Optimizing Adjuvant Radiation for Breast Cancer: The Story of Hypofractionation

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Overview of Talk

- History and Rationale for Hypofractionation
- Clinical Evidence for Hypofractionation
- Clinical and Research Implications

*Whelan et al. *Semin Radiat Oncol* Oct 2008

Radiotherapy Fractionation

- **Early 1900's:** radiotherapy initially delivered in single/few fractions
  - Increased toxicity, limited tumor control
- **1920-1930:** experience in France with multiple fractions over longer duration in H&N cancer
  - Less toxicity, increased tumor control
- Fractionation of radiation adopted based on empiric observation
- Before the era of randomized trials

Radiobiology of Fractionation

The “4 Rs”

- **Repair of sub lethal damage**
- **Repopulation**
- **Reassortment of cells within the cell cycle**
- **Reoxygenation**

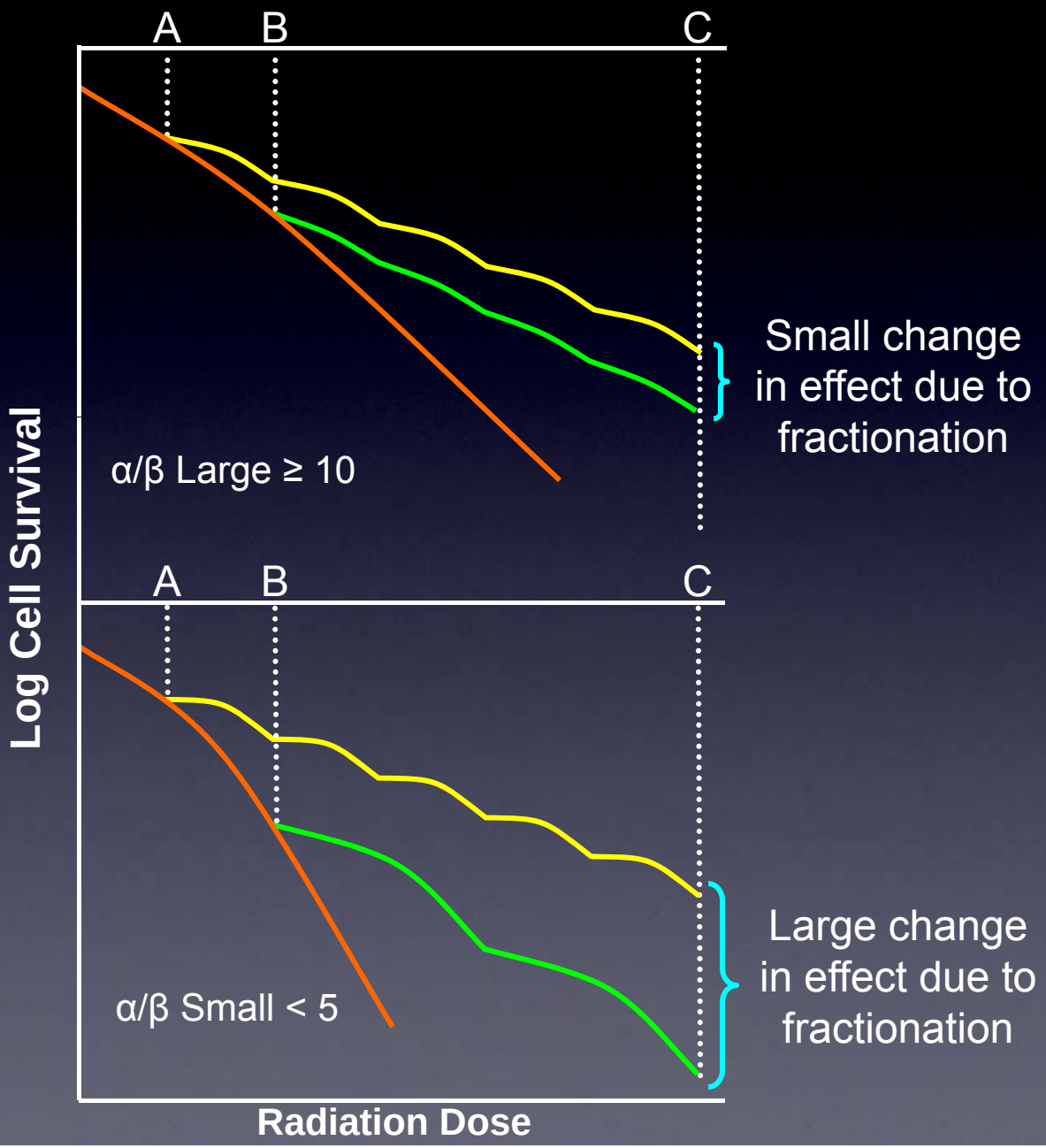
Effect of Fractionation Can Be Predicted

- Effected by size of fraction, total dose of radiation and overall treatment time
- Linear quadratic model
- Biological Effective Dose (BED) =

$$\text{Total Dose (TD)}\ (1 + \frac{\text{fraction size}}{\alpha/\beta}) - F(T)$$

