

# AWBI in Breast Cancer

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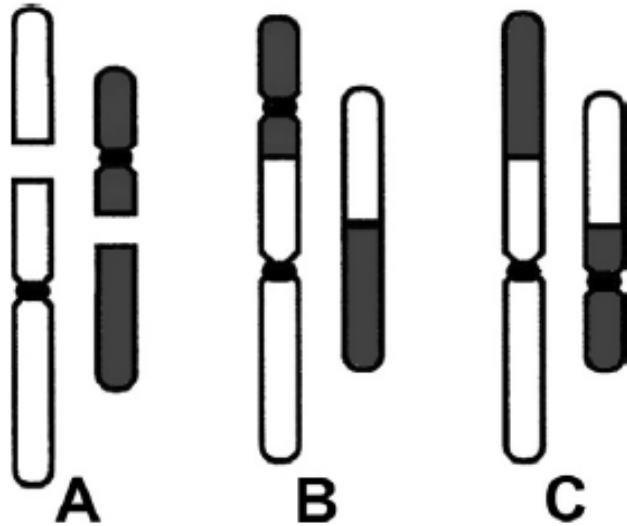
# Introduction

## Prospective randomized trials comparing Lumpectomy Alone vs. with WBRT

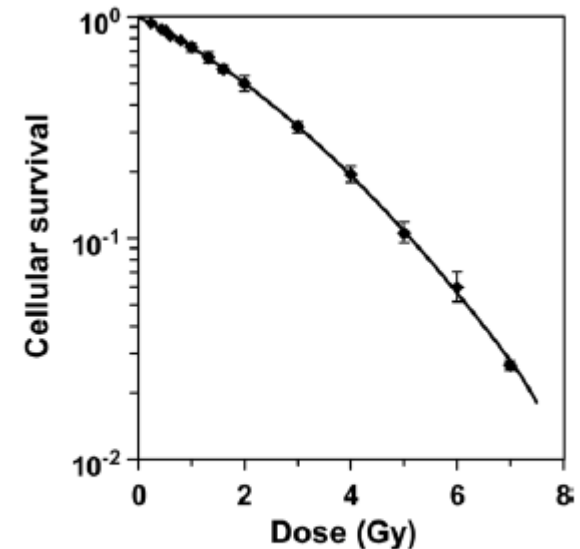
Trial	N	F/U (yr)	op	Breast recurrence (%)		% reduction
				BCS	BCS + RT	
Sweden	381	10	Q	24	9	63
Milan III	579	10	Q	24	6	75
NSABP-B06	1262	20	L	39	14	64
Ontario	837	7.6	L	35	11	69
Scottish	585	7.7	L	25	5	80
England	399	>5	L	35	13	63
Finland	152	6.7	L	18	8	56
NSABP-B21	1009	8	L	16.5	2.8*	83

\* Patients received tamoxifen

# Linear-Quadratic (LQ) model for radiotherapy



**Figure 1** Examples of binary misrepair. Figure 1A shows 2 chromosomes; each has 1 DSB, shown as a gap. Centromeres, which are needed for proper transmission of chromosomes to daughter cells at mitosis, are shown as black constrictions. Most DSBs are correctly restituted, but a few undergo binary misrepair. As shown in Figure 1B, binary misrepair can result in a dicentric chromosome aberration, which generally destroys the clonogenic viability of the cell. In about half the binary misrepair events, the 2 DSB shown in Figure 1A lead to a translocation, shown in Figure 1C; translocations involve large-scale rearrangements and can cause potentially precarcinogenic alterations in cellular phenotype, but most do not impair cellular survival.

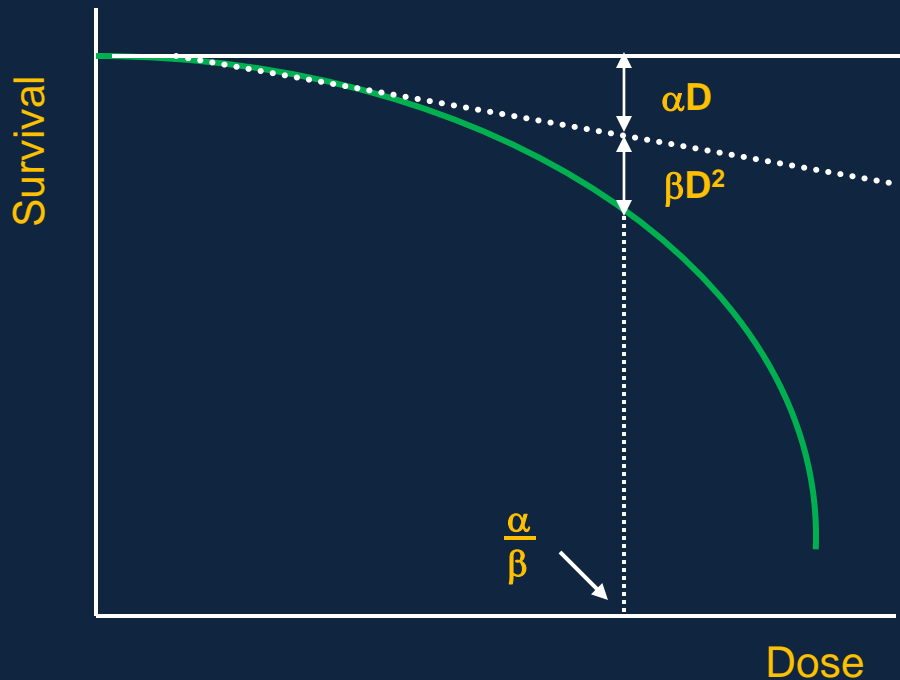


**Figure 2** Survival of x-irradiated CHO cells, determined by flow cytometry population counting, 5 days after treatment.<sup>22</sup> The curve is the corresponding LQ model fit.

