Breast Cancer Radiotherapy: Clinical challenges in 2011 from a European Perspective

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Radiotherapy in Early Breast Cancer

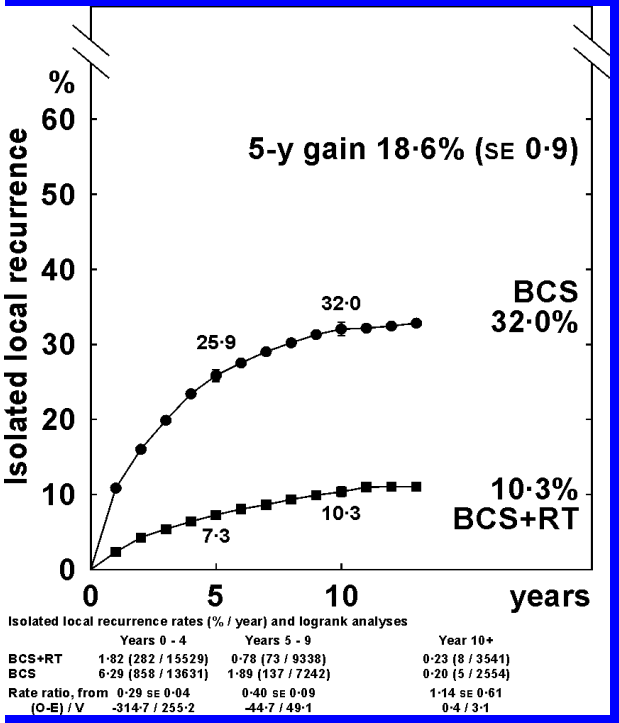
- Why do we do it?
- Who should we Treat?
- What areas should we Treat?
- Whole breast vs partial Breast?
- Dose/Fractionation?

Early Breast Cancer Trialists' Collaborative Group (EBCTCG) Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials

EBCTCG Lancet 2005; 366: 2087-2106

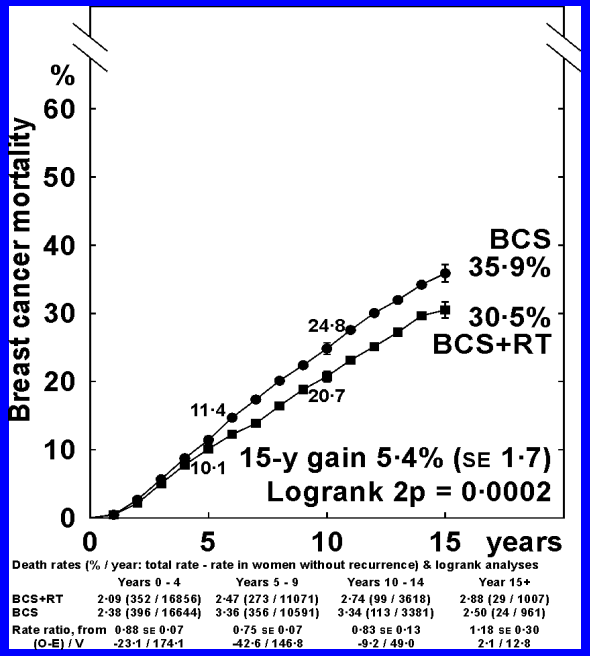
Radiotherapy after breast-conserving surgery, generally with axillary clearance (BCS±RT) in all women (node-negative or node-positive)

(7311 women, 17% with node-positive disease)



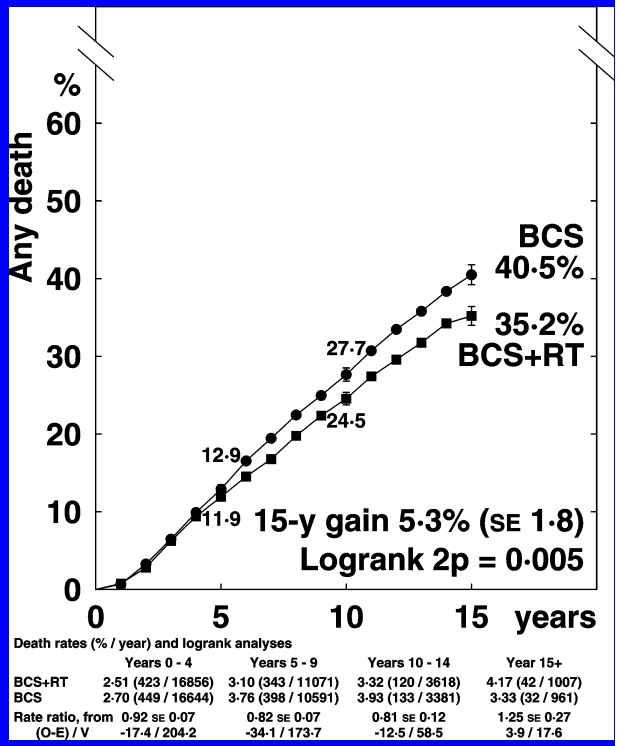
Isolated local recurrence rates (% / year) and logrank analyses

	Years 0 - 4	Years 5 - 9	Year 10+
BCS+RT	1·82 (282 / 15529)	0·78 (73 / 9338)	0·23 (8 / 3541)
BCS	6·29 (858 / 13631)	1·89 (137 / 7242)	0·20 (5 / 2554)
Rate ratio, from	0·29 SE 0·04	0·40 SE 0·09	1·14 SE 0·61
(O-E) / V	-314·7 / 255·2	-44·7 / 49·1	0·4 / 3·1



Death rates (% / year: total rate - rate in women without recurrence) & logrank analyses

	Years 0 - 4	Years 5 - 9	Years 10 - 14	Year 15+
BCS+RT	2·09 (352 / 16856)	2·47 (273 / 11071)	2·74 (99 / 3618)	2·88 (29 / 1007)
BCS	2·38 (396 / 16644)	3·36 (356 / 10591)	3·34 (113 / 3381)	2·50 (24 / 961)
Rate ratio, from	0·88 SE 0·07	0·75 SE 0·07	0·83 SE 0·13	1·18 SE 0·30
(O-E) / V	-23·1 / 174·1	-42·6 / 146·8	-9·2 / 49·0	2·1 / 12·8

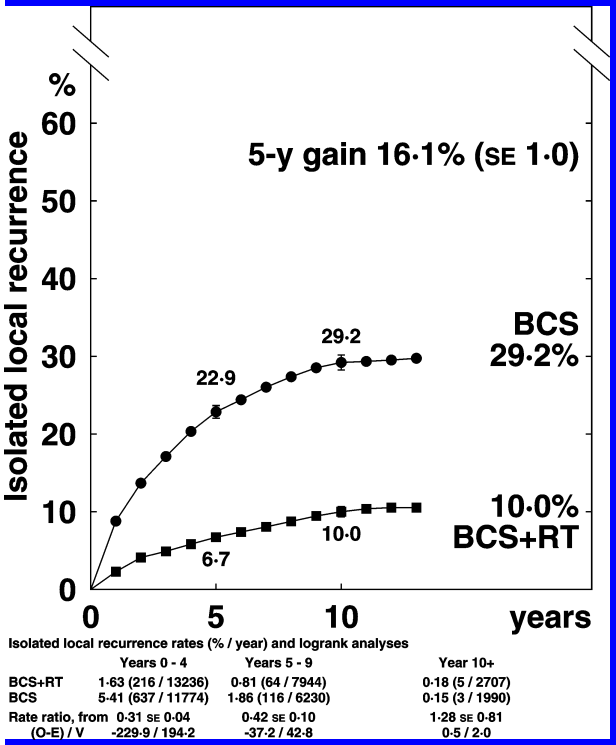


Death rates (% / year) and logrank analyses

	Years 0 - 4	Years 5 - 9	Years 10 - 14	Year 15+
BCS+RT	2·51 (423 / 16856)	3·10 (343 / 11071)	3·32 (120 / 3618)	4·17 (42 / 1007)
BCS	2·70 (449 / 16644)	3·76 (398 / 10591)	3·93 (133 / 3381)	3·33 (32 / 961)
Rate ratio, from	0·92 SE 0·07	0·82 SE 0·07	0·81 SE 0·12	1·25 SE 0·27
(O-E) / V	-17·4 / 204·2	-34·1 / 173·7	-12·5 / 58·5	3·9 / 17·6

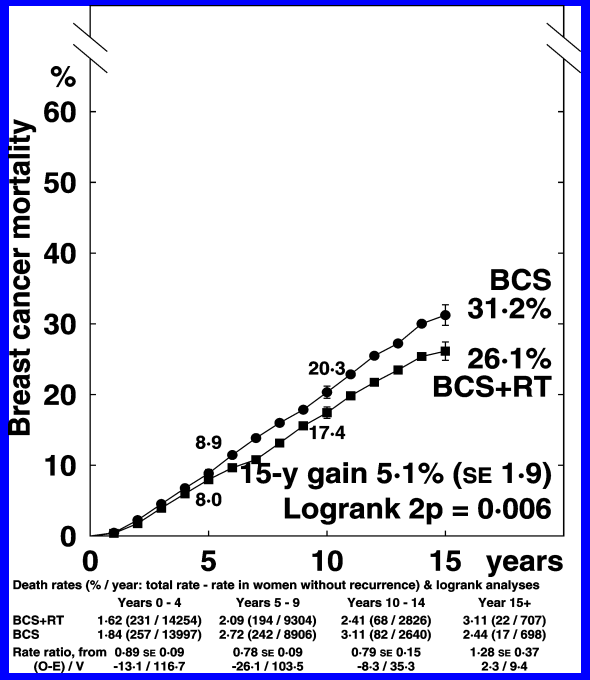
Radiotherapy after breast-conserving surgery, generally with axillary clearance (BCS±RT) in women with node-negative disease

(6097 women)



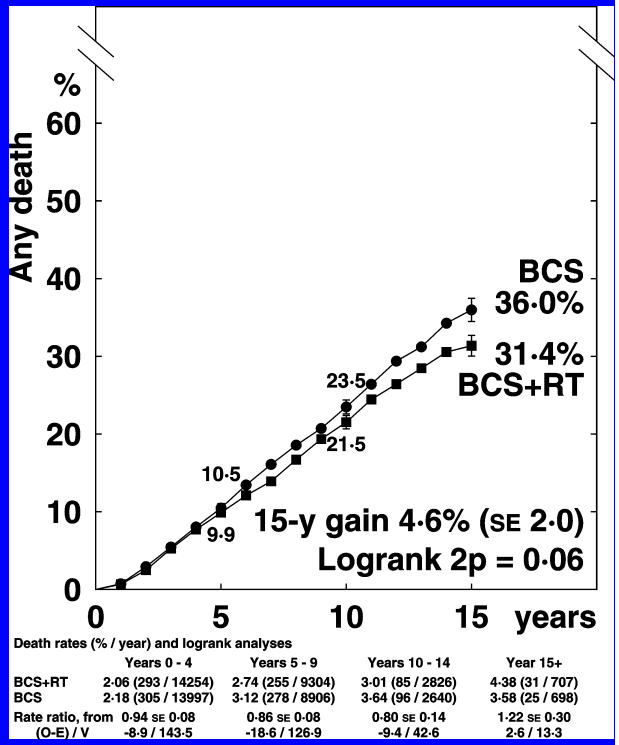
Isolated local recurrence rates (% / year) and logrank analyses

	Years 0 - 4	Years 5 - 9	Year 10+
BCS+RT	1·63 (216 / 13236)	0·81 (64 / 7944)	0·18 (5 / 2707)
BCS	5·41 (637 / 11774)	1·86 (116 / 6230)	0·15 (3 / 1990)
Rate ratio, from	0·31 SE 0·04	0·42 SE 0·10	1·28 SE 0·81
(O-E) / V	-229·9 / 194·2	-37·2 / 42·8	0·5 / 2·0



Death rates (% / year: total rate - rate in women without recurrence) & logrank analyses

	Years 0 - 4	Years 5 - 9	Years 10 - 14	Year 15+
BCS+RT	1·62 (231 / 14254)	2·09 (194 / 9304)	2·41 (68 / 2826)	3·11 (22 / 707)
BCS	1·84 (257 / 13997)	2·72 (242 / 8906)	3·11 (82 / 2640)	2·44 (17 / 698)
Rate ratio, from	0·89 SE 0·09	0·78 SE 0·09	0·79 SE 0·15	1·28 SE 0·37
(O-E) / V	-13·1 / 116·7	-26·1 / 103·5	-8·3 / 35·3	2·3 / 9·4

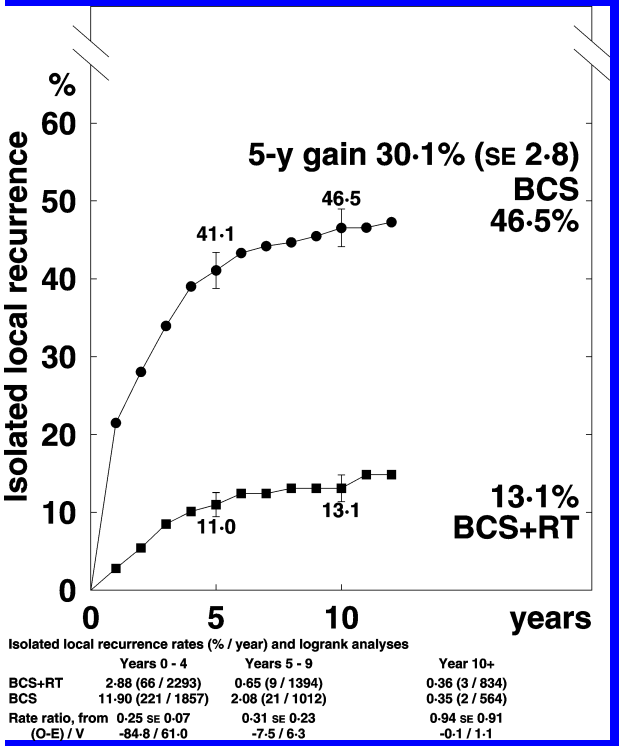


Death rates (% / year) and logrank analyses

	Years 0 - 4	Years 5 - 9	Years 10 - 14	Year 15+
BCS+RT	2·06 (293 / 14254)	2·74 (255 / 9304)	3·01 (85 / 2826)	4·38 (31 / 707)
BCS	2·18 (305 / 13997)	3·12 (278 / 8906)	3·64 (96 / 2640)	3·58 (25 / 698)
Rate ratio, from	0·94 SE 0·08	0·86 SE 0·08	0·80 SE 0·14	1·22 SE 0·30
(O-E) / V	-8·9 / 143·5	-18·6 / 126·9	-9·4 / 42·6	2·6 / 13·3

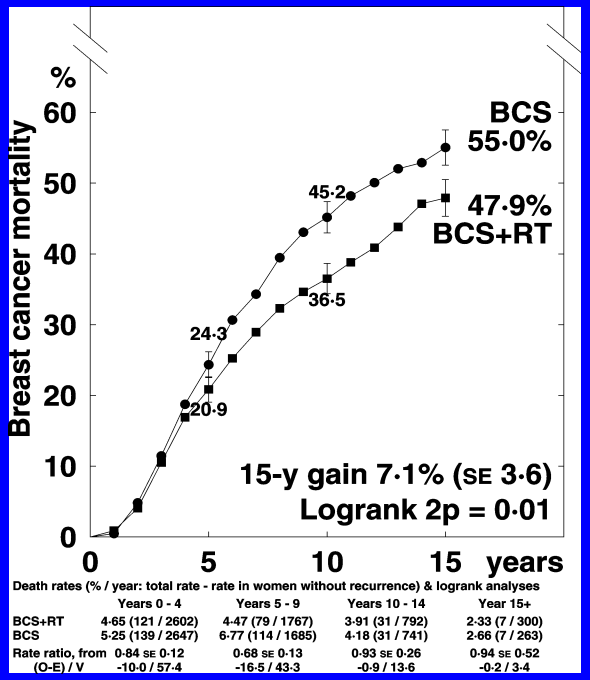
Radiotherapy after breast-conserving surgery, generally with axillary clearance (BCSΔRT) in women with node-positive disease

