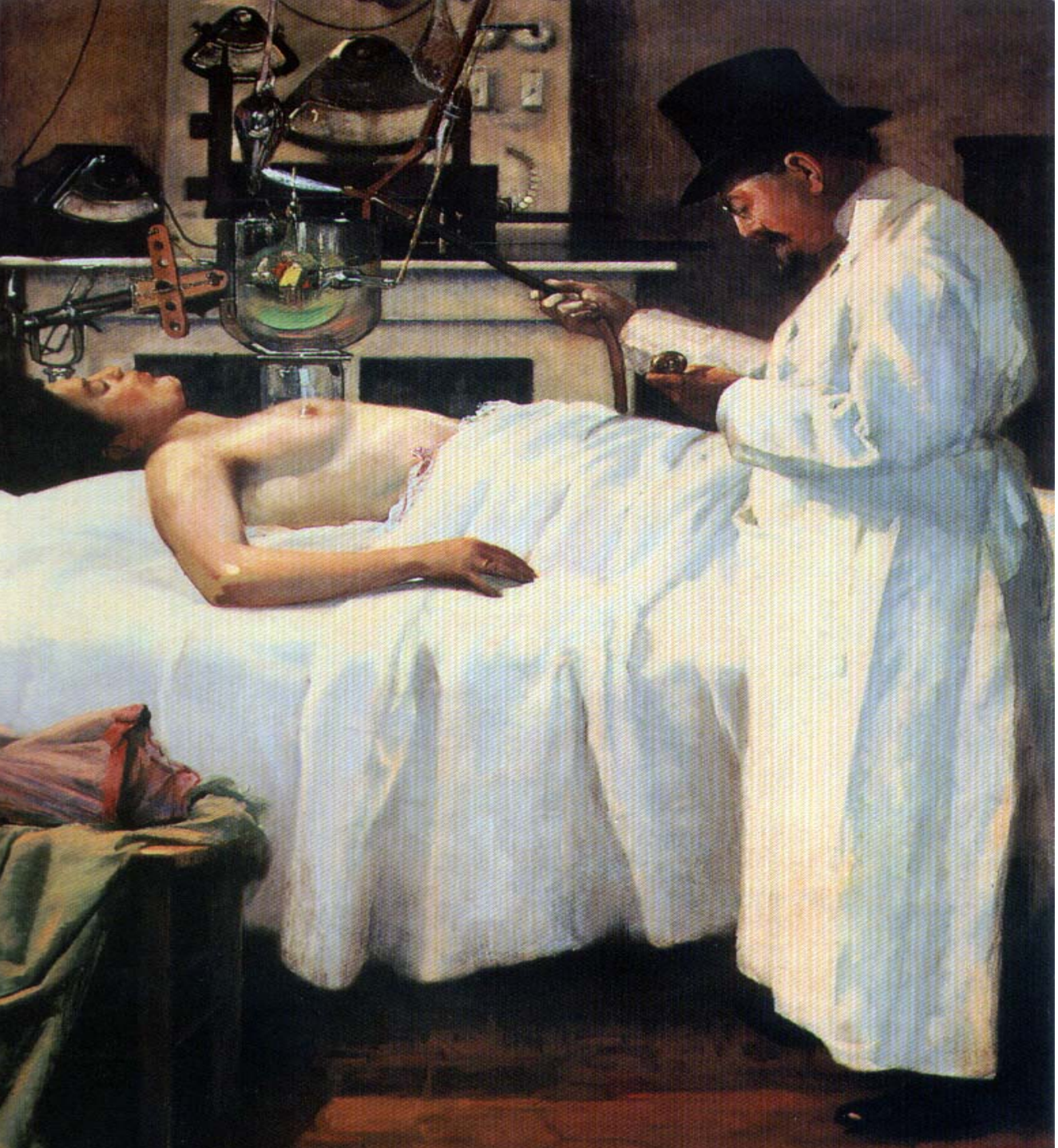
Breast Radiotherapy, the British experience. A case for hypofractionation.

Murray Brunt
University Hospital of North Staffordshire
Vienna, 15 October 2010




ERECTED AND SUPPORTED BY

The Cancer Centre

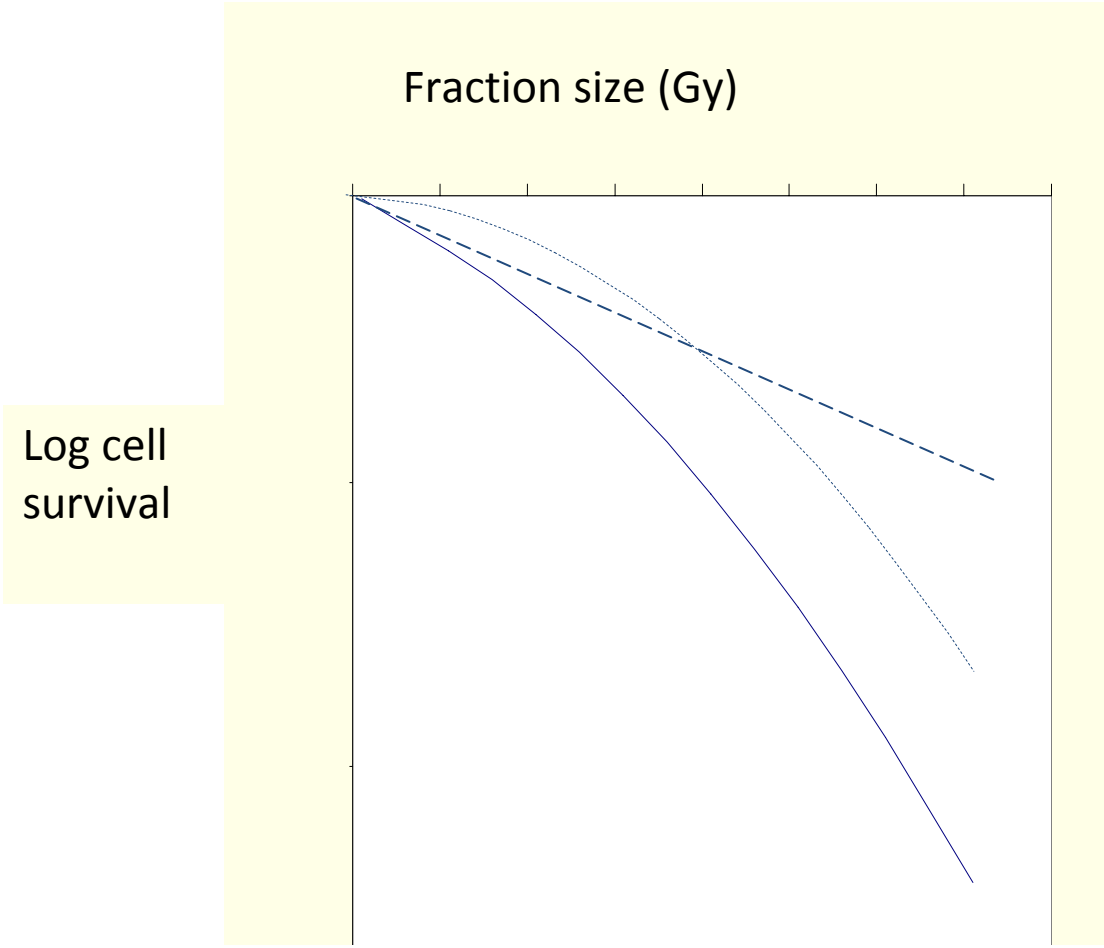
Randomised Trials (N >7000)

Trial	Test arms	
	Fraction size (Gy)	Total dose(Gy)
Ontario	2.7	42.5
RMH/GOC	3.3	42.9
START A	3.0/3.2	39.0/41.6
START B	2.7	40.0