$$S = e^{-\alpha D - \beta D^2}$$

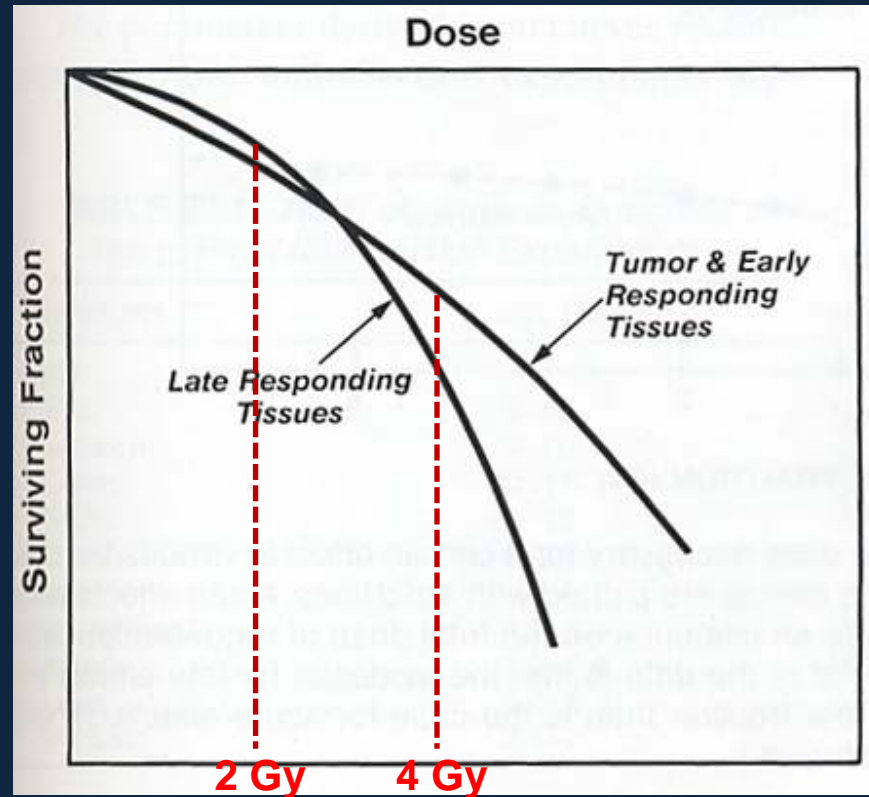
## $\alpha/\beta$ ratio

- linear ( $\alpha$ ) and the quadratic ( $\beta$ ) component of cell killing are equal.
- $\alpha D = \beta D^2$



- Early or tumor: less curved
  - linear ( $\alpha$ ) is steeper,  $\alpha/\beta$  is large (10 Gy)
- Late: more curved
  - linear small, quadratic ( $\beta$ ) is big,  $\alpha/\beta$  is small (2-3 Gy)

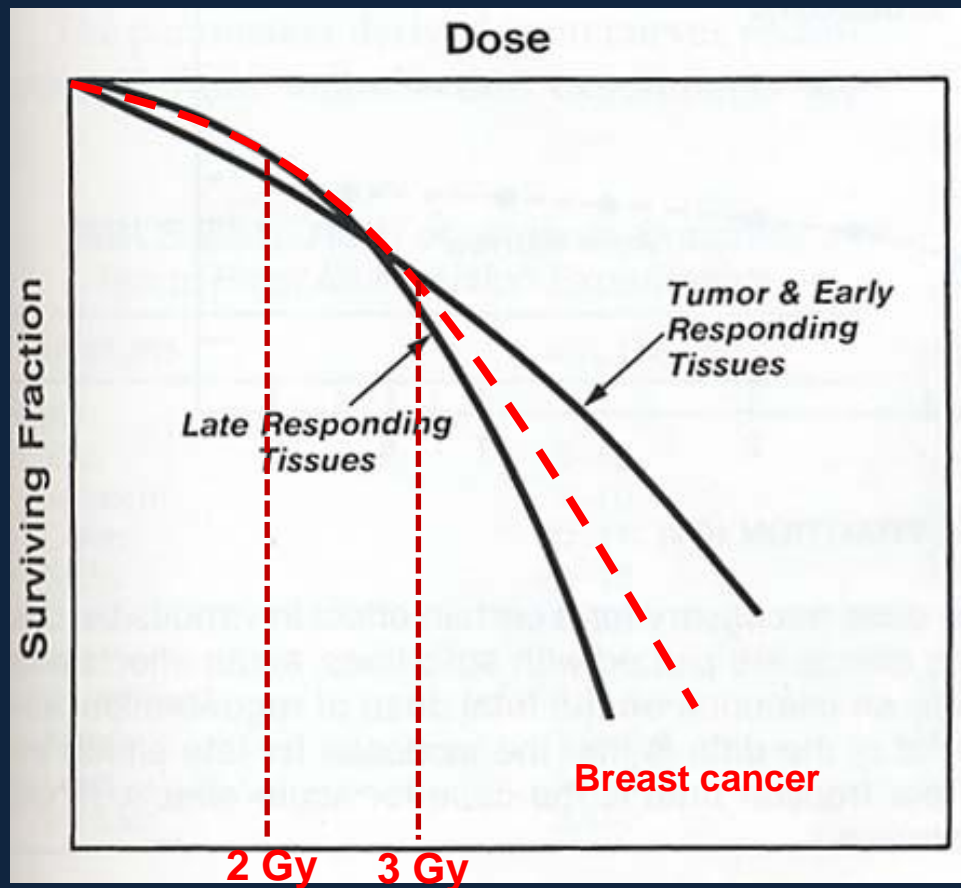
# Dose-response Relationship



Dose-response relationship for late responding tissues is more curved.  
→ Larger  $\alpha/\beta$  ratio for early responding tissues.

# $\alpha/\beta$ ratio of Breast

	$\alpha/\beta$ ratio, Gy
Conventional	
Tumor	10
Normal tissue effect	3
In vitro human breast ca. cell lines	4
*Locoregional tumor control	4.6
Change in photographic breast appearance	3.4

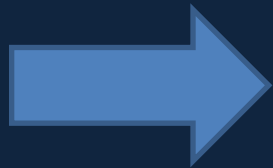


$\alpha/\beta$  ratio of breast cancer: 4.6 Gy  
 breast normal tissue: 3.4 Gy

➔ conventional (2Gy) and hypo (3Gy) fractionation  
 - No big difference of effectiveness and toxicity

# Hypofractionated RT

- 1) Shorter total treatment time
- 2) More convenient for patient ( Time and \$ )
- 3) Less resource intensive



**1) Treatment Outcome ?**

**2) Cosmetic effect ?**



# Randomized trials of breast hypofractionation

	RMH/GOC	START A	START B	Canadian
Site	UK	UK	UK	Canada
Years accrual	1986–98	1998–2002	1999–2001	1993–96
Standard arm	50 Gy/25F	50 Gy/25F	50 Gy/25F	50 Gy/25F
Experimental arm A	42.9 Gy/13F	41.6 Gy/13F	40 Gy/15F	42.5 Gy/16F
Experimental arm B	39 Gy/13F	39 Gy/13F	N/A	N/A
Mean age (years)	54.5	57.2	57.4	Not reported
Node + (%)	32.7	28.8	22.8	0
Mastectomy (%)	0	15	8	0
Tumor size ≥ T2 (%)	42.5 <sup>a</sup>	48.6	35.9	20
Boost (%)	74.5	60.6	42.6	0
Chemotherapy (%)	13.9	35.5	22.2	11
Regional RT (%)	20.6	14.2	7.3	0