(1214 women)



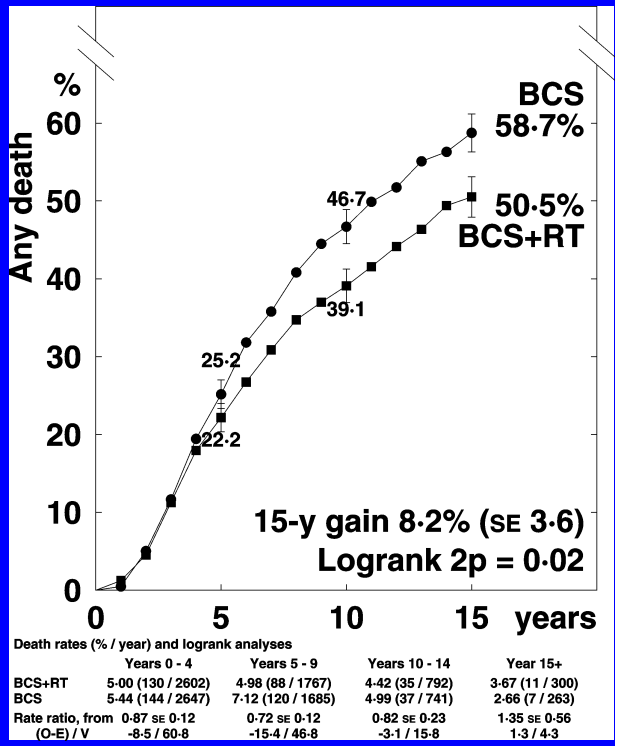
Isolated local recurrence rates (% / year) and logrank analyses

	Years 0 - 4	Years 5 - 9	Year 10+
BCS+RT	2·88 (66 / 2293)	0·65 (9 / 1394)	0·36 (3 / 834)
BCS	11·90 (221 / 1857)	2·08 (21 / 1012)	0·35 (2 / 564)
Rate ratio, from (O-E) / V	0·25 SE 0·07 -84·8 / 61·0	0·31 SE 0·23 -7·5 / 6·3	0·94 SE 0·91 -0·1 / 1·1



Death rates (% / year: total rate - rate in women without recurrence) & logrank analyses

	Years 0 - 4	Years 5 - 9	Years 10 - 14	Year 15+
BCS+RT	4·65 (121 / 2602)	4·47 (79 / 1767)	3·91 (31 / 792)	2·33 (7 / 300)
BCS	5·25 (139 / 2647)	6·77 (114 / 1685)	4·18 (31 / 741)	2·66 (7 / 263)
Rate ratio, from (O-E) / V	0·84 SE 0·12 -10·0 / 57·4	0·68 SE 0·13 -16·5 / 43·3	0·93 SE 0·26 -0·9 / 13·6	0·94 SE 0·52 -0·2 / 3·4

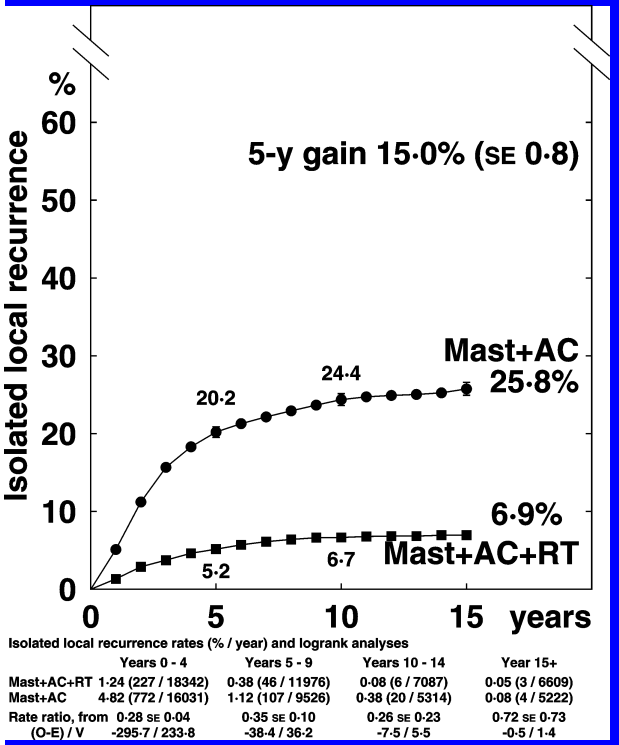


Death rates (% / year) and logrank analyses

	Years 0 - 4	Years 5 - 9	Years 10 - 14	Year 15+
BCS+RT	5·00 (130 / 2602)	4·98 (88 / 1767)	4·42 (35 / 792)	3·67 (11 / 300)
BCS	5·44 (144 / 2647)	7·12 (120 / 1685)	4·99 (37 / 741)	2·66 (7 / 263)
Rate ratio, from (O-E) / V	0·87 SE 0·12 -8·5 / 60·8	0·72 SE 0·12 -15·4 / 46·8	0·82 SE 0·23 -3·1 / 15·8	1·35 SE 0·56 1·3 / 4·3

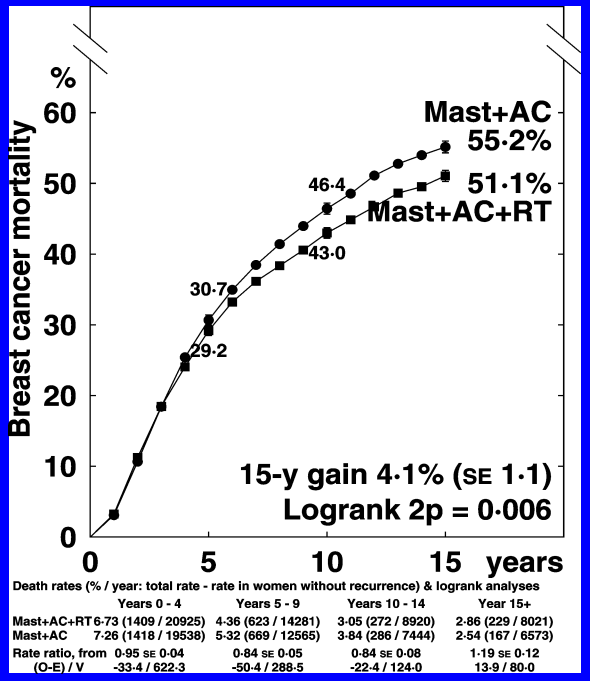
Radiotherapy after mastectomy with axillary clearance (Mast+AC±RT) in all women

(9933 women, 86% with node-positive disease)



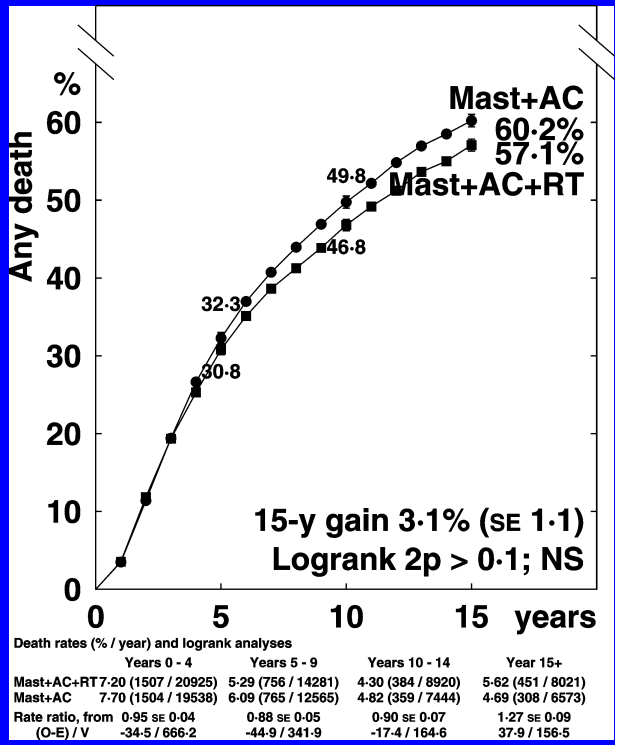
Isolated local recurrence rates (% / year) and logrank analyses

	Years 0 - 4	Years 5 - 9	Years 10 - 14	Year 15+
Mast+AC+RT	1·24 (227 / 18342)	0·38 (46 / 11976)	0·08 (6 / 7087)	0·05 (3 / 6609)
Mast+AC	4·82 (772 / 16031)	1·12 (107 / 9526)	0·38 (20 / 5314)	0·08 (4 / 5222)
Rate ratio, from	0·28 SE 0·04	0·35 SE 0·10	0·26 SE 0·23	0·72 SE 0·73
(O-E) / V	-295·7 / 233·8	-38·4 / 36·2	-7·5 / 5·5	-0·5 / 1·4



Death rates (% / year: total rate - rate in women without recurrence) & logrank analyses

	Years 0 - 4	Years 5 - 9	Years 10 - 14	Year 15+
Mast+AC+RT	6·73 (1409 / 20925)	4·36 (623 / 14281)	3·05 (272 / 8920)	2·86 (229 / 8021)
Mast+AC	7·26 (1418 / 19538)	5·32 (669 / 12565)	3·84 (286 / 7444)	2·54 (167 / 6573)
Rate ratio, from	0·95 SE 0·04	0·84 SE 0·05	0·84 SE 0·08	1·19 SE 0·12
(O-E) / V	-33·4 / 622·3	-50·4 / 288·5	-22·4 / 124·0	13·9 / 80·0

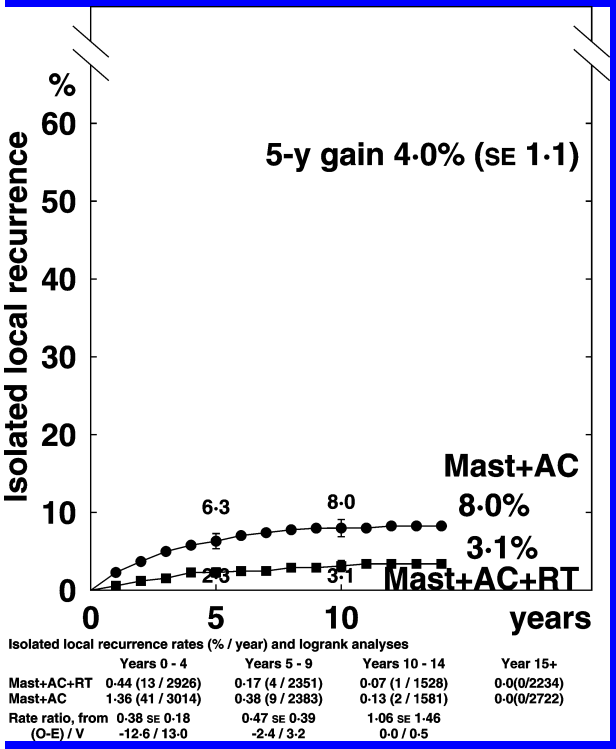


Death rates (% / year) and logrank analyses

	Years 0 - 4	Years 5 - 9	Years 10 - 14	Year 15+
Mast+AC+RT	7·20 (1507 / 20925)	5·29 (756 / 14281)	4·30 (384 / 8920)	5·62 (451 / 8021)
Mast+AC	7·70 (1504 / 19538)	6·09 (765 / 12565)	4·82 (359 / 7444)	4·69 (308 / 6573)
Rate ratio, from	0·95 SE 0·04	0·88 SE 0·05	0·90 SE 0·07	1·27 SE 0·09
(O-E) / V	-34·5 / 666·2	-44·9 / 341·9	-17·4 / 164·6	37·9 / 156·5

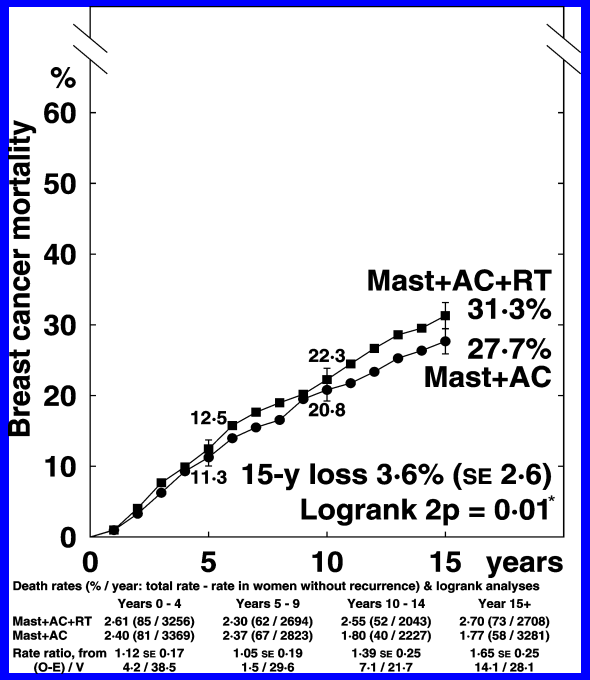
Radiotherapy after mastectomy with axillary clearance (Mast+AC±RT) in women with node-negative disease

(1428 women)



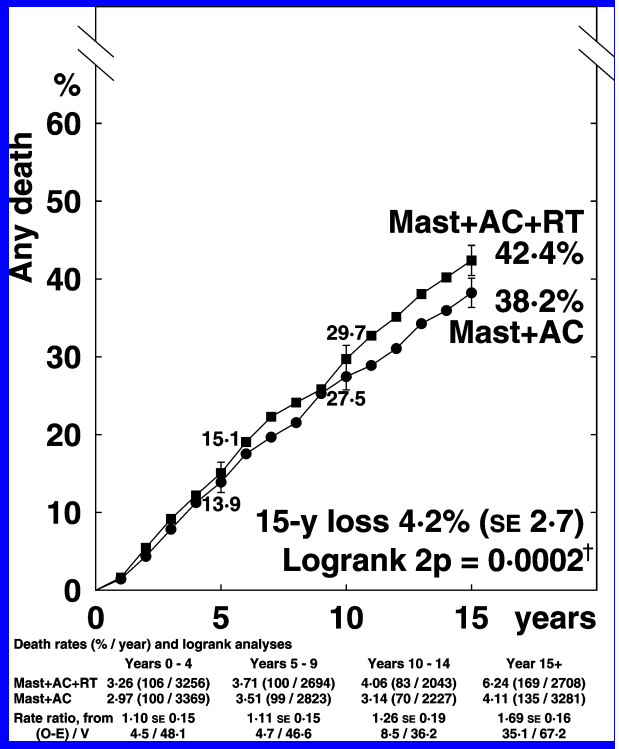
Isolated local recurrence rates (% / year) and logrank analyses

	Years 0 - 4	Years 5 - 9	Years 10 - 14	Year 15+
Mast+AC+RT	0·44 (13 / 2926)	0·17 (4 / 2351)	0·07 (1 / 1528)	0·0(0/2234)
Mast+AC	1·36 (41 / 3014)	0·38 (9 / 2383)	0·13 (2 / 1581)	0·0(0/2722)
Rate ratio, from	0·38 SE 0·18	0·47 SE 0·39	1·06 SE 1·46	
(O-E) / V	-12·6 / 13·0	-2·4 / 3·2	0·0 / 0·5	



Death rates (% / year: total rate - rate in women without recurrence) & logrank analyses

	Years 0 - 4	Years 5 - 9	Years 10 - 14	Year 15+
Mast+AC+RT	2·61 (85 / 3256)	2·30 (62 / 2694)	2·55 (52 / 2043)	2·70 (73 / 2708)
Mast+AC	2·40 (81 / 3369)	2·37 (67 / 2823)	1·80 (40 / 2227)	1·77 (58 / 3281)
Rate ratio, from	1·12 SE 0·17	1·05 SE 0·19	1·39 SE 0·25	1·65 SE 0·25
(O-E) / V	4·2 / 38·5	1·5 / 29·6	7·1 / 21·7	14·1 / 28·1



Death rates (% / year) and logrank analyses

	Years 0 - 4	Years 5 - 9	Years 10 - 14	Year 15+
Mast+AC+RT	3·26 (106 / 3256)	3·71 (100 / 2694)	4·06 (83 / 2043)	6·24 (169 / 2708)
Mast+AC	2·97 (100 / 3369)	3·51 (99 / 2823)	3·14 (70 / 2227)	4·11 (135 / 3281)
Rate ratio, from	1·10 SE 0·15	1·11 SE 0·15	1·26 SE 0·19	1·69 SE 0·16
(O-E) / V	4·5 / 48·1	4·7 / 46·6	8·5 / 36·2	35·1 / 67·2

Proportional and absolute reductions produced by radiotherapy

Radiotherapy produced similar *proportional* reductions in local recurrence in all women (irrespective of age or tumour characteristics) and in all major trials of ±RT (recent or older; with or without systemic therapy), so large *absolute* reductions in local recurrence were seen only if the control risk was large.