- Affect of fraction size modified by inherent sensitivity (α/β ratio) of the tumor or normal tissue

Cell Survival Curves



Choice of Fractionation ~ Therapeutic Ratio

- **Maximize tumor cell kill and limit normal tissue damage**
- **If α/β ratio of tumor is high (often 10 or greater) and > α/β ratio of normal tissue (often < 5) a lower dose per fraction *(hyperfractionation)* is preferred**
  - **e.g., squamous cancer of head and neck, lung**
- **If α/β ratio of tumor is $\leq$ normal tissue then a larger dose per fraction *(hypofractionation)* is preferred**
  - **e.g., prostate cancer, breast cancer**

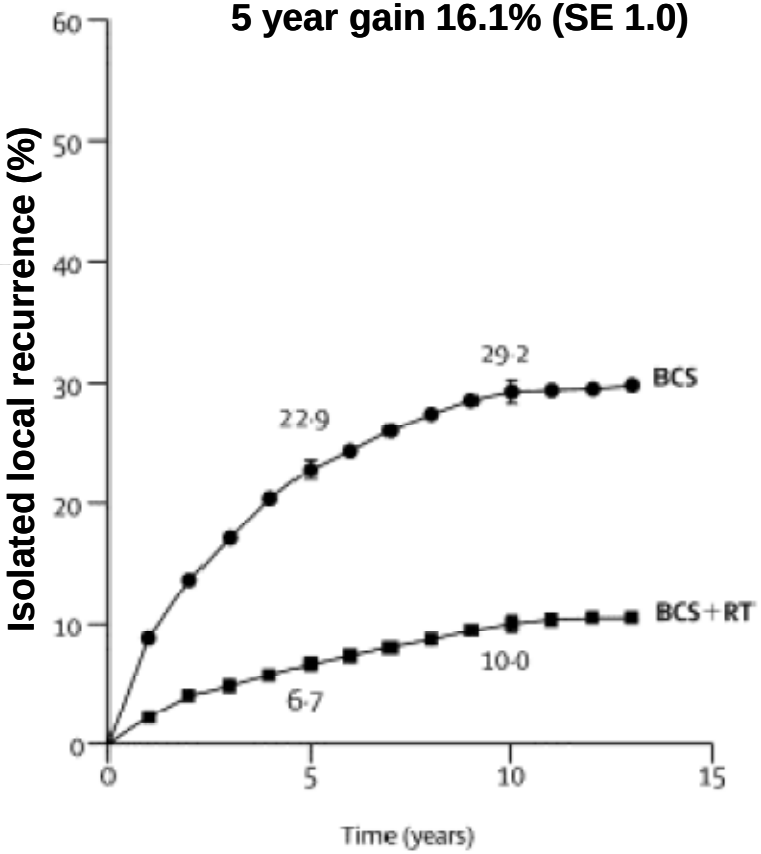
Whole Breast Irradiation

- Integral part of breast conserving therapy
- Reduces the risk of local recurrence and prevents subsequent mastectomy

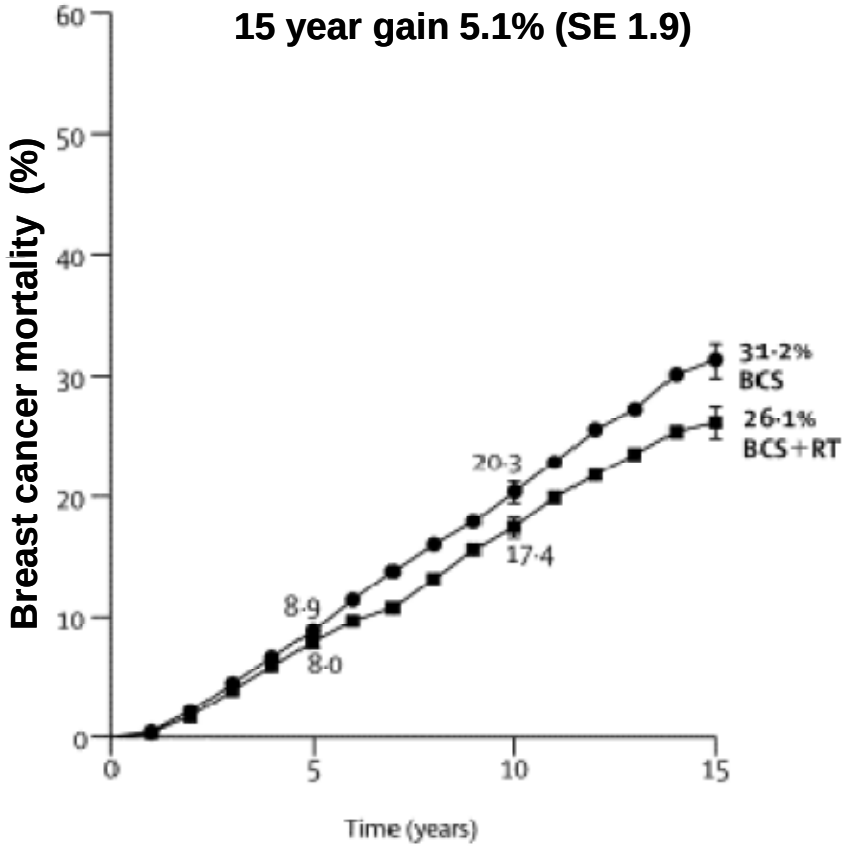
Whole Breast Irradiation

6097 women with BCS and node negative disease

5 year gain 16.1% (SE 1.0)