Other UK Trials

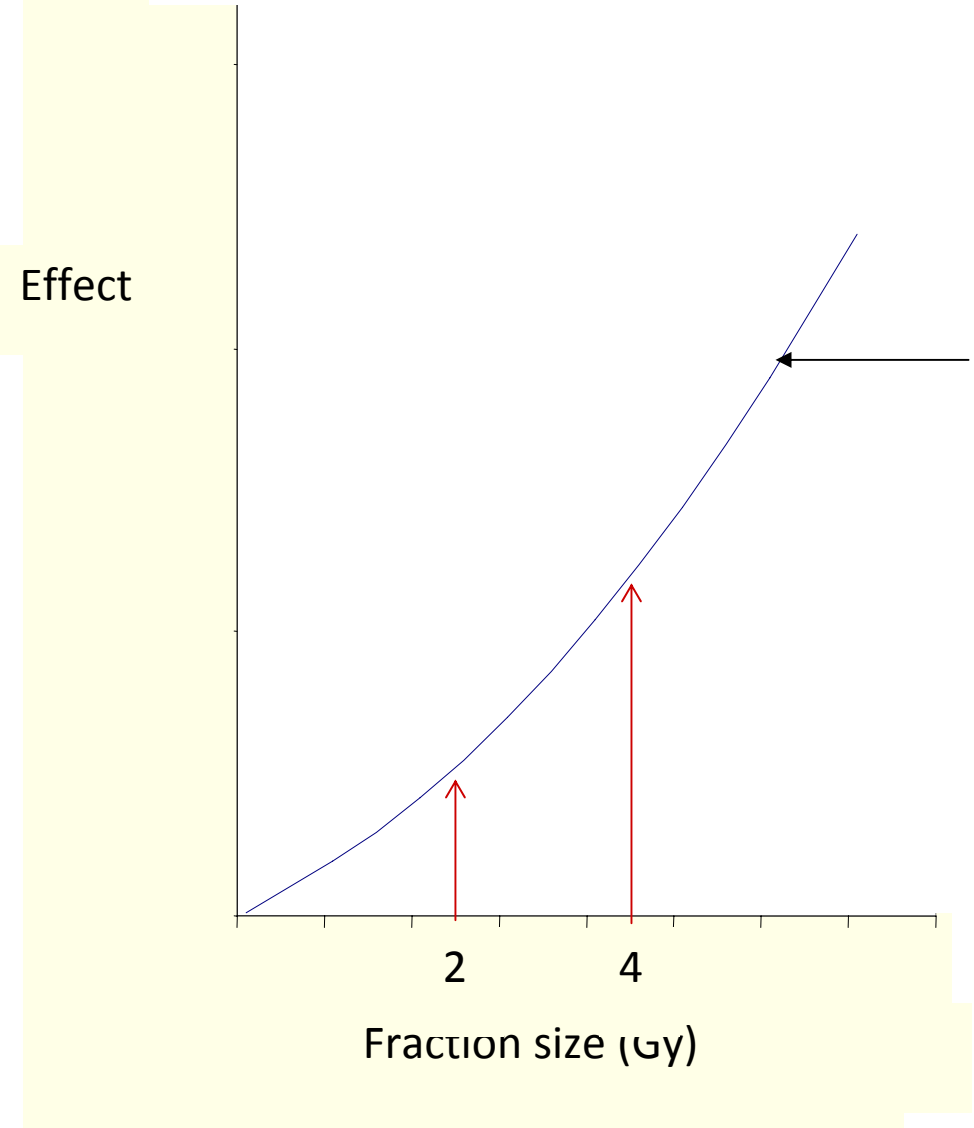
- FAST
- IMPORT HIGH
- FAST FORWARD

Cell survival is well described using linear and quadratic components



Survival $\propto$
$\alpha D + \beta D^2$

Early Reacting Normal Tissues (NT): Insensitive to Fraction Size



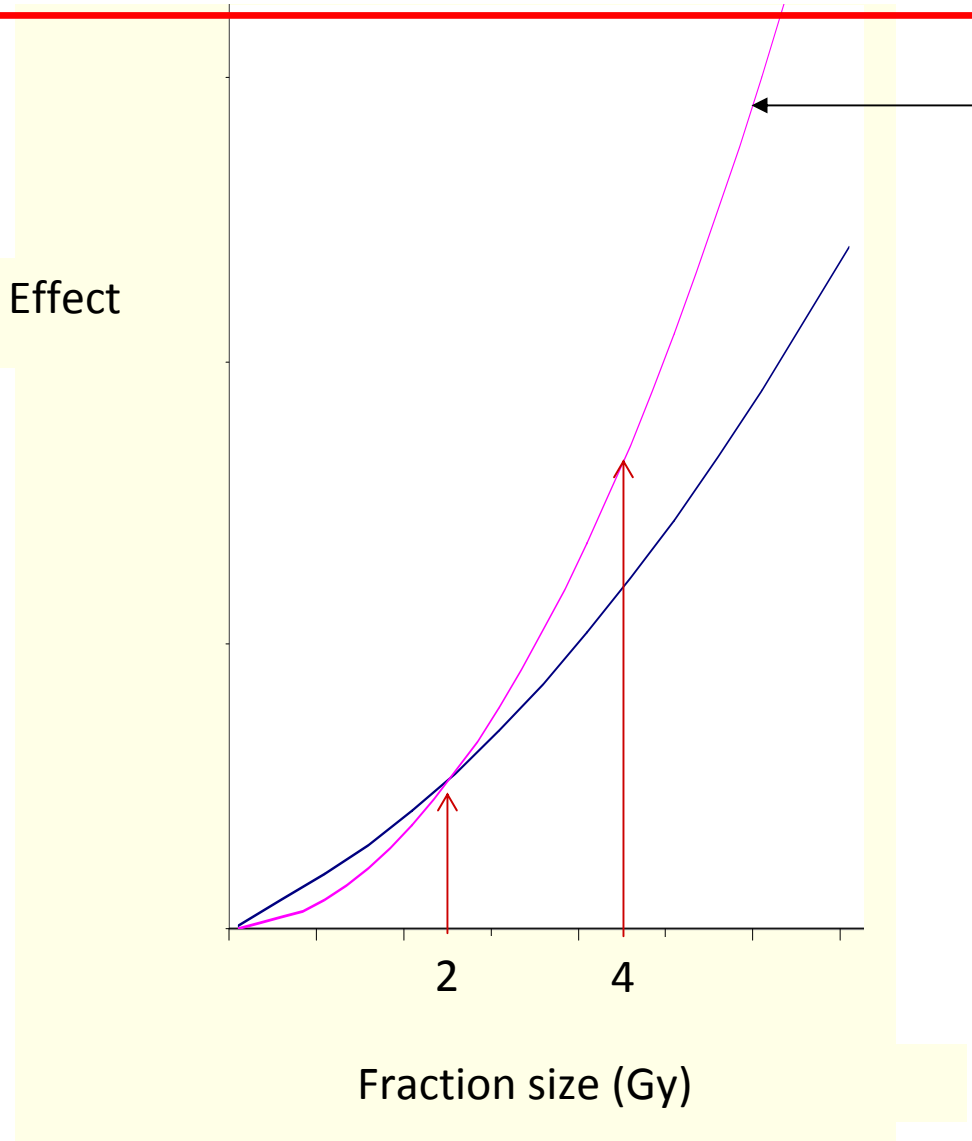
Early reacting NT

Double the fraction size

Double the effect

Many cancers respond like this, too

Late Reacting Normal Tissues (NT): Sensitive to Fraction Size



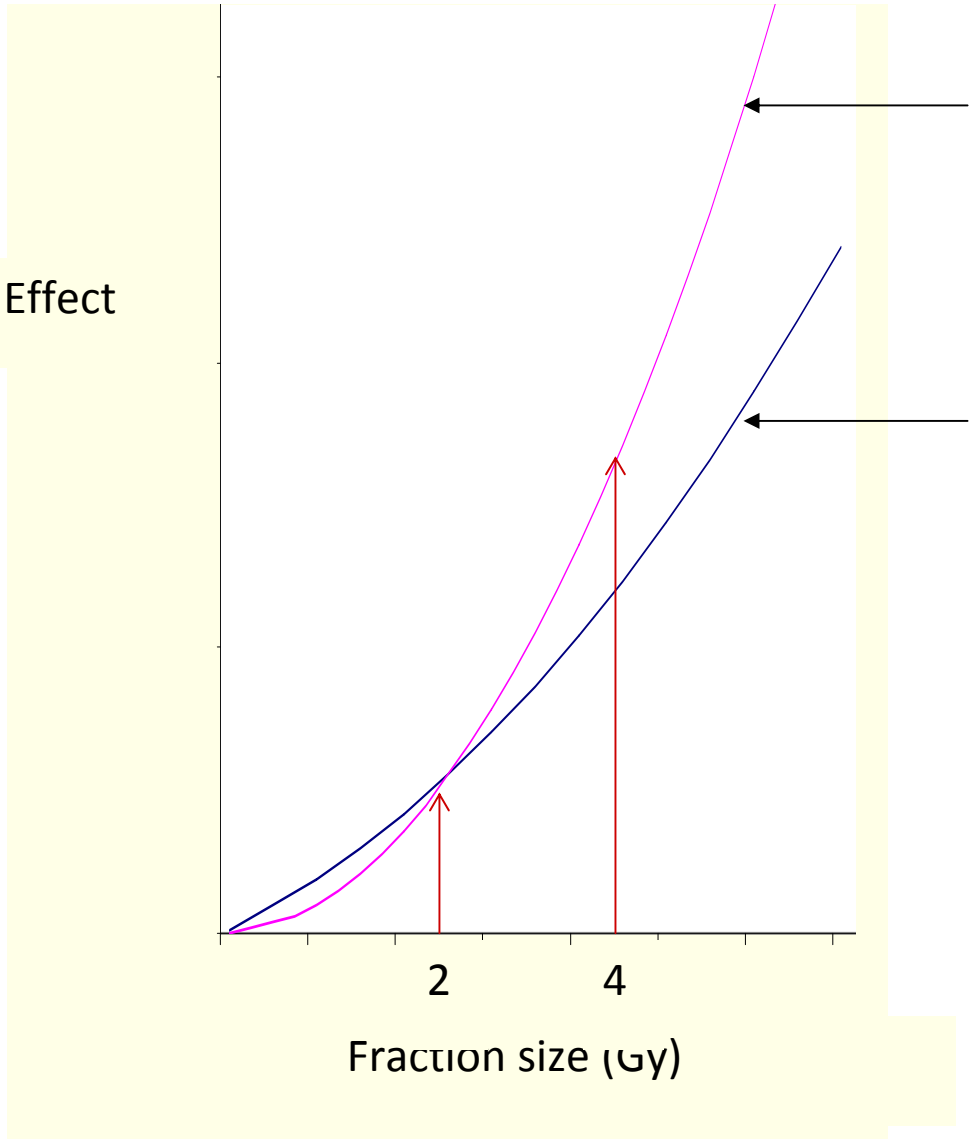
Late reacting NT

More upward curvature

Curvature described by polynomial:

Effect = $\alpha D + \beta D^2$

Standard Model….



Late NT effects

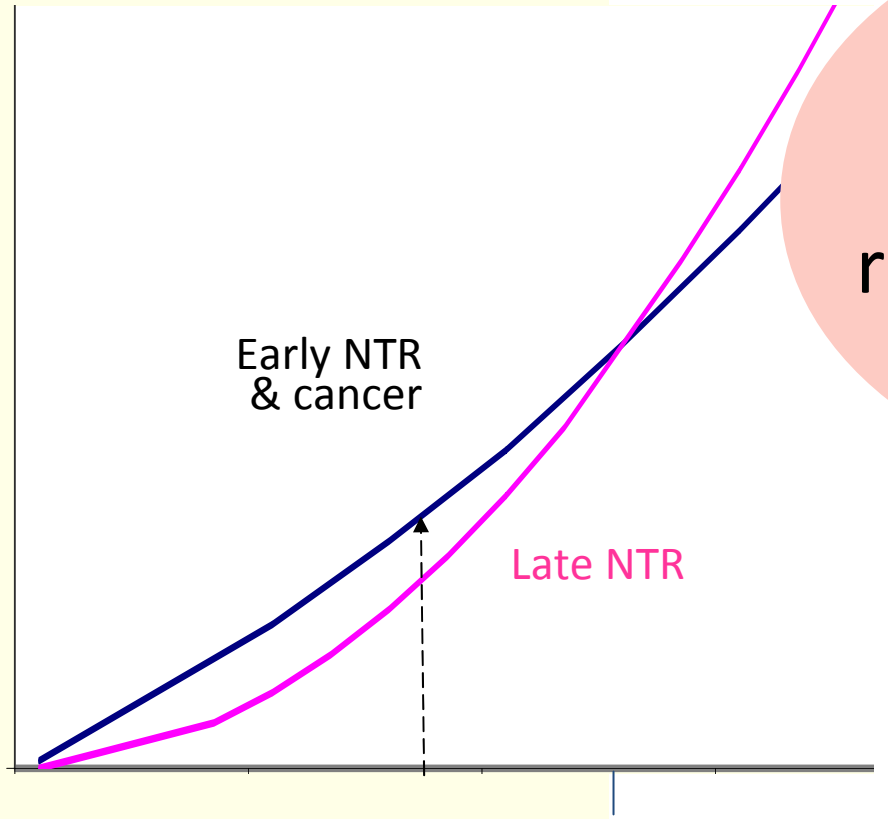
α/β ratio low <10 Gy

Early NT effects

Cancers

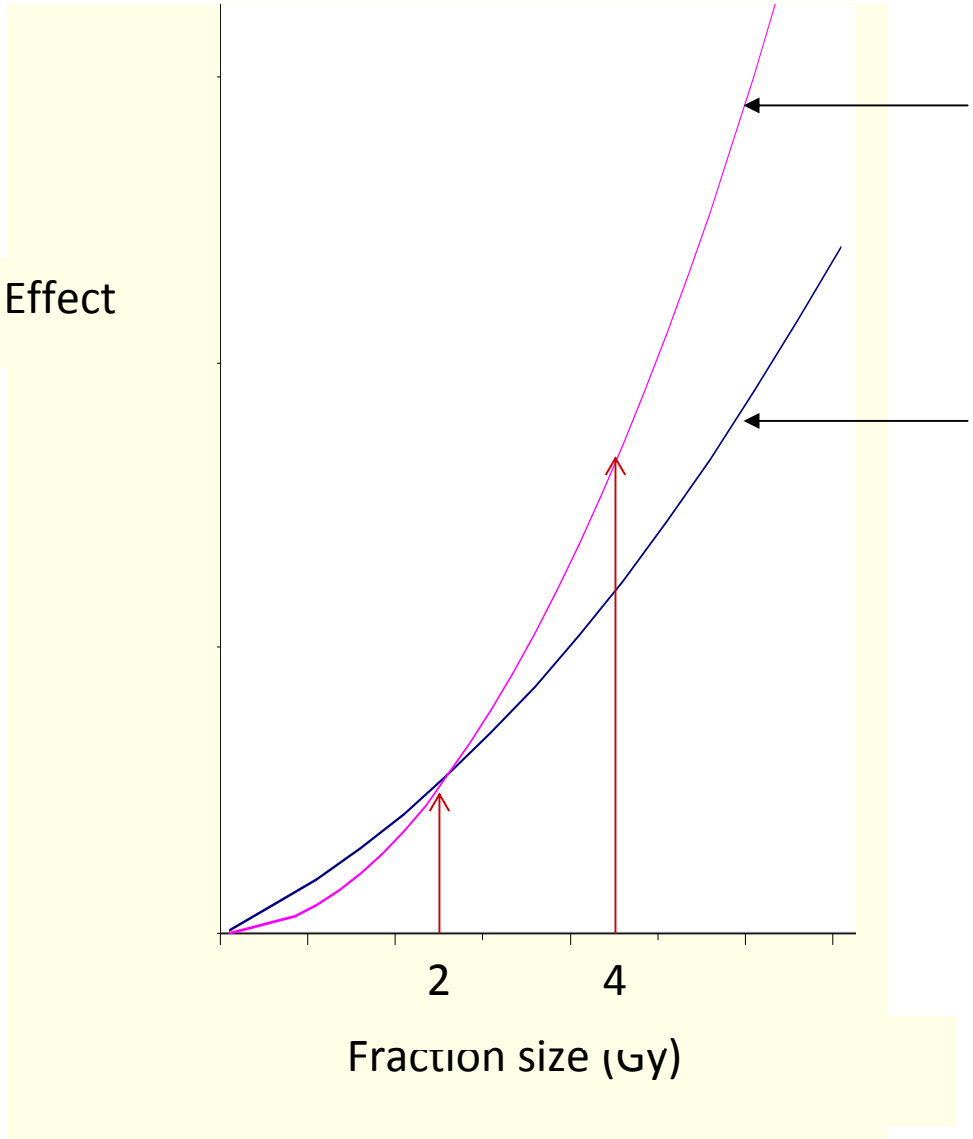
α/β ratio high ≥10 Gy

Standard Model



"Fractions < 2 Gy spare late NTR relative to tumour"

Standard Model Faces a Challenge….



Late NT effects

Breast cancer?

α/β ratio low <10 Gy

Early NT effects

Head & Neck cancer

α/β ratio high ≥10 Gy

Hypothesis

"Breast cancer is
as sensitive to fraction size
as the late-reacting
normal tissues"

If true, small fractions spare
breast cancer as much as
the late-reacting NT

RMH/GOC Trial Design

Total Dose (Gy)	Fraction size (Gy)	Fraction number	Time (week)
*39.0	3.0	13	5
50.0	2.0	25	5
º42.9	3.3	13	5

* equivalent to 50Gy/25F if α/β value = 2 Gy

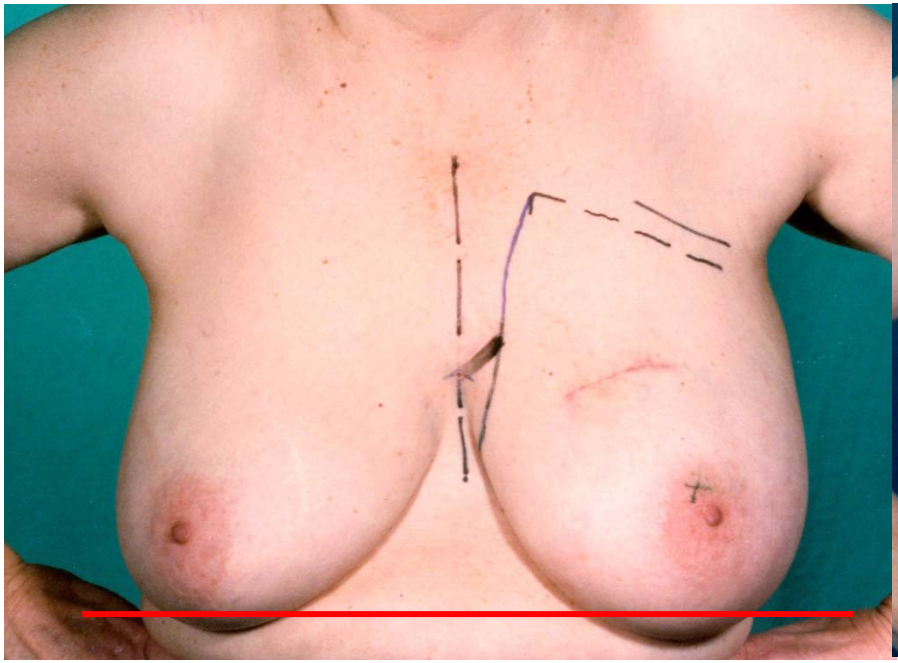
º equivalent to 50Gy/25F if α/β value = 6 Gy