Interpretation

In these trials, avoidance of a local recurrence in the conserved breast after BCS and avoidance of a local recurrence elsewhere (eg, the chest wall or regional nodes) after mastectomy were of comparable relevance to 15-year breast cancer mortality.

Differences in local treatment that substantially affect local recurrence rates would, in the hypothetical absence of any other causes of death, avoid about one breast cancer death over the next 15 years for every four local recurrences avoided, and should reduce 15-year overall mortality.

Conclusions

These trials of radiotherapy and of the extent of surgery show that, in the hypothetical absence of other causes of death, about one breast cancer death over the next 15 years would be avoided for every four local recurrences avoided.

Although the management of early breast cancer continues to change, it is reasonable to assume that this approximate four-to-one relationship will continue to apply and will still be of relevance to future treatment choices.

Problems with Radiotherapy

- Who and Which areas should we treat?
- Side Effects
- 1. Short term (tired, skin effects, inconvenient..)
- 2. Long term
- (breast shrinkage,tenderness,skin changes, lymphoedema, lung fibrosis, rib fracture, cardiac morbidity, second malignancies, ?other vascular effects….).

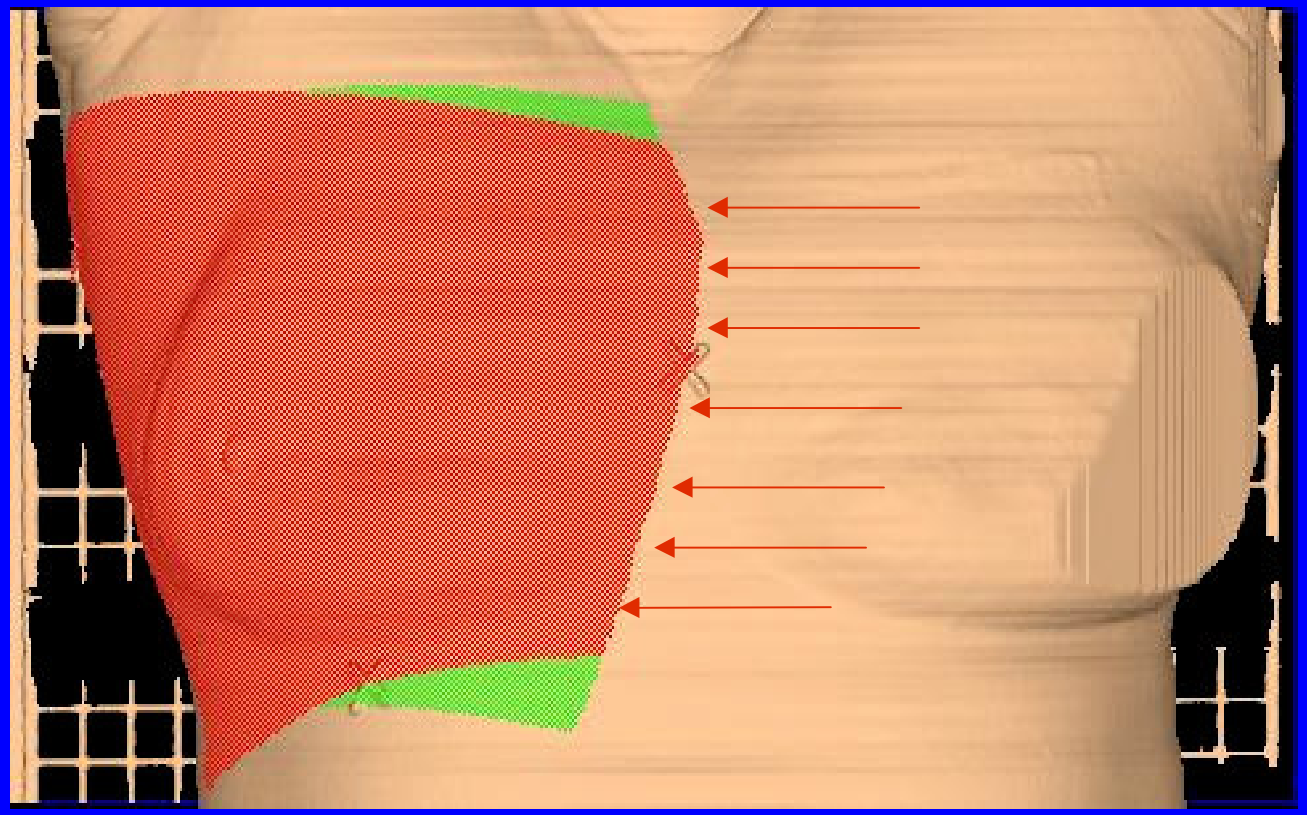
Can we reduce side effects/inconvenience of Radiotherapy?

- Altered fractionation regimes (START/FAST trials)
- Cardiac shielding
- Partial breast irradiation
- Newer techniques (IMRT)

Partial Breast Radiotherapy

Is this a rationale option?

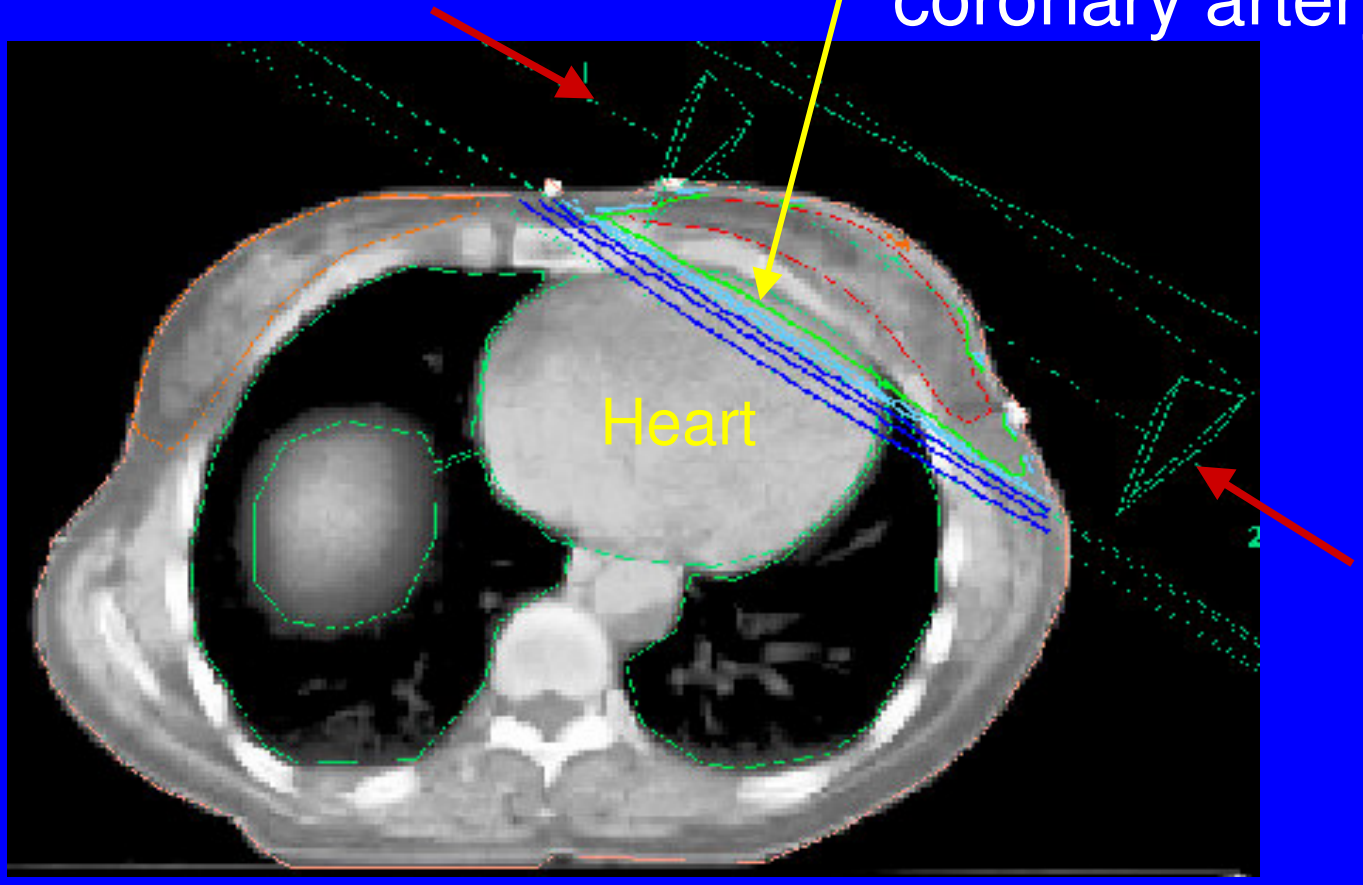
Exposure of Multiple Non-Target Tissues



Radiotherapy Adverse Effects

- High dose effects (cell killing)
  - Atrophy & fibrosis
  - Breast, muscles, ribs, lung, heart
  - Dose threshold
- Low dose effects (mutagenesis)
  - Carcinogenesis
  - No dose threshold

Cardiac Injury: Little Evidence of a Volume Effect

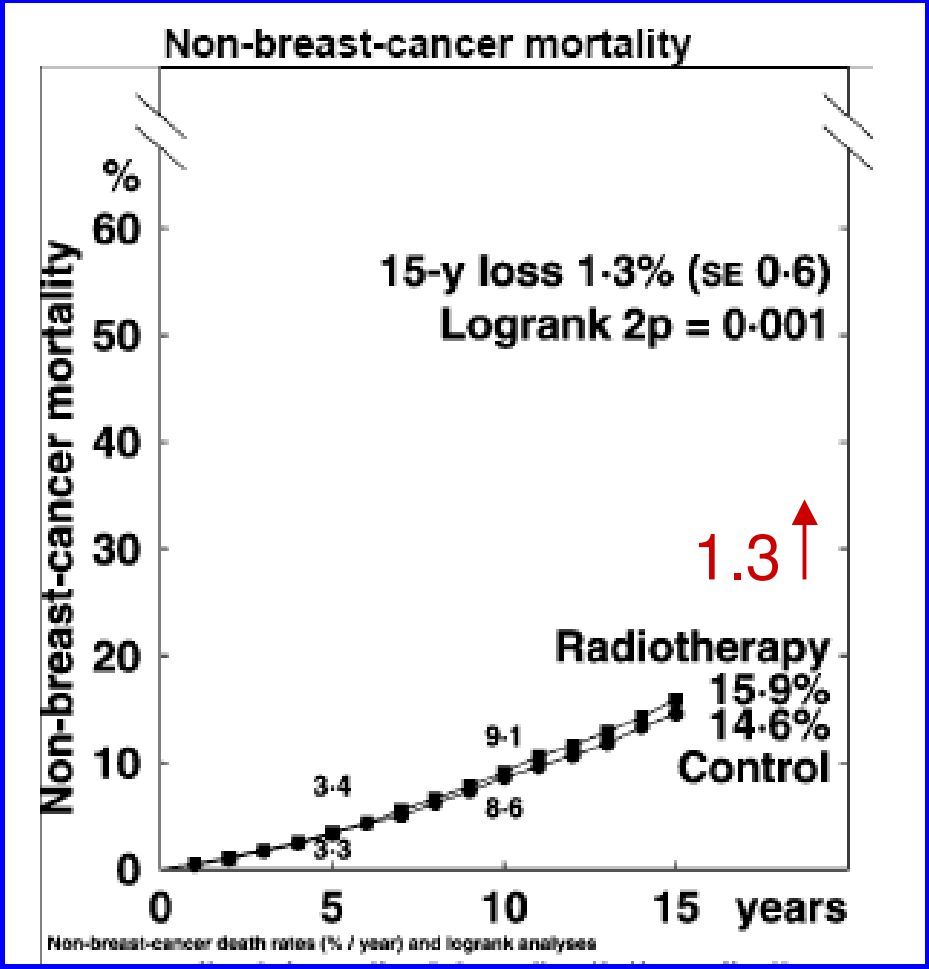


Causes of Excess Non-Breast Cancer Mortality (N=23,500)

Cause of death	No. Events	Ratio of events	2p
Heart	1106	1.27	0.0001
CVA	345	1.12	0.3
Lung Ca	156	1.78	0.0004

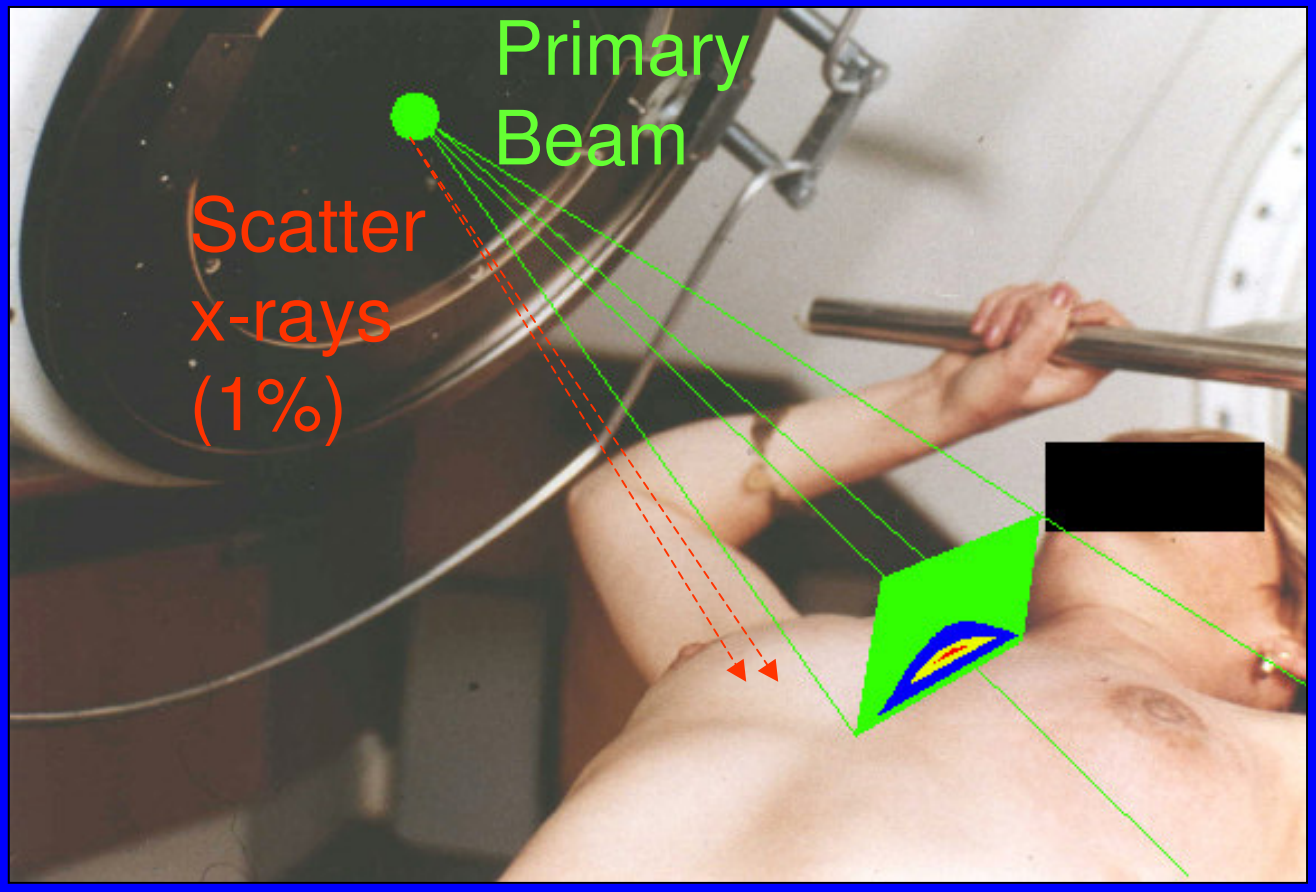
EBCTCG, Lancet 2005; 366, 2087-2106

Effect of RT on Non-Breast Cancer Mortality (N=29,623)