15 year gain 5.1% (SE 1.9)



EBCTCG *Lancet* 2005; 366: 2087-2106

Whole Breast Irradiation

- Despite the benefits it is estimated that 20-30% of woman do not receive it
  - Inconvenience
  - Cost

Fractionation for Whole Breast Irradiation

- **Commonly given as 45-50 Gy/25 fractions at 1.8-2 Gy / frac / day ± boost irradiation (10-16 Gy/5-8 frac)**
- **Close to tolerance of normal tissue**
- **1960's: adopted higher fraction sizes (2.5-2.7 Gy) because of limited resources → increased toxicity**
- **Centers in the UK and Canada adopted similar fraction size but *reduced total dose* with limited toxicity and good local control**

Clinical Evidence for Hypofractionation

- Indirect comparisons from randomized trials of whole breast RT
- Prospective cohort studies
  - Single institution
  - Multi institution
- Direct comparisons from randomized trials of hypofractionation

Summary of RCTs of Breast RT

Study	Number of Patients	RT	Frac (Gy)	FU Yrs	Local Rec %	RR
NSABP	1137	50 Gy/25	2.0	12	10 v 35	.29
Uppsala -Örebro	381	54 Gy/27	2.0	9	9 v 24	.39
OCOG	837	40 Gy/16 + 12.5 Gy/5	2.5	8	11 v 35	.31
Milan	567	50 Gy/25 + 10 Gy/5	2.0	9	6 v 24	.25
Scottish	585	50 Gy/20-25 + 10-30 Gy	2.5	6	6 v 24	.25
Finland	152	50 Gy/25	2.0	7	8 v 18	.44

Single Institution Cohort Studies

Study	Patients	Fractionation Schedule	Median Follow-up (y)	Local Recurrence (%)	Cosmetic Outcome at 5 years (% excellent/ good)
Ash et al. 1995	339 node –ve	40 Gy/15 frac/ 3 weeks	7	13.8	66
Yamada et al. 1999	183 node –ve and +ve	40 Gy/15 frac/ 3 weeks	5	13	NR
Shelley et al. 2000	294 node –ve	40 Gy/16 frac/ 3 weeks	5	3.5	77

Multi-Institution Cohort Studies

Study	Patients	Fractionation Schedule	Median Follow-up (y)	Local Recurrence (%)	Cosmetic Outcome at 5 years (% excellent/ good)
Olivotto et al. 1996	186 node –ve	44 Gy/15 frac/ 3 weeks	5	6	89
Clarke et al. 1996	416 node –ve	40 Gy/16 frac/ 3 weeks (+ boost)	7.6	11	NR

Dose/Fraction and BED*

Schedule Gy/frac	Fraction Size (Gy)	BED* α/β=3.5	BED α/β=10
5000/25	2.0	78	60
4250/16	2.7	75	52

*** time factor not included**

Ontario Clinical Oncology Group (OCOG) Trial of Accelerated Hypofractionated Whole Breast Irradiation (AHWBI)