RMH/GOC Trial Endpoints

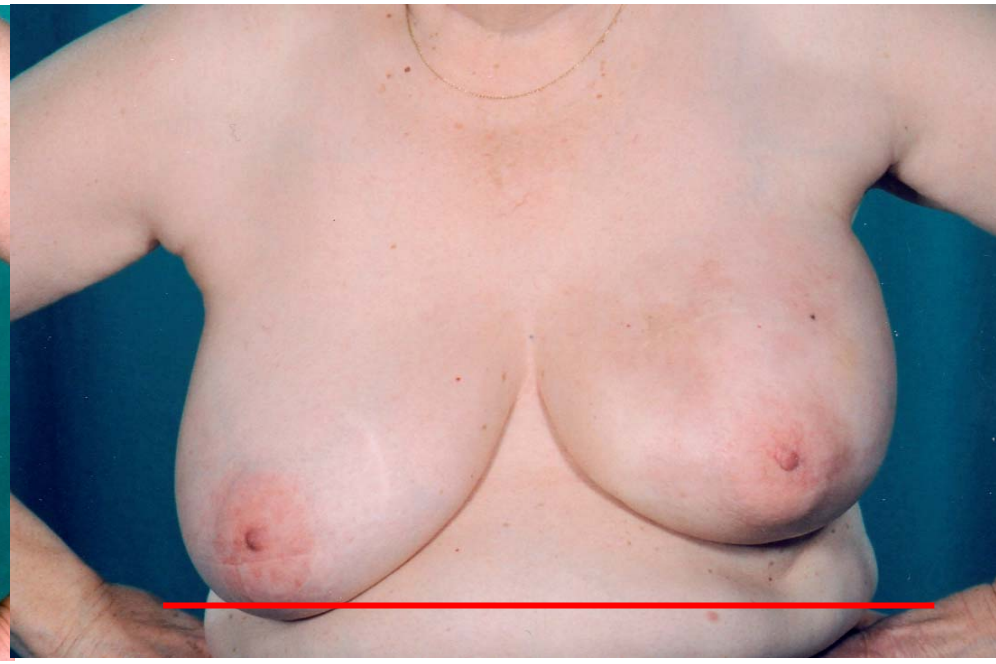
- Primary:
  - Change in breast appearance
- Secondary:
  - Breast shrinkage, oedema, telangiectasia, induration
  - Tumour control

Late Normal Tissue Responses e.g. Breast Shrinkage (Fat Atrophy)

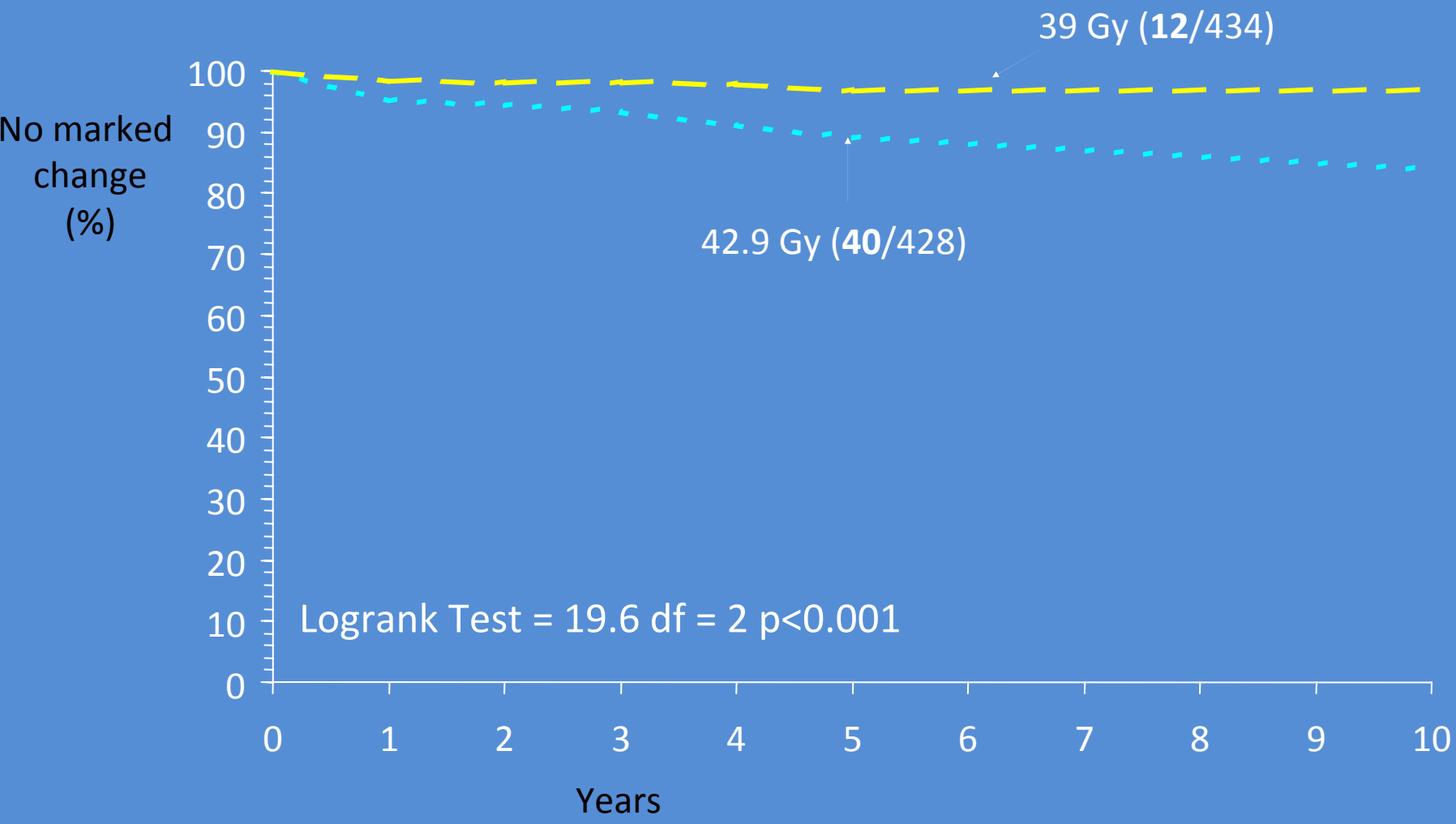
Before RT



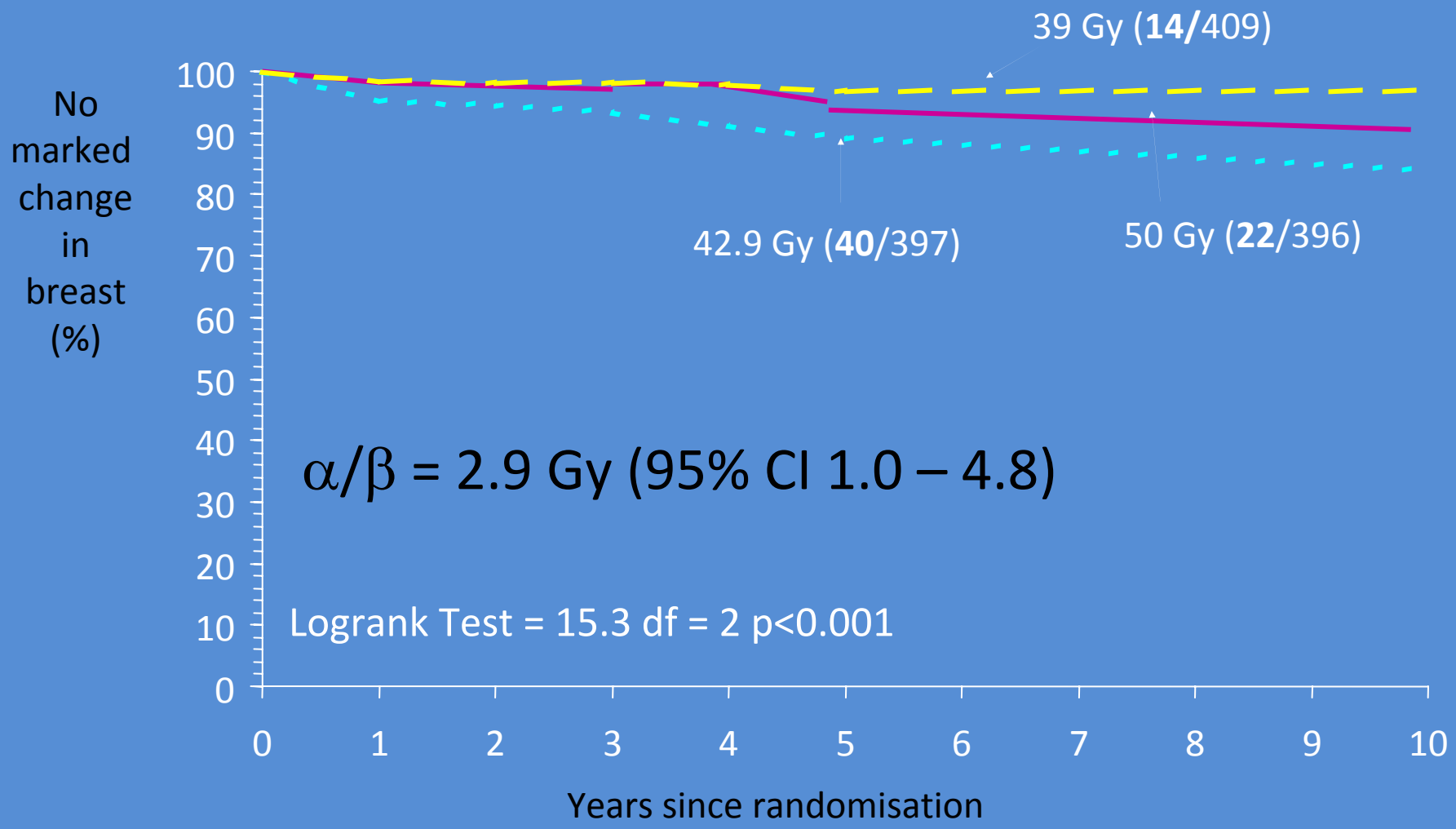
Several years later…



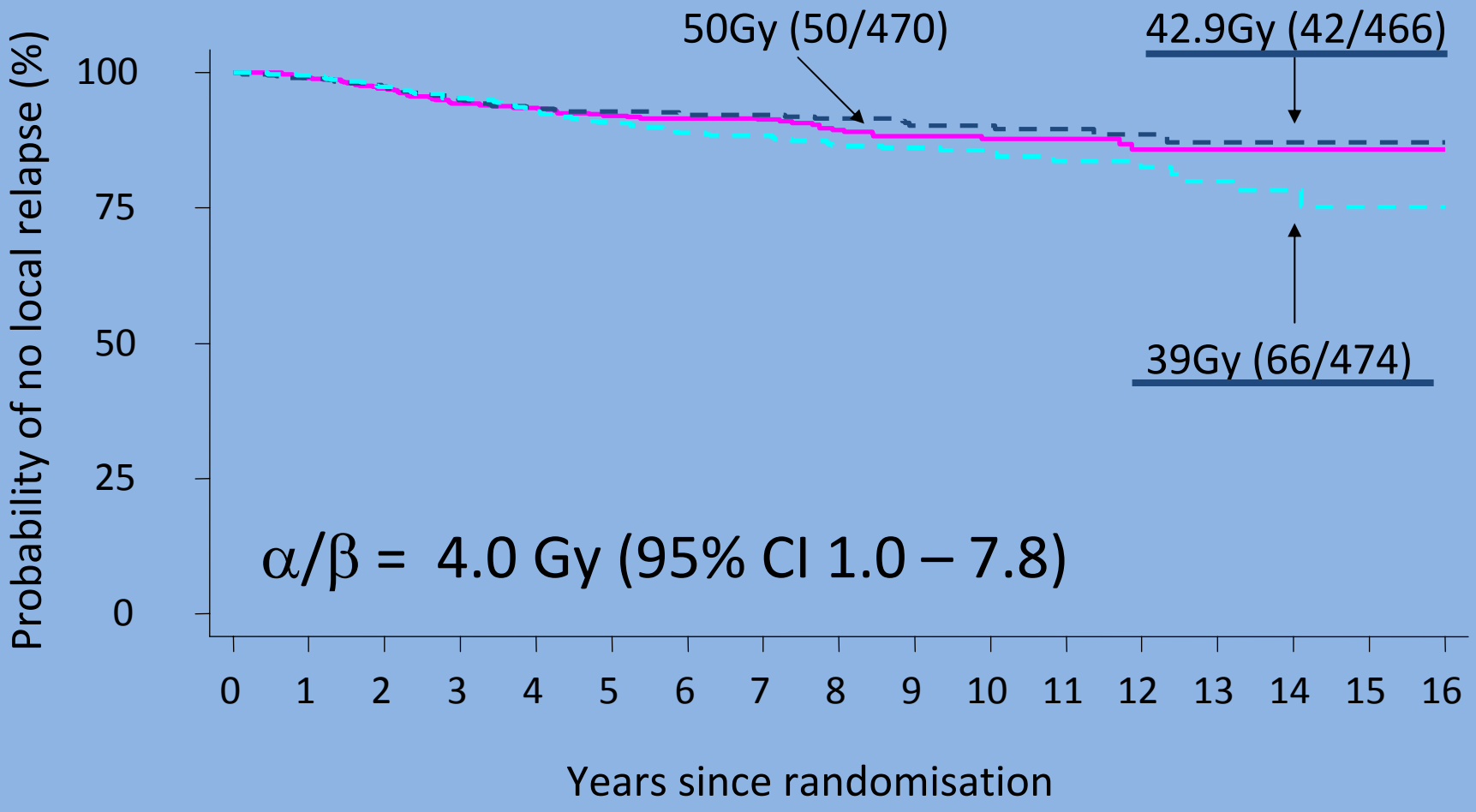
Marked Change in Breast Appearance (n=1410)



Marked Change in Breast Appearance



Local tumour relapse



Owen, Lancet Oncology, 2006

Fractionation Sensitivity of Late Side Effects and Tumour Control

Effect	α/β value (95% C.I.)
Any change in breast appearance	3.6 Gy (1.8 – 5.4)
Palpable breast induration	3.1 Gy (1.8 – 4.4)
Tumour control	4.1 Gy (1.0 – 9.7)

Background

START pilot study (N=1410) suggests that

- 13 fractions of 3.2Gy (41.6 Gy) cause the same level of late adverse effects as 25 fractions of 2.0Gy (50 Gy) [1]
- Tumour response (local control) is as sensitive to fraction size as the late adverse effects [2]

If confirmed, radiation fractions > 2.0Gy have advantages in breast cancer

1. Yarnold J et al. Radiother. Oncol 2005; 75: 9-17
2. Owen R et al. Lancet Oncol 2006; 7: 467-71

START Trials: Aim

To test the benefits of fraction sizes >2.0Gy in terms of:

