Hypofractionation radiotherapy in breast cancer

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Radiotherapy in Breast ca: Dose-Time relationship

- Lionel Cohen-with personal observation and review of published data
- Breast cancer is more radiosensitive than skin cancer
- Fractionated regimen with treatment over 3 weeks is more effective
- No improvement in therapeutic ratio by prolonging the treatment time and increasing dose beyond skin tolerance
- Single dose of 1200r is curative

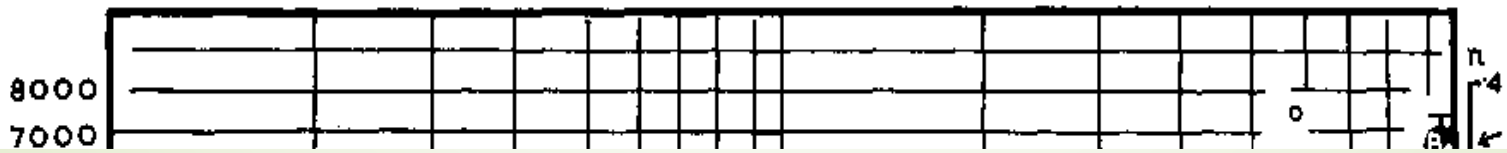
BJR:1952; Vol 25, No 300, 636-642

Lionel Cohen-Review

neither the overall time nor the size of the
e were available. There remained the 29
ons listed in Table II from which relevant
d be extracted.
ble II the minimum tumour doses (calcu-
d the number of fractions (usually daily)
together with the proportion of cases cured
articular combination of treatment factors.
e-operative irradiation this cure rate is
given by the author and is usually based
gical examination of the surgical specimen.
st-operative irradiation one can estimate

fluctuations of undetermined magnitude.)

The diverse set of data in Table II can
dered comparable by estimating, from
rates given, the actual *median* curative doses
series of cases. Assuming, as we have sho
true for our personally observed cases,
dosage distribution is practically lognormal
the standard deviation factor is about t
magnitude ($f=1{\cdot}11$), one can estimate
giving a 50 per cent. cure rate (M.L.D.) by c
the given dose by the appropriate probit f
this way we were able to calculate the 26 v



Small white circles represent cured cases; black circles, failures.

Adjuvant breast Hypofractionation RT: Background

- EBCTCG-systematic overview confirms adjuvant radiotherapy after primary surgery reduced LRR and breast cancer death
- For many decades schedules of adjuvant RT commonly used was 50Gy/25#/5weeks (+/- boost RT)
- At least 13 randomised studies testing adjuvant breast hypofractionated RT versus standard regimen were reported.
- 2.7Gy/# for 15 or 16# over 3 to 3.2 weeks hypofractionated regimen were confirmed safe & efficient and replaced standard schedule in many countries
- Hypofractionated schedule is convenient and cost effective to both patient and health services

NSABP-04 TRIAL

TWENTY-FIVE-YEAR FOLLOW-UP OF A RANDOMIZED TRIAL COMPARING RADICAL MASTECTOMY, TOTAL MASTECTOMY, AND TOTAL MASTECTOMY FOLLOWED BY IRRADIATION

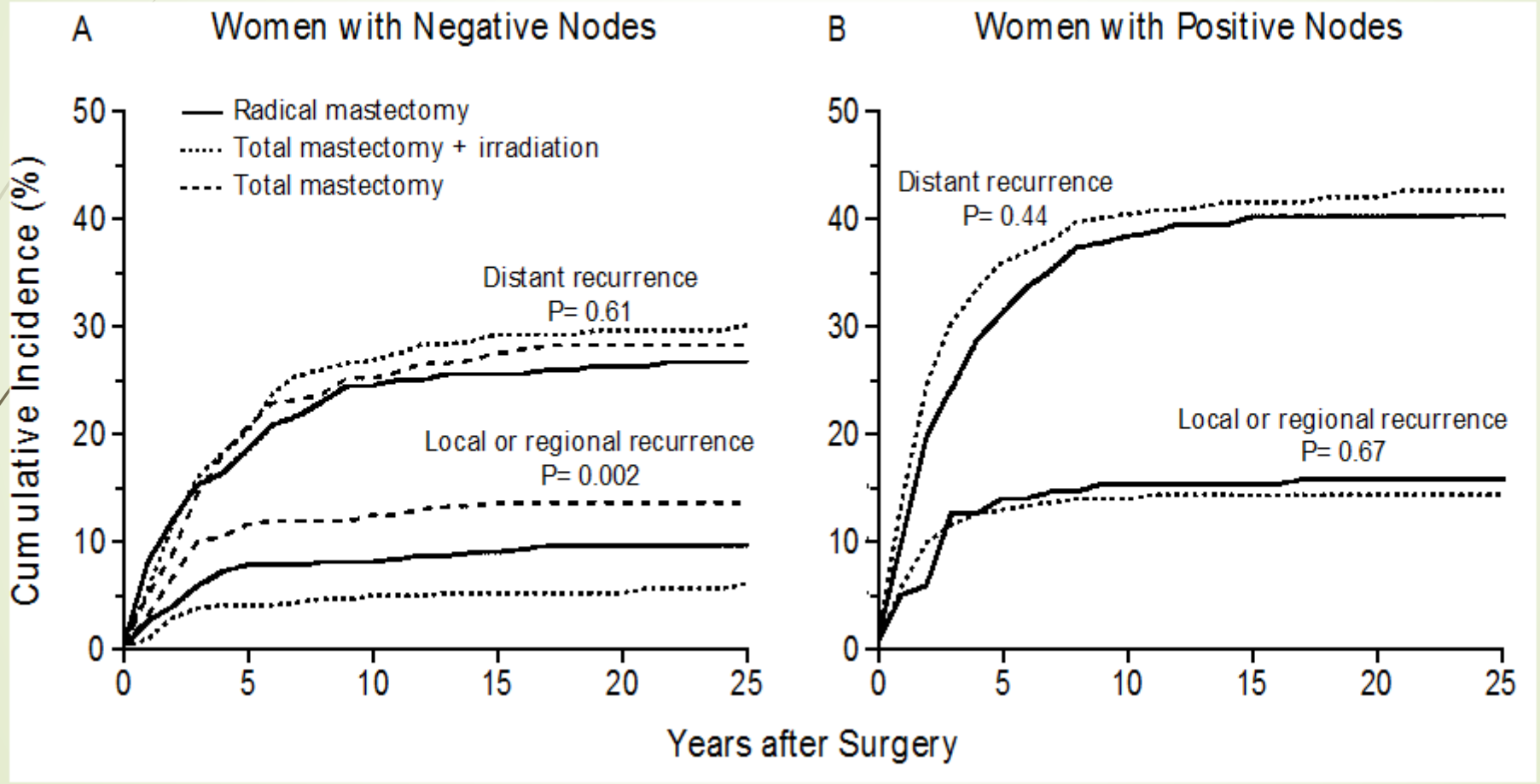
BERNARD FISHER, M.D., JONG-HYEON JEONG, PH.D., STEWART ANDERSON, PH.D., JOHN BRYANT, PH.D., EDWIN R. FISHER, M.D., AND NORMAN WOLMARK, M.D.