1,234 patients
T_{1-2}, N_0
with clear margins post BCS

50 Gy/25 frac/5 wks [2 Gy]

42.5 Gy/16 frac/3 wks [2.7 Gy]

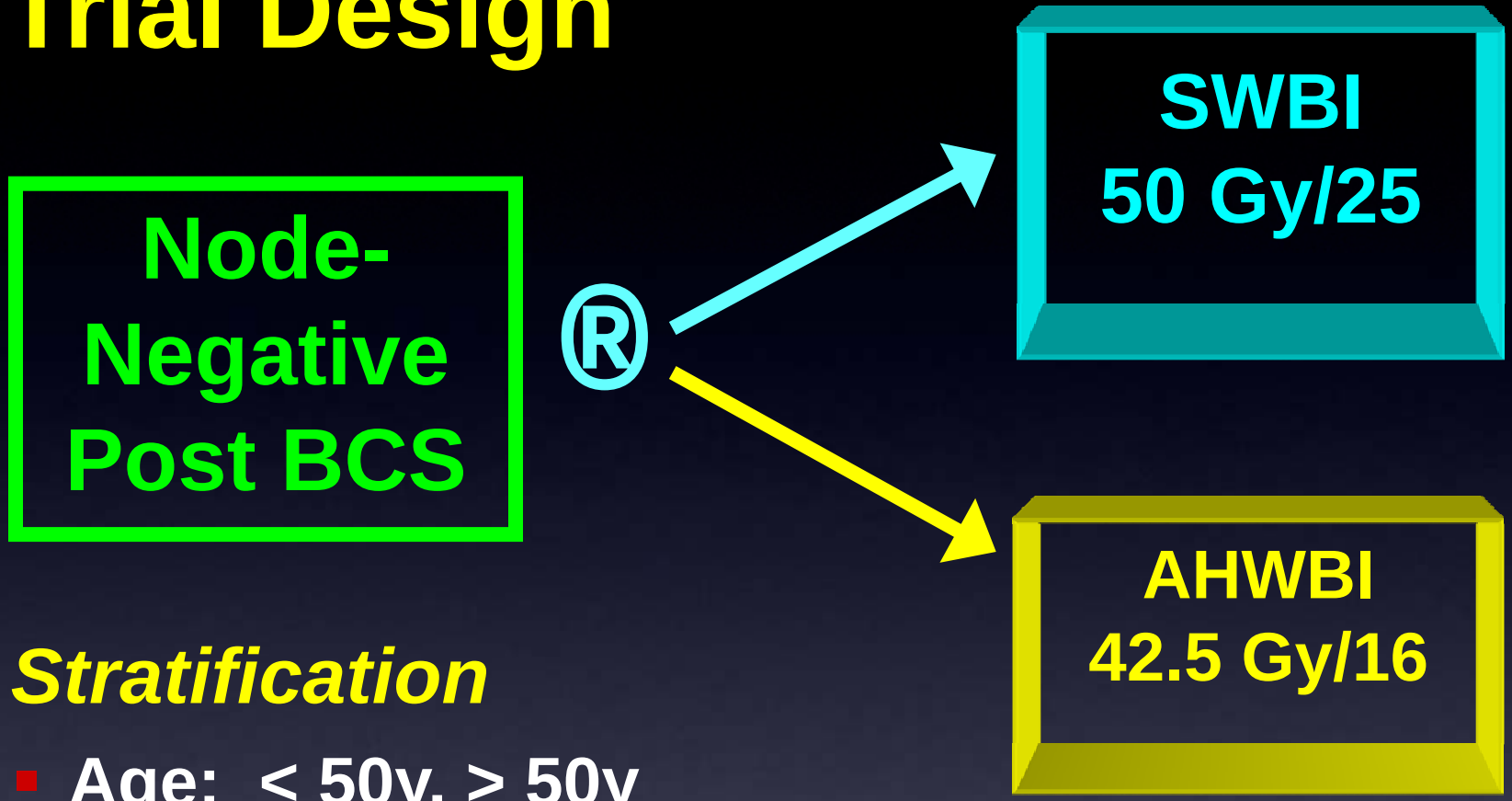
Patients accrued from 1993-1996

Background

- 5 year results of the RCT comparing standard WBI - 50 Gy / 25 / 35 days (2 Gy) vs. AHWBI - 42.5 Gy / 16 / 22 days (2.7 Gy)*
  - 3% local recurrence
  - Similar cosmetic outcome
- Concern remained re: long-term morbidity