- local-regional tumour control
- late normal tissue responses
- quality of life & cost-effectiveness

in patients with early breast cancer

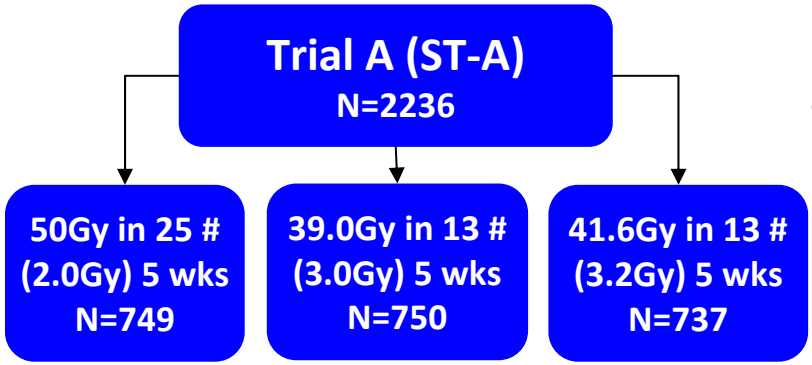
Sensitivity to fraction size indicated by α/β ratio:

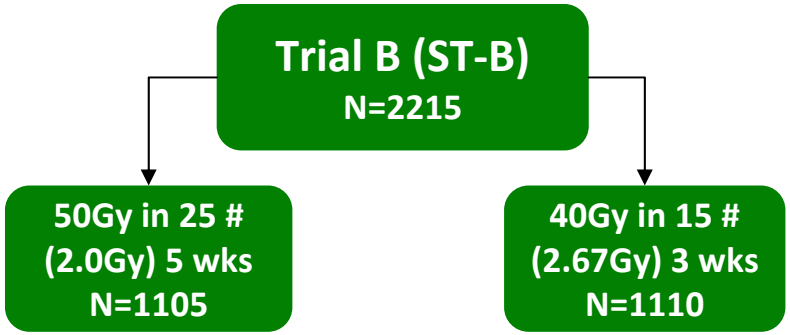
< 10 = sensitive

≥ 10 = insensitive

START Trials: design and endpoints

Women with completely excised invasive breast cancer, T1-3 N0-1 M0





	Number of patients Trial A	Trial B
Primary endpoint:		
local-regional relapse	**2236**	**2215**
Secondary endpoints:		
normal tissue effects (NTEs)	**2236**	**2215**
-annual physician assessments of induration, shrinkage, oedema		
-photographs (baseline, 2y & 5y)	**1291**	**1094**
quality of life EORTC Breast, body image, HADS (baseline, 6m, 1y, 2y, 5y)	**1129**	**1079**
Additional endpoints:		
disease-free survival	**2236**	**2215**
overall survival		

Recruitment from 35 UK centres between Jan 1999 & Oct 2002

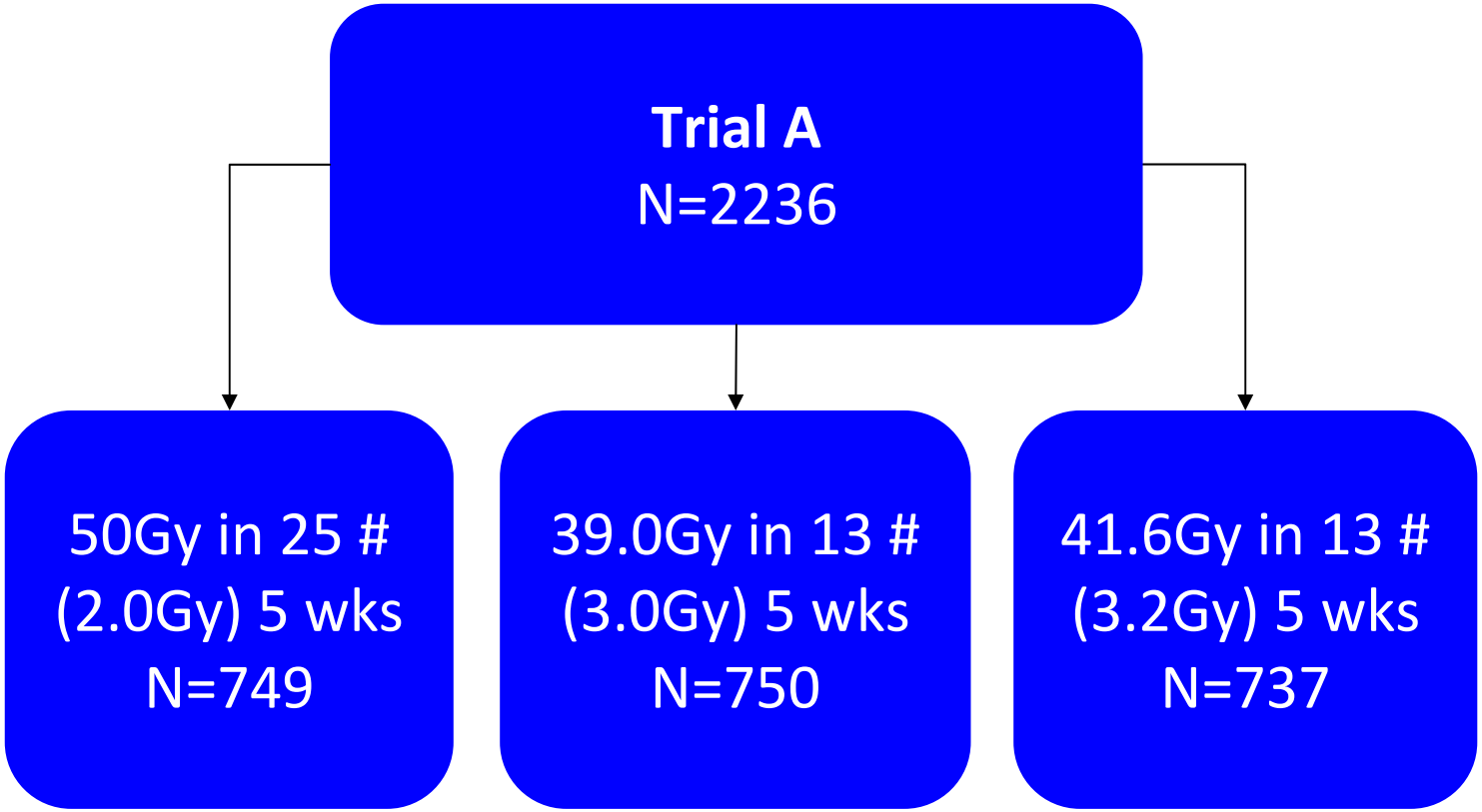
Sample size rationale

	Trial A	Trial B
Sample size	2000	1840
5-yr local-regional (LR) relapse rate after 50Gy/25 fractions	10%	10%
Magnitude of difference in LR rate to detect / exclude	5%	5% ↑ after 40Gy
Significance	2-sided α=0.05	1-sided α=0.025
Power	80%	95%

Baseline Characteristics

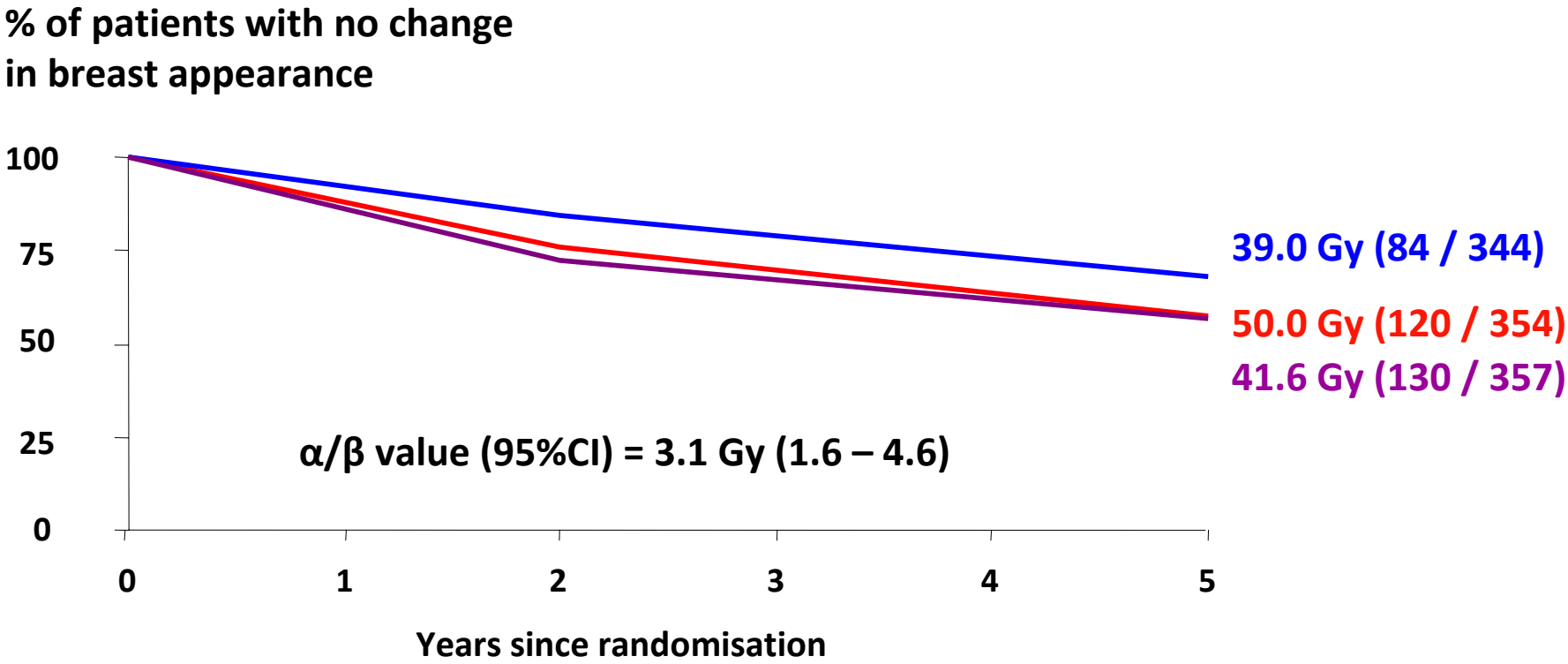
	Trial A (2236)	Trial B (2215)
Mean age (yrs)	57.2	57.4
Interquartile range	[50.7 – 64.5]	[51.2 – 64.0]
Conservation surgery	85%	92%
pT size < 2 cm	51%	64%
2-3 cm	27%	26%
3+ cm	22%	10%
Grade 3	28%	23%
Node +ve	29%	23%
Breast boost given	52%	40%
Lymphatic RT given	15%	8%
Chemotherapy	36%	22%
Tamoxifen	79%	87%

START Trial A (ST-A)



5.1 years median follow-up

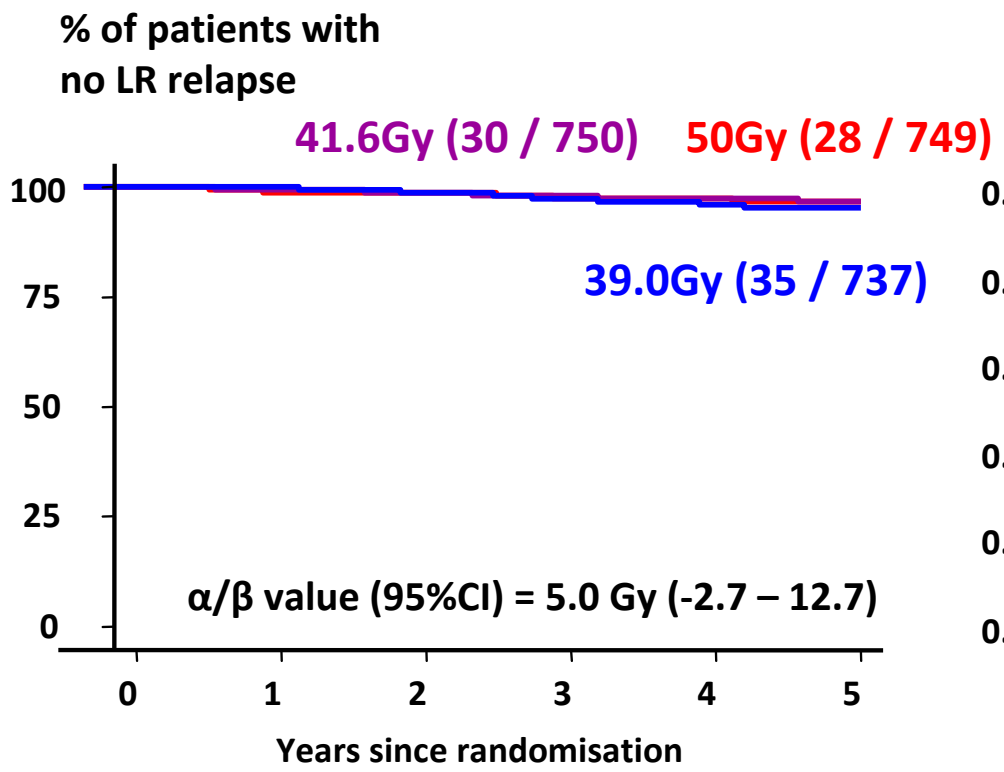
Trial A: Change in breast appearance (photos)