N Engl J Med, Vol. 347, No. 8 • August 22, 2002

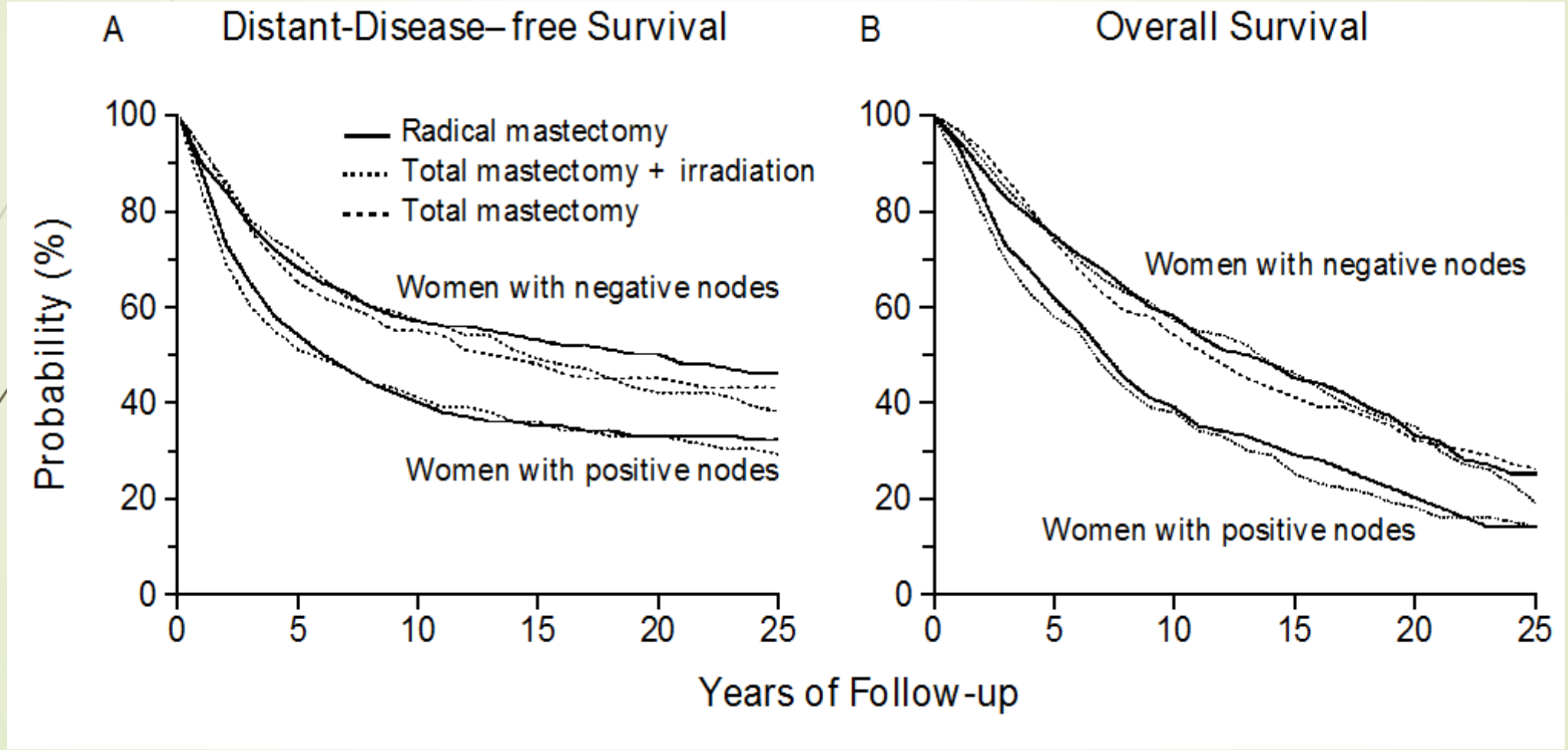
NSABP-04 TRIAL: Results

- Between July 1971 to September 1974
- 1765 women with operable breast cancer were randomized
- Radical mastectomy, Total mastectomy with or without regional irradiation
- Patients with clinically positive LN had ALND
- RT dose 50Gy/25# to chest wall & SCF and 10-20Gy boost for positive LN, 45Gy/25# to IMC
- No difference in DFS, RFS, OS and distant recurrence rate
- RT significantly reduced locoregional recurrence.

NSABP-04 TRIAL



NSABP-04 TRIAL



NSABP-06 TRIAL

FIVE-YEAR RESULTS OF A RANDOMIZED CLINICAL TRIAL COMPARING TOTAL MASTECTOMY AND SEGMENTAL MASTECTOMY WITH OR WITHOUT RADIATION IN THE TREATMENT OF BREAST CANCER

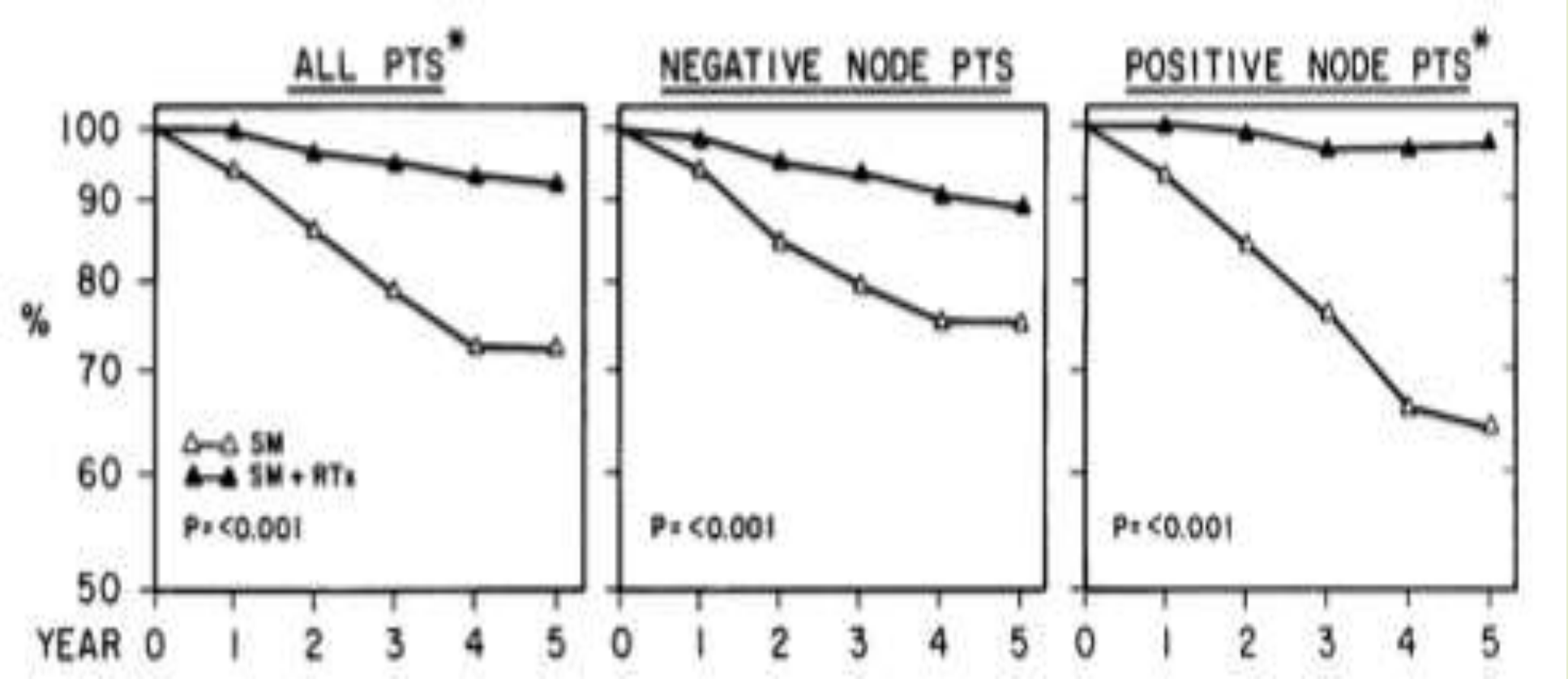
BERNARD FISHER, M.D., MADELINE BAUER, PH.D., RICHARD MARGOLESE, M.D., ROGER POISSON, M.D.,