* Whelan et al. *JNCI* 2002

Trial Design



Stratification

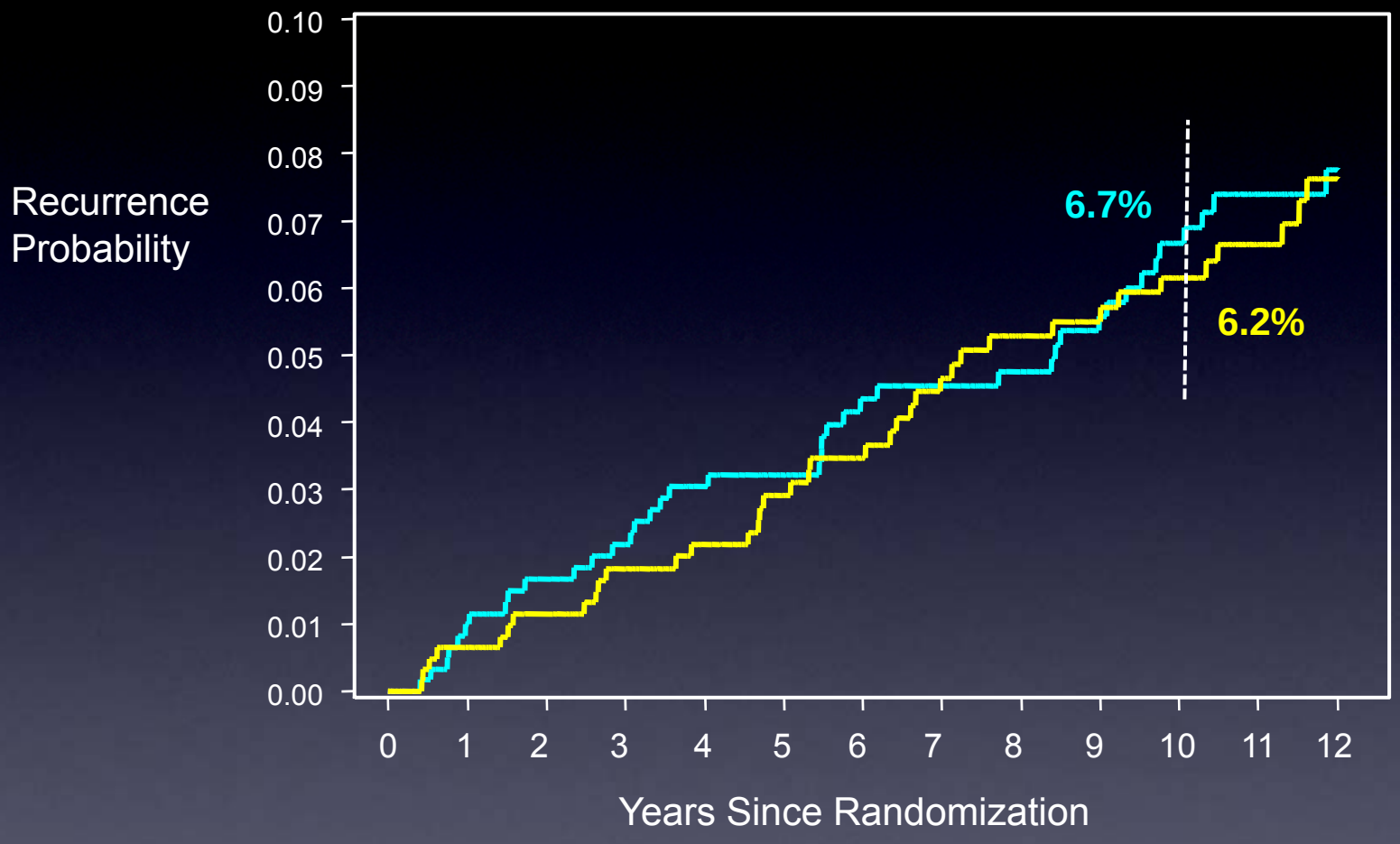
- Age: < 50y, ≥ 50y
- Size: ≤ 2cm, > 2cm
- Systemic therapy: Tamoxifen, chemo, none
- Center

Median follow-up is 12 years

Baseline Characteristics

	SWBI n=612		AHWBI n=622	
	n	(%)	n	(%)
Age < 50 yrs	148	(24)	157	(25)
Tumor size ≥ 2 cm	203	(33)	190	(31)
ER negative	157	(26)	165	(26)
Tumor grade high	116	(21)	117	(20)
Tamoxifen	266	(41)	265	(41)
Chemotherapy	72	(11)	75	(11)

Local Recurrence



At Risk:

SWBI	612	597	578	562	550	533	499	485	470	449	410	317	218
AHWBI	622	609	592	569	548	524	500	472	447	430	406	330	214

Cosmetic Outcome By Time and Treatment*

	Baseline	3 Year	5 Year	10 Year
SWBI	83% **(604)**	77% **(498)**	79% **(423)**	71% **(216)**
AHWBI	84% **(616)**	77% **(518)**	78% **(448)**	70% **(235)**

*** % excellent or good** (# evaluable)

RTOG/EORTC Late Radiation Morbidity by Time and Treatment (%)*

	3 Year		5 Year		10 Year	
	G2	G3	G2	G3	G2	G3
Skin						
SWBI	2	<1	3	<1	5	3
AHWBI	2	0	3	<1	6	3
Subcu. tissue						
SWBI	4	1	5	1	7	4
AHWBI	4	<1	4	1	9	3

* % grade 2 (G2) and grade 3 (G3)

Cause of Death*

	SWBI (n=612)		AHWBI (n=622)	
Cancer related	13.2%	(81)	13.7%	(85)
Non-cancer related	7.4%	(45)	5.9%	(37)
TOTAL	20.6%	(126)	19.6%	(122)

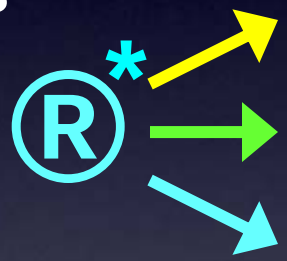
* % (n)

OCOG Trial Summary

- Demonstrated excellent local control
- Was not associated with long-term morbidity
  - Skin and soft tissue toxicity
  - Breast cosmesis
  - Non-cancer deaths

UK Trial✦ of Hypofractionated Whole Breast Irradiation

1,410 patients
T_{1-3}, N_{0-1}
with clear margins post BCS



50 Gy/25 frac/5 wks [2 Gy]

42.9 Gy/13 frac/5 wks [3.3 Gy]

39 Gy/13 frac/5 wks [3.3 Gy]

Median follow-up 9.7 years

✦ Owen, Yarnold et al., *Lancet Oncol* 2006; 7:467-71

* Boost radiation permitted

UK Study – Baseline Characteristics

	%
Age < 50	30.3
Tumor Size > 2 cm	42.5
Node +ve	32.7*
Tamoxifen	65.1
Chemo	11.9
Boost Irradiation	75.5
Locoreg. Irradiation	21.0