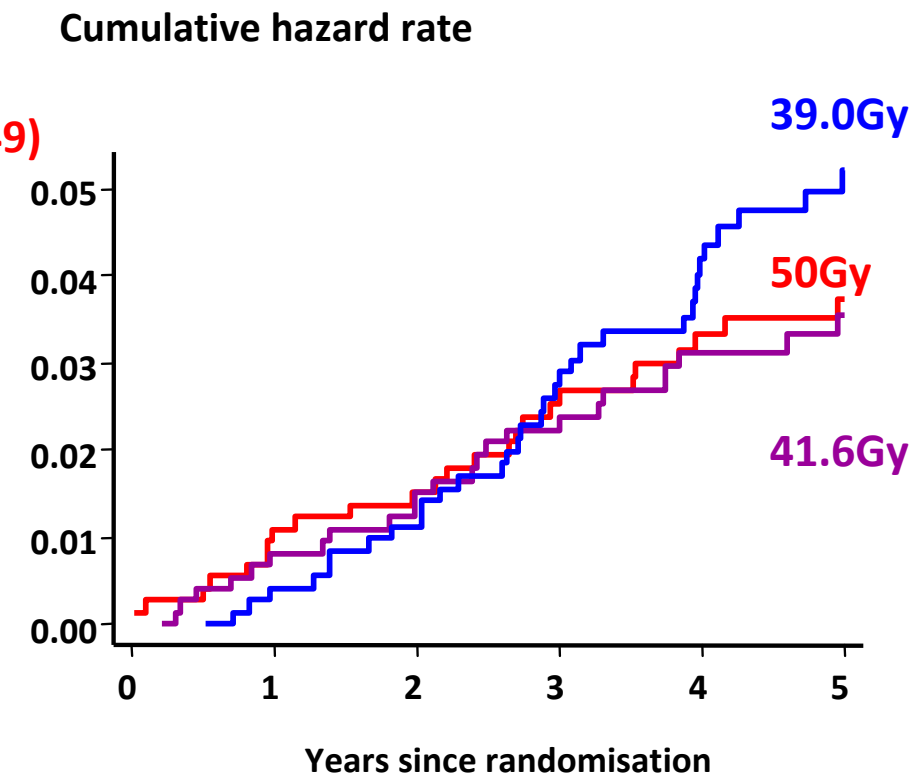


Numbers at risk:	*Yr 0*	*Yr 2*	*Yr 5*
	1055	*1047*	*448*

	Hazard Ratios (95%CI)	Absolute difference at 5 yr (95%CI)
41.6 Gy vs 50 Gy	1.09 (0.85 – 1.40)	+2.8% (- 5.0% – 11.5%)
39.0 Gy vs 50 Gy	0.69 (0.52 – 0.91)	-10.8% (-17.6% – 2.9%)

Trial A: Local-regional (LR) tumour relapse





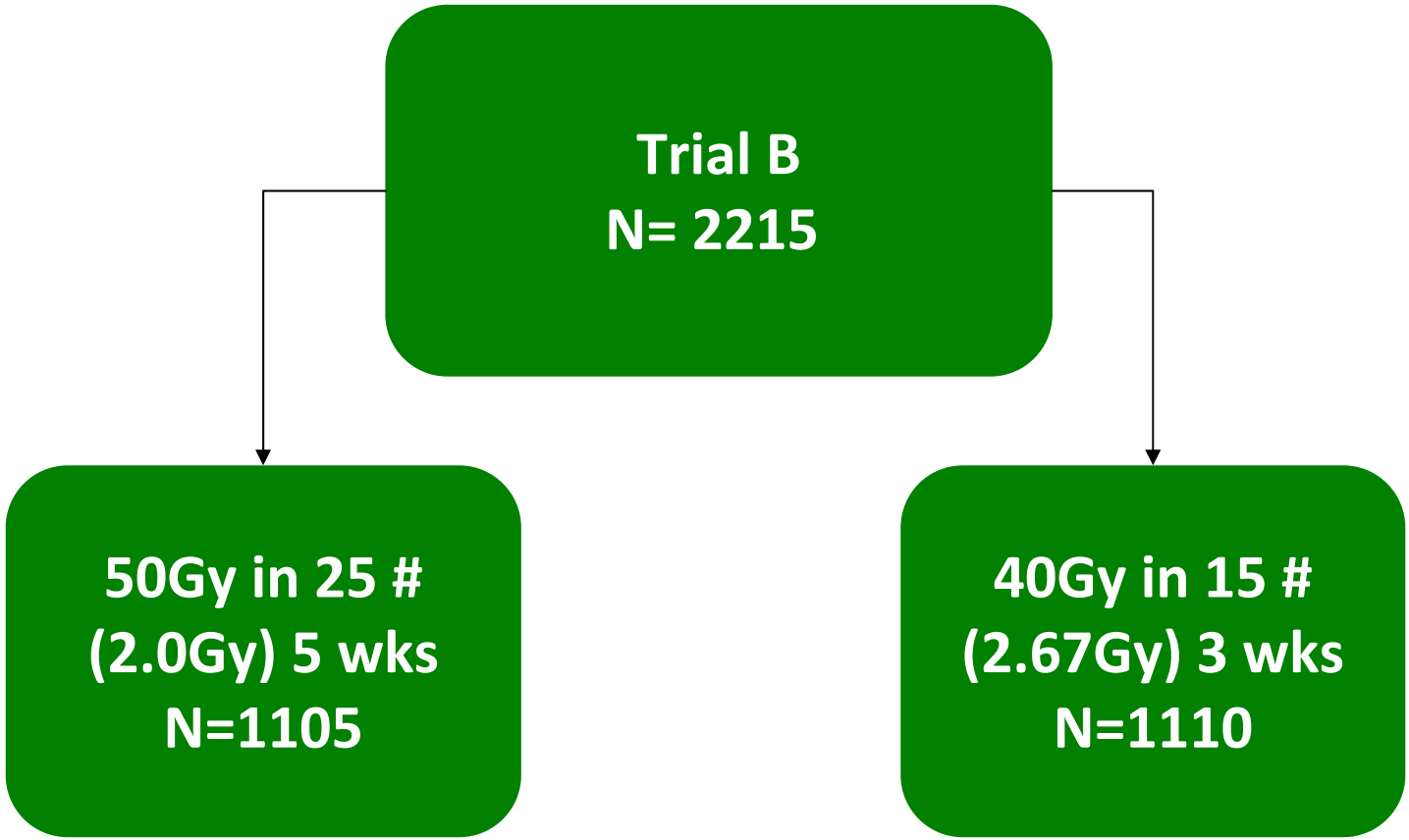
Number at risk:	*Yr 0*	*Yr 1*	*Yr 2*	*Yr 3*	*Yr 4*	*Yr 5*
	2236	*2175*	*2107*	*2008*	*1784*	*1231*

	Hazard Ratios (95%CI)	Absolute difference at 5 years (95%CI)
41.6 Gy vs. 50 Gy	1.05 (0.63 – 1.75)	+0.2% (-1.3% – 2.6%)
39 Gy vs. 50 Gy	1.26 (0.77 – 2.08)	+0.9% (-0.8% – 3.7%)

Survival

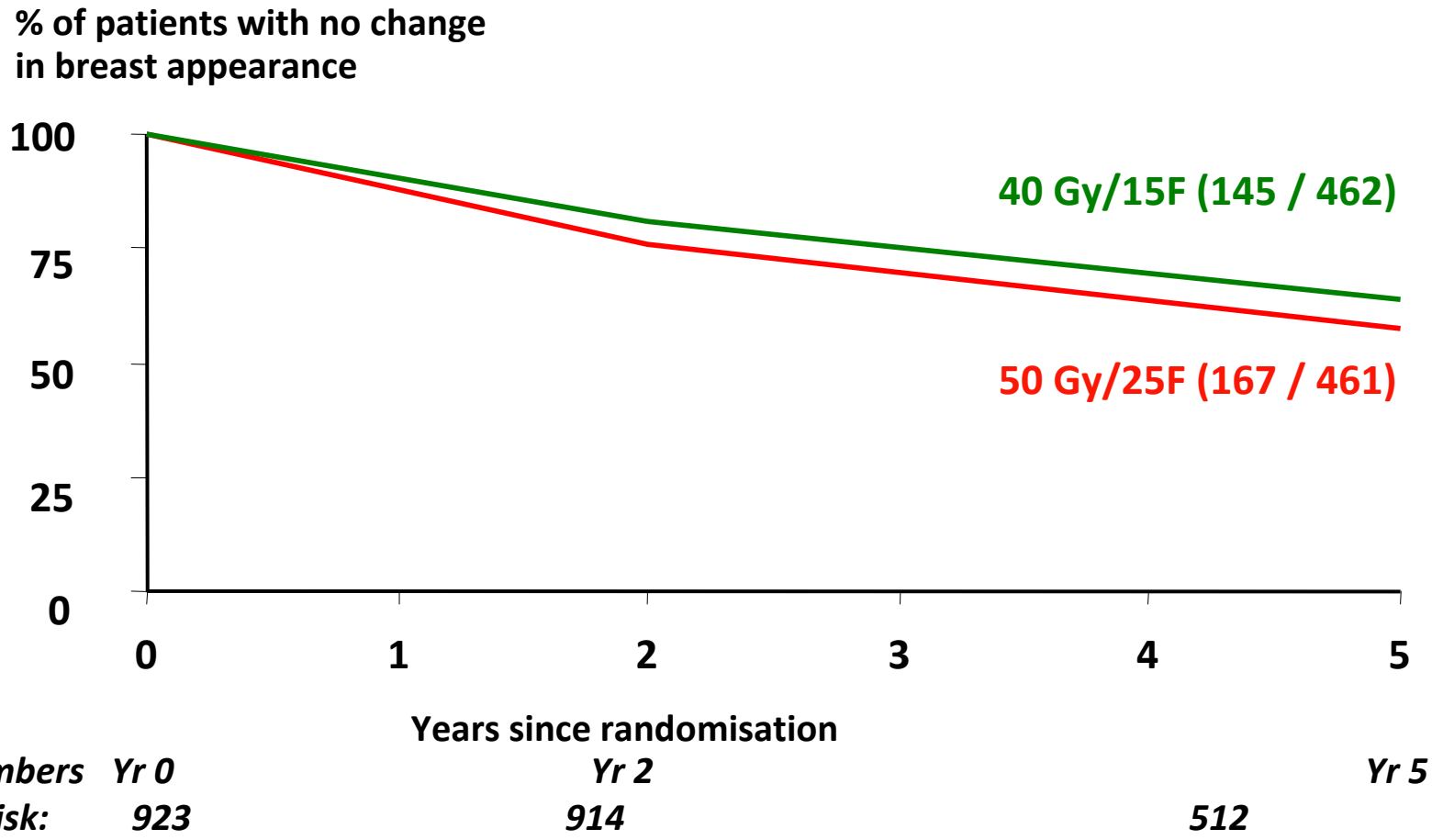
Endpoint	Fr. schedule	Estimated % with event by 5 years (95% CI)	Crude HR (95% CI)	Wald test p-value
Loco regional recurrence	50 Gy 41.6 Gy 39 Gy	3.6 (2.2-5.1) 3.5 (2.1-4.3) 5.2 (3.5-6.9)	1 1.05 (0.63-1.75) 1.26 (0.77-2.08)	- 0.86 0.35
Distant relapse	50 Gy 41.6 Gy 39 Gy	9.8 (7.5-12.0) 9.5 (7.3-11.7) 11.9 (9.5-14.4)	1 0.92 (0.66-1.28) 1.29 (0.95-1.76)	- 0.64 0.10
All cause mortality	50 Gy 41.6 Gy 39 Gy	11.1 (8.7-13.4) 11.3 (8.9-13.7) 10.7 (8.3-13.1)	1 1.04 (0.77-1.40) 1.00 (0.74-1.36	- 0.81 0.99

START Trial B (ST-B)



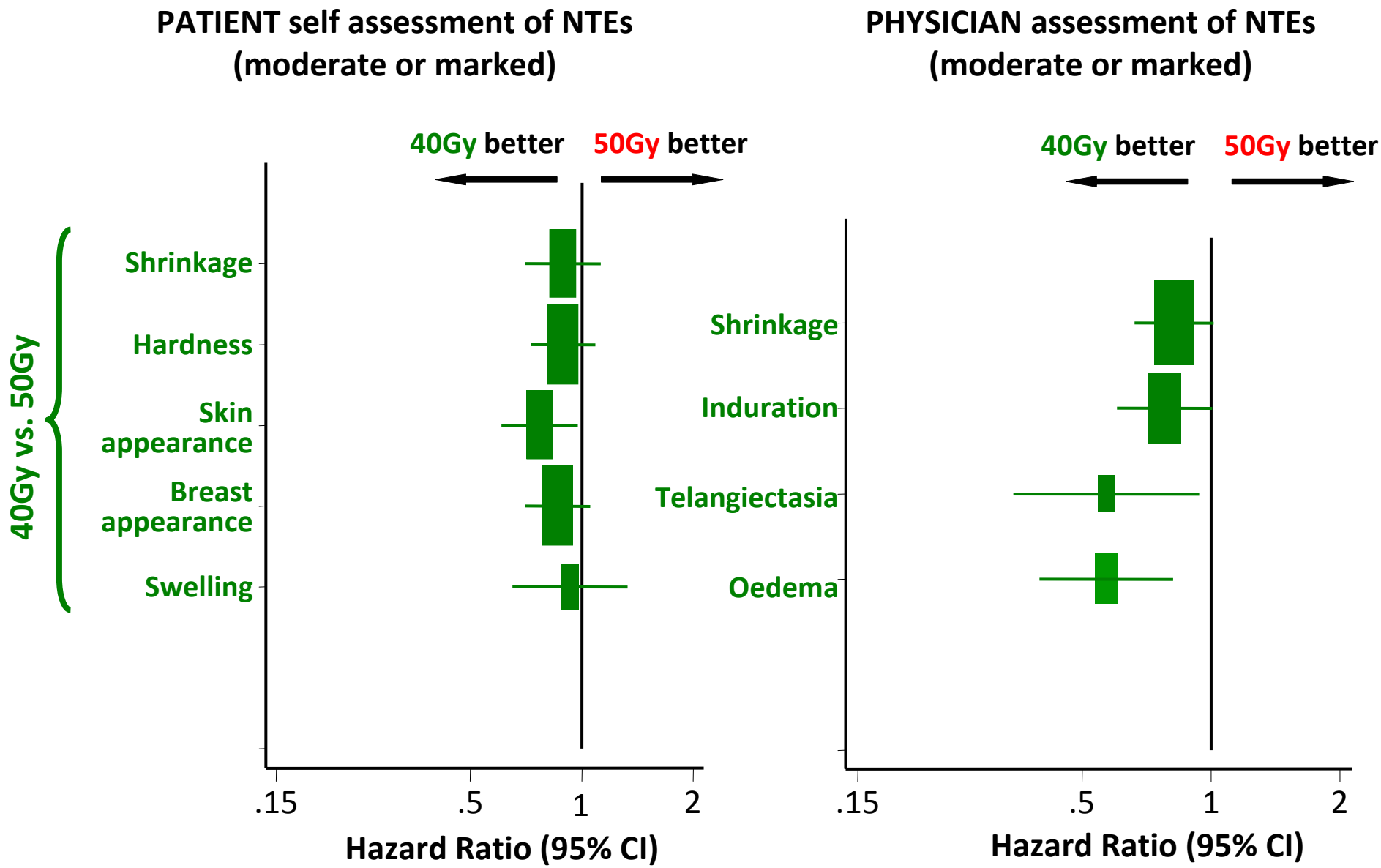
6.0 years median follow-up

Trial B: Change in breast appearance (photos)