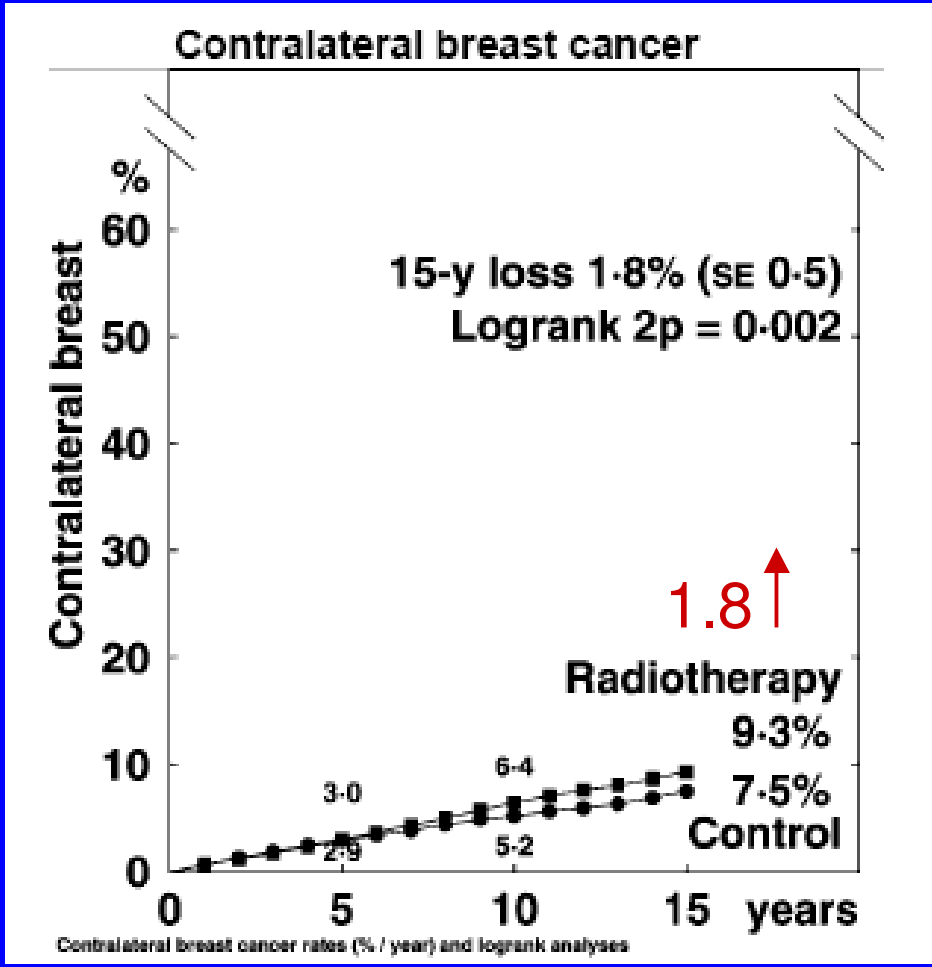


EBCTCG, Lancet 2005; 366, 2087-2106

Low Dose Effects of Radiation Scatter Outside Treatment Volume



Effect of RT on Contralateral Breast Cancer (N=29,623)

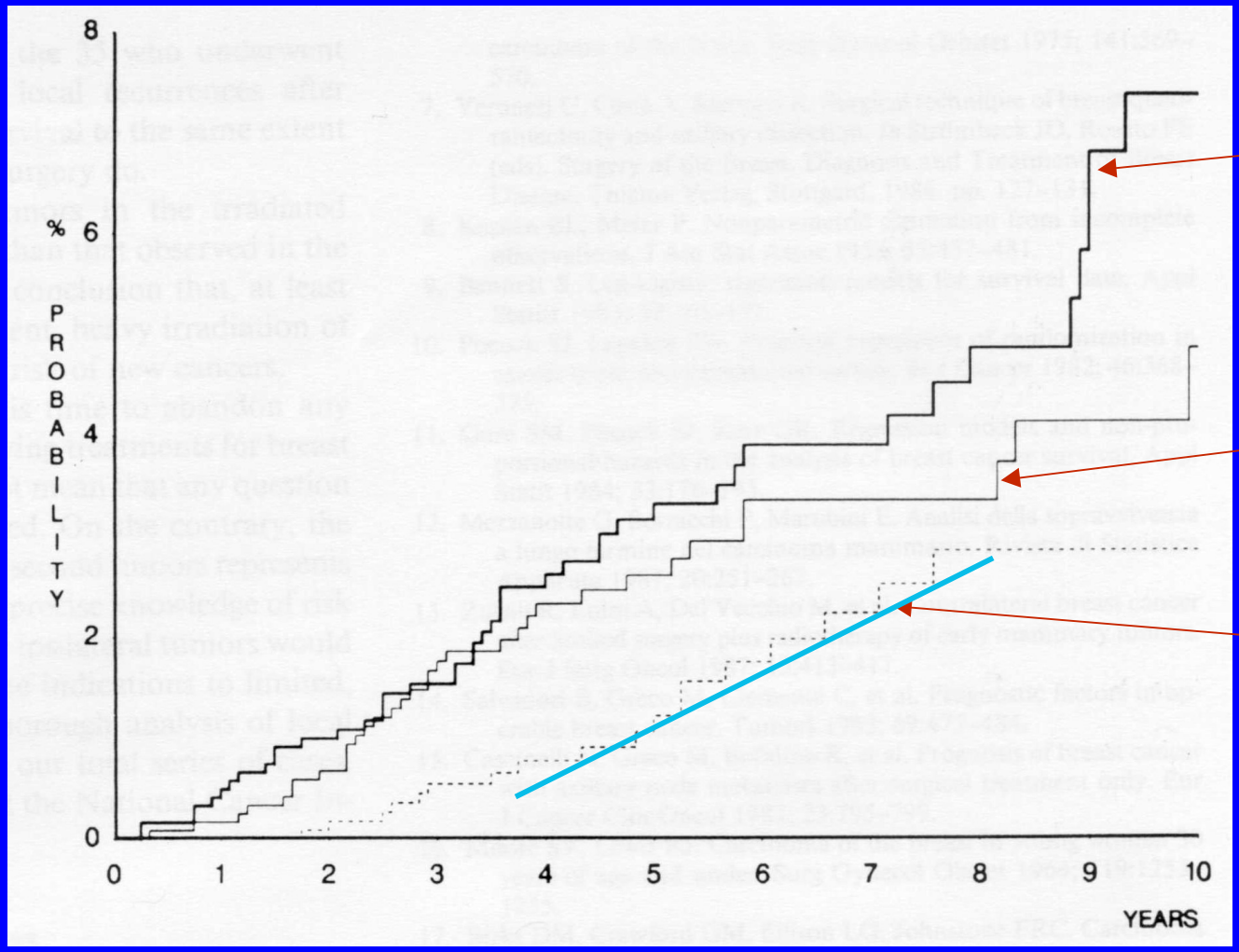


EBCTCG, Lancet 2005; 366, 2087-2106

The Case For Partial Breast RT (PBRT)

- PBRT targets 75% of local relapse risk
- WBRT does not reduce the residual 25% relapse risk
  - mostly new primary tumours
- PBRT reduces complications
  - less damage to healthy breast
  - less injury to ribs, muscle, lung, heart

Cumulative Probability of Relapse after Tumour Excision + RT (N=1,232)



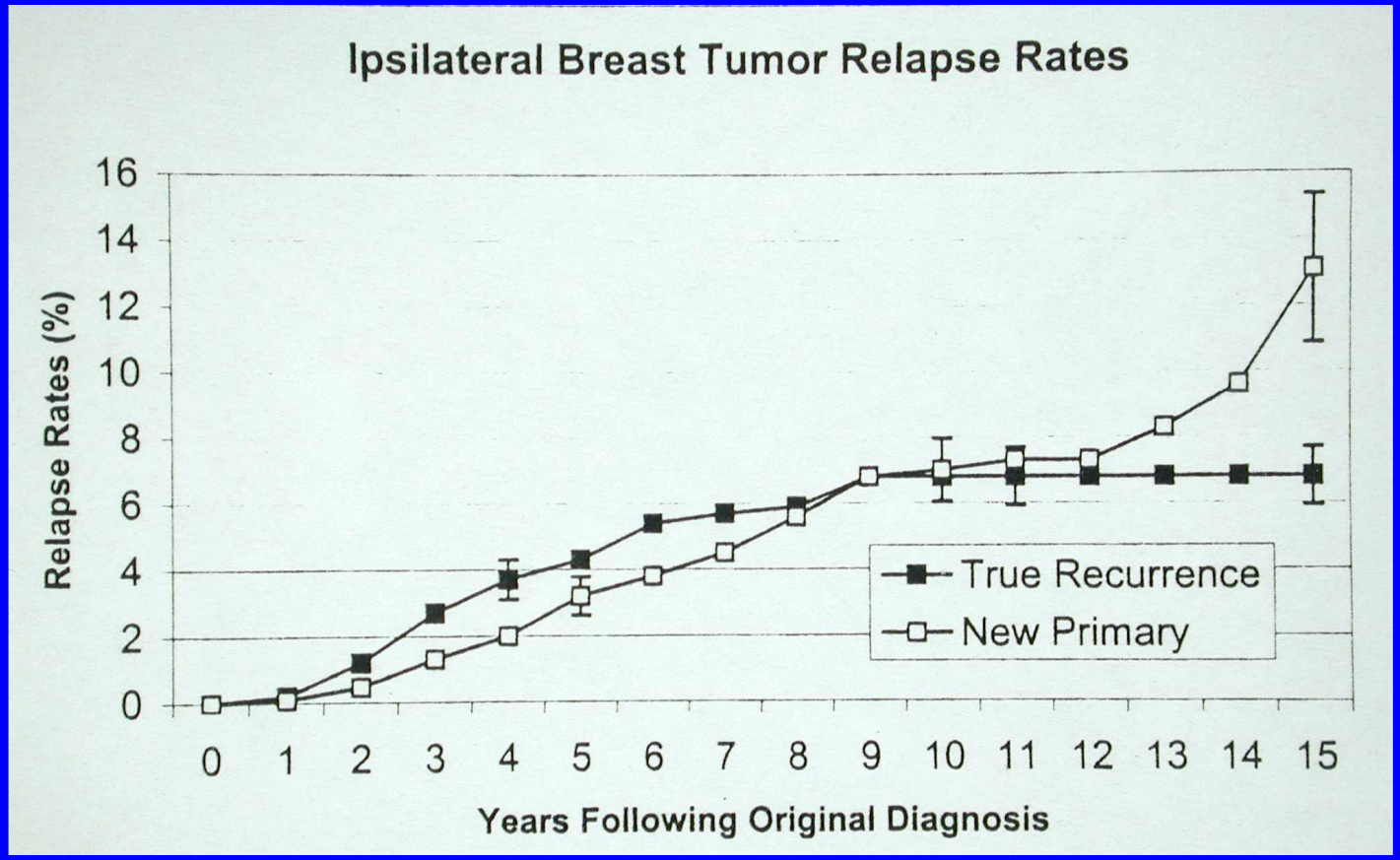
Contralateral primary

Ipsilateral index quadrant

Ipsilateral other quadrant

Veronesi U. Ann Surg, 1990

True Recurrence & New Primary After Local Excision + Breast RT

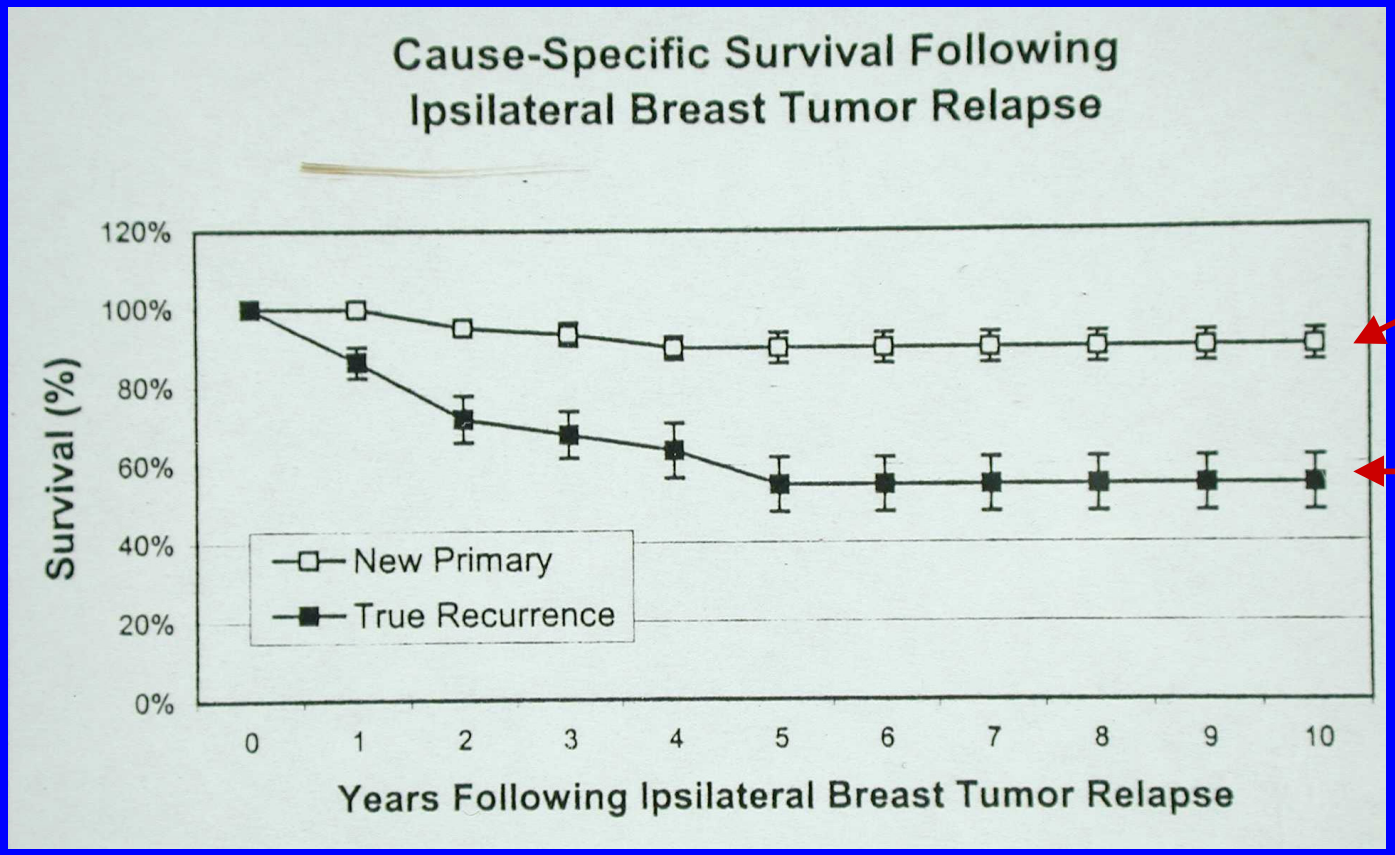


New primary (N= 70)

Recurrence (N= 60)

Smith TE, IJROBP, 2000, 48, 1281-89

True Recurrence & New Primary After Local Excision + Breast RT



70 'new primaries'

60 'true recurrences'