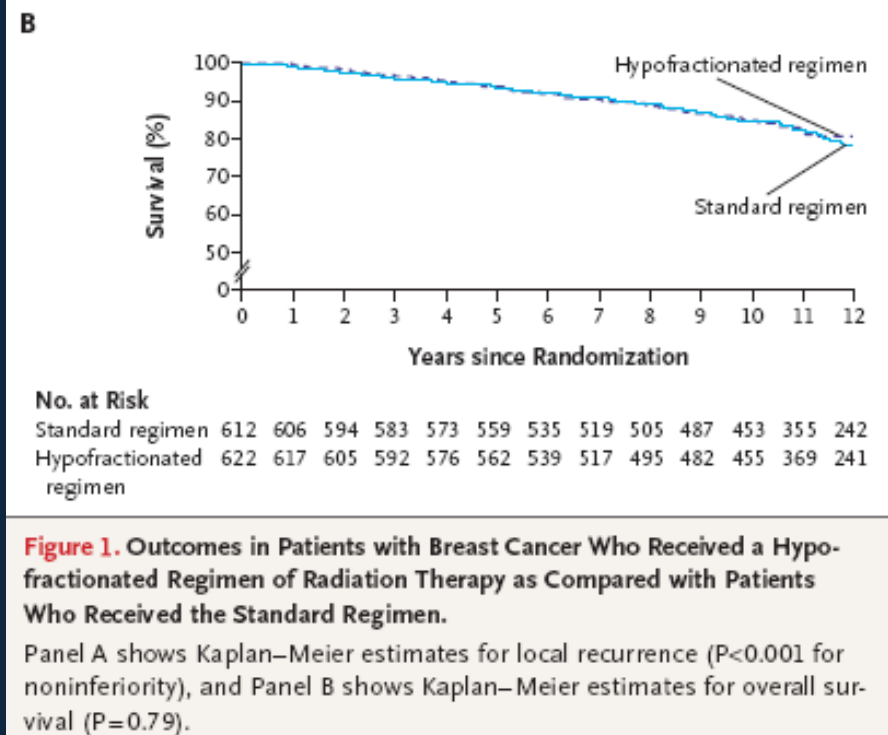
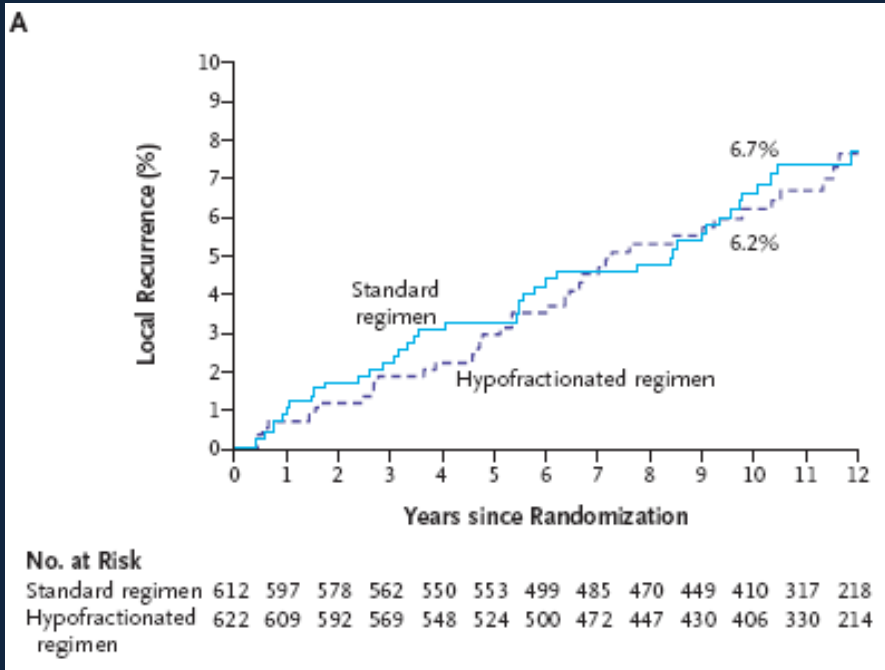
N	1410	2236	2215	1234
Daily dose	3.3/3	3.2/3	2.67	2.66
Weeks	5/5	5/5	3	3.5

***Hypofractionation achieves equivalent local control to  
'standard' fractionation.***

	Total dose(Gy) / fractionation	Daily dose /total weeks	5yr local recurrence (%)	10yr local recurrence (%)
RMH/GOC	50/25 39/13 42.9/13	2Gy/5wks 3Gy/5wks 3.3Gy/5wks		12.1 14.8 9.6
START A	50/25 39/13 41.6/13	2Gy/5wks 3Gy/5wks 3.2Gy/5wks	3.6 5.2 3.5	8yr, no diff. btw arms
START B	50/25 40/15	2Gy/5wks 2.67Gy/3wks	3.3 2.2	8yr, no diff. btw arms
Canadian	50/25 42.5/16	2Gy/5wks 2.66Gy/3.5wks	3.2 2.8	6.7 6.2

# Long-Term Results of Hypofractionated Radiation Therapy for Breast Cancer

Timothy J. Whelan, B.M., B.Ch., Jean-Philippe Pignol, M.D., Mark N. Levine, M.D.,



*Hypofractionation achieves equivalent normal tissue effects compared to 'standard' fractionation.*

RMH/GOC

START A

START B

Canadian

Total dose (Gy)/fraction	Excellent/good cosmesis or no change (%)		Marked change (% or HR*)		Moderate/marked induration (% or HR*)		Skin toxicity (% or HR*)	
	5 yr	10 yr	5 yr	10 yr	5 yr	10 yr	5 yr	10 yr
50/25	60.4	46.6	6.4	9.8	23.1	36.3	12.0	18.1
<u>42.9/13</u>	54.3	42.0	11.2	15.6	35.6	51.1	13.0	18.0
39/13	69.7	43.9	3.9	6.6	16.0	27.7	5.6	12.0
50/25	59.0		1.0*		1.0*		1.0*	
<u>41.6/13</u>	58.1		1.09*		1.09*		0.83*	
39/13	65.9		0.69*		0.79*		0.63*	
50/25	58.8		1.0*		1.0*		1.0*	
40/15	64.5		0.83*		0.88*		0.76*	
50/25	79.2	71.3			6.1	10.4	3.3	7.7
42.5/16	77.9	69.8			4.7	11.9	3.2	8.9

Fractional dose > 3 Gy showed a little higher cosmetic change and induration

## IMPACT OF FRACTION SIZE ON CARDIAC MORTALITY IN WOMEN TREATED WITH TANGENTIAL RADIOTHERAPY FOR LOCALIZED BREAST CANCER

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Table 4. Relative risk (95% confidence interval) of cardiovascular death by age, fraction size, and laterality

Age (y)	Fraction size (Gy)	Laterality	Cumulative incidence of cardiac death at 10-y follow-up (%)	Relative risk* at 10-y follow-up
All ages	≤2	Right	1.01	<b>1.00</b>
		Left	0.96	0.95 (0.24–3.78)
	>2	Right	1.73	<b>1.00</b>
		Left	1.86	1.07 (0.68–1.69)
≤60	≤2	Right	0.00	<b>1.00</b>
		Left	0.00	N/A
	>2	Right	0.70	<b>1.00</b>
		Left	0.34	0.49 (0.15–1.62)
>60	≤2	Right	2.68	<b>1.00</b>
		Left	2.37	0.90 (0.23–3.53)
	>2	Right	3.05	<b>1.00</b>
		Left	3.74	1.22 (0.75–2.01)

\* Relative risk of cardiac death for women with left-sided compared with right-sided breast cancer adjusted for age and fraction size.