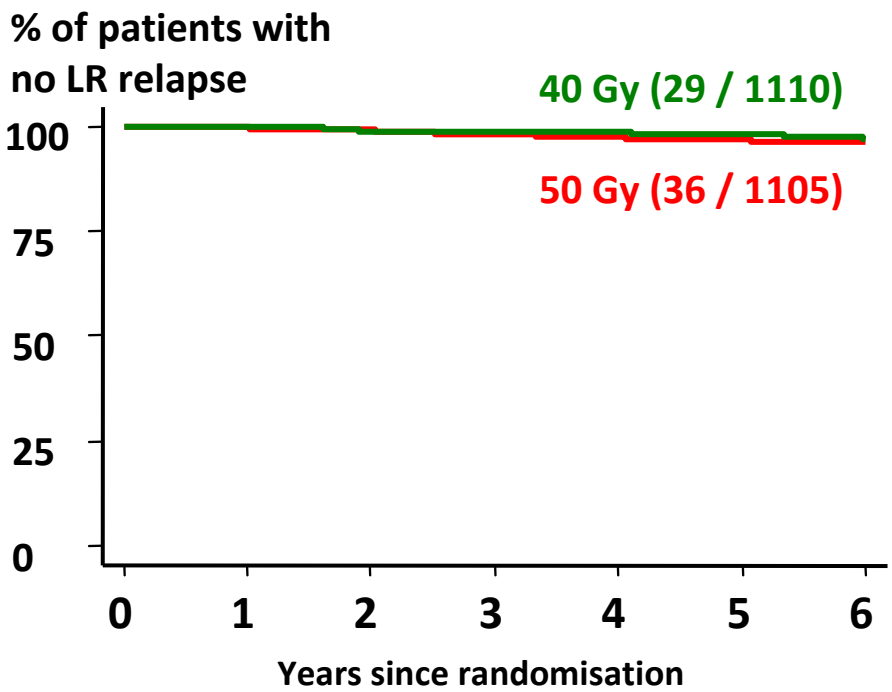


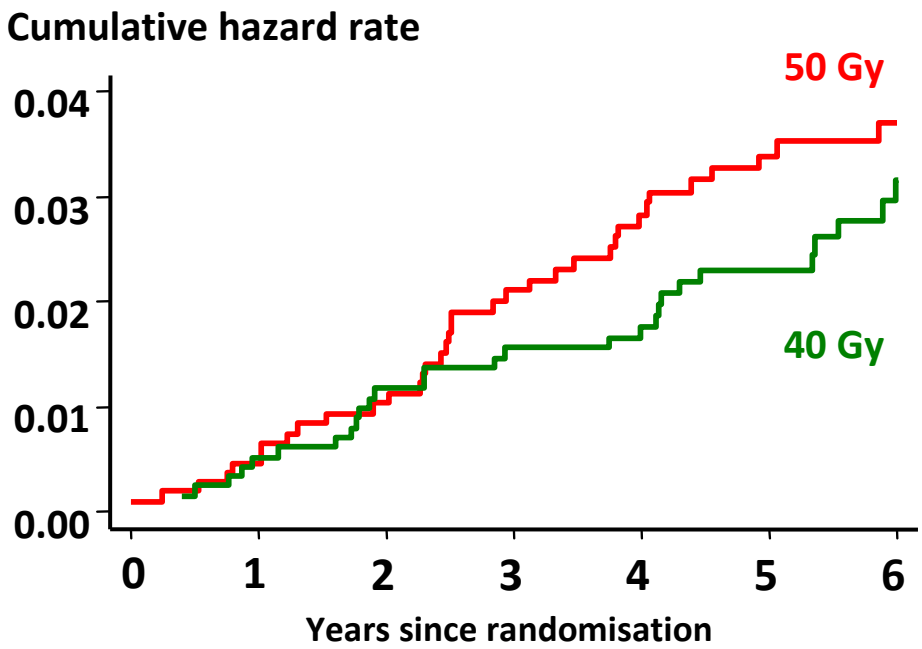
	Hazard Ratios (95%CI)	Absolute difference at 5 yr (95%CI)
40 Gy vs. 50 Gy	0.83 (0.66 – 1.04)	-5.6% (-11.8% – 1.2%)

Trial B : Late normal tissue effects



Trial B : Local-regional (LR) tumour relapse





Numbers at risk:

Yr 0	*Yr 1*	*Yr 2*	*Yr 3*	*Yr 4*	*Yr 5*	*Yr 6*
2215	*2158*	*2098*	*2007*	*1903*	*1589*	*884*

	Hazard Ratio (95%CI)	**Absolute difference at 5 yr (95%CI)**
40 Gy vs. 50 Gy	**0.79 (0.48 – 1.29)**	**-0.6% (-1.7% – 0.9%)**

Survival: Trial B

Endpoint	Fr. schedule	Estimated % with event by 5 years (95% CI)	Crude HR (95% CI)	Wald test p-value1
Loco regional recurrence	50 Gy 40 Gy	3.3 (2.2-4.4) 2.0 (1.1-2.8)	1 0.72 (0.43-1.21)	0.21
Distant relapse	50 Gy 40 Gy	10.2 (8.4-12.1) 7.6 (6.0-9.2)	1 0.69 (0.53-0.91)	0.01
All cause mortality	50 Gy 40 Gy	11.0 (9.1-12.9) 8.0 (6.7-9.4)	1 0.76 (0.59-0.98)	0.03

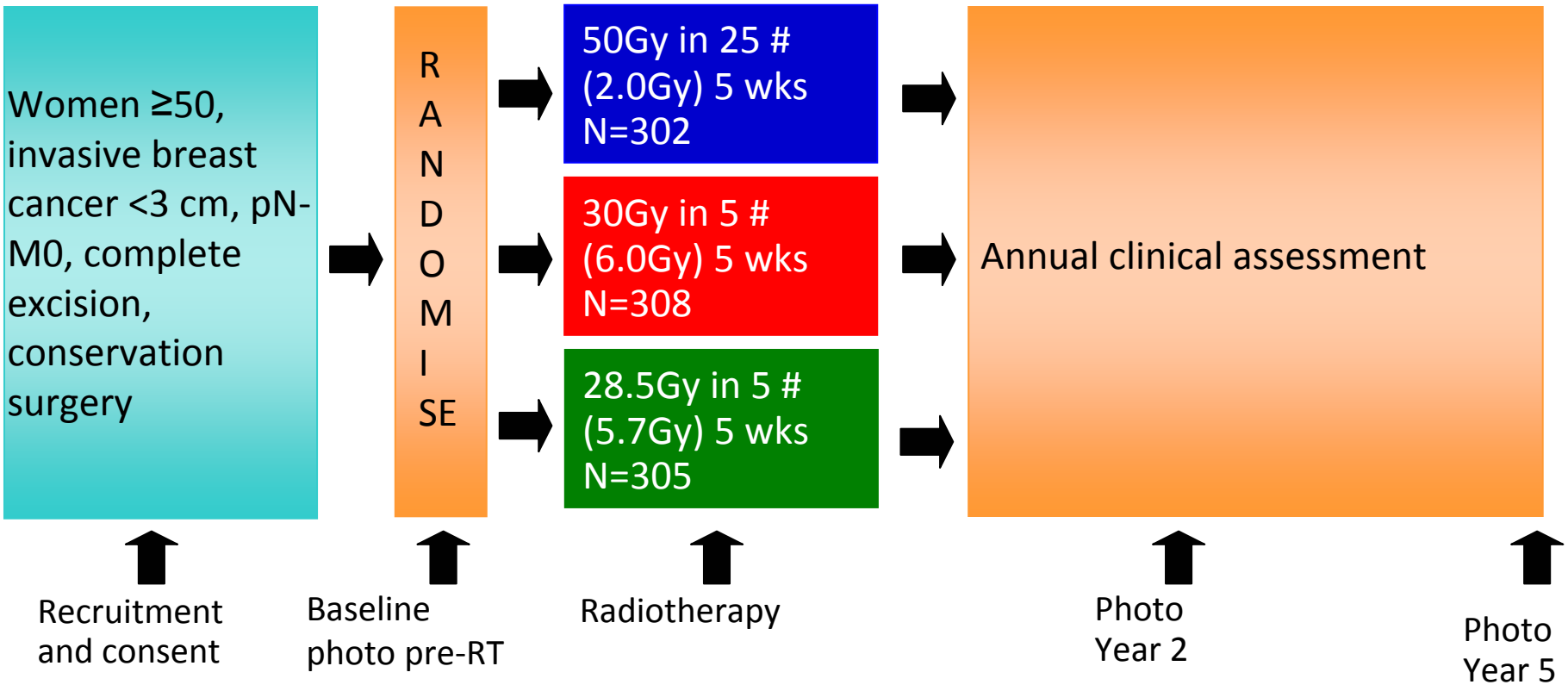
FAST Trial: Aim

To test a 5-fraction regimen of whole breast RT against 25 fractions of 2Gy after local excision of early breast cancer in terms of:

- late normal tissue responses

- local tumour control

FAST Trial: Design



Primary Endpoint:

- Photographic change in breast appearance at 2 years
- NONE, MILD, MARKED change compared with pre-RT baseline (Clin Oncol 2008;20:497-501)

Secondary Endpoints:

- Change in photographic breast appearance at 5 years
- Annual clinical assessments of breast induration, shrinkage, oedema
- Local tumour relapse

FAST Trial: Sample size

Assume:

- 20% change in breast appearance at 2 years
- Detect 10% difference between test groups (90% power, 5% significance)
- Allow for 10% loss to follow-up / unevaluable

300 patients required per group = 900

Patients and follow-up

- 915 patients at 18 UK centres 2004-'07
  - Mean age 63 years (range 50-88)
  - 71% ductal histology
  - 81% <2cm tumour size
  - 88% grade 1 or 2
  - 11% no adjuvant therapy
  - 89% endocrine therapy
- 98.9% patients received allocated treatment
- All patients had 3D dose compensation*
- Median follow up 2.3 years

* All centres had to undergo a rigorous QA programme before trial initiation

Acute Skin Reactions

RTOG grade	50Gy (%) N=110	30Gy (%) N=111	28.5Gy (%) N=106
0 or 1	53.7	85.6	89.7
2=tender/bright erythema +/- dry desquamation	35.5	11.7	8.5
3=patchy moist desquamation	10.9	2.7	1.9

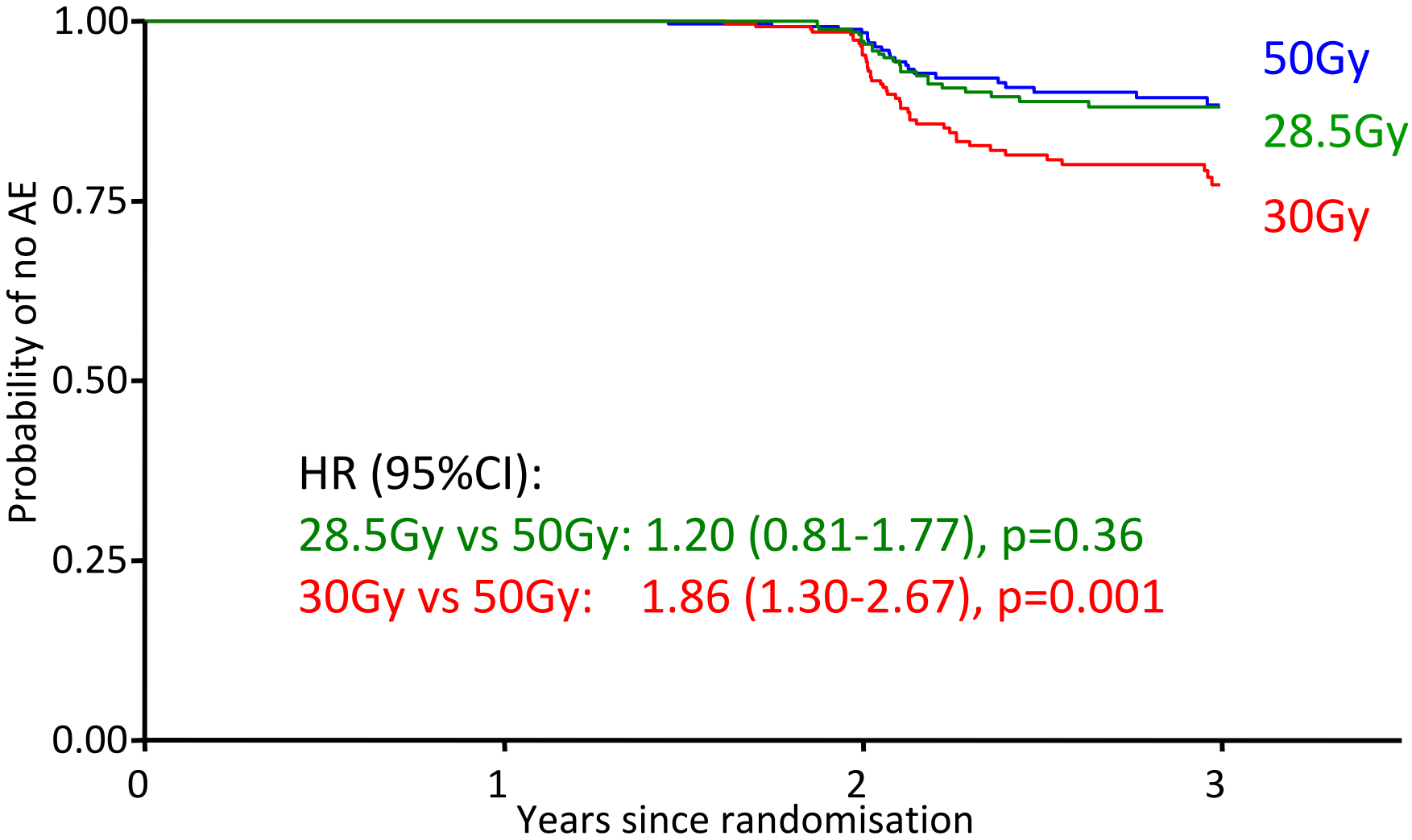
No patients had grade 4 toxicity reported (confluent moist desquamation)

Change in Photographic Breast Appearance

Change at 2 years	50Gy (%) N=229		30Gy (%) N=232		28.5Gy (%) N=225	
None	79.5		66.8		76.0	
Mild	18.8	20.5	24.1	33.2	20.0	24.0
Marked	1.7		9.1		4.0	
P-values vs. 50Gy			<0.001		0.22	

77% of 2-year assessments currently available

Moderate/marked Radiotherapy Adverse Effects in Breast*



*Includes shrinkage, induration, telangiectasia, oedema & other.
Year 1 events excluded - mostly reflect surgical and acute transient RT effects.