ICR-Local Recurrence-Free Survival

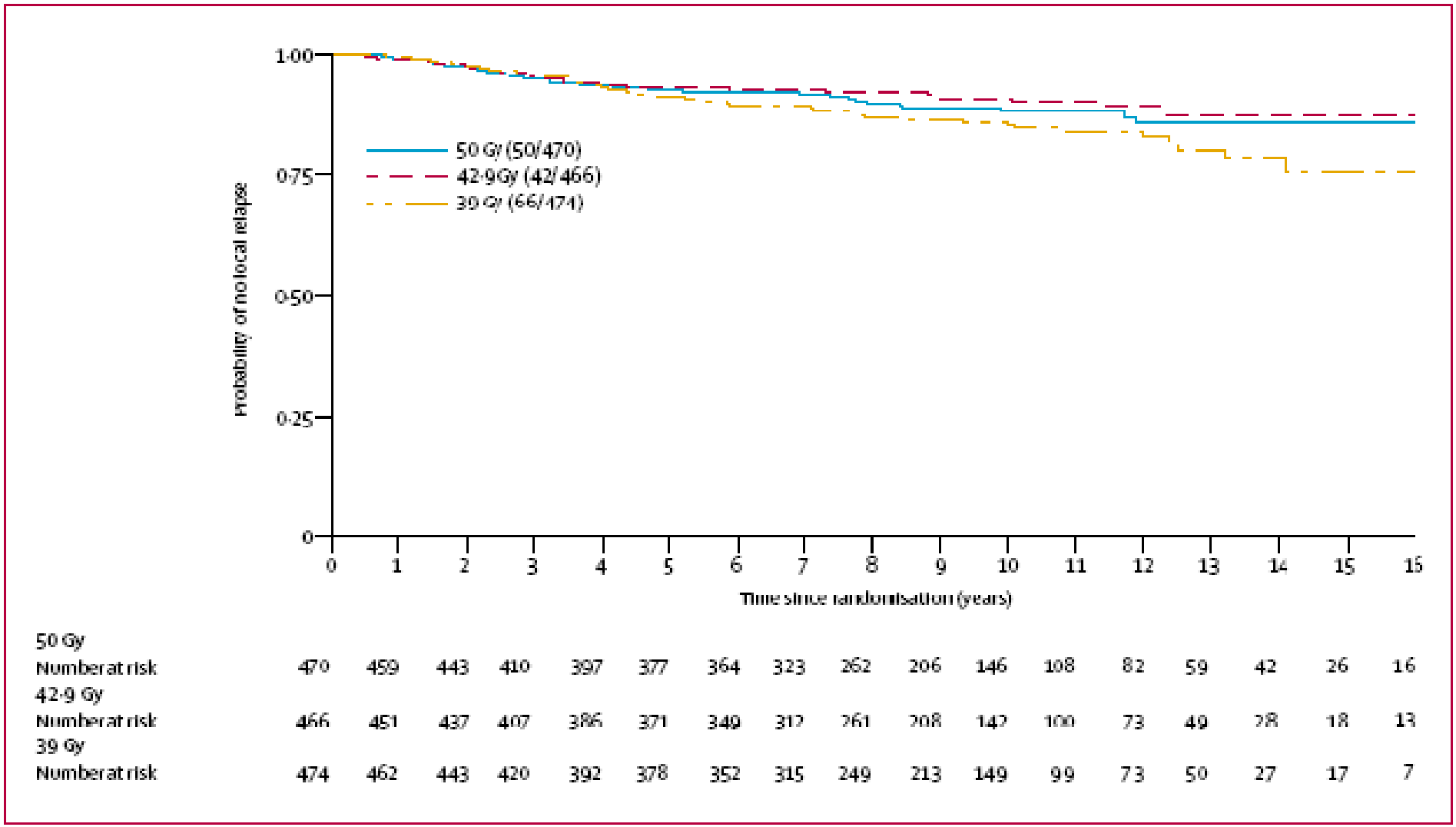


Figure 2: Local ipsilateral relapse in the breast according to fractionation schedule