***Hypofractionated adjuvant RT did not significantly increase the risk of cardiac mortality.***

## DCIS, retrospective data.

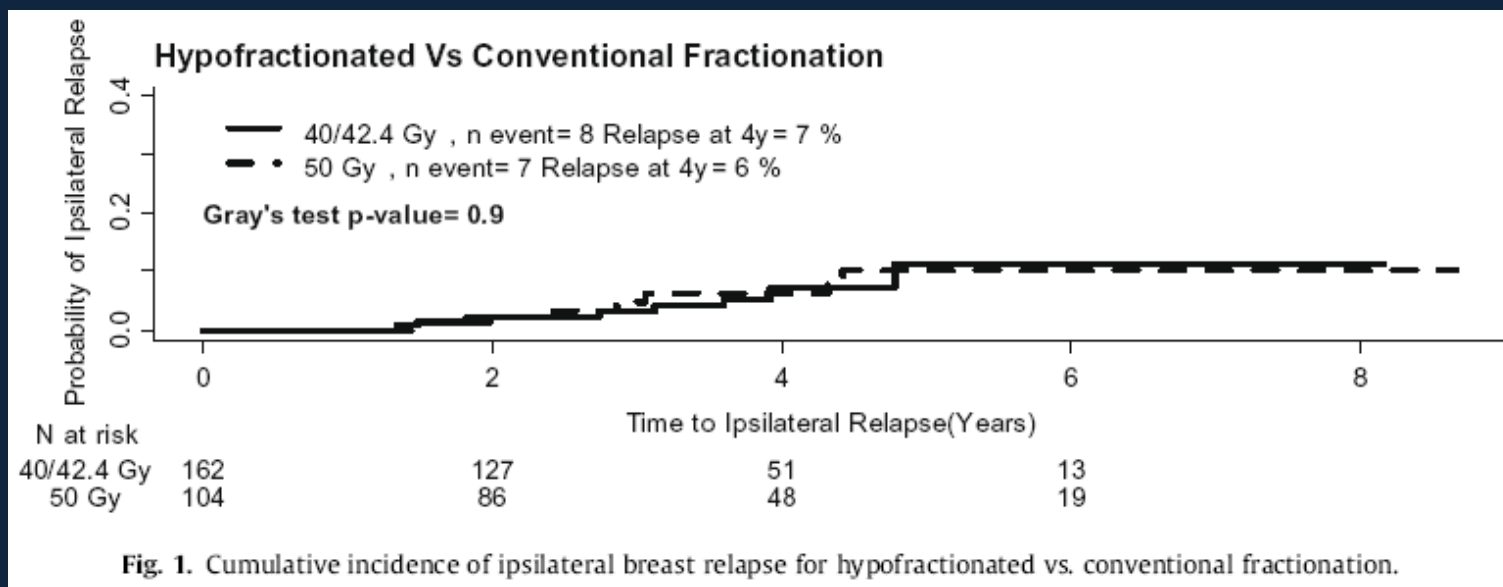
- Conventional 50Gy/25fx (n=104)
- AWBI 42.4Gy/16fx or 40Gy/16fx+ 12.5Gy boost (n=162)

Ductal carcinoma in situ

Local control with conventional and hypofractionated adjuvant radiotherapy after breast-conserving surgery for ductal carcinoma in-situ <sup>☆</sup>

Deborah Williamson <sup>a</sup>, Robert Dinniwel <sup>a</sup>, Sharon Fung <sup>b</sup>, Melania Pintilie <sup>b</sup>, Susan J. Done <sup>c</sup>, Anthony W. Fyles <sup>a,\*</sup>

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## NCC trial (NCCCTS-07-267)

- Phase II Study of Accelerated Whole Breast Irradiation (AWBI) after Lumpectomy in Patients with Stage I and II Breast Cancer
- Accrual of patients: 277 (2007. 5-2009. 7)
- Whole Breast 39 Gy / 13 fractions + Tumor Bed Boost 9 Gy / 3 fractions

BED calculation according to START trial  $\alpha/\beta$  ratio

	total dose (Gy)	fx. dose (Gy)	fx. number	tx. Time (weeks)	tumor BED ( $\alpha/\beta=4.6\text{Gy}$ )	late BED ( $\alpha/\beta=3.4\text{ Gy}$ )
Conventional 50.4Gy+boost 10Gy	60.4	1.8	33	6.5	84.5	93.0
Conventional 50.4Gy	50.4	1.8	28	5.5	70.1	77.1
Conventional 50.0Gy	50.0	2.0	25	5	71.7	79.4
AWBI, 39Gy (RMH & START A)	39.0	3.0	13	5	64.4	73.4
AWBI, 42.9Gy (RMH)	42.9	3.3	13	5	73.7	84.5
AWBI, 41.6Gy (START A)	41.6	3.2	13	5	70.5	80.8
AWBI, 40Gy (START B)	40.0	2.7	15	3	63.2	71.4
AWBI, 48Gy (NCC-267)	48.0	3.0	16	3	79.3	90.4

# NCCCTS-07-267: Scheme

NCC Conventional RT 60.4 Gy / daily dose 1.8Gy / 33 fractions / 6.6 weeks

Whole breast (28 fx)



NCC Hypofractionated RT 48 Gy / daily dose 3.0 Gy / 16 fractions / 3.2 weeks

Whole breast (13 fx)