Fractionation Sensitivity (α/β estimates)

- Change in breast appearance (photographs):

  $\alpha/\beta = 2.4$Gy (95% CI 1.0–3.9)

- Breast shrinkage (clinical):

  $\alpha/\beta = 2.7$Gy (95% CI 1.6–3.7)

If $\alpha/\beta = 2.5$Gy

28.5Gy in 5F ≡ 51.9Gy in 2.0Gy fractions

Relapse and Survival

At median follow up of 2.3 years - disease outcome is currently immature:

- 2 patients with local relapse
- 2 patients with regional relapse
- 10 patients with metastatic disease
- 15 patient deaths (8 from breast cancer)

FAST Conclusions

- Using α/β estimate, one can identify a 5F schedule of whole breast RT $\equiv$ 50Gy/25F in terms of adverse effects of late reacting normal tissues
- Local relapse rate currently very low
- Follow-up continuing

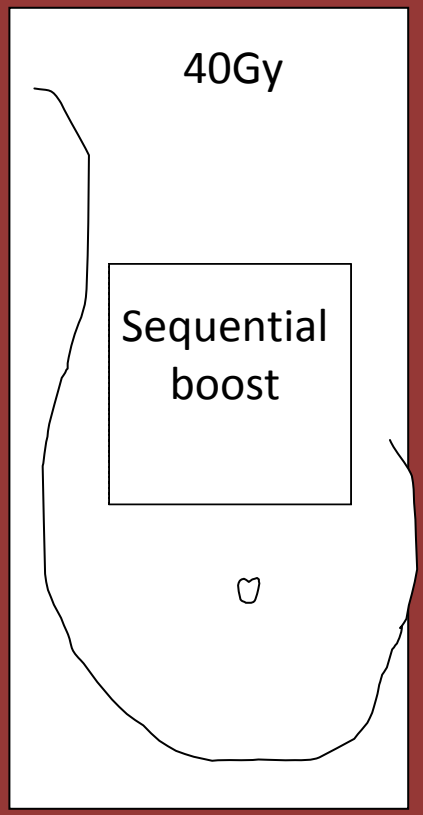
IMPORT HIGH: Aim

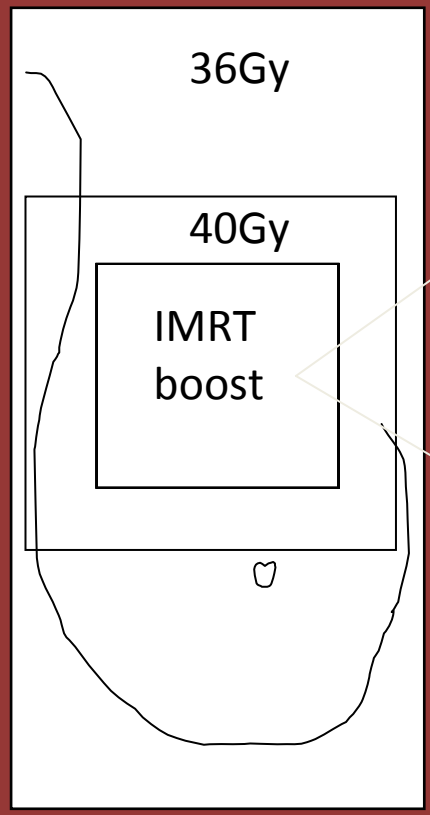
- To test dose escalated IMRT after conservation surgery for women with higher than average local recurrence risk early breast cancer

IMPORT HIGH Trial (showing physical doses)

Control

Test





Subrandomise Boost dose

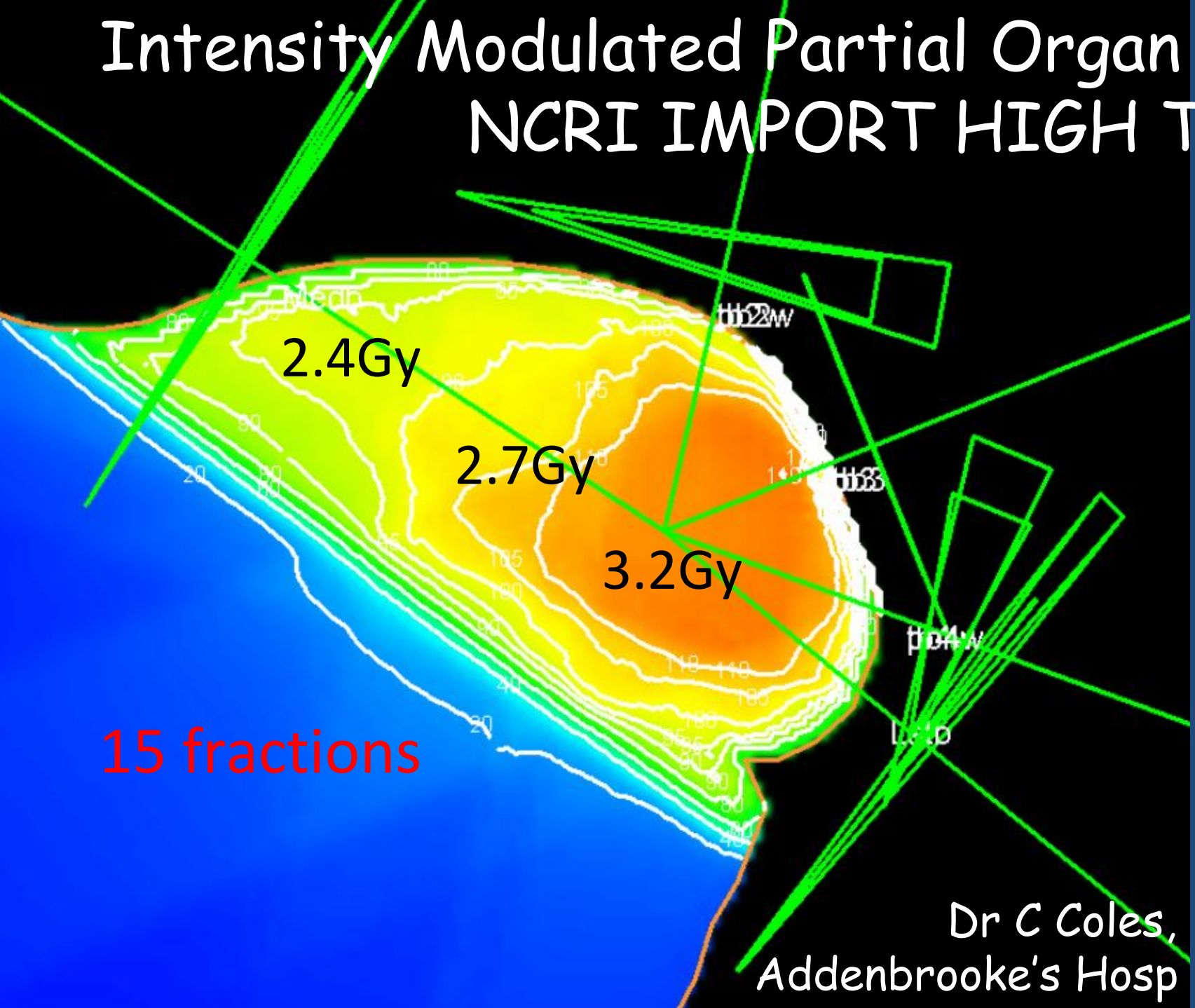
48Gy/15F (3.2Gy/F)

vs

53Gy/15F (3.5Gy/F)

No boost	15F	15F
Boost	15 + 8F	15F

Intensity Modulated Partial Organ RT: NCRI IMPORT HIGH Trial



Dr C Coles,
Addenbrooke's Hosp

IMPORT HIGH: Endpoints

- **Primary**
  - **Palpable induration**
- **Secondary**
  - **Other late adverse effects & QL**
  - **Local tumour control**
  - **Location of tumour relapse**
  - **Contralateral primary tumours**
  - **Regional and distant metastases**

Hypofractionation: the Future

- Likely that breast cancer is as sensitive to fraction size as the critical late-reacting normal tissues
- Likely that patients can be safely and effectively treated to a lower total dose with fewer fractions

What are the limits of this approach?

FAST Forward Trial (N=4000)

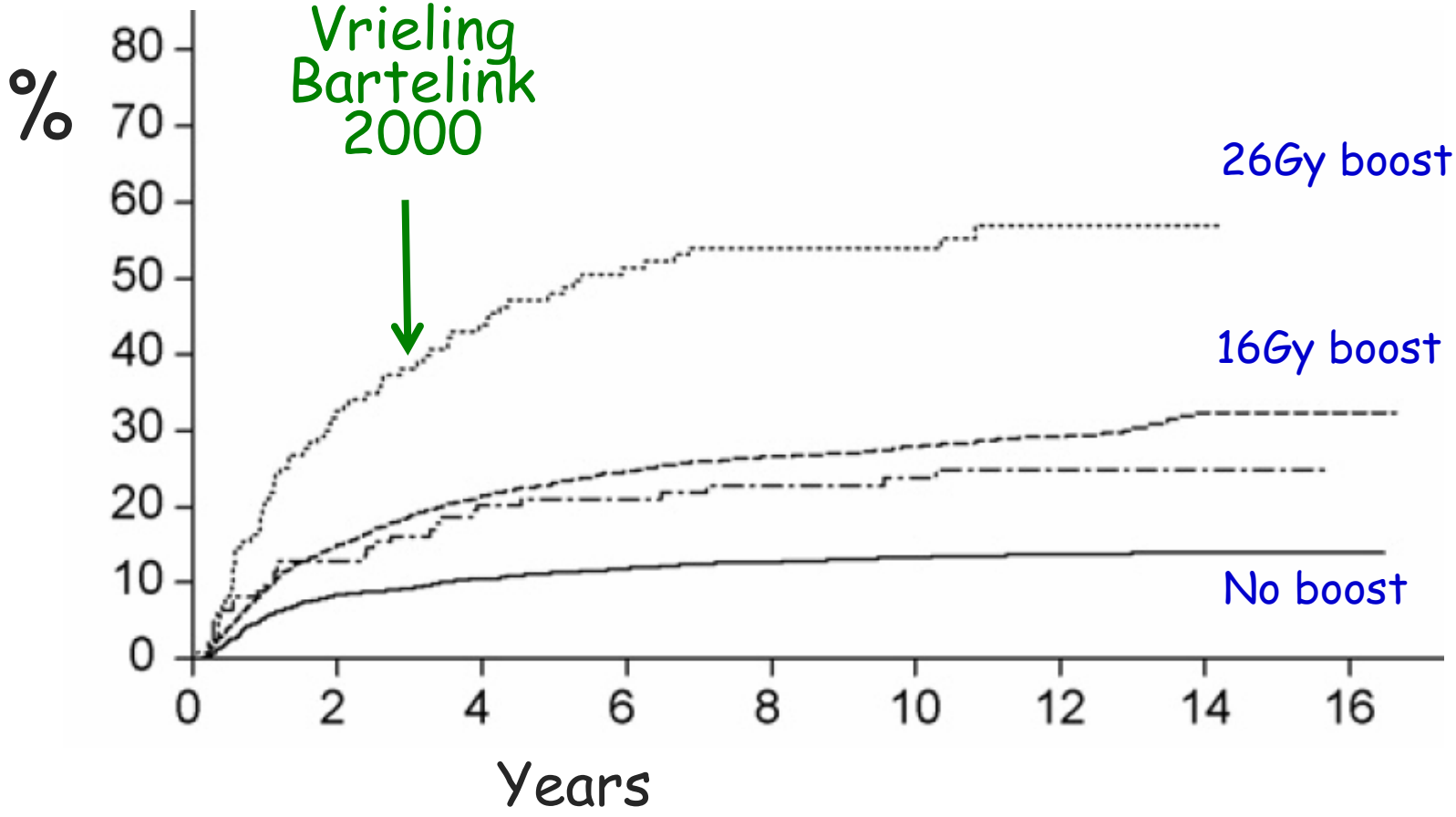
	TD (Gy)	N	# (Gy)	T
Control 1	40.0	15	2.67	3 weeks
Test 1	27.0	5	5.4	5 days
Test 2	26.0	5	5.2	5 days

Primary endpoint: local tumour control

Criticisms?