*N Engl J Med, Vol. 312, No. 11 · **March 14**, 1985*

NSABP-06 TRIAL: Results

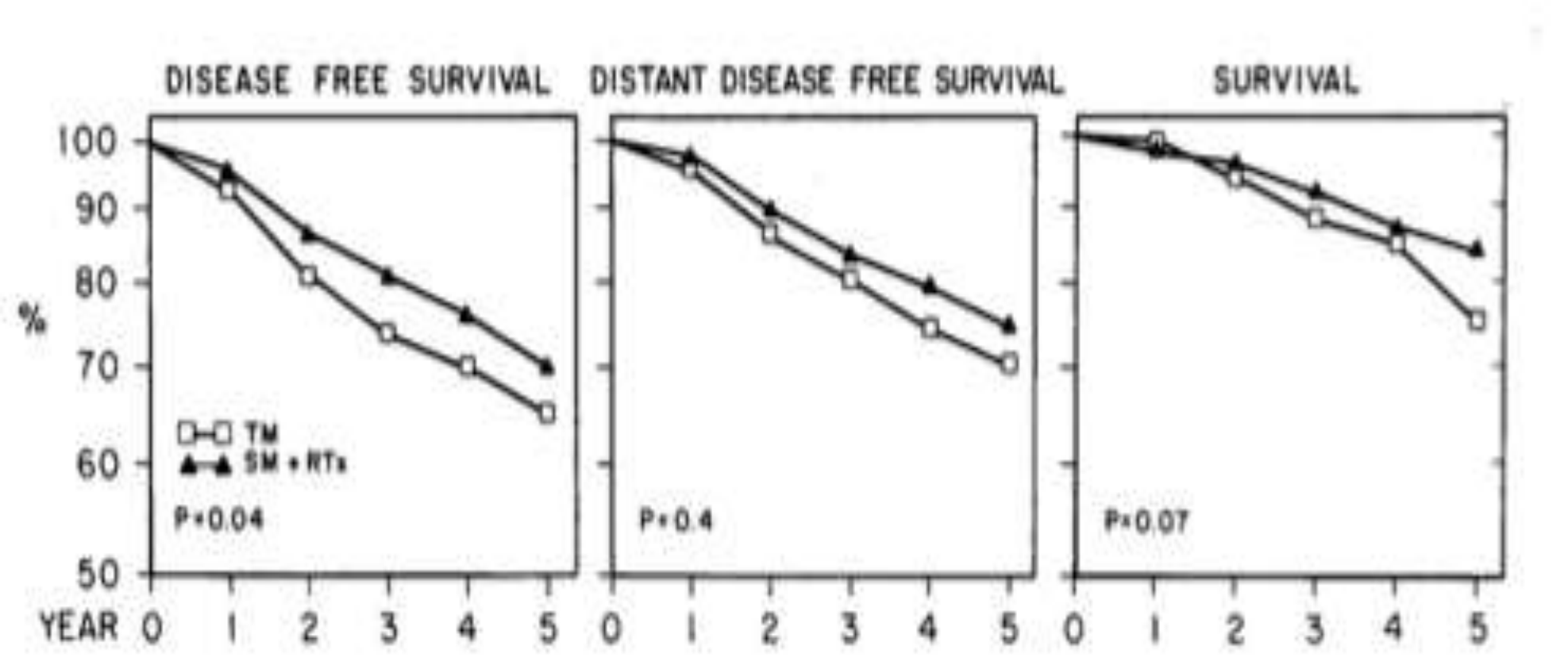
- Started in 1976
- Total of 1843 patients randomized
- Stage I & II breast cancer, tumor <4cm
- Mastectomy, segmentectomy with or without breast irradiation.
- ALL patient had ALND and patient with positive nodes received chemotherapy
- Breast RT of 50Gy/25# over 5 wks; No boost and LN irradiation
- DFS, Distant DFS and OS in segmentectomy group is no worse than mastectomy
- Breast irradiation significantly reduced the local recurrence

NSABP-06 TRIAL



Percentage of patients remaining free of breast tumor after segmentectomy or segmentectomy plus irradiation

NSABP-06 TRIAL



DFS, Distant DFS and OS of patients treated by Total mastectomy or by segmentectomy plus irradiation

EBCTCG- A meta-analysis

EFFECTS OF RADIOTHERAPY AND SURGERY IN EARLY BREAST CANCER

An Overview of the Randomized Trials

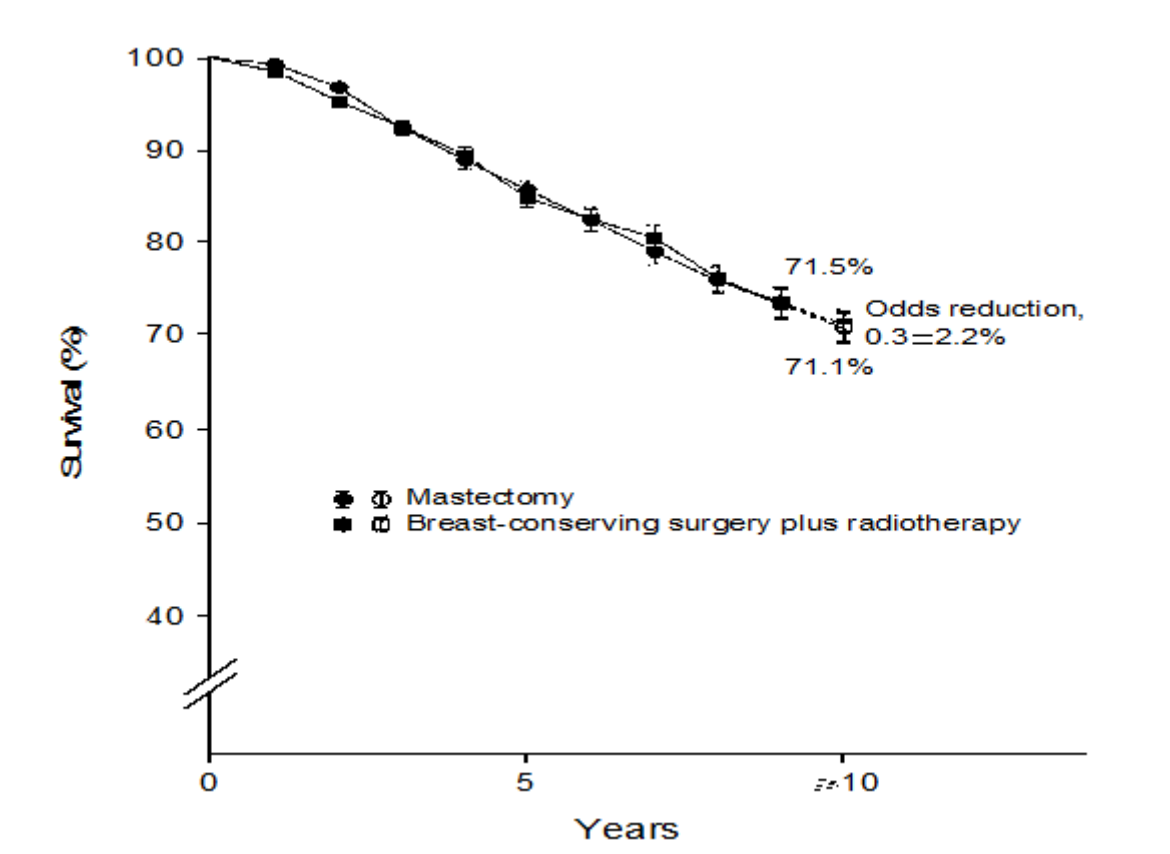
EARLY BREAST CANCER TRIALISTS' COLLABORATIVE GROUP*

N Engl J Med 1995;333:1444-55.

EBCTCG- A meta-analysis

- Mortality data from 36 randomized trials were analyzed
- Comparing surgery with or without RT in EBC
- Total of 29715 women
- Radiotherapy reduced the risk of local recurrence by 3 times c/w surgery alone
- RT prevents one death for every 4 local recurrence reduction at 10 years
- No difference in long term OS

EBCTCG- A meta-analysis



Ten-Year Survival among Approximately 3100 Women in Seven Randomized Trials Comparing Mastectomy with Breast-Conserving Surgery plus Radiotherapy.

Hypofractionation in Breast Ca RT

- **Ontario Clinical Oncology Group Trial**

Randomized Trial of Breast Irradiation Schedules After Lumpectomy for Women With Lymph Node-Negative Breast Cancer