# Patient Characteristics (N=277)

Median FU: 3.1 years

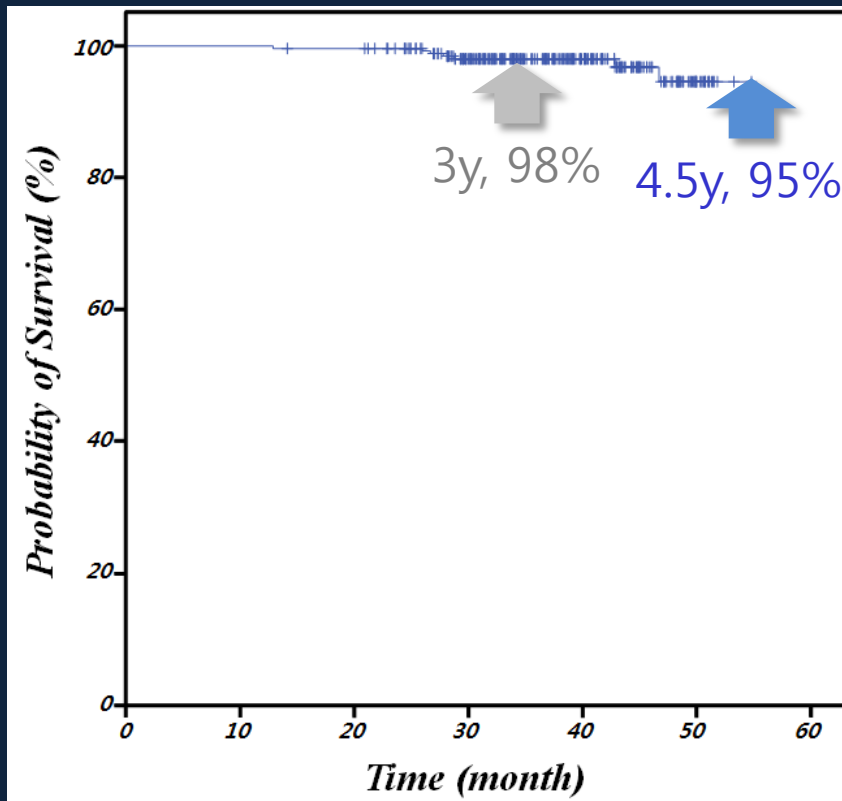
Characteristics	No.	%
<b>Age</b>		
30-39	16	6
40-49	100	36
≥ 50	161	58
Median	53 yo	
<b>Menopause</b>		
Pre	146	53
Peri	7	3
Post	124	44
<b>Tumor location</b>		
Right	148	53
Left	129	47
<b>Histology</b>		
Ductal	244	88
Others	33	12

Characteristics	No.	%
<b>pT stage</b>		
pT1	195	70
pT2	82	30
<b>pN stage</b>		
pN0	239	86
pN1mi	23	8
pN1a	15	5
<b>EIC</b>		
Yes	113	41
No	137	49
Unknown	27	10
<b>Grade</b>		
Low	22	8
Intermediate	171	62
High	78	28
Unknown	6	2

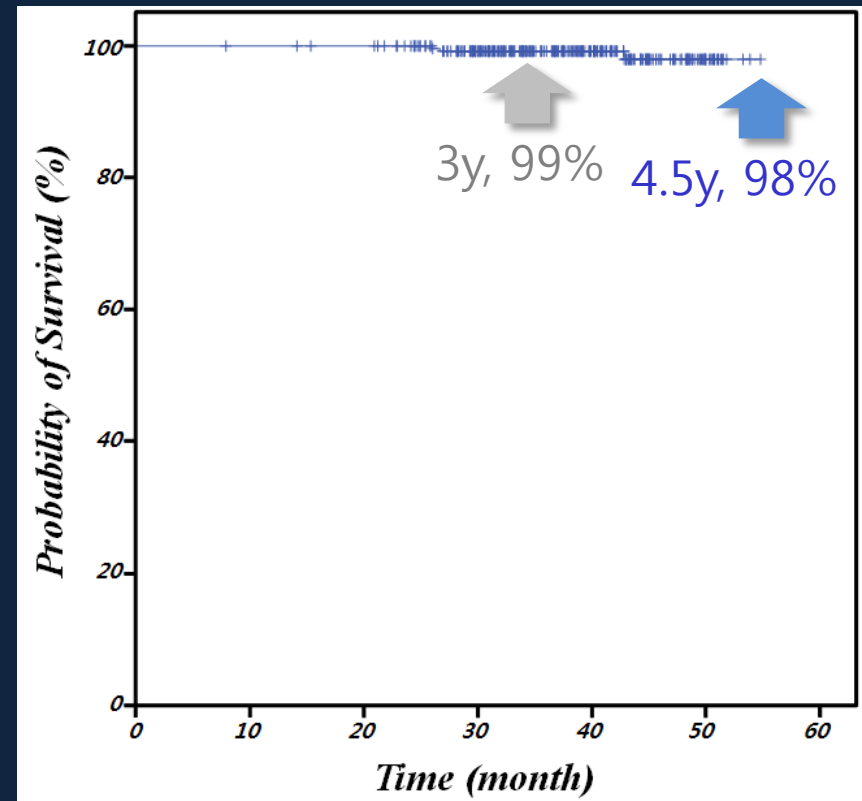
Characteristics	No.	%
<b>ER status</b>		
Positive	206	74
Negative	71	26
<b>Hormonal therapy</b>		
Yes	214	77
No	63	23
<b>Adj. Chemotherapy</b>		
Yes	205	74
No	72	26

