Radiotherapy of breast cancer: from the first tryouts to today's state of the art.
ESTRO guidelines for regional target volume definition.

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Oslo, Febr 13 th 2015

Contents

- History of the role of RT in breast cancer
  - Effect on Local control and/or survival ?
  - Specific issues:
    - Indication for RT in pN1 disease
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  - History of BCT
    - Less treatment in low risk BC ?

- From conventional simulation to state of the art techniques

- ESTRO delineation guidelines

History of radiotherapy in breast cancer

- Radiotherapy started with Rontgen, Mr. and Mrs. Curie, Becquerel (late 19th century)

- Emil Grubbe (1875-1960)
- After noting peeling of his hands exposed to x-rays, a medical student in Chicago named Emil Grubbe convinced one of his professors to allow him to irradiate a cancer patient, a woman named Rose Lee, suffering from locally advanced breast cancer. By doing so, Grubbe became the World's first Radiation Oncologist

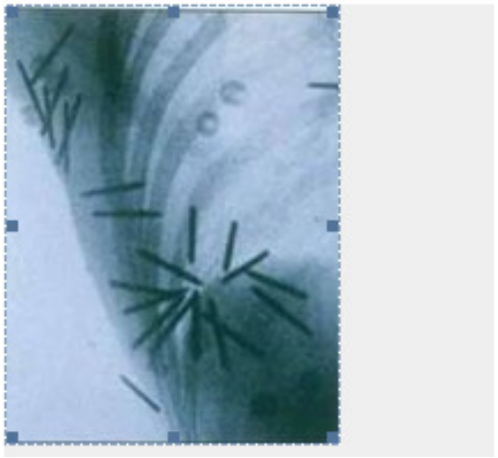
History of radiotherapy in breast cancer

- Many early advocates of Radiation Therapy thus relied instead on the placement of radioactive sources in close proximity or even within the tumor, a technique known as brachytherapy [Brachytherapy].

- In many tumors, for example cervical and uterine cancers, brachytherapy became the mainstay of treatment (as it so remains to this day).

- First report in Pubmed on RT in breast cancer from 1938 – Brodeur from Ottawa

Breast Brachytherapy (1920s)



Radiotherapy of cancer of the breast
dr. P. Brodeur, Ottawa, 1938

- In 1922, W. Sampson Handley said:

"In a number of cases of cancer the efforts of the surgeon, *if unsupported by those of the radiologist*, would be unavailing, and of course the converse proposition is equally true."

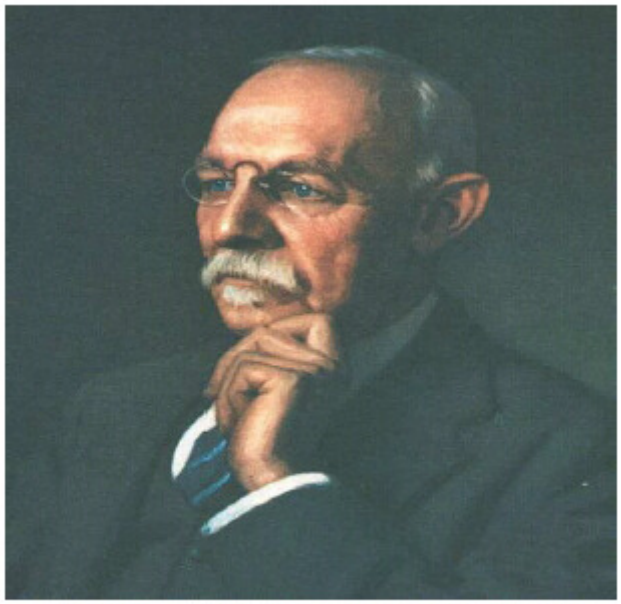
- In 1938 Brodeur wrote :

"These lines written in 1922, are still the fundamentals of proper treatment of breast cancers"…