ICR- Change in Breast Appearance

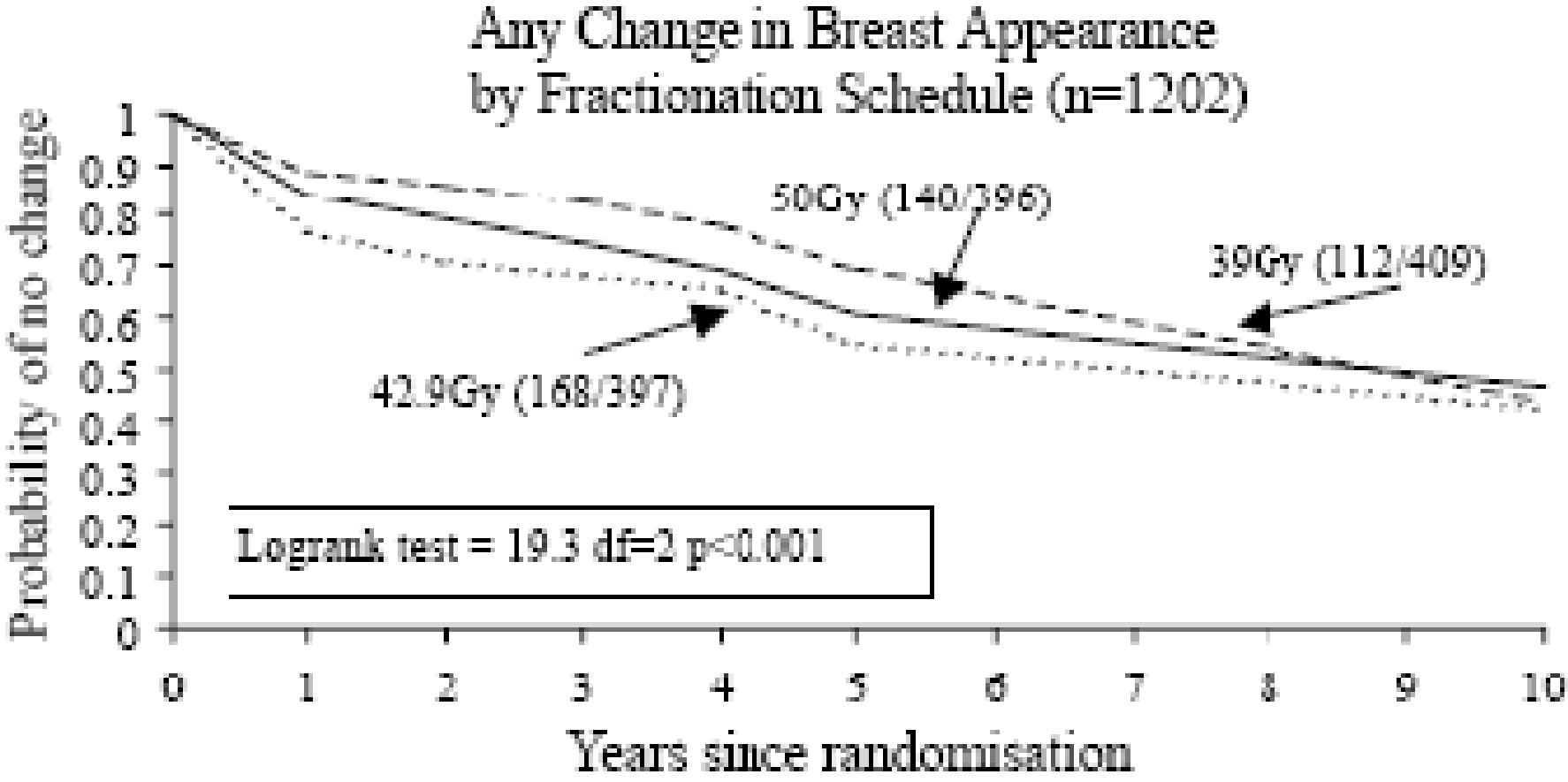


Fig. 2. Probability of any change in breast appearance late radiation effect ten years after radiotherapy by fractionation schedule.

RCT's of Hypofractionated Whole Breast Irradiation

Study	Radiation Treatment	No. of Pts.	Median F/U (yrs)	Local Rec. (%)	Toxicity Br (%)
OCOG, 2002*	50 Gy/25 frac/5 wks	612	12	6.7	29
	42.5 Gy/16 frac/3 wks	622		6.2	30
ICR, 2006**	50 Gy/25 frac/5 wks	470	9.7	12.1	40
	42.9 Gy/13 frac/5 wks	466		9.6	46
	39 Gy/13 frac/5 wks	474		14.8	30
Start A***	50 Gy/25 frac/5 wks	749	5.1	3.7	42
	41.6 Gy/13 frac/5 wks	737		3.5	42
	39 Gy/13 frac/5 wks	750		5.3	31
Start B***	50 Gy/25 frac/5 wks	1105	6.0	3.7	40
	40 Gy/15 frac/3 wks	1110		3.2	33

*Whelan et al., *JNCI* 94:1143-1150, 2002. **Owen, Yarnold et al., *Lancet Oncol* 7:467-71, 2006. Dewer, Yarnold et al., *ASCO* 2007

Conclusions

Hypofractionation

- **Excellent local control**
- **No increase in long-term morbidity**
- **More convenient**
- **Less costly**

Cost Comparison*

Cost	WBI+B	WBI	AHWBI	APBI-3DCRT
Payer	9,500	7,400	**5,400**	7,200
Patient	1,400	1,100	**700**	500
TOTAL	10,900	8,500	**6,100**	7,700