# Results : *Survival analysis*

## Disease Free Survival

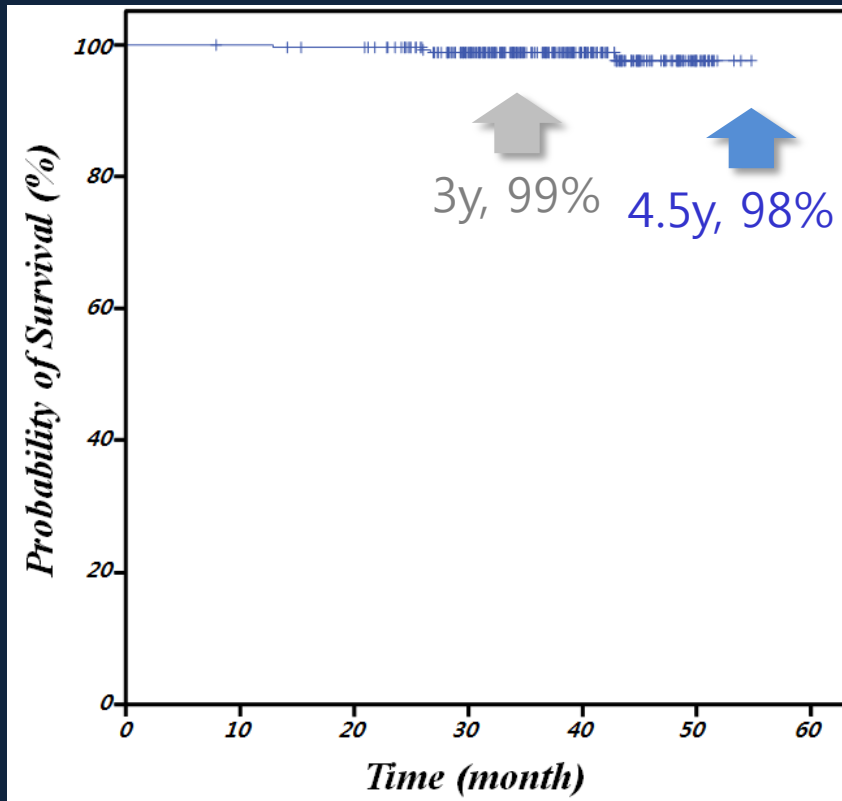


## IBTR-free survival

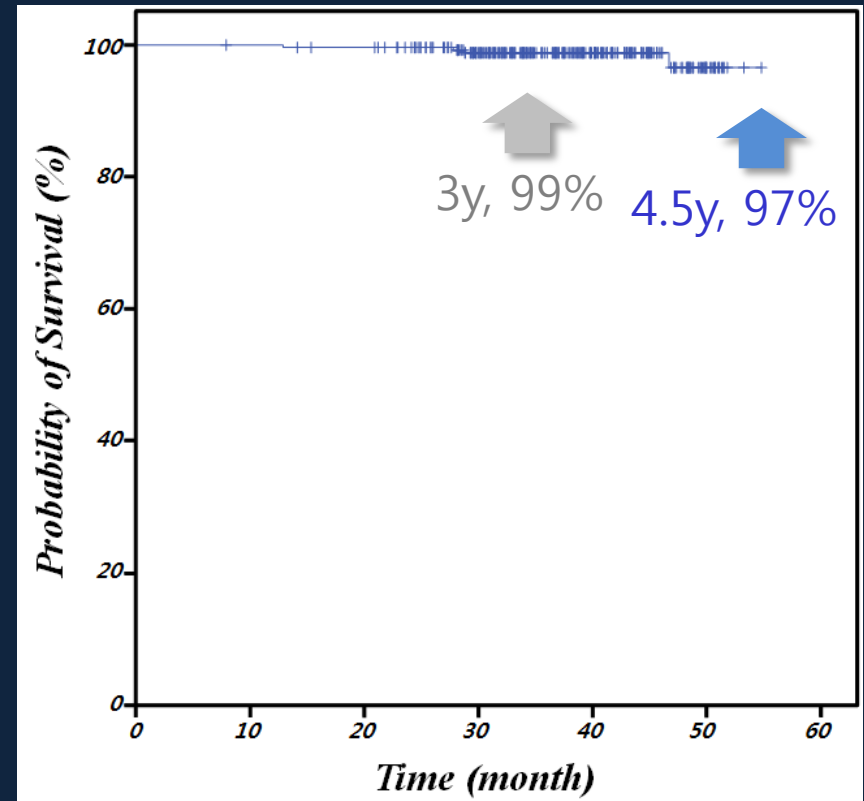


# Results : *Survival analysis*

## LRR-free survival

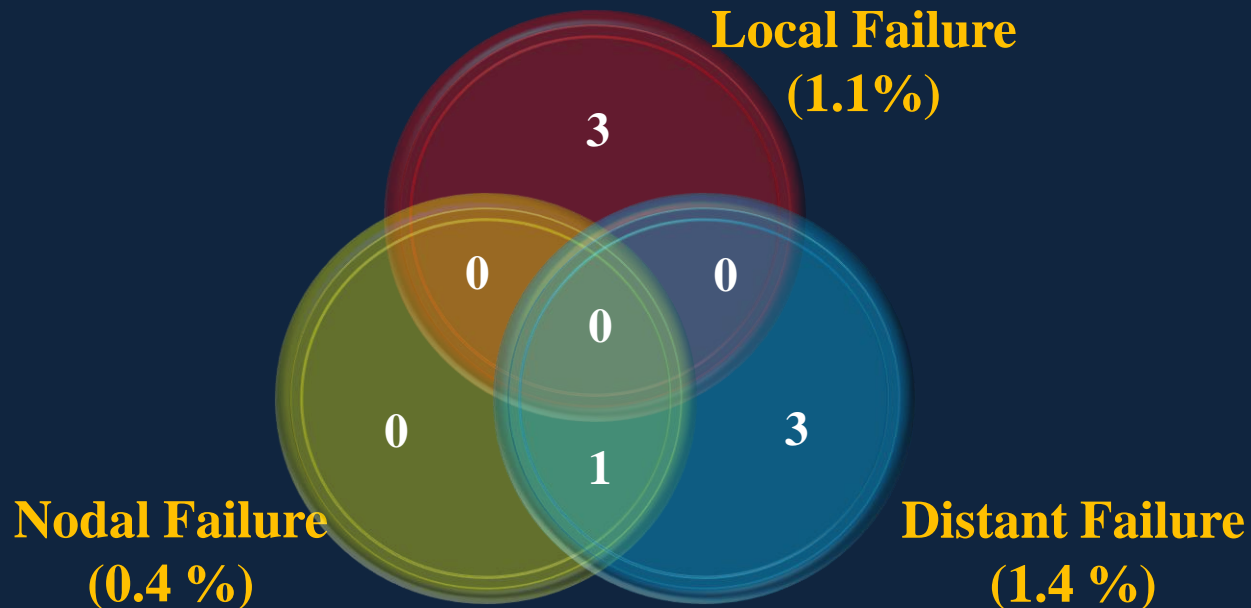


## Distant relapse-free survival



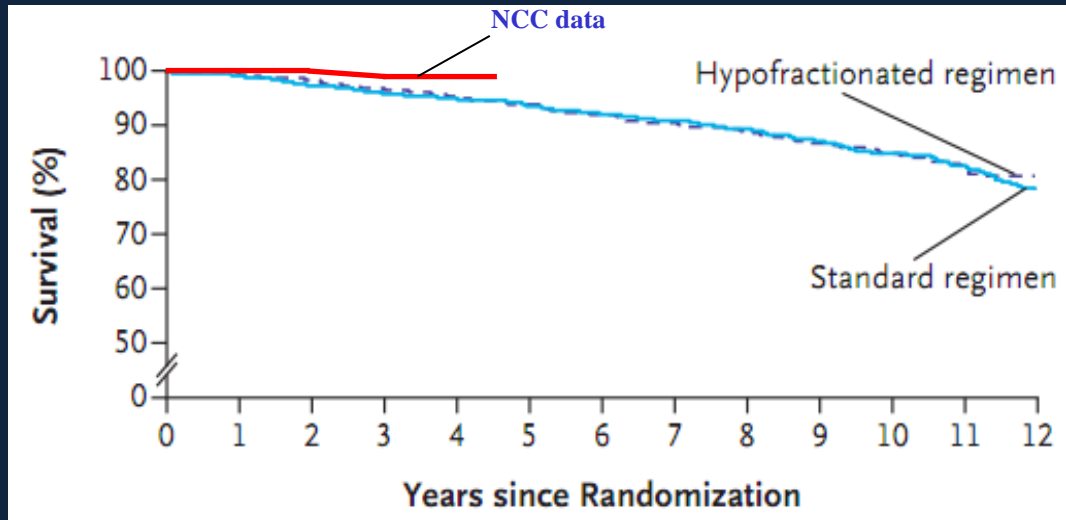
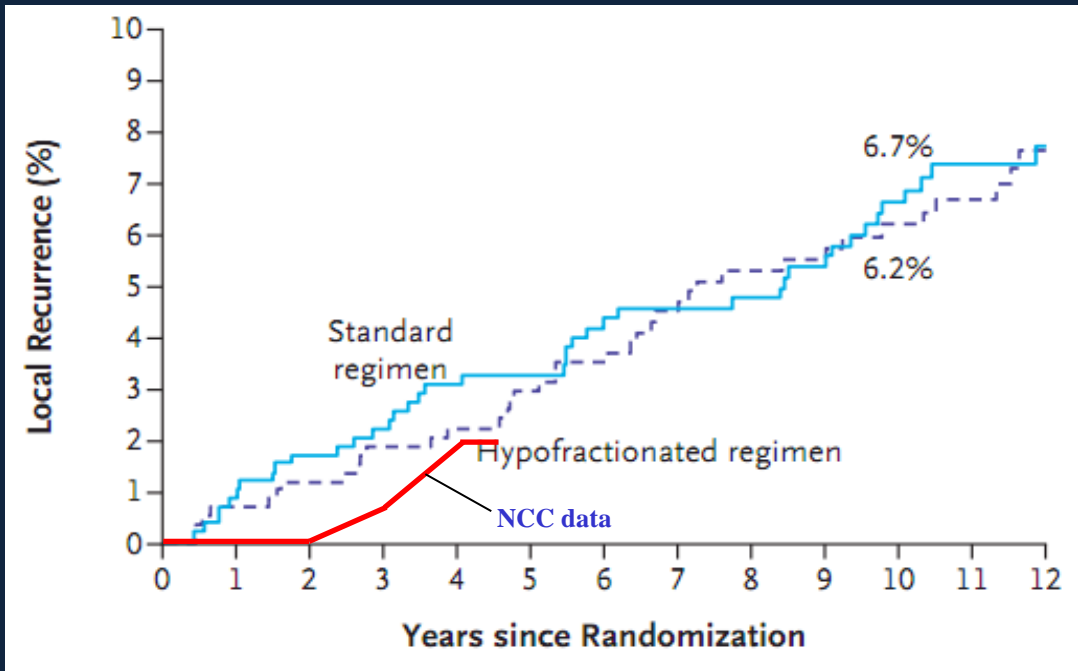
# Results : *Recurrence pattern*