Smith TE, IJROBP, 2000, 48, 1281-89

Ipsilateral Breast Relapse after Breast Cons. Surgery (BCS) +/- RT

- 2,544 patients treated by BCS at NCI, Milan 1970 – 89

Site in relation to primary tumour	No. (%)
≤ 2cm from scar	142 (74)
Other quadrant	43 (23)
Undetermined	6 (3)

Salvadori B, BJS,1999, 86, 84-87

The Case For Partial Breast RT (PBRT)

- PBRT targets 75% of local relapse risk
- WBRT does not reduce the residual 25% relapse risk
  - mostly new primary tumours
- PBRT reduces complications
  - less damage to healthy breast
  - less injury to ribs, muscle, lung, heart

Results of Multicatheter Accelerated Partial Breast RT Phase II Studies

Study	No.	TD (Gy) HD/LDR	FU (yr)	Loc. Rel (%)
Polgar '04	45	30/36	6.8	6.7
Chen '06	199	50/33	6.4	1.2
Patel '05	240	33	3.0	1.7
Ott, '07	274	50/32	2.7	0.7

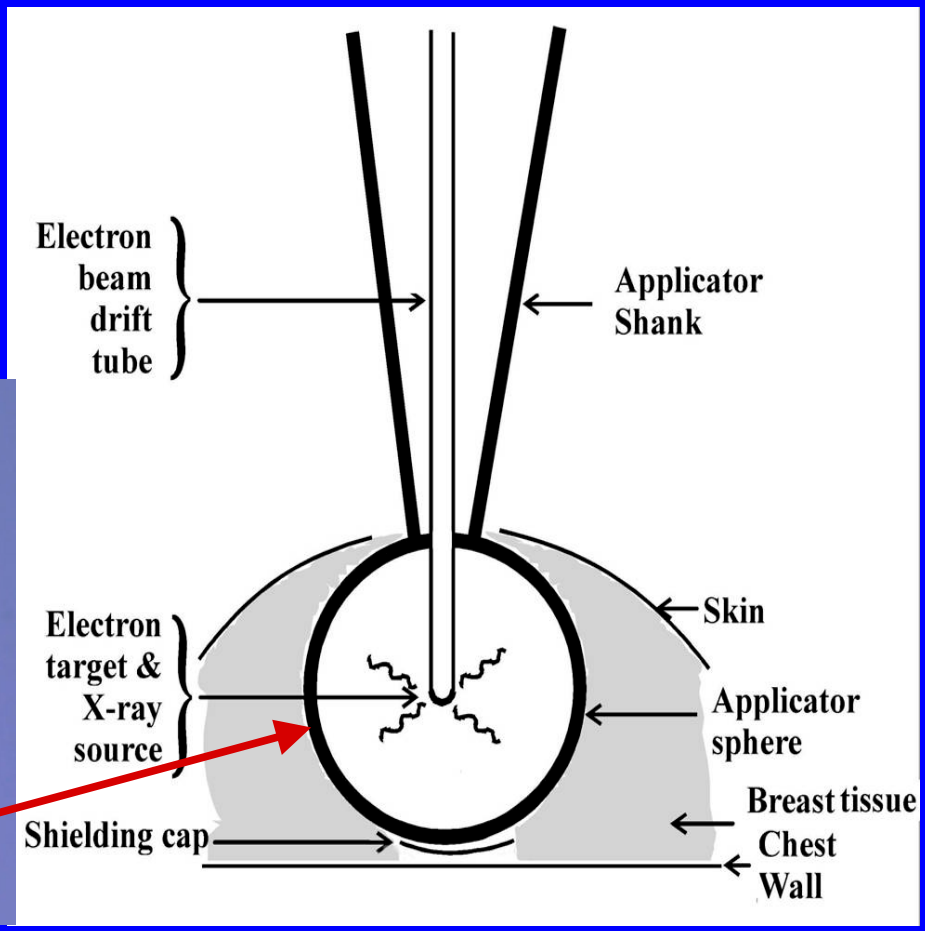
Phase III Trials of Partial Breast RT

Trial	Target accrual	Partial Breast Test Arms	Time
NSABP-39	9000	Multi-source ^{192}Ir Single source ^{192}Ir External beam RT	5 d 5 d 5 d
TARGIT	2000	Intraoperative x-rays	1 d
ELIOT	2000	Intraoperative electrons	1 d
IMPORT LOW	2000	External beam IMRT	3 w
GEC-ESTRO	1170	Multi-source ^{192}Ir (HDR) Multi-source ^{192}Ir (PDR)	3.5-4 d 2.5-3.5d

ELIOT in Action:
Intra-Operative Electron Therapy

http://www.ieo.it/inglese/innovazioni/eliot.htm

TARGIT

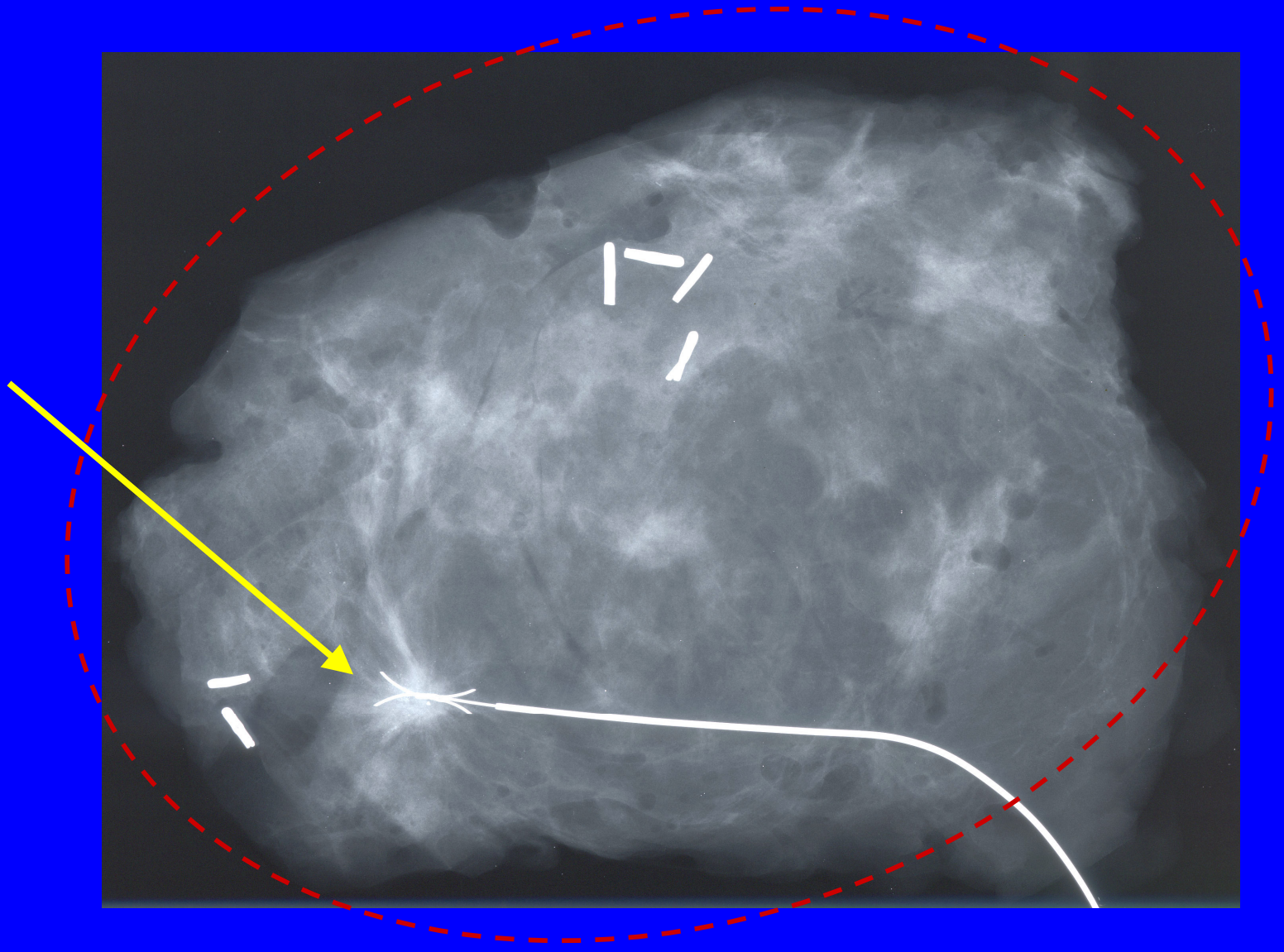


25 minutes

Uncertainties: Volume & Dose

- What is the optimal target volume?
  - Is the target defined by the wall of the excision cavity?
  - What additional margin is needed?
- Dose is an added variable: 21Gy×1 or 3.85Gy×10

Sometimes the Tumour is Near an Edge!



TARGIT A TRIAL
RESULTS MEDIAN FU 4 YEARS

EXTERNAL BEAM

1119 PATIENTS

- 1025 RECEIVED EBRT
- LR 5 PATIENTS(0.95%)
- SERIOUS TOXICITY 3.9%

INTRAOPERATIVE

1113 PATIENTS

- 996 RECEIVED
- 854(86%) IORT ONLY
- 14% ADDITIONAL EBRT
- LOC REC 6PTS(1.4%)
- SERIOUS TOXICITY 3.3%

However lots of Linear accelerators around! IMPORT LOW

Whole / Partial Breast Irradiation

For women at low risk of local tumour relapse

IMPORT LOW Trial Schema

•Female age =50
•Primary breast conservation surgery+/- adjuvant systemic therapy for early breast cancer
•Tumour = 2.0cm pT1a-c

<u>Other inclusions</u>
•Invasive adenocarcinoma, unifocal, Grade I or II
•Min. margin = 2mm,
•no lympho-vascular invasion(removed later)
•Axillary lymph node –ve pN0 (1-3 nodes allowed later)
(sentinel node biopsy & isolated tumour cells < 2.0mm allowed)
•No blood borne mets

IMPORT LOW Trial Schema

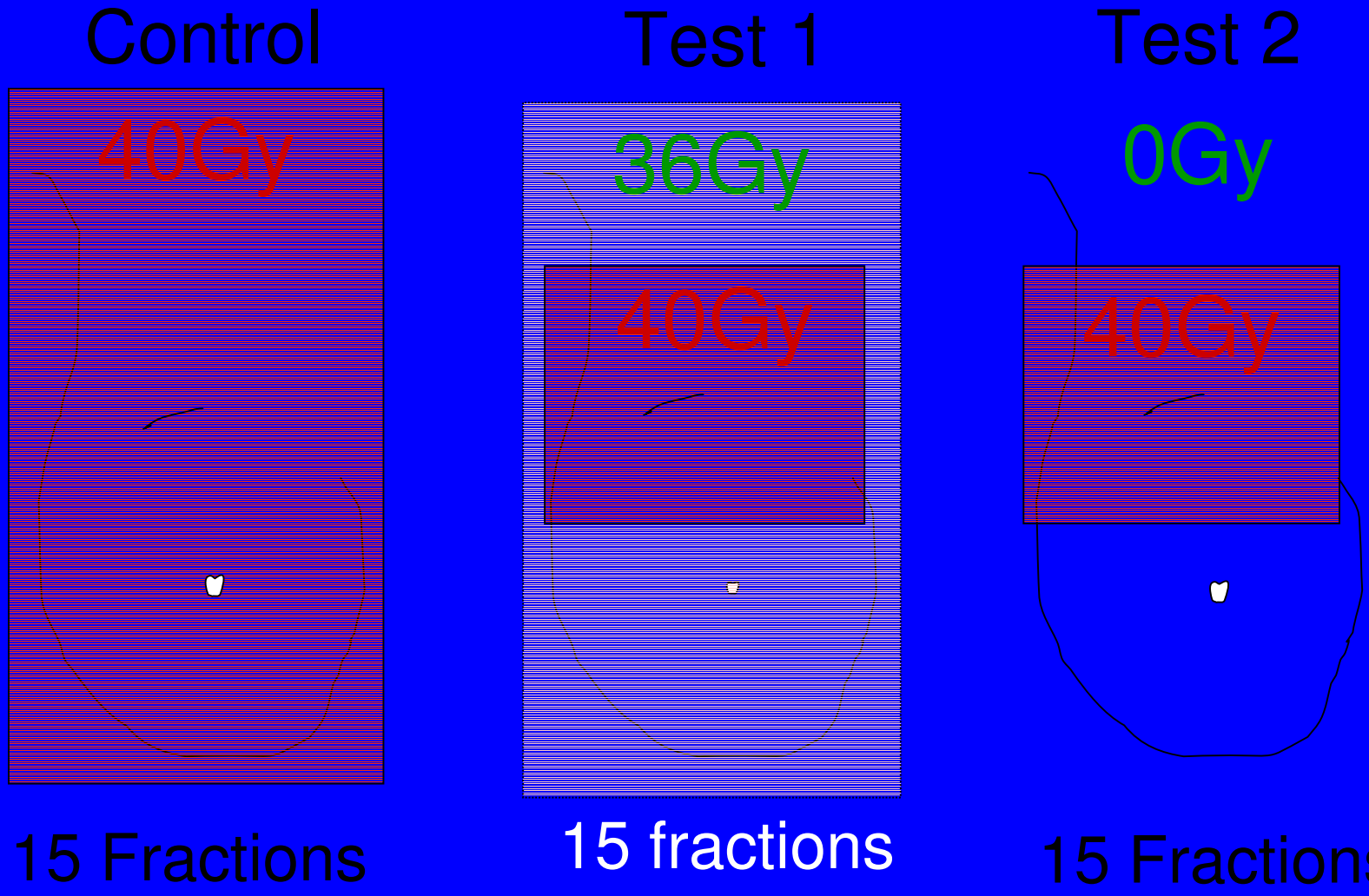
EXCLUSIONS

- Previous malignancy
- Mastectomy
- Invasive carcinoma of classical lobular type
- Primary endocrine therapy or chemotherapy

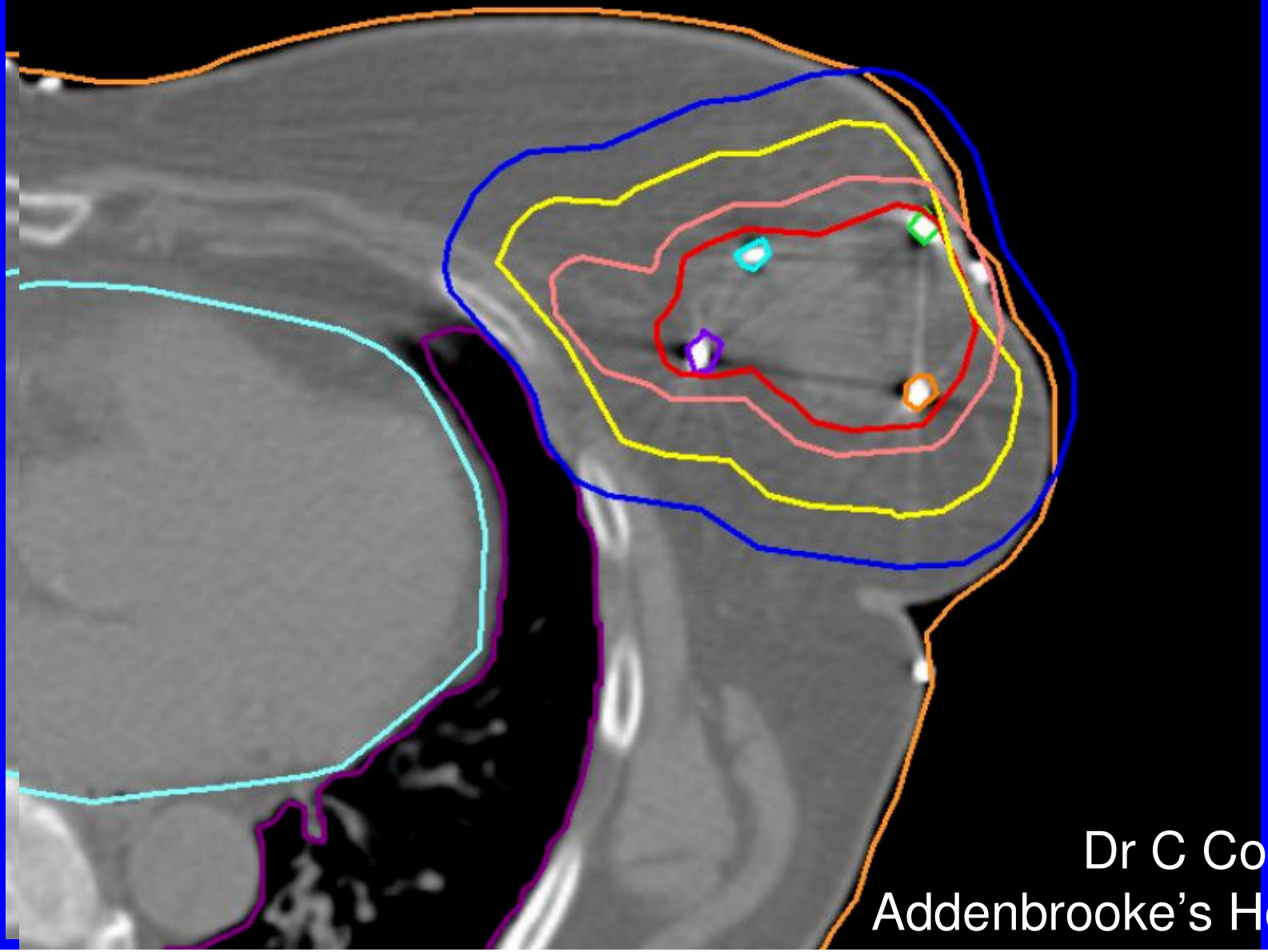
(neo-adjuvant endocrine therapy permissible
if tumour < 2cm and all other inclusion criteria met.)