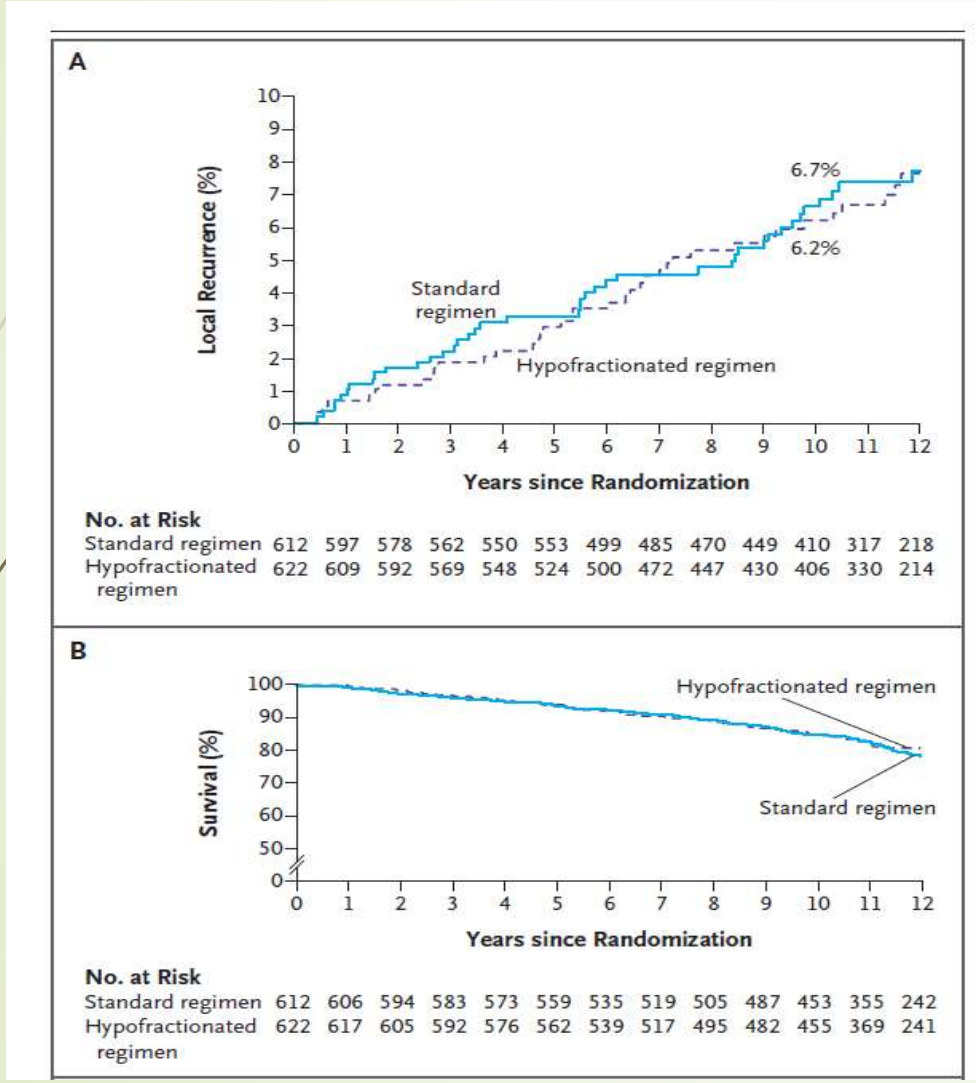
Timothy Whelan, Robert MacKenzie, Jim Julian, Mark Levine, Wendy Shelley, Laval Grimard, Barbara Lada, Himu Lukka, Francisco Perera, Anthony Fyles, Ethan Laukkanen, Sunil Gulavita, Veronique Benk, Barbara Szechtman

J Natl Cancer Inst 2002, 94(15):1143-50

Ontario Clinical Oncology Group Trial

- 1234 patients, between April 1992 to September 1996
- 50Gy/25fx/35 days vs 42.5Gy/16 fx/22 days
- T1 –T2 tumors; all node negative
- Large breasted women excluded (separation > 25 cm)
- Non-inferiority with 80% power to rule out 5% increase in local recurrence

Ontario Clinical Oncology Group Trial-Results



Median follow-up: 12 years

Tam : 41%
Chemo: 11%

Whelan et al NEJM 362 (6), 2010

Long-term Toxicity

Site and Grade	5 Yr		10 Yr	
	Standard Regimen (N=424)	Hypofractionated Regimen (N=449)	Standard Regimen (N=220)	Hypofractionated Regimen (N=235)
	percent of patients			
Skin				
0†	82.3	86.1	70.5	66.8
1	14.4	10.7	21.8	24.3
2	2.6	2.5	5.0	6.4
3	0.7	0.7	2.7	2.5
Subcutaneous tissue				
0‡	61.4	66.8	45.3	48.1
1	32.5	29.5	44.3	40.0
2	5.2	3.8	6.8	9.4
3	0.9	0.9	3.6	2.5

No difference in skin & subcutaneous toxicities

Long Term Cosmetic Results

Table 2. Global Cosmetic Outcome, Assessed According to the EORTC Scale.*

Rating	Baseline			5 Yr			10 Yr		
	Standard Regimen (N=604)	Hypofractionated Regimen (N=616)	Absolute Difference (95% CI)	Standard Regimen (N=423)	Hypofractionated Regimen (N=448)	Absolute Difference (95% CI)	Standard Regimen (N=216)	Hypofractionated Regimen (N=235)	Absolute Difference (95% CI)
	percent of patients		*percentage points*	*percent of patients*		*percentage points*	*percent of patients*		*percentage points*
Excellent	46.3	46.8		34.3	36.4		27.8	30.6	
Good	36.3	37.0		44.9	41.5		43.5	39.2	
Fair	15.1	14.6		17.3	19.0		25.5	25.4	
Poor	2.3	1.6		3.5	3.1		3.2	4.8	
Excellent or good	82.6	83.8	−1.2 (−5.4 to 3.1)	79.2	77.9	1.3 (−4.2 to 6.7)	71.3	69.8	1.5 (−6.9 to 9.8)

* Absolute differences were calculated as the value in the group that received the standard regimen minus the value in the group that received the hypofractionated regimen. EORTC denotes European Organization for Research and Treatment of Cancer.

No difference in long-term cosmetic result

UK Start trials

The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials

Joanne S Haviland, J Roger Owen, John A Dewar, Rajiv K Agrawal, Jane Barrett, Peter J Barrett-Lee, H Jane Dobbs, Penelope Hopwood, Pat A Lawton, Brian J Magee, Judith Mills, Sandra Simmons, Mark A Sydenham, Karen Venables, Judith M Bliss, John R Yarnold*, on behalf of the START Trialists' Group†*

Haviland JS et al. Lancet Oncol 2013; 14: 1086–94

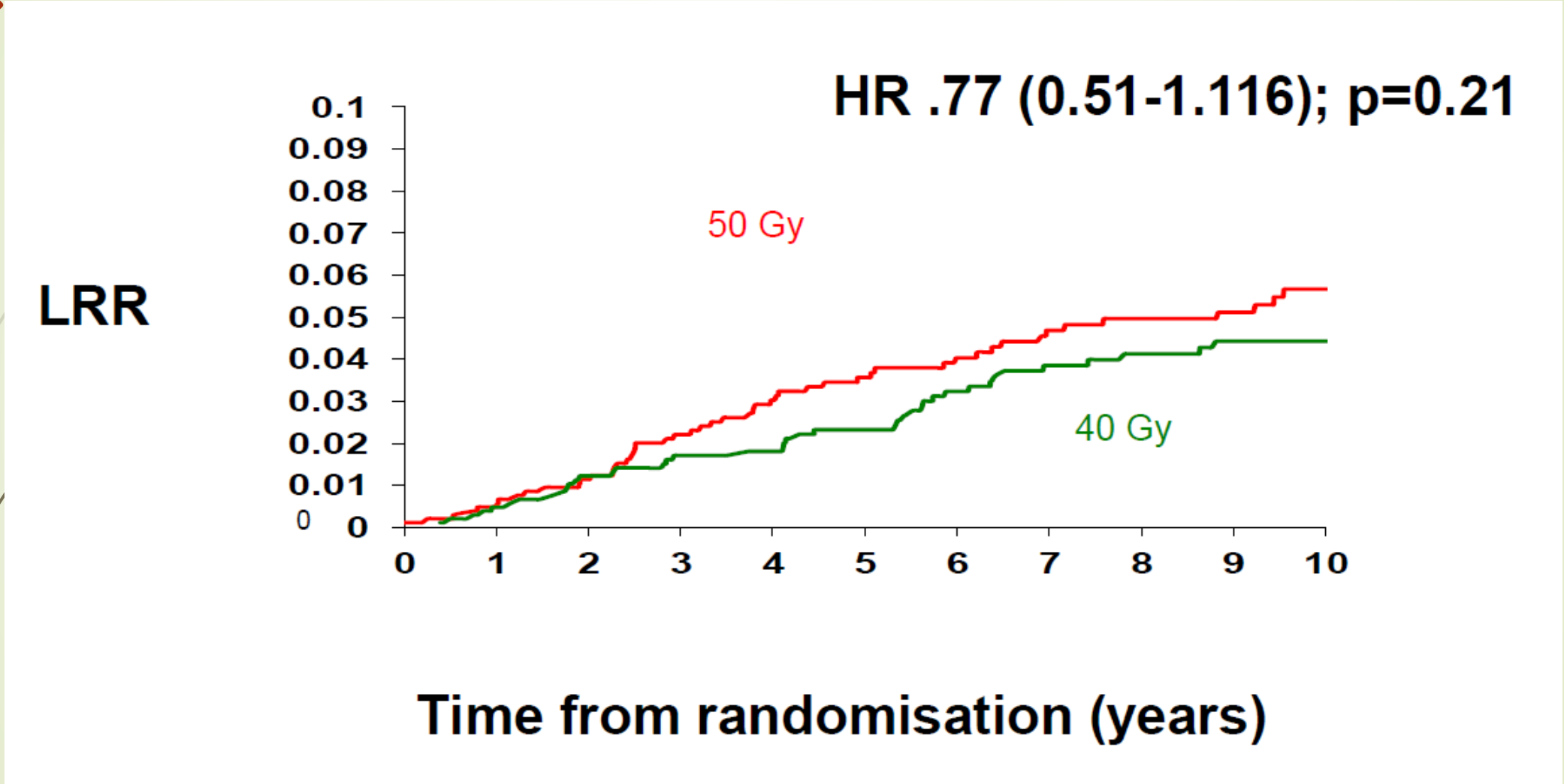
UK Start B trial

- N=2215 patients, from 1999 to 2002
- Median follow-up: 9.9 years
- Standard Arm: 50Gy/25# over 5 weeks
- Experimental arm: 40.05Gy/15# over 3 weeks
- pT1-3 pN0-1 M0 EBC patients were included
- 23 centres in the UK participated