- Recurrence : *Total 7 patients*



# Comparison with other studies

	<b>NCC</b>	<b>START A</b>	<b>START B</b>	<b>Canadian</b>
<b>Patient, n</b>	277	2236	2216	1234
<b>Stage</b>	T1-2 N0-1 M0	T1-3a N0-1 M0	T1-3a N0-1 M0	T1-2 N0 M0
<b>Median F/U</b>	3.1 years	5.1 years	6 years	12 years
<b>Dose schedule</b>	<b>39 Gy / 13 F + 9 Gy / 3F (Boost)</b>	<b>A : 39 Gy / 13F B : 41.6 Gy / 13F C : 50 Gy / 25F</b>	<b>A : 40 Gy / 15 F B : 50 Gy / 25F</b>	<b>A : 42.5 Gy / 16 F B : 50 Gy / 25F</b>
<b>Boost RT</b>	100%	61%	43%	0%
<b>Results</b>	<b>4.5-year LRR - 2.4%</b>	<b>5-year LRR - 39 Gy : 5.2% - 41.6 Gy : 3.5% - 50 Gy : 3.6%</b>	<b>5-year LRR - 40 Gy : 2.2% - 50 Gy : 3.3%</b>	<b>10-year LRR - 42.5 Gy : 6.2% - 50 Gy : 6.7%</b>



# Cosmesis

	Total dose(Gy) / fractionation	Excellent/Good Cosmesis or no change (%) (5 year)
RMH/GOC	50/25 39/13 42.9/13	60.4 54.3 69.7
START A	50/25 39/13 41.6/13	59.0 58.1 65.9
START B	50/25 40/15	58.8 64.5
Canadian	50/25 42.5/16	79.2 77.9
NCC, Korea	39/13+boost 9/3	80.2 (3 year)

# Skin toxicity

	Total dose(Gy) / fractionation	Moderate /Marked Induration (%)		Skin toxicity (%)	
		5 yr	10 yr	5 yr	10 yr
RMH/GOC	50/25	23	36	12	18.1
	39/13	36	51	13	18
	42.9/13	16	28	5.6	12
START A	50/25	1.0		1.0	
	39/13	1.09		0.83	
	41.6/13	0.69 (HR)		0.63	
START B	50/25	1.0		1.0	
	40/15	0.83 (HR)		0.76	
Canadian	50/25	6.1	10.4	3.3	7.7
	42.5/16	4.7	11.9	3.2	8.9
NCC, Korea	39/13+boost 9/3	2.7 (3yr)		Grade 1 (3yr) Hyperpigmentation	1.8
				breast pain	7.1
				induration	2.7



# ASTRO guideline



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**CLINICAL INVESTIGATION**

**Breast**

## FRACTIONATION FOR WHOLE BREAST IRRADIATION: AN AMERICAN SOCIETY FOR RADIATION ONCOLOGY (ASTRO) EVIDENCE-BASED GUIDELINE

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FRANK A. VICINI, M.D., FACR.,||| JULIA R. WHITE, M.D.,## AND BRUCE G. HAFFTY, M.D.\*\*\*

Table 1. Evidence supports the equivalence of hypofractionated whole breast irradiation with conventionally fractionated whole breast irradiation for patients who satisfy all of these criteria\*

1. Patient is 50 years or older at diagnosis.
2. Pathologic stage is T1–2 N0 and patient has been treated with breast- conserving surgery.
3. Patient has not been treated with systemic chemotherapy.
4. Within the breast along the central axis, the minimum dose is no less than 93% and maximum dose is no greater than 107% of the prescription dose ( $\pm 7\%$ ;) (as calculated with 2-dimensional treatment planning without heterogeneity corrections).

Table 4. Characteristics of patients enrolled on clinical trials comparing hypofractionated whole breast irradiation with conventionally fractionated whole breast irradiation

	Canada (18, 19, 21) N = 1,234	RMH/GOC (17, 20) N = 1,410	START A (10) N = 2,236	START B (16) N = 2,215
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**Conclusion:** Data were sufficient to support the use of HF-WBI for patients with early-stage breast cancer who met all the aforementioned criteria. For other patients, the task force could not reach agreement either for or against the use of HF-WBI, which nevertheless should not be interpreted as a contraindication to its use.

Age $\geq 50$ years	929	75%	987	70%
pT1–2	1,234	100%	1,324	94%
pN0	1,234	100%	564	40%
Chemotherapy not used	1,098	89%	1,214	86%
Central axis inhomogeneity –7% to +7%	1,234	100%	1,410	100%
High tumor grade	233	19%		

Abbreviations: CF = conventional fractionation; HF = hypofractionation; RMH/GOC = randomized, multicenter, phase III trial comparing hypofractionated whole breast irradiation with conventionally fractionated whole breast irradiation; START = standardization of breast radiotherapy; WBI = whole-breast irradiation.