- Concurrent chemo-radiation

Intensity Modulated Partial Organ RT: UK IMPORT Low Risk Trial (N=1960)

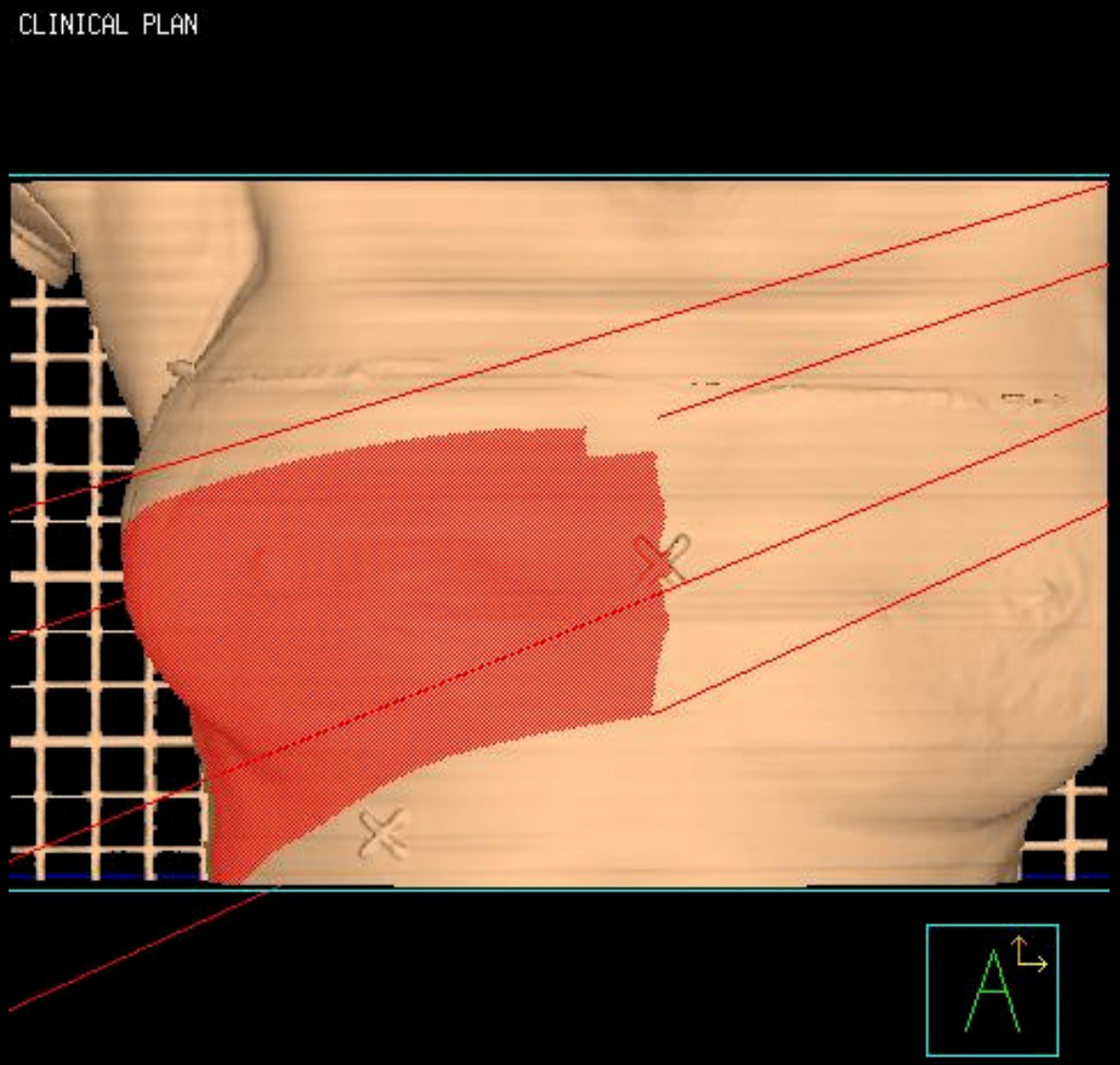


IMPORT LOW: Quadrant PTV

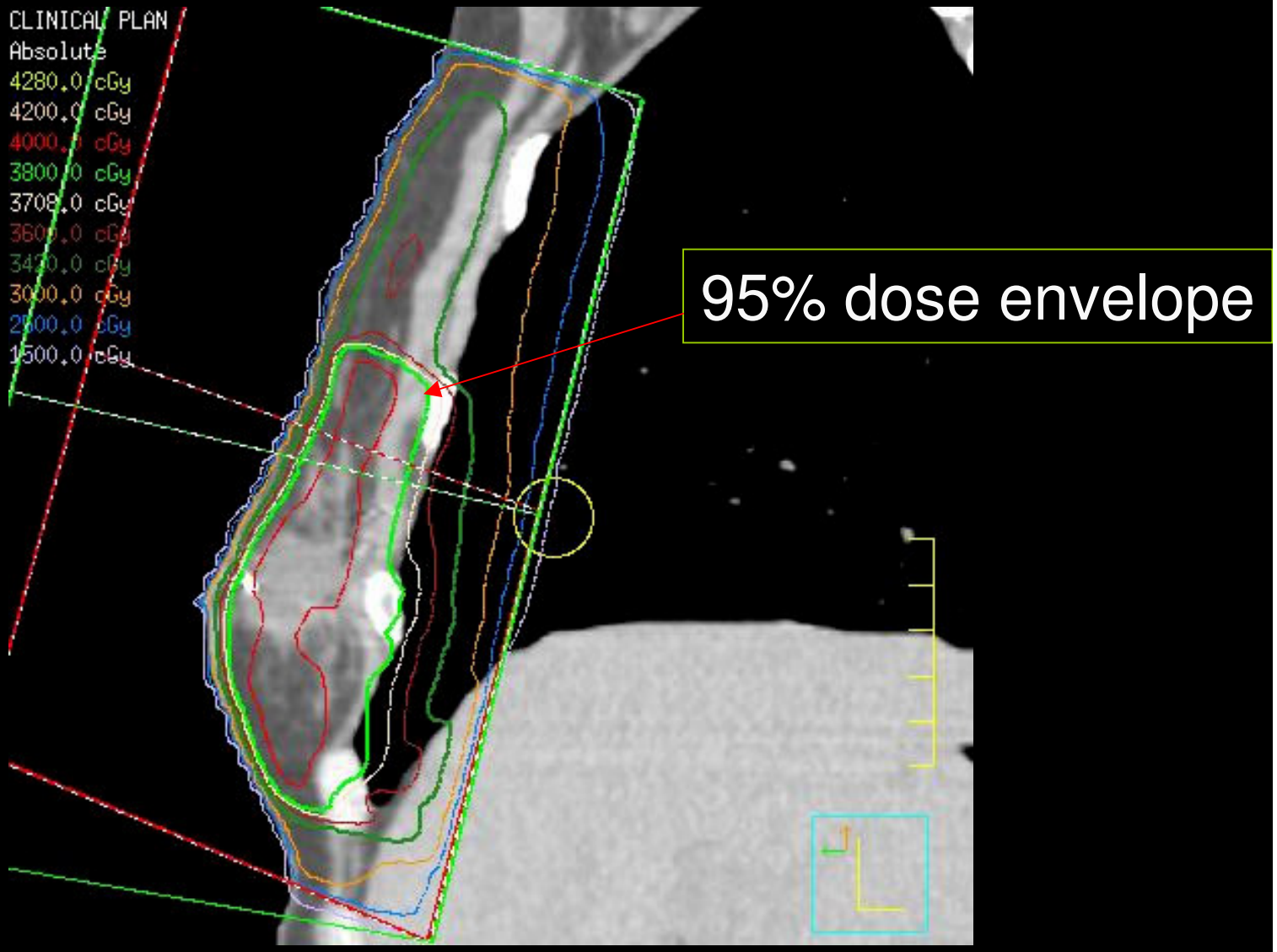


Dr C Coles,
Addenbrooke's Hosp.

Medial Tangential Field to Right Breast



Upper Breast Excluded From Treatment



Radiotherapy Update on Fractionation, Intensity Modulated Radiotherapy (IMRT), & Nodal Disease

50 Gy in 25 fractions of 2 Gy is still widely used

If fraction size is increased >2 Gy, total dose must be reduced to match the level of adverse effects

If fractions >2 Gy are used, and total dose is reduced to match the late adverse effects of 50Gy/25F

What happens to tumour control?

Dogma

"Cancers are relatively insensitive to fraction size"

Reduction in total dose needed to match late adverse effects of 50Gy/25F under-doses the cancer

right?

The Institute of Cancer Research
ICR-CTSU

Hypofractionation for early breast cancer: First results of the UK standardisation of breast radiotherapy (START) trials

JR Yarnold, JS Haviland, JA Dewar RK Agrawal, JM Bliss, P Hopwood, B Magee, JR Owen, MA Sydenham, K Venables,

on behalf of the START Trialists

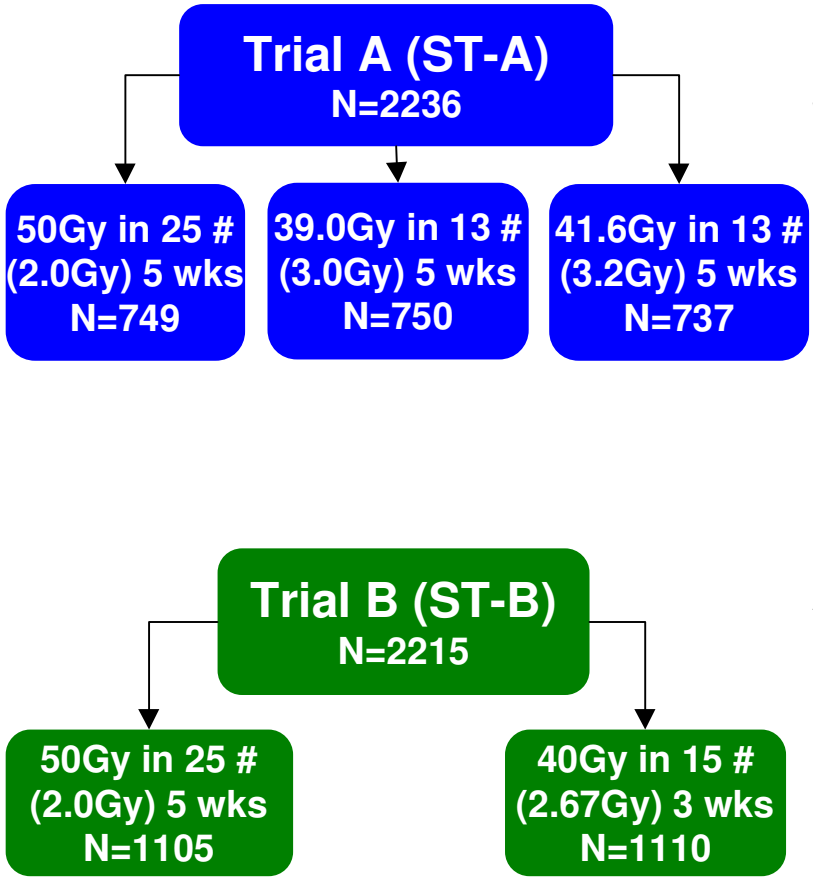
CANCER RESEARCH UK

MRC Medical Research Council

DH Department of Health

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)		
-annual physician assessments of induration, shrinkage, oedema	**2236**	**2215**
-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		

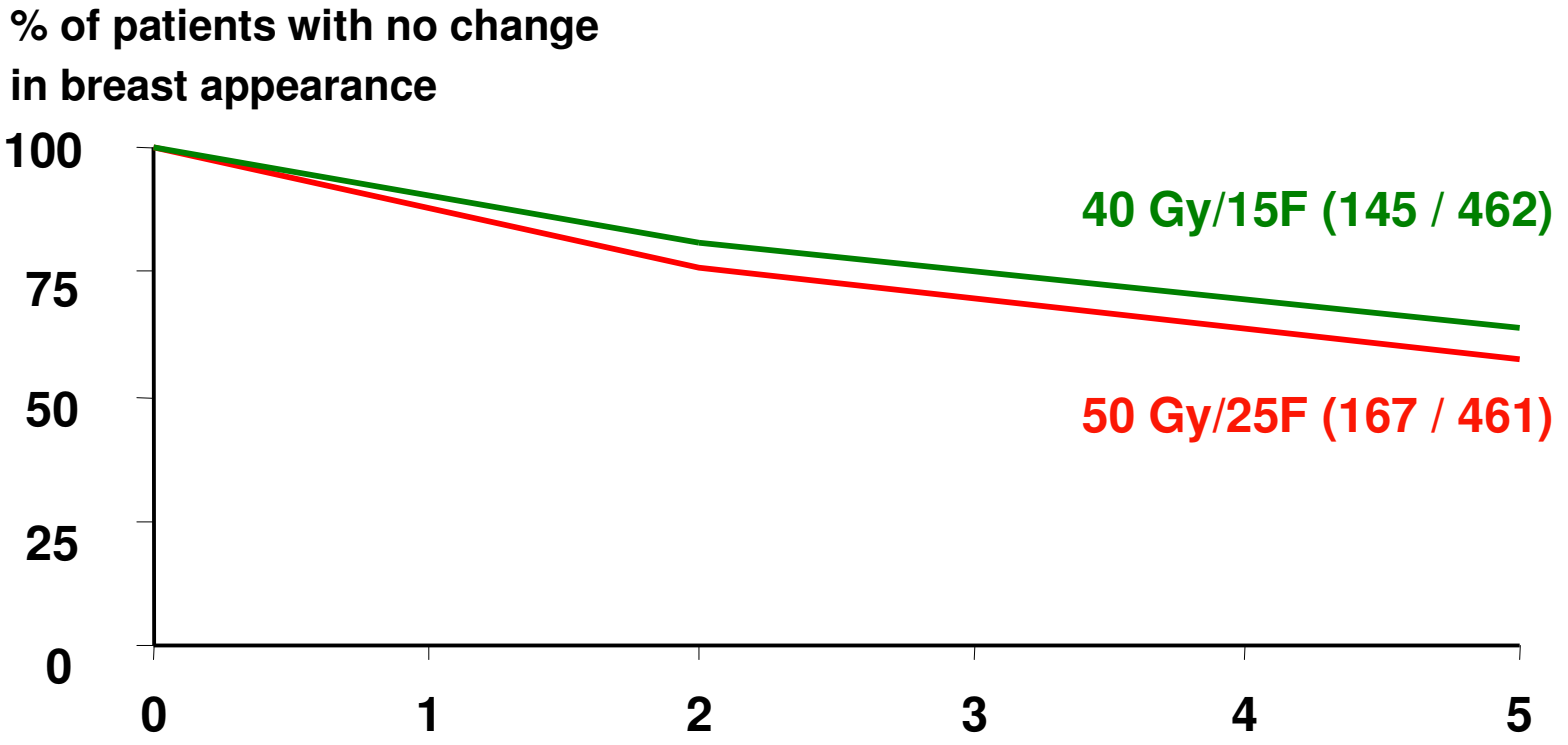
Recruitment from 35 UK centres between Jan 1999 & Oct 2002