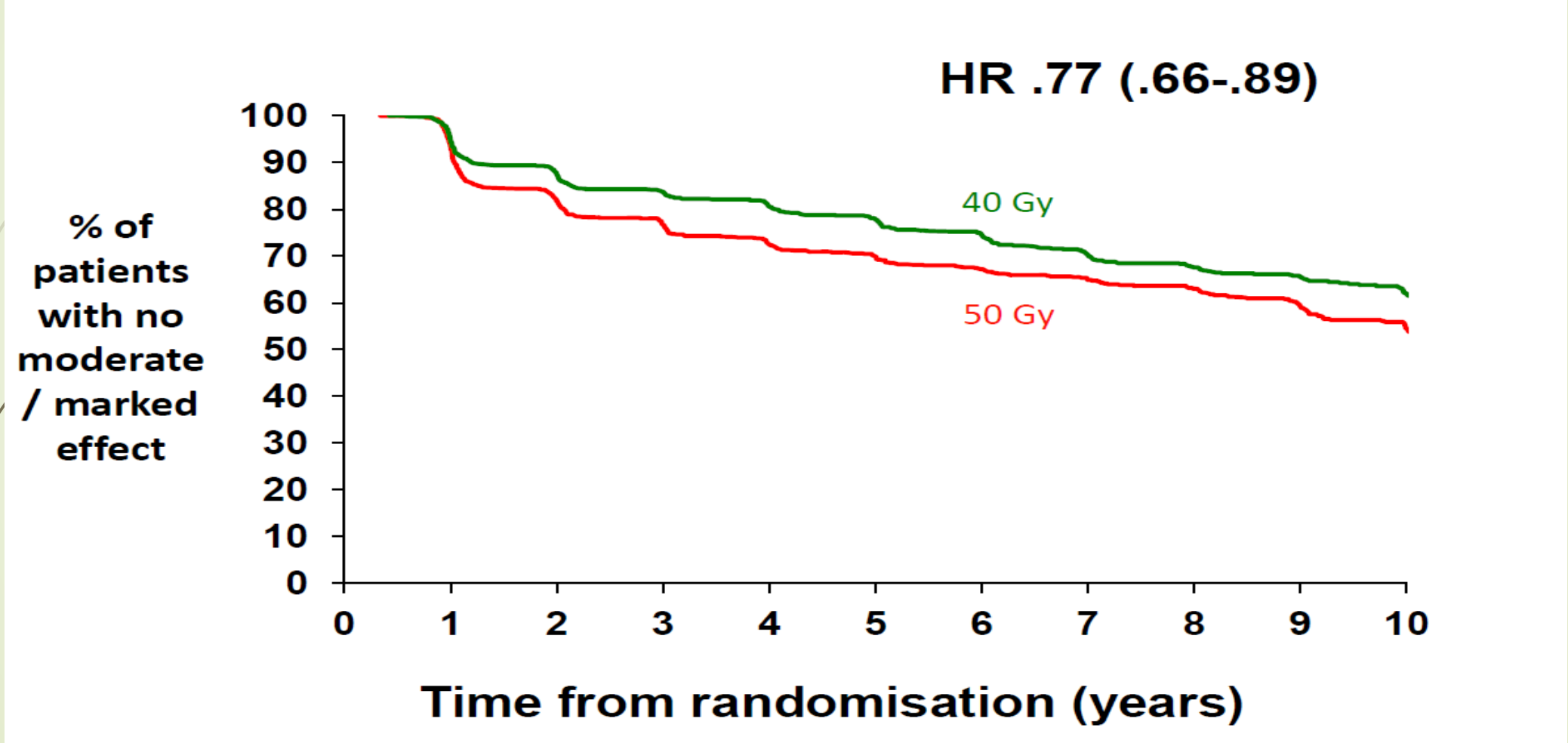
START A Trail: Experimental arm includes 39Gy/13# or 41.6Gy/13# over 5 weeks

Haviland JS et al. Lancet Oncol 2013; 14: 1086–94

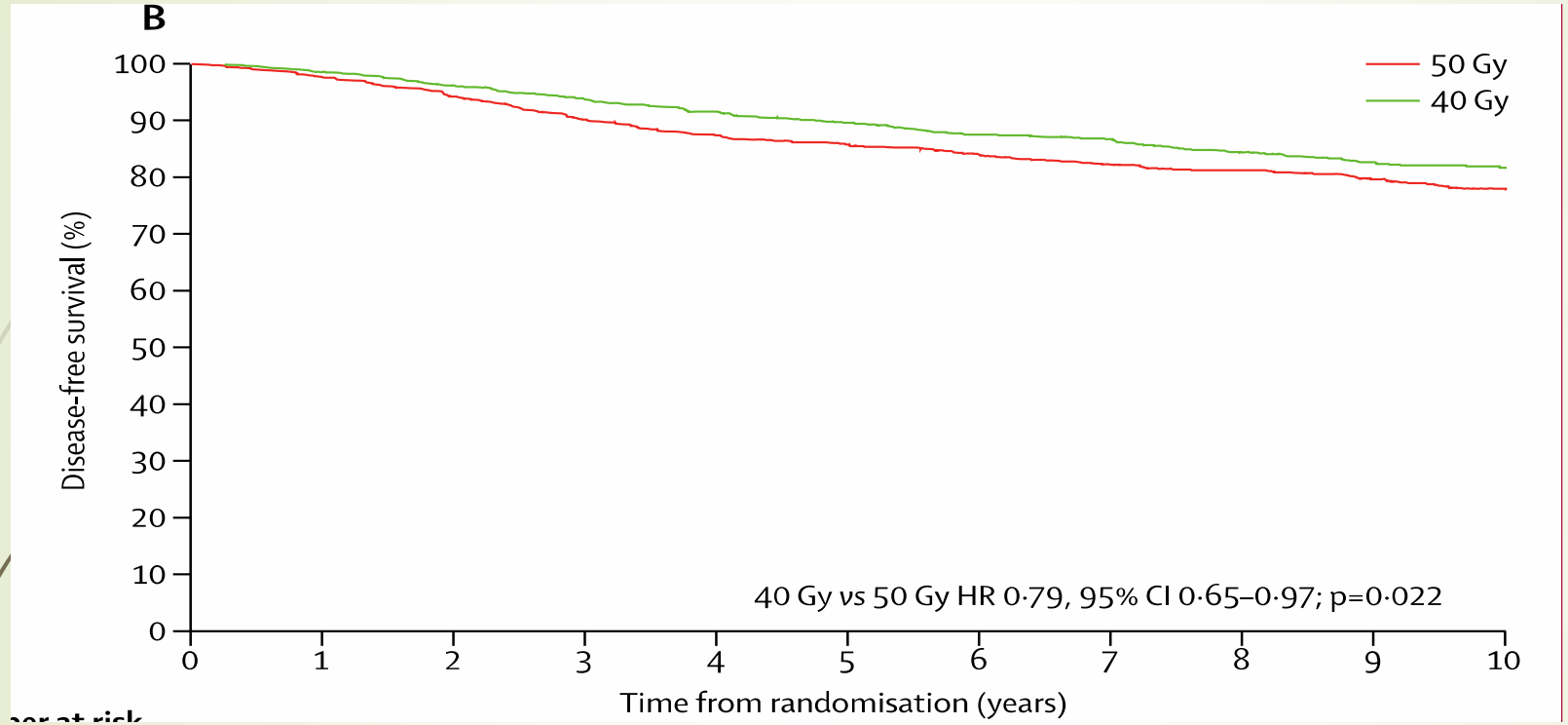
Start B: Cumulative Incidence LRR



Start B: Marked/Moderate Cosmetic Defect



Start B: Disease free survival



Fast forward trial

Hypofractionated breast radiotherapy for 1 week versus 3 weeks (FAST-Forward): 5-year efficacy and late normal tissue effects results from a multicentre, non-inferiority, randomised, phase 3 trial