“The 50Gy in 25 fractions prescription does not have the advantage of convenience for patients nor the advantage of a reduced biological effectiveness associated with the ‘extended’ fractionation schedule and, in our view should no longer be the ‘standard’ for whole breast RT following BCS. ”

*Holloway CL. The breast 19:163-7, 2010*

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Practice Guidelines  
in Oncology – V.2.2010

**Invasive Breast Cancer**

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[Breast Cancer TOC](#)  
[Staging, Discussion, References](#)

#### PRINCIPLES OF RADIATION THERAPY

##### Whole Breast Radiation:

Target delineation includes the majority of the breast tissue, and is best done by both clinical assessment and CT-based treatment planning. A uniform dose distribution is the objective, using compensators such as wedges, forward planning using segments, or intensity modulated radiation therapy (IMRT). The breast should receive a dose of 45-50 Gy in 1.8 - 2 Gy per fraction, or 42.5 Gy at 2.66 Gy per fraction. A boost to the tumor bed is recommended in patients at higher risk for local failure, (age < 50, positive axillary nodes, lymphovascular invasion, or close margins). This can be achieved with brachytherapy or electron beam or photon fields. Typical doses are 10-16 Gy at 2 Gy/fx. All dose schedules are given 5 days per week.

# APBI vs. AWBI

	APBI	AWBI
Inclusion criteria	Very selective, most favorable group	Wider applicability
Treated volume	Partial volume of breast	Whole breast
Level of evidence available	Level II	Level I
Technique	Usually invasive	Non-invasive
Learning Curve	Yes	No
Local control	Acceptable	Acceptable
Survival	No mature randomized data	Acceptable

# Cost comparison

- ◆ Suh WW et al.
  - 2003 Medicare Fee Schedule

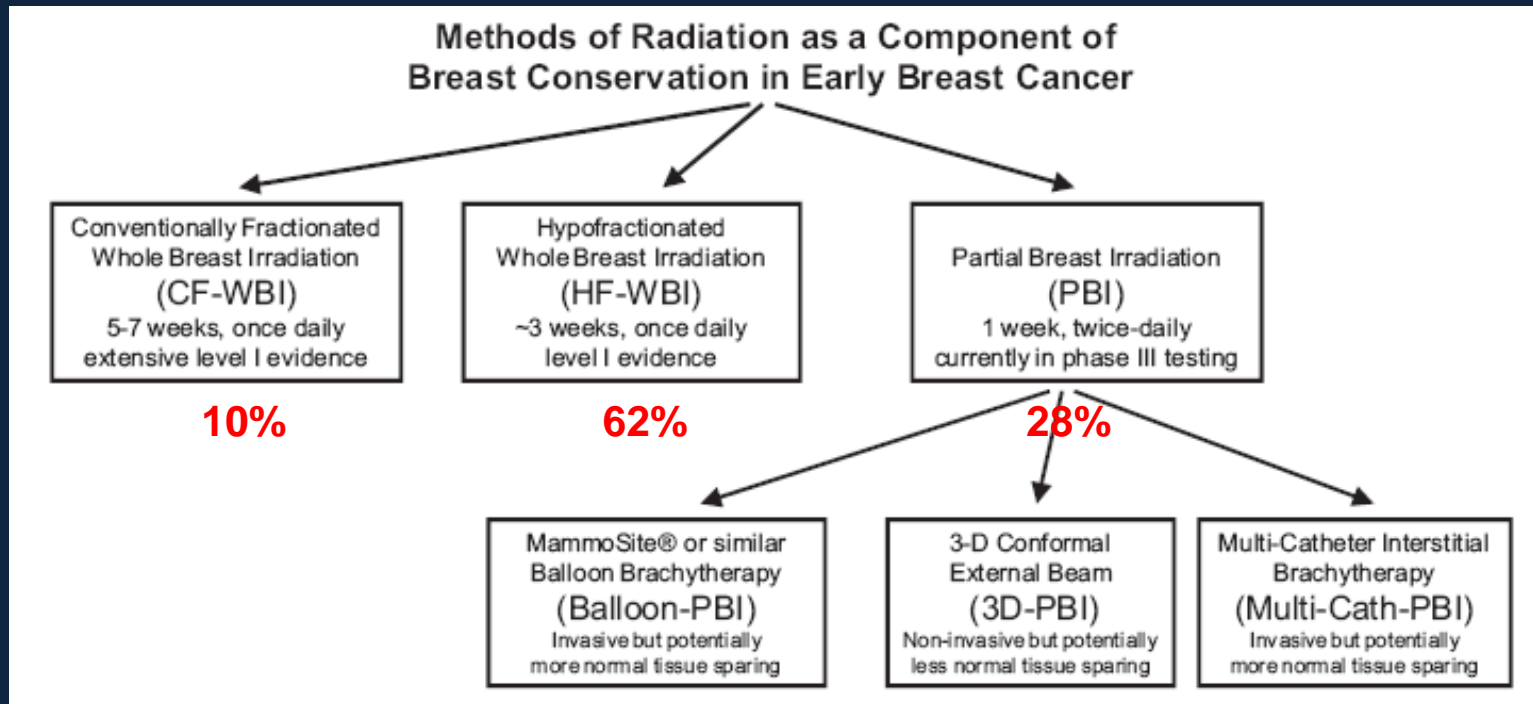
Table 5. Summary of total direct RT costs for eight treatment regimens

Cost	Whole breast				Partial breast			
	WBRT-B (\$)	WBRT (\$)	WBRT-AC (\$)	WBRT-IMRT (\$)	APBI-IC (\$)	APBI-IT (\$)	APBI-3D-CRT (\$)	APBI-IMRT (\$)
<b>Payer's</b>								
Technical	7,500	5,800	4,100	15,600	15,800	13,000	5,000	7,100
Professional	2,000	1,600	1,300	2,300	2,000	3,800	2,200	2,100
Subtotal	9,500	7,400	5,400	17,900	17,800	16,800	7,200	9,200
<b>Patient's</b>								
Time	900	700	500	900	300	300	300	300
Transport	500	400	200	500	200	200	200	200
Subtotal	1,400	1,100	700	1,400	500	500	500	500
<b>Society's</b>								
Total	10,900	8,500	6,100	19,300	18,300	17,300	7,700	9,700

*Abbreviations:* RT = radiotherapy; WBRT-B = whole-breast RT with boost; WBRT-AC = WBRT on accelerated schedule; IMRT = intensity-modulated RT; APBI = accelerated partial-breast irradiation; IC = partial-breast HDR brachytherapy technique based on the MammoSite Radiation Therapy System; HDR = high dose rate; IT = interstitial; 3D-CRT = three-dimensional conformal RT.

# Patient preference

- ◆ Hoopes DJ et al.
  - 1,807 patients respond



# Questions to be solved (AWBI)

- DCIS
- Boost
- Regional radiotherapy
- Women with large breasts
- Late toxicities: brachial plexopathy, lymphedema, heart