UK START Trial 'B' (N=2215)

(6.0 years median follow up)

Total Dose (Gy)	Fraction size (Gy)	Fraction number	Time (week)
50.0	2.0	25	5
40.0	2.67	15	3

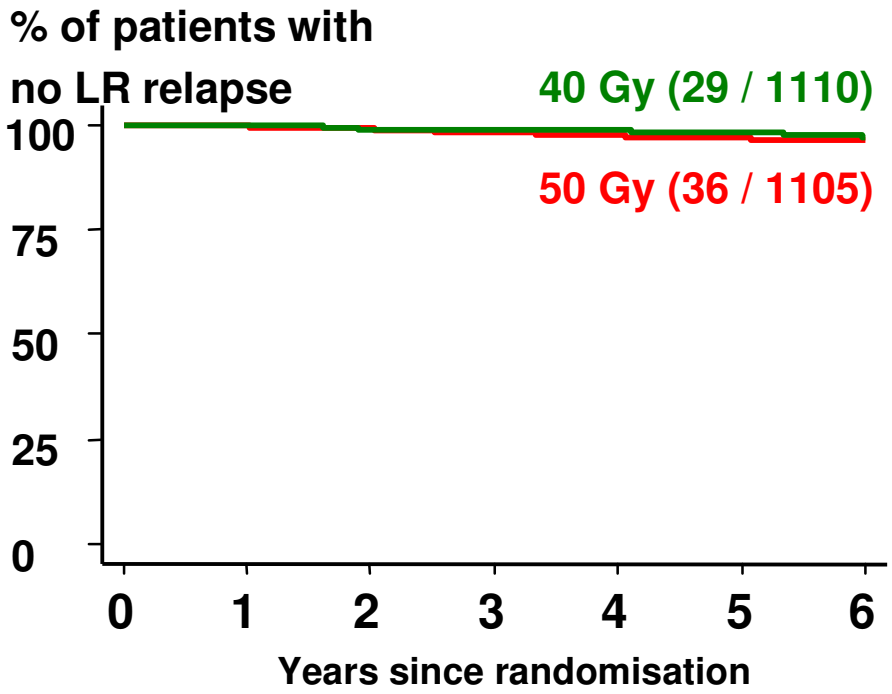
Trial B: Change in breast appearance (photos)

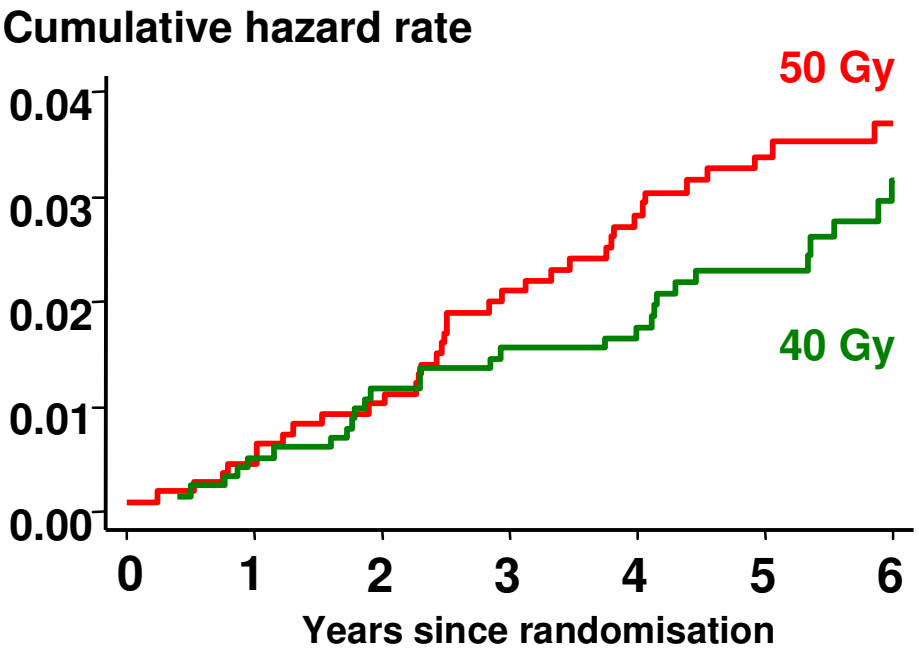


Number at risk:	*Yr 0*	*Yr 2*	*Yr 5*
	923	*914*	*512*

	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 : Local-regional (LR) tumour relapse





Number 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%)

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?

A 5-fraction regimen of adjuvant radiotherapy for women with early breast cancer: Updated analysis of the randomised UK FAST Trial

(ISRCTN62488883, CRUKE/04/015)

J Yarnold, AM Brunt, M Sydenham, J Bliss,
C Coles, L Gothard, A Harnett, J Haviland,
J Morden, I Syndikus, D Wheatley

On behalf of the FAST Trialists

ICR
The Institute of Cancer Research

CANCER RESEARCH UK

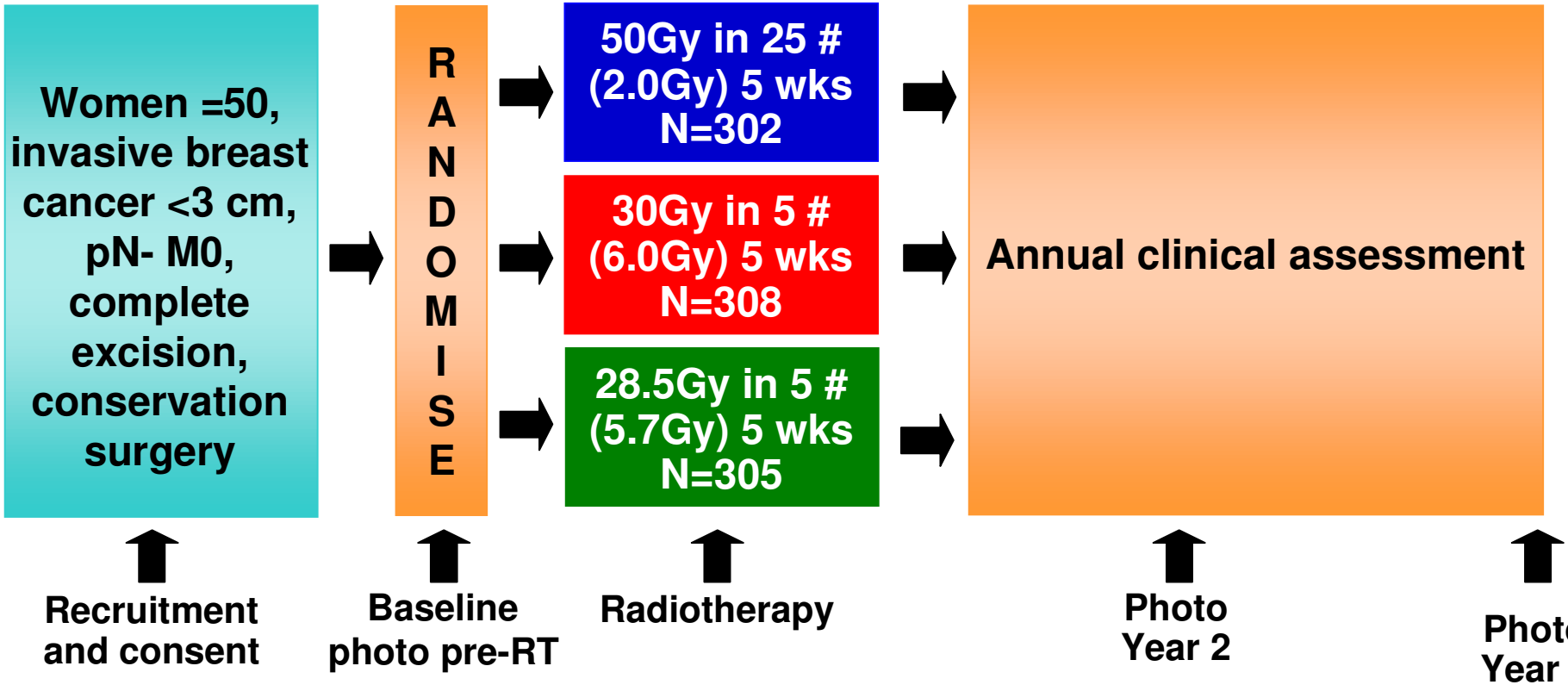
NCRI
National Cancer Research Institute

FAST Trial:
Aim

To test a 5-fraction regimen of whole breast RT against 25 fractions of 2.0Gy 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 at 2 years (NONE, MILD, MARKED change) compared with pre-RT baseline

Secondary Endpoints:

•Photographic change in breast at 5 years

•Annual clinical assessments of breast induration, shrinkage, oedema

•Local tumour relapse

Patients and Follow-up

- 915 patients at 18 UK centres 2004-'07
  - Mean age 63 years (range 50-88)
  - 77% ductal histology
  - 82% <2cm tumour size
  - 89% grade 1 or 2
  - 11% no adjuvant therapy
  - 89% endocrine therapy
- 98.7% patients received allocated treatment
- All patients had 3D dose compensation*
- Median follow up 3.1 years

* RT Quality assurance programme at every centre before trial initiation

Acute Skin Reactions

RTOG grade	50Gy (%) N=110	30Gy (%) N=111	28.5Gy (%) N=106
0 or 1	53.6	85.6	89.6
2=tender/bright erythema +/- dry desquamation	35.5	11.7	8.5
3=patchy moist desquamation	10.9	2.7	1.9

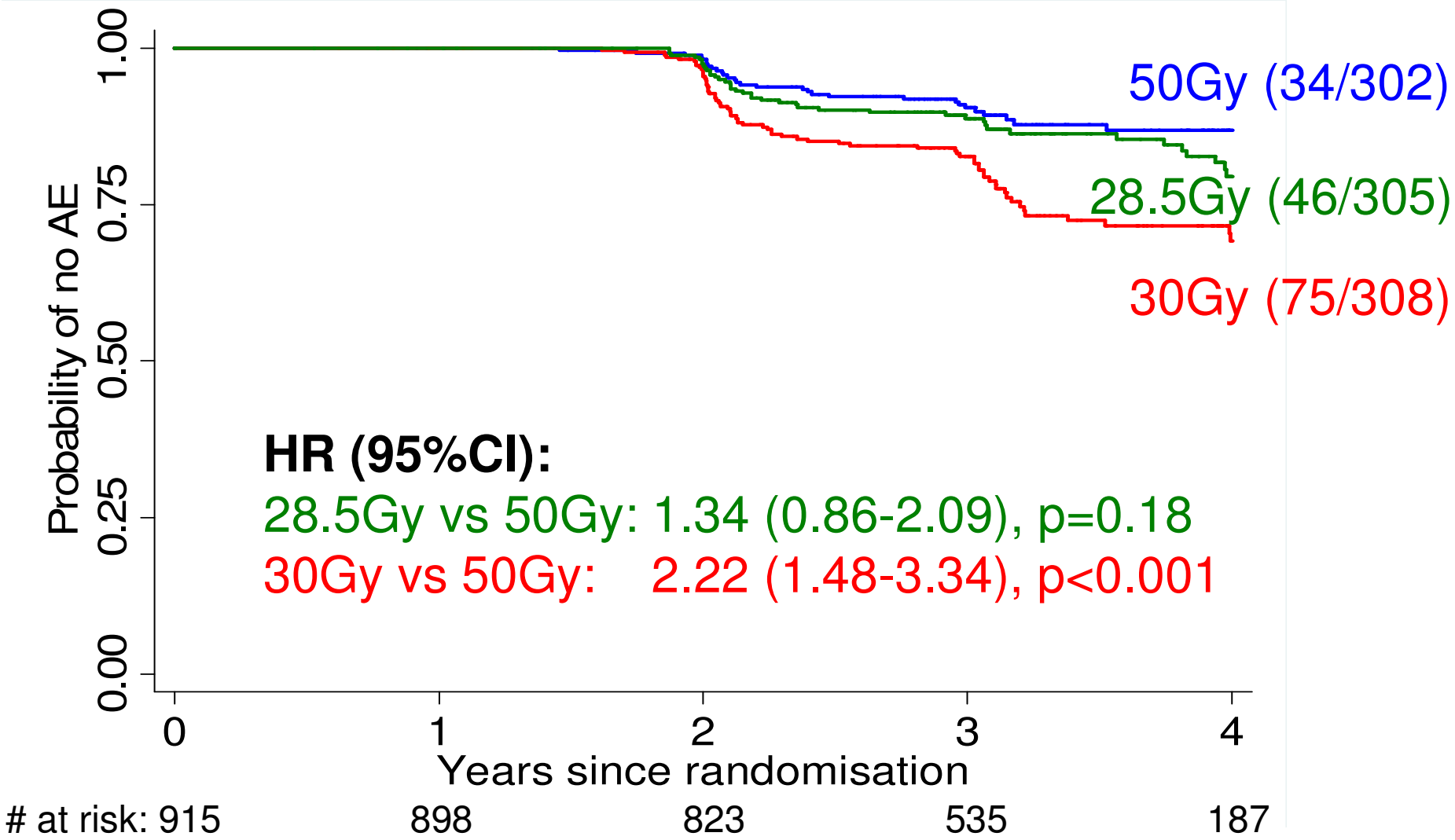
No grade 4 toxicity reported (confluent moist desquamation)

Change in Photographic Breast Appearance

Change at 2 years	50Gy N=236	30Gy N=244	28.5Gy N=236
None	79.2	66.0	76.3
Mild or Marked	20.8	34.0	23.7
P-values vs. 50Gy		<0.001	0.26

80% of 2-year assessments currently available

Moderate/Marked Adverse Effects*



*Breast shrinkage, induration, telangiectasia, oedema & other.
Year 1 events excluded due to high % of surgical & transient RT effects.