Adrian Murray Brunt, Joanne S Haviland*, Duncan A Wheatley, Mark A Sydenham, Abdulla Alhasso, David J Bloomfield, Charlie Chan, Mark Churn, Susan Cleator, Charlotte E Coles, Andrew Goodman, Adrian Harnett, Penelope Hopwood, Anna M Kirby, Cliona C Kirwan, Carolyn Morris, Zohal Nabi, Elinor Sawyer, Navita Somaiah, Liba Stones, Isabel Syndikus, Judith M Bliss†, John R Yarnold†, on behalf of the FAST-Forward Trial Management Group*

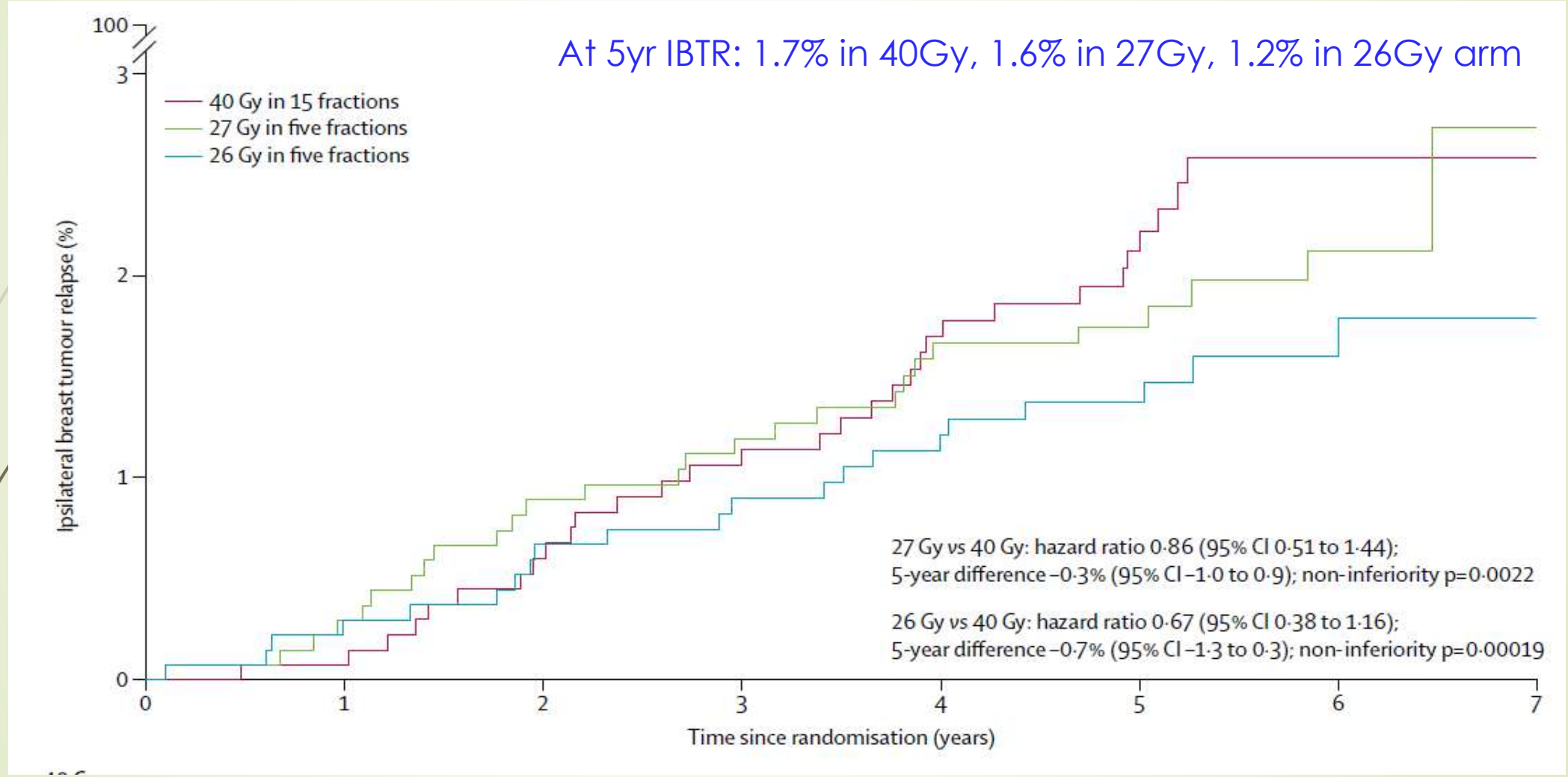
Brunt et al; Lancet Oncology-April 2020

Fast forward trial

- From Nov 2011 to June 2014
- 97 (47 RT & 50 referring) hospitals in UK participated
- Total of 4096 patients enrolled
- pT1-3, pN0-1, M0, after BCS or mastectomy were eligible
- Patients randomised to;
  - 40Gy/15#/3wks (n=1361)
  - 27Gy/5#/1wk (n=1367)
  - 26Gy/5#/1wk (n=1368)
  - No SCF RT
- Median follow-up 71.5 months

Fast forward trial: Results

At 5yr IBTR: 1.7% in 40Gy, 1.6% in 27Gy, 1.2% in 26Gy arm



Fast forward trial: 26Gy/5# is better

	Number of moderate or marked events/total number of assessments over follow-up	Odds ratio for schedule (95% CI)	p value for comparison with 40 Gy	p value for comparison between 27 Gy and 26 Gy	Odds ratio for years of follow-up (95% CI); p value
Any adverse event in the breast or chest wall*	..	..	..	..	0·98 (0·96–1·00); 0·055
40 Gy	651/6121 (10·6%)	1 (ref)	..	..	..
27 Gy	1004/6303 (15·9%)	1·55 (1·32–1·83)	<0·0001	..	..
26 Gy	774/6327 (12·2%)	1·12 (0·94–1·34)	0·20	0·0001	..
Breast distortion†	..	..	..	..	0·99 (0·95–1·02); 0·38
40 Gy	232/5724 (4·0%)	1 (ref)	..	..	..
27 Gy	363/5953 (6·1%)	1·51 (1·15–1·97)	0·0028	..	..
26 Gy	299/5945 (5·0%)	1·20 (0·91–1·60)	0·19	0·083	..
Breast shrinkage†	..	..	..	..	1·03 (1·00–1·06); 0·023
40 Gy	330/5728 (5·8%)	1 (ref)	..	..	..
27 Gy	503/5944 (8·5%)	1·50 (1·20–1·88)	0·0004	..	..
26 Gy	369/5943 (6·2%)	1·05 (0·82–1·33)	0·71	0·0018	..
Breast induration (tumour bed)†	..	..	..	..	1·00 (0·96–1·04); 0·95
40 Gy	185/5713 (3·2%)	1 (ref)	..	..	..
27 Gy	304/5948 (5·1%)	1·56 (1·19–2·05)	0·0013	..	..
26 Gy	236/5937 (4·0%)	1·19 (0·90–1·59)	0·23	0·047	..
Breast induration (outside tumour bed)†	..	..	..	..	0·96 (0·90–1·02); 0·17
40 Gy	45/5712 (0·8%)	1 (ref)	..	..	..
27 Gy	137/5943 (2·3%)	2·79 (1·74–4·50)	<0·0001	..	..
26 Gy	97/5930 (1·6%)	1·90 (1·15–3·14)	0·013	0·059	..
Telangiectasia	..	..	..	..	1·21 (1·14–1·29); <0·0001
40 Gy	63/6087 (1·0%)	1 (ref)	..	..	..
27 Gy	100/6272 (1·6%)	1·68 (1·07–2·65)	0·025	..	..
26 Gy	102/6300 (1·6%)	1·53 (0·96–2·43)	0·070	0·65	
Breast or chest wall oedema	..	..	..	..	0·73 (0·69–0·78); <0·0001
40 Gy	89/6097 (1·5%)	1 (ref)	..	..	..
27 Gy	217/6287 (3·4%)	2·18 (1·57–3·03)	<0·0001	..	..
26 Gy	155/6318 (2·4%)	1·47 (1·03–2·09)	0·032	0·0097	..
Breast or chest wall discomfort	..	..	..	..	0·93 (0·89–0·97); 0·0003
40 Gy	234/6086 (3·8%)	1 (ref)	..	..	..
27 Gy	269/6285 (4·3%)	1·10 (0·86–1·40)	0·44	..	..
26 Gy	250/6309 (4·0%)	0·98 (0·76–1·26)	0·86	0·35	..