*** Suh et al. *IJROBP* 62:790-96, 2005**

Clinical Implications

Consider Hypofractionation

- For women of all age groups
- When using boost irradiation
- In patients treated with tamoxifen and/or chemotherapy

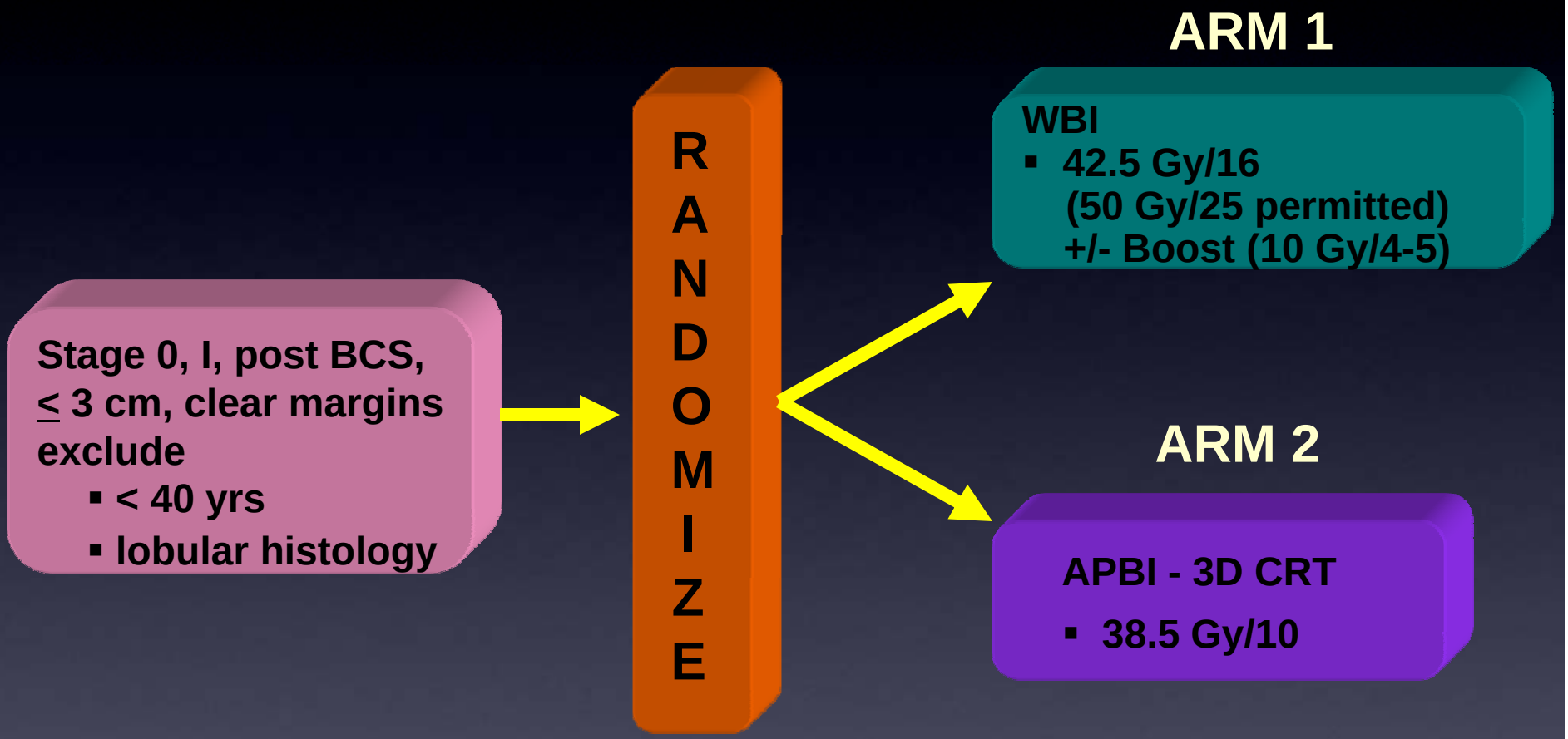
Avoid Hypofractionation

- Large breasted women
- When axillary/SC irradiation considered
- ? Intensive chemotherapy

Research Implications

- FAST trial will evaluate 30 Gy/5 frac (6 Gy) and 28.5 Gy/5 frac (5.7 Gy)
- IMRT to deliver hypofractionation with concurrent boost
- Partial breast irradiation

Randomized Trial of Accelerated Partial Breast Irradiation* RAPID



Sample size = 2128

*Formerly Canadian Trial of Accelerated Partial Breast Irradiation

Hypofractionation

- Recent resurgence based on radiobiology; technology advances; quality of life considerations
- Supported by single institution and multi-institution cohort studies, indirect and direct comparisons in RCTs
- Long-term data show that it is safe and effective
- New technical approaches are exploring hypofractionated PBI