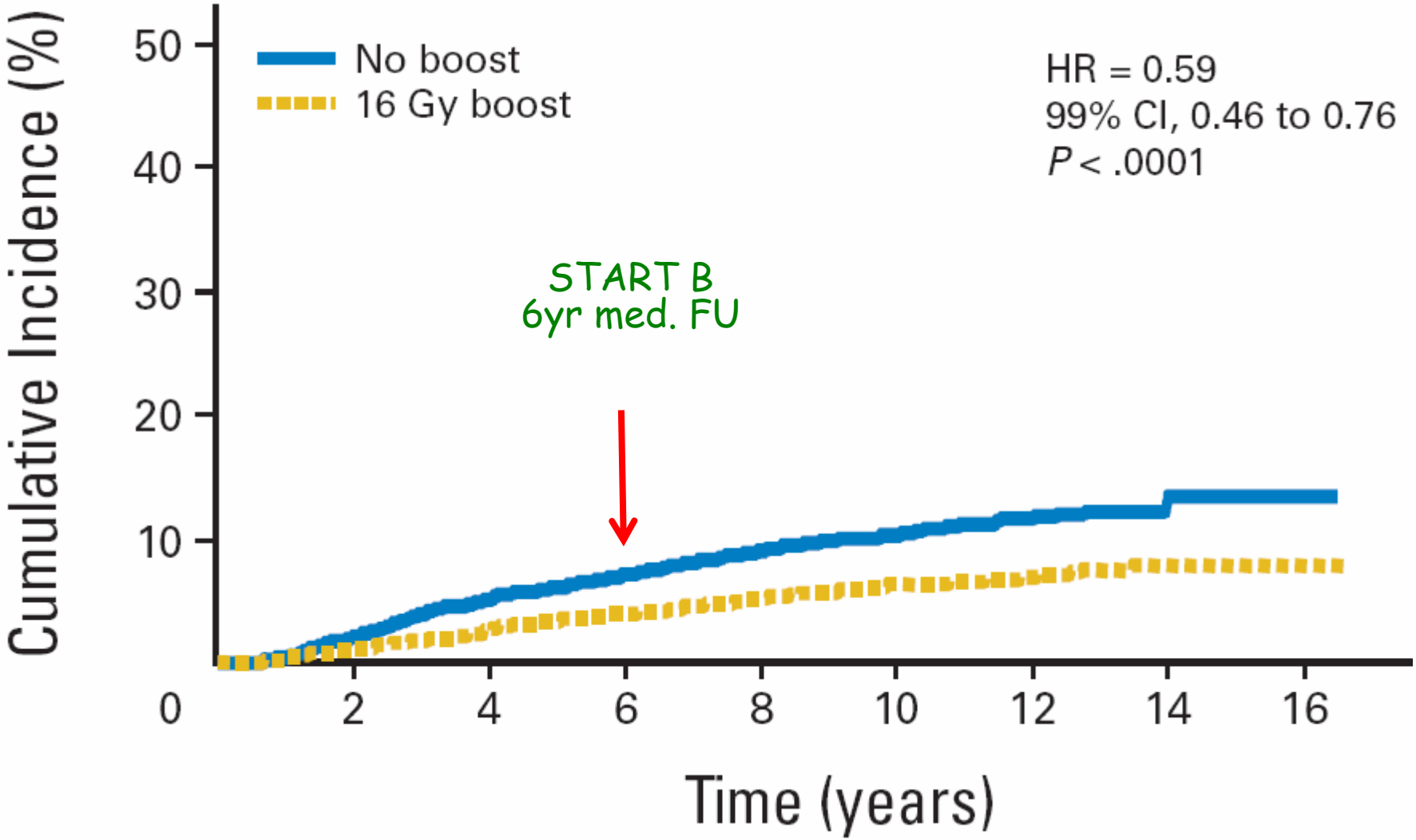
- “Your results are too early”

Moderate or Severe Fibrosis in EORTC Boost Trial (N=5318)



Vrieling et al, Radioth Oncol, 55; 2000, 219-32
Poortmans et al, Cancer Radiotherapie, 12; 2008, 565-70

Local Tumour Relapse in EORTC Boost Trial (N=5318)



Bartelink et al JCO, 2007, 25; 3259-65

Ontario Trial (N=1234)

Total Dose (Gy)	Fraction size (Gy)	Fraction number	Time (week)
50.0	2.0	25	5
42.5	2.66	16	3

Whelan 2002, JNCI, 94, 1143-50

Ontario trial

- Postoperative RT after conservation
- Node –ve, clear margins
- 50 Gy 25f 5 weeks vs. 42.5 Gy 16f 3 weeks
- 1234 patients recruited 1993-6
- Median follow up 140 months

Ontario Trial: Results

- 5-year local relapse-free survival
  - 96.8% after 50 Gy/25F
  - 97.2% after 42.5 Gy/16F
- 5-year excellent/good breast cosmesis
  - 77.4% after 50 Gy/25F
  - 76.8% after 42.5 Gy/16F

Whelan 2002, JNCI, 94, 1143-50

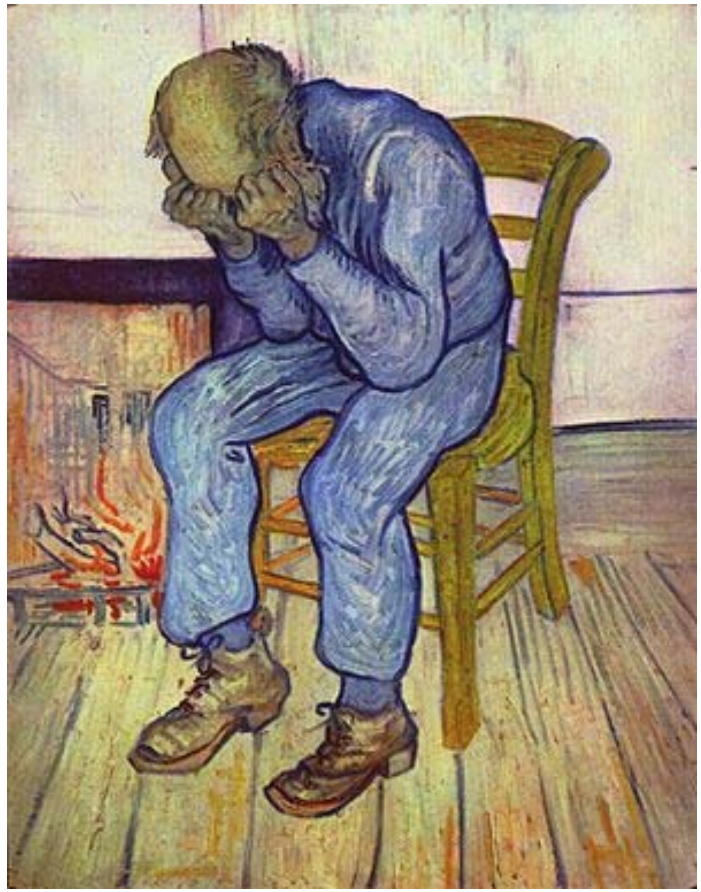
Ontario trial

10 year results	50 Gy	42.6 Gy
Local recurrence %	6.7	6.2
Overall survival %	84.6	86.4
% excellent cosmesis	71	70

There Must be Other Things to Worry About…….

- Double trouble?
- Acute reactions?

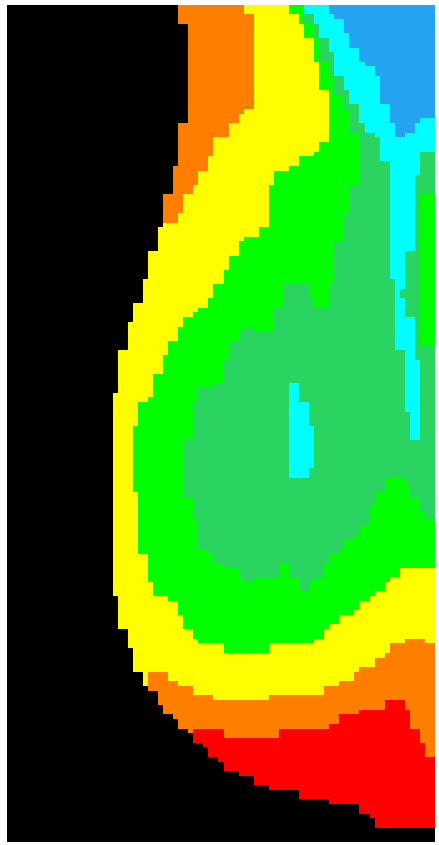
Relax…



'Double Trouble' is Bad, but larger Fractions **Do Not** Make it Much Worse

50 Gy/25F
2.0 Gy to 100%

52.5 Gy/25F
2.1 Gy to 105%



50 Gy in 25 Fractions to 100%

25F of 2.1 Gy to 105%
α/β=2.5 Gy

54 Gy in 2.0 Gy F
to 105%

5 fractions of 5.6 Gy to 100%

5F of 5.9 Gy to 105%
α/β=2.5 Gy

55 Gy in 2.0 Gy F
to 105%

Is this Clinically Relevant?

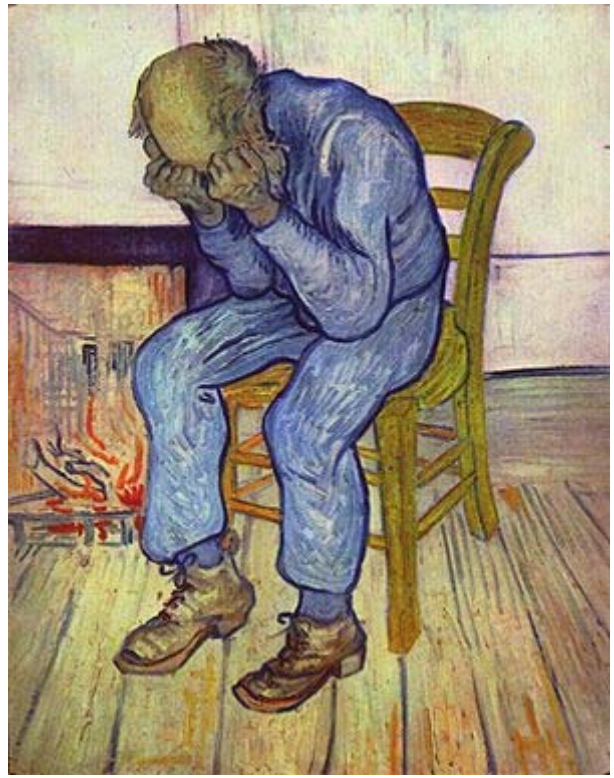
- 25F → 54 Gy to 105%
- 5F → 55 Gy to 105%

To whole breast; perhaps

To a small partial volume; no!

There Must be Other Things to Worry About…….

- Acute reactions?



Acute Reactions are Milder !

RTOG grade	50Gy/25F/5W (%) N=110	28.5Gy/5F/5W (%) N=106
3=patchy moist desquamation	10.9	1.9
4=confluent moist desquamation	0	0

FAST Trial; Brunt, M. ECCO 2009

"Hypofractionation
Should be Standard of Care
in Breast Cancer"

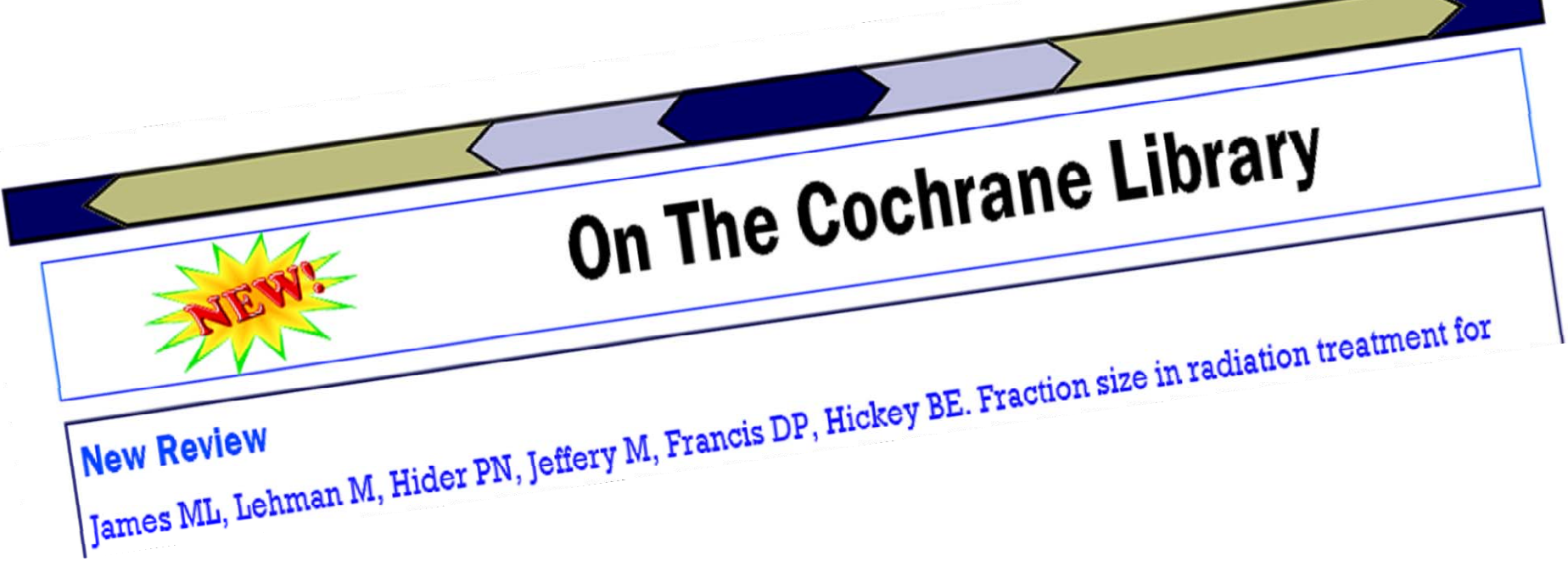
QED

Thank you for your kind attention

Learn the correct lessons from history….

Danish post-mast. trial 1978-80

- 22F vs 12F
- 22F arm, 52 Gy median TD
- 12F arm, 48 Gy median TD
- 12F arm matched 22F for erythema
- late effects much more severe
  - ≅ 70 Gy/35F



"We have evidence from two high quality trials that the use of unconventional fractionation regimes (> 2.0 Gy per fraction) does not affect breast appearance or toxicity & does not seem to affect local recurrence....."

Cochrane Database of Systematic Reviews, 2008

Other Benefits

Acceleration
Convenience
Partial breast RT
40 Gy/15F gentler on brachial plexus than 50 Gy/25F!
Synchronous boost

Conclusions

Women should be offered the benefits of hypofractionation

- 40 Gy in 15 fractions is
  - Safe
  - Effective
  - Convenient
  - Economical

Meta-analysis of START Pilot Trial & START Trial A

- Tumour relapse (294 events/3646 pts):
  - Adjusted α/β = 4.6 Gy (95%CI 1.1-8.1)
- Adverse effects (754 events/2257 pts):
  - Adjusted α/β = 3.4 Gy (95%CI 2.3-4.5)

- Data suggest that small fractions spare the cancer as much as healthy tissues!

START Lanc Onc 2008; 7: 331-41

Ontario Trial : Implications for Fractionation Sensitivity

- If schedules are truly iso-effective for both tumour & NT effects,

  α/β value = 3 Gy

  (if no time effect)

Radiotherapy – increasing fraction size

60 Gy over 8 weeks + 30 Gy boost (Montague 1968)

Complications	**5 fractions per week**	**3 fractions per week**
Chest wall necrosis, fibrosis, rib fracture.	3%	13%

Linear-Quadratic model