Fast forward trial: 26Gy/5# is better

	Number of patients reporting moderate or marked event at baseline/total*	Number of moderate or marked events/total number of assessments over 3–60 months of follow-up	Odds ratio for schedule (95% CI)	p value for comparison with 40 Gy	p value for comparison between 27 Gy and 26 Gy	Odds ratio for years of follow-up (95% CI); p value
Protocol-specific items						
Breast appearance changed	..	..	..	..	..	1·03 (1·01–1·05); 0·0010
40 Gy	170/573 (29·7%)	778/2480 (31·4%)	1 (ref)	..	..	..
27 Gy	177/583 (30·4%)	929/2550 (36·4%)	1·22 (1·02–1·46)	0·033	..	..
26 Gy	155/581 (26·7%)	770/2563 (30·0%)	0·91 (0·75–1·10)	0·33	0·0018	..
Breast smaller	..	..	..	..	..	1·11 (1·09–1·13); <0·0001
40 Gy	96/560 (17·1%)	585/2445 (23·9%)	1 (ref)	..	..	..
27 Gy	106/576 (18·4%)	606/2520 (24·0%)	1·05 (0·85–1·29)	0·67	..	..
26 Gy	90/574 (15·7%)	515/2542 (20·3%)	0·81 (0·65–1·00)	0·053	0·017	..
Breast harder or firmer	..	..	..	..		0·95 (0·93–0·97); <0·0001
40 Gy	94/558 (16·8%)	499/2446 (20·4%)	1 (ref)	..	..	..
27 Gy	105/572 (18·4%)	690/2512 (27·5%)	1·42 (1·17–1·72)	0·0003	..	..
26 Gy	95/566 (16·8%)	626/2534 (24·7%)	1·22 (1·00–1·48)	0·048	0·1007	..
Skin appearance changed	..	..	..	..	..	0·96 (0·93–0·99); 0·0080
40 Gy	78/577 (13·5%)	345/2505 (13·8%)	1 (ref)	..	..	..
27 Gy	61/586 (10·4%)	392/2571 (15·2%)	1·03 (0·83–1·28)	0·77	..	..
26 Gy	67/580 (11·5%)	338/2576 (13·1%)	0·90 (0·72–1·13)	0·37	0·23	..

IORT-TARGIT A trial

Long term survival and local control outcomes from single dose targeted intraoperative radiotherapy during lumpectomy

(TARGIT-IORT) for early breast cancer: TARGIT-A randomised clinical trial

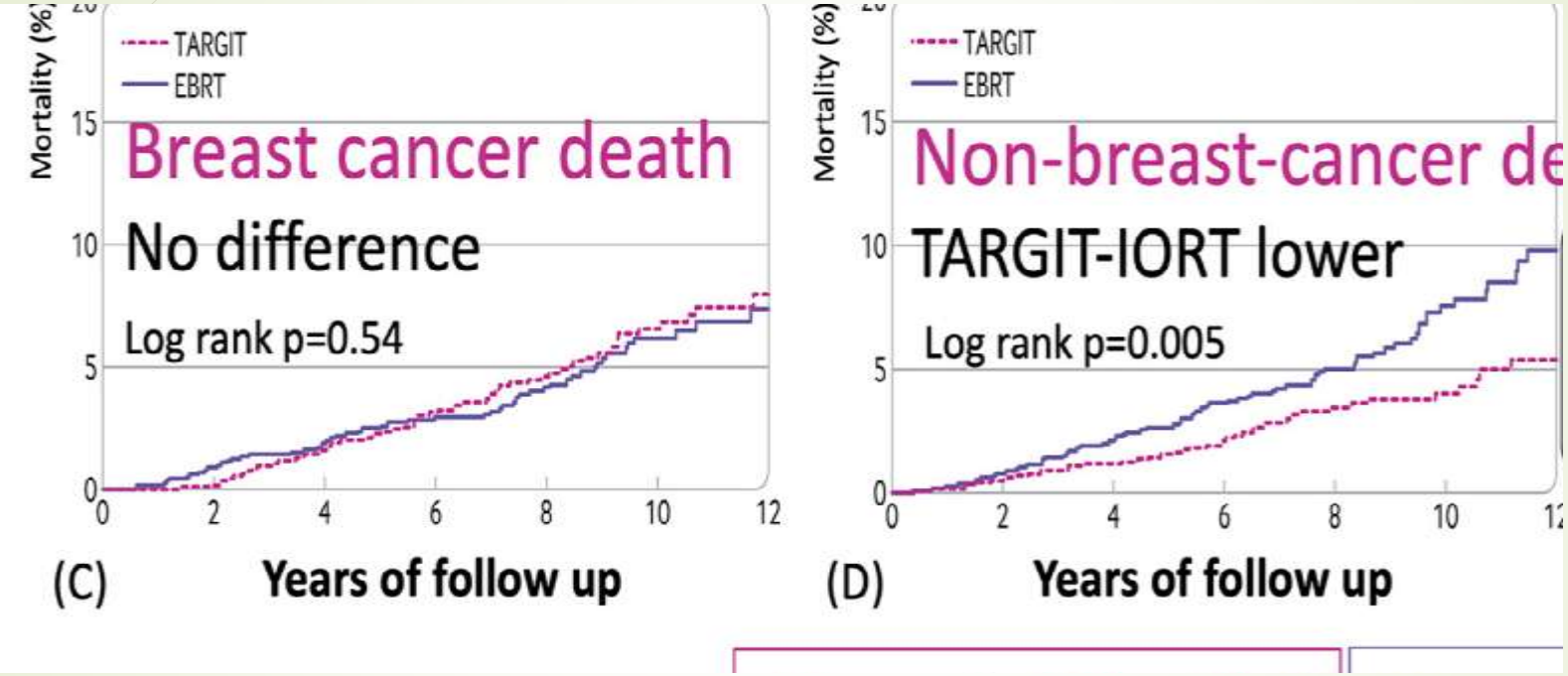
Jayant S Vaidya et al.