Relapse and Survival

At median follow up of 3.1 years - disease outcome is currently immature:

- 2 patients with local relapse
- 3 patients with regional relapse
- 17 patients with metastatic disease
- 23 patient deaths (10 from breast cancer)

Proposed 'FAST Forward' Trial (N=4000)

	TD (Gy)	N	# (Gy)	T
Control 1	40	15	2.7	3 weeks
Test 1:	27.0	5	5.4	5 days
Test 2	26.0	5	5.2	5 days

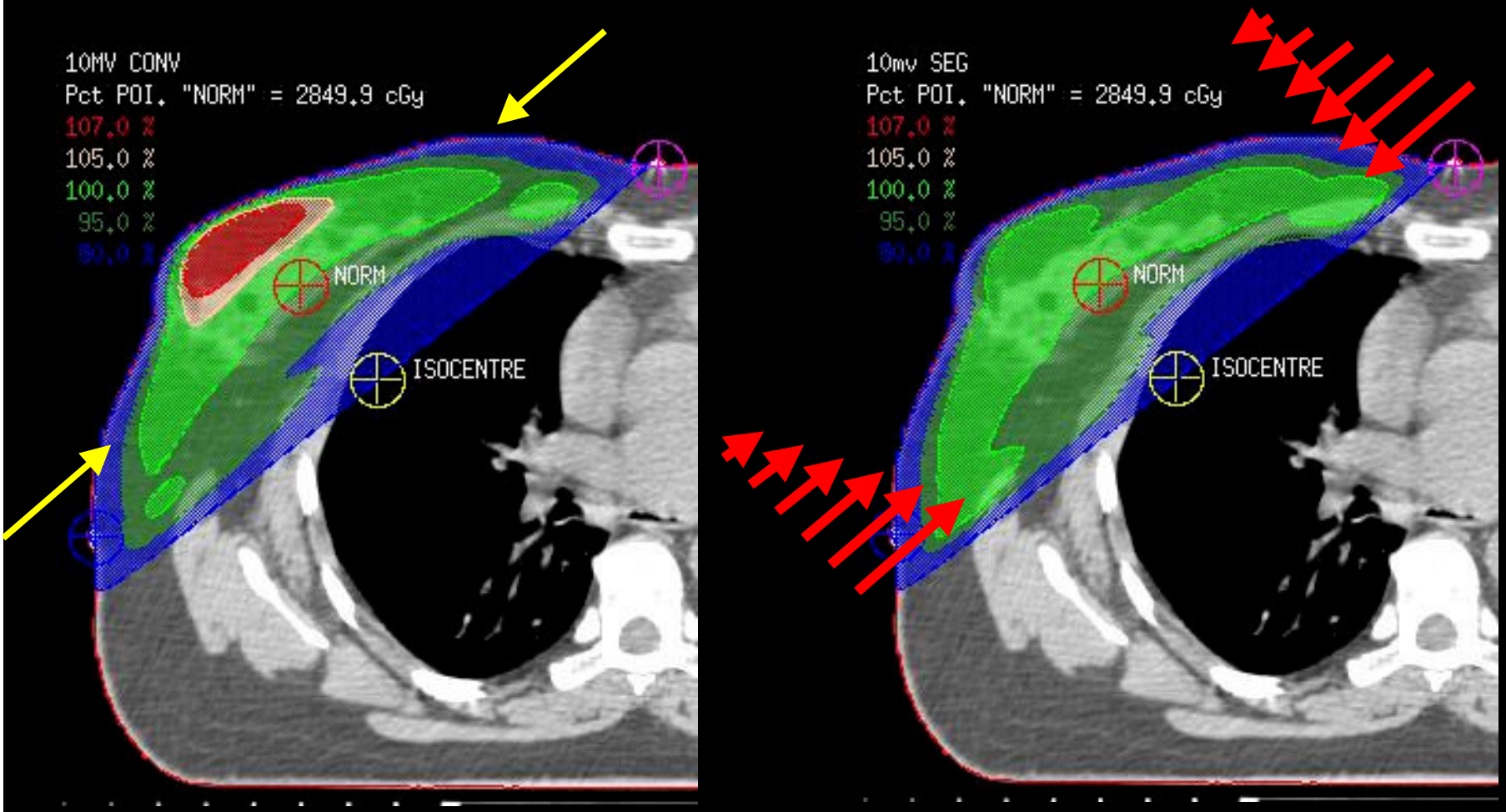
Outcome Predictions

- No penalty using fraction sizes > 2.0 Gy
- Shorter schedules may counter tumour proliferation
- Relevant to physical developments in radiotherapy…….. Intensity Modulated Radiotherapy (IMRT)

Intensity Modulated Radiotherapy

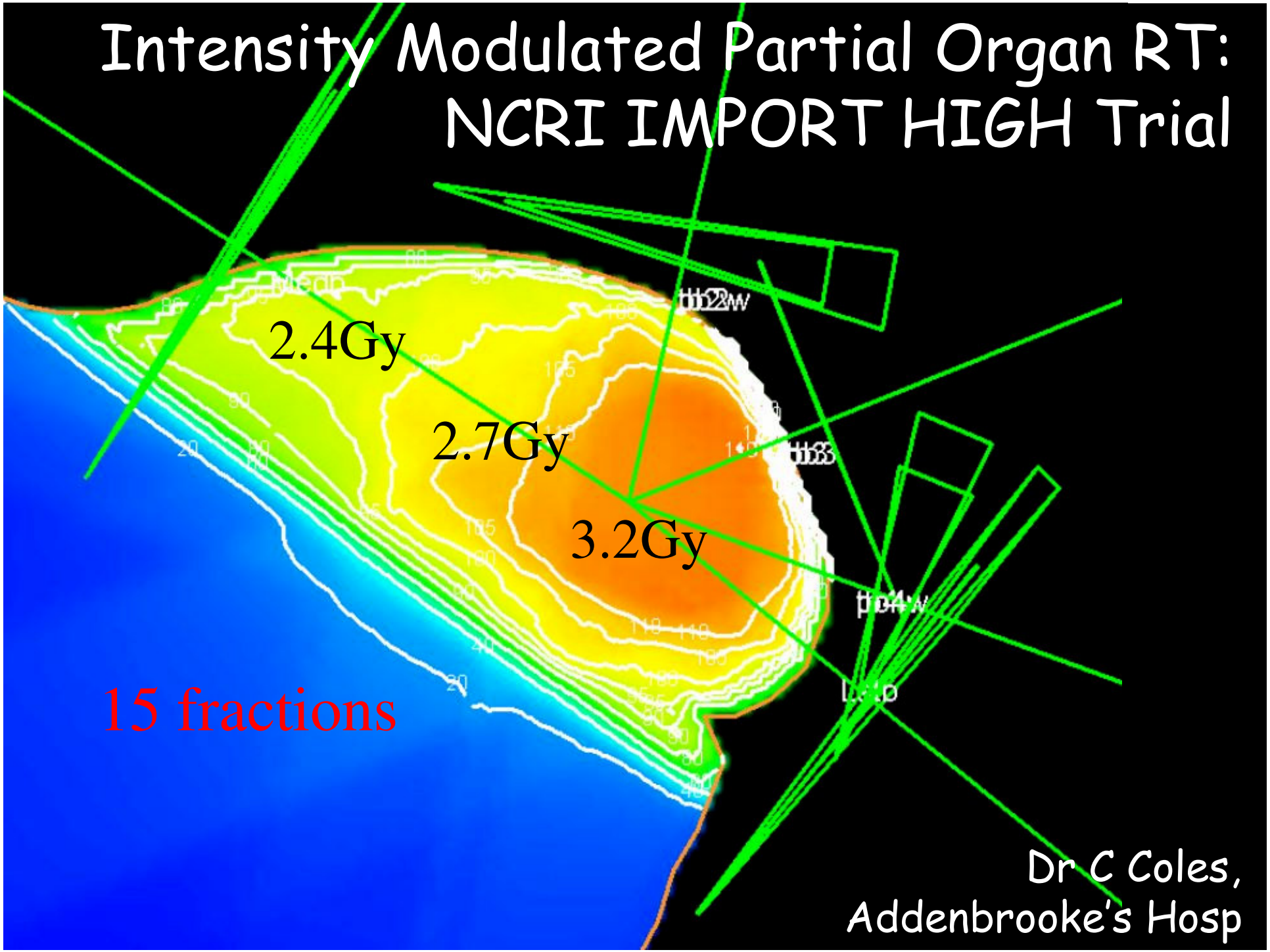
- Conventional RT delivers inhomogeneous dose throughout breast/nodes.
- Hot spots = more toxicity
- Cold spots = increased risk of recurrence
- IMRT can deliver homogenous dose with less late side effects without compromising local control

Modify the Beam Profile to Ensure Dose Uniformity



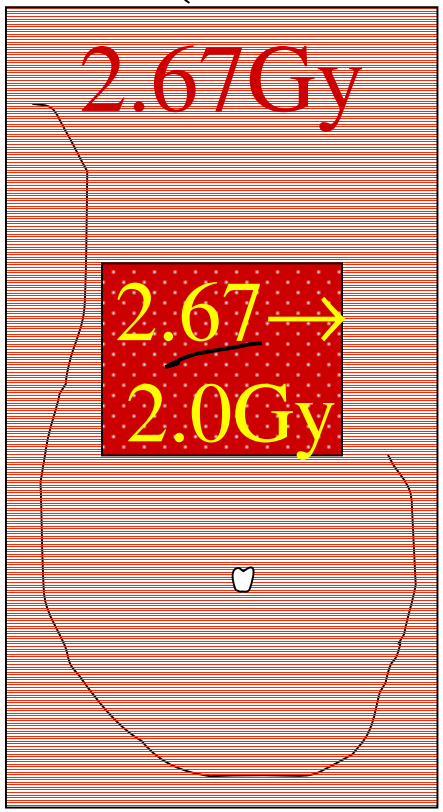
Introduce Planned Variation in Dose Across Target Volume (in 3D)

- Adjust dose intensity more closely to local relapse risk in breast
  - Higher in the vicinity of tumour bed (IMPORT HIGH)
  - Lower in other quadrants
- So, adjust fraction size in preference to fraction number


Intensity Modulated Partial Organ RT:
NCRI IMPORT HIGH Trial
2.4Gy
2.7Gy
3.2Gy
15 fractions
Dr C Coles,
Addenbrooke's Hosp

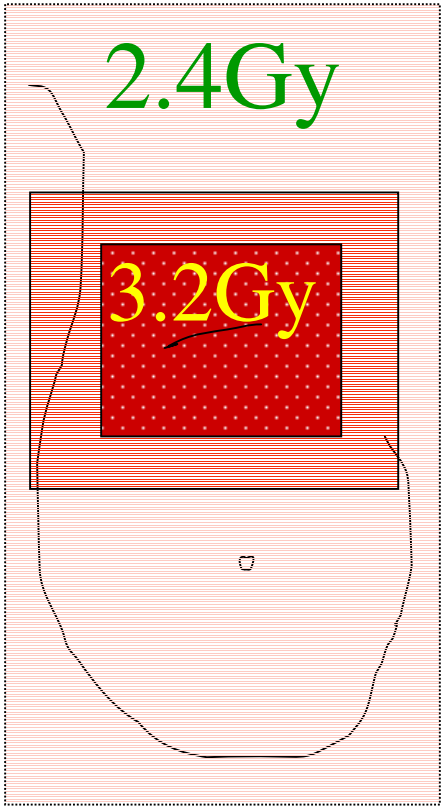
IMPORT HIGH Trial (N=900)

Sequential boost (Control)



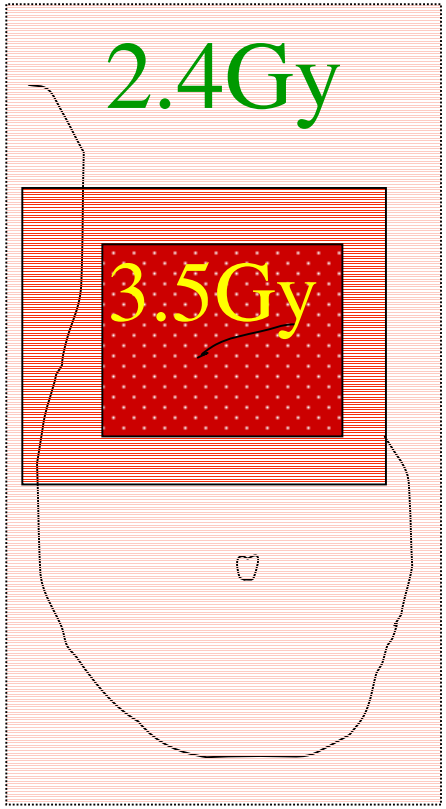
15+8 Fractions

Concomitant Boost Test 1



15 Fractions

Concomitant Boost Test 2



15 Fractions

Conclusions

- Lower total dose in fewer, larger fractions appear as safe & effective as 50 Gy in 25 fractions
- Adjusting fraction size a good way to adjust dose intensity
- A 5-day schedule of partial breast radiotherapy is a realisable research objective

Nodal Irradiation

- Who needs it?
- Most Studies Whole breast/ Chest wall
- Danish post Mastectomy studies included Internal Mammary Chain (imc) and Supraclavicular fossa(scf)
- MA.20 Study (T.Whelan ASCO 2011)

WHOLE BREAST RT +/- IMC+SCF RT

	WHOLE BREAST 916 PTS	**BREAST +NODAL RT 916 PTS**
ISOLATED LR	94.5%	96.8%
DFS	84%	89.7%
DISTANT DFS	87%	92.4%
OS	90.7%	92.3%

CONCLUSIONS

- Radiotherapy reduces risk of relapse by 75%
- Radiotherapy improves survival
- Usually well tolerated
- Should be offered to most patients
- EBRT remains stardard of care (just!)
- Modest Hypofractination is standard of care

CONCLUSIONS

- Further Research to identify who gains most (Who can be spared?)
- Partial Breast RT promising
- Hypofractination Trials should be supported
- Who can be spared Surgery (Post CR after neoadjuvant Chemo)

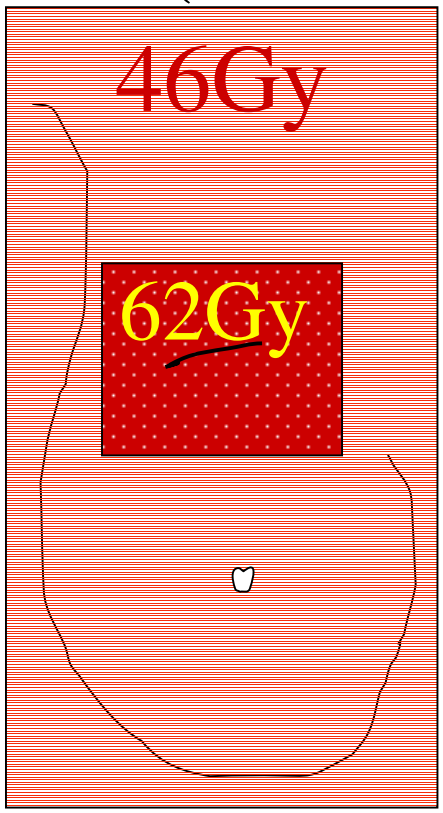
CONCLUSIONS

- THANK YOU

- ANY QUESTIONS?

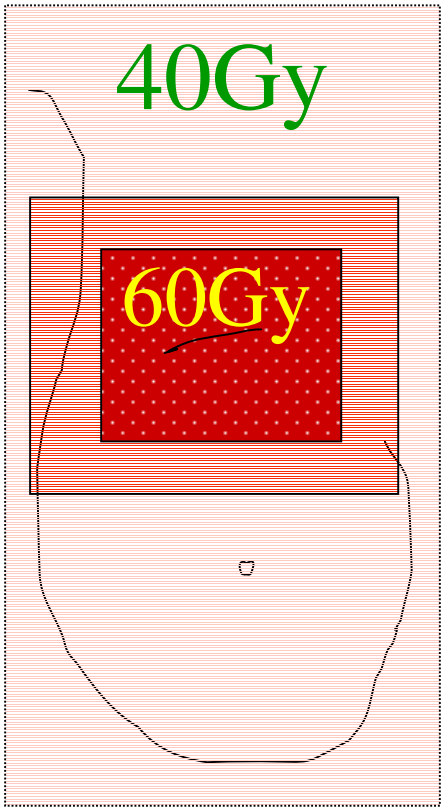
IMPORT HIGH: Total Doses in 2.0Gy Equivalents Assuming a/β = 3.0Gy

Sequential boost (Control)

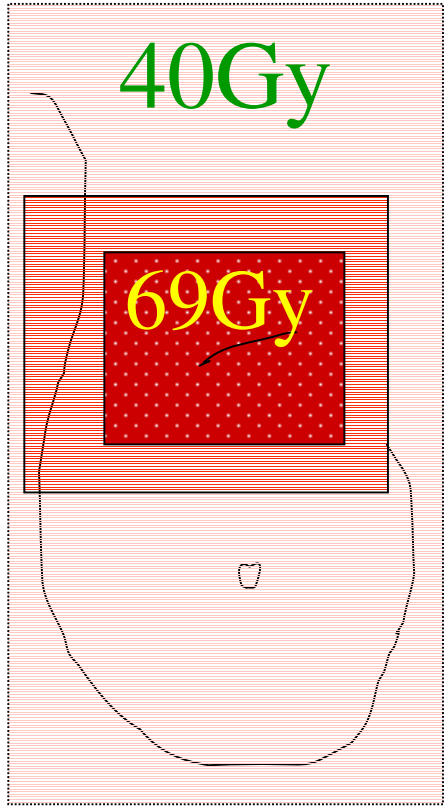


Concomitant boost

Test 1



Test 2



Primary endpoint: Induration at boost site