BMJ 2020;370: 2836

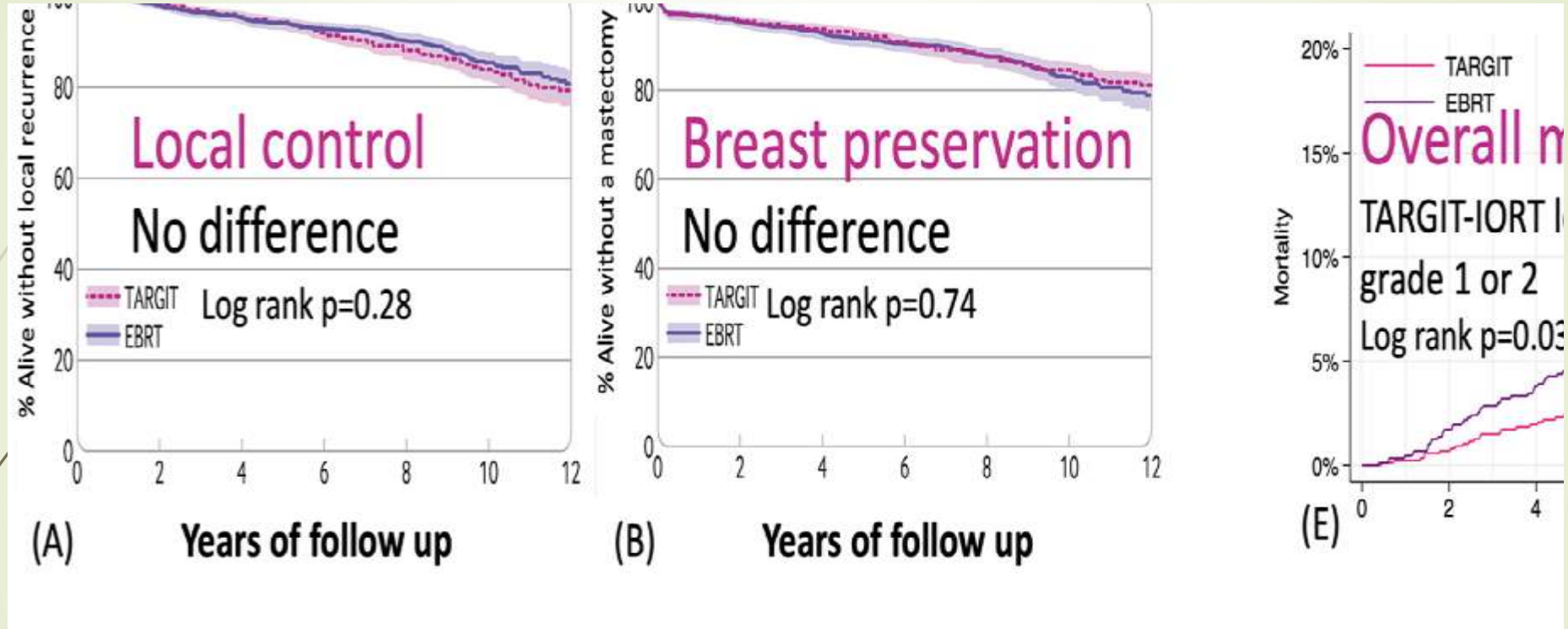
TARGIT A trial-Results

- 2298 women, aged 45years and older
- Between March 2000 to June 2012, international study
- IDC up to 3.5cm, cN0-N1, eligible for BCS
- Randomised to IORT or EBRT
- EBRT-daily fractionated course of 3-6 weeks
- IORT- by Intrabeam device, 50kV x-rays, tumor bed surface receives 20Gy/1#
- Patients with high risk pathology features received EBRT to whole breast
- Median FU 8.6yrs (max 18.9yrs)

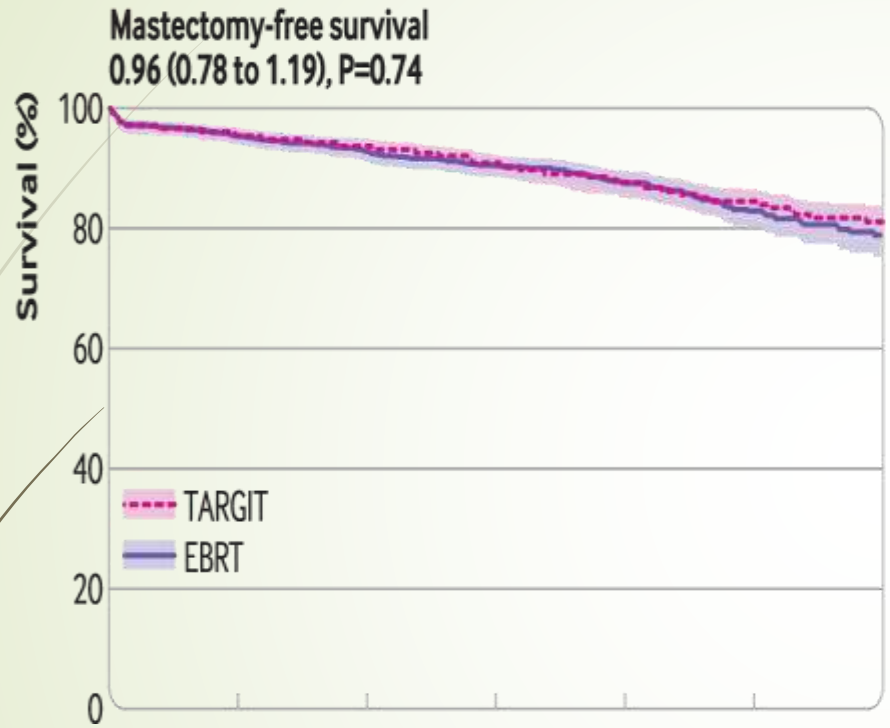
TARGIT A trial-Results

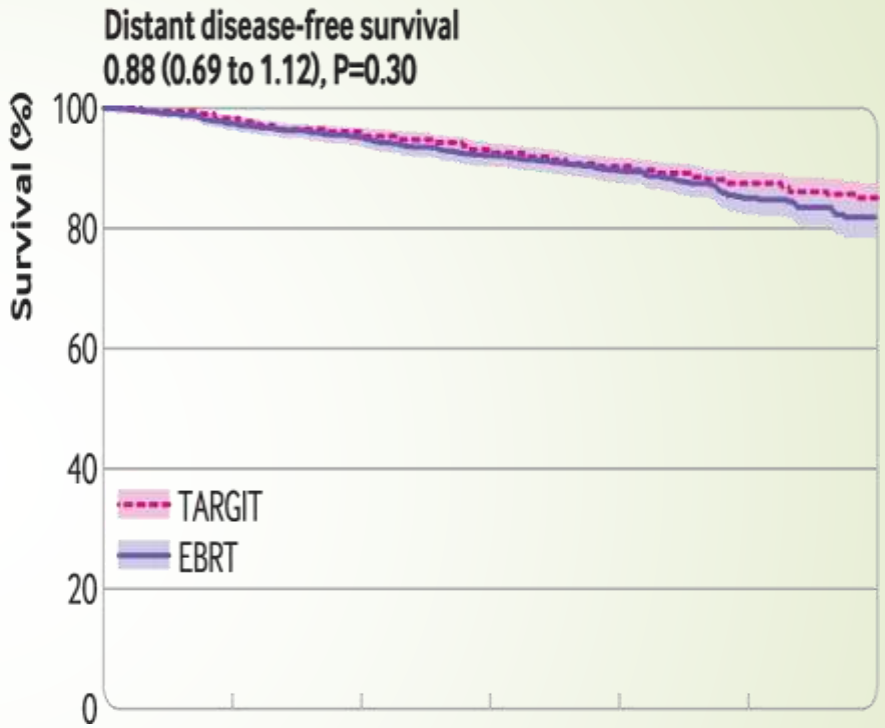


TARGIT A trial-Results



TARGIT A trial-Results





TARGIT A trial-Results

- **CONCLUSION**

  For patients with early breast cancer who met our trial selection criteria, risk adapted immediate single dose TARGIT-IORT during lumpectomy was an effective alternative to EBRT, with comparable long term efficacy for cancer control and lower non-breast cancer mortality. TARGIT-IORT should be discussed with eligible patients when breast conserving surgery is planned.

Omission of adjuvant RT

- Safe omission of radiotherapy after breast-conserving surgery
  - can be considered in women deemed to be at very low risk of local recurrence
  - T1, N0, Grade 1 & 2
  - ER + PR+ Her2 –
  - >65 years
  - willing to take adjuvant endocrine therapy for 5 years
  - willing to have regular mammographic follow up to year 10.

NICE Guideline- July 2018

- Consider omitting radiotherapy for women who:
- have had breast-conserving surgery for invasive breast cancer with clear margins **and**
- have a very low absolute risk of local recurrence (defined as women aged 65 and over with tumours that are T1N0, ER-positive, HER2-negative and grade 1 to 2) **and**
- are willing to take adjuvant endocrine therapy for a minimum of 5 years.

NCCN-Clinical practice guidelines in Oncology

- The National Comprehensive Cancer Network clinical guidelines allow for the use of lumpectomy plus tamoxifen/AI without breast irradiation in
  - women greater than or equal to 70 years of age
  - clinically node negative
  - ER positive
  - T1 breast cancer
  - pathological negative margin required
  - category I data

Breast cancer-Version 5.2020 published July 15, 2020

PRIME II Trail

- RT + hormonal therapy vs hormonal therapy alone
- Age greater than 65
- Tumour < 3.0 cm, N0
- HR positive
- Margins >1 mm
- Grade 3 or LVI permitted (not both)
- N=1326 patients

Kunkler I, Lancet Oncol. 2015 Mar;16(3):266-73

PRIME II: 5-year Results

	RT	NO RT	P
IBTR (%)	1.3	4.1	0.001
DM (%)	.3	1.0	NS
OS (%)	94.2	93.8	NS

Omission of adjuvant RT-Other trials

- CALGB 9343
  - 650 pts, >70yrs, Tam or Tam+RT, median FU 12.6yrs
  - No difference in MFS, DMFS & OS
  - LRR free survival 90% & 98%
- Princess Margaret Hospital trial
  - 769pts, >50yrs, Tam or Tam +RT, T1 & T2 disease
  - No difference in OS
  - At 8 yrs, LRR 17.6% vs 3.5%

Hughes KS et al JCO 2013, 45: 2615

Fyles, A. et al. NEJM 2004;351:963-970

Thank you