Brodeur, 1938

History of surgery and radiotherapy in breast cancer

- Breast surgery started with Halsted
  - Removal of Breast, Muscles and Nodes

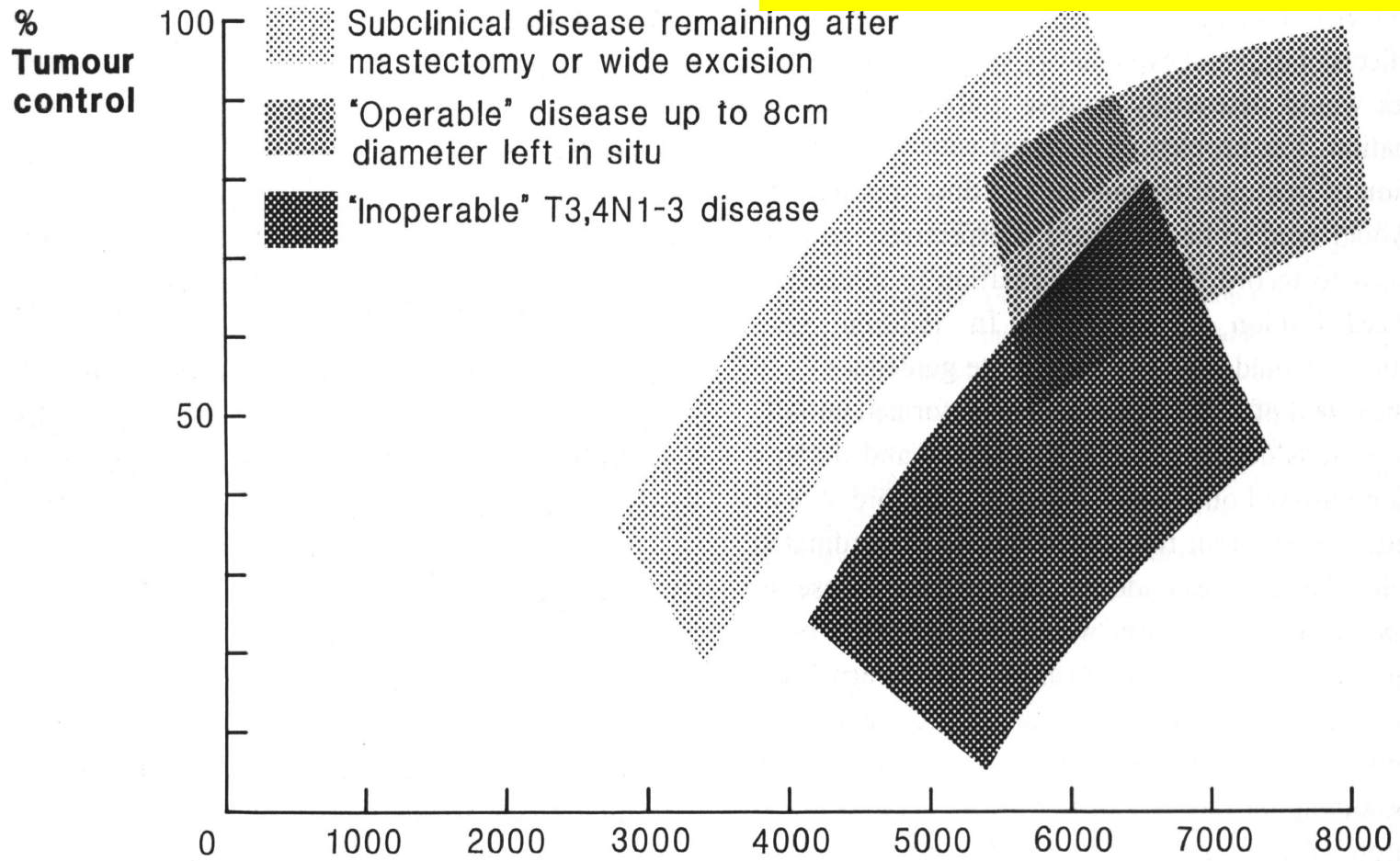


William Halsted (1852-1922)

Radiotherapy for inoperable locally advanced breast cancer

Dose-effect relations in breast cancer

RT should be combined with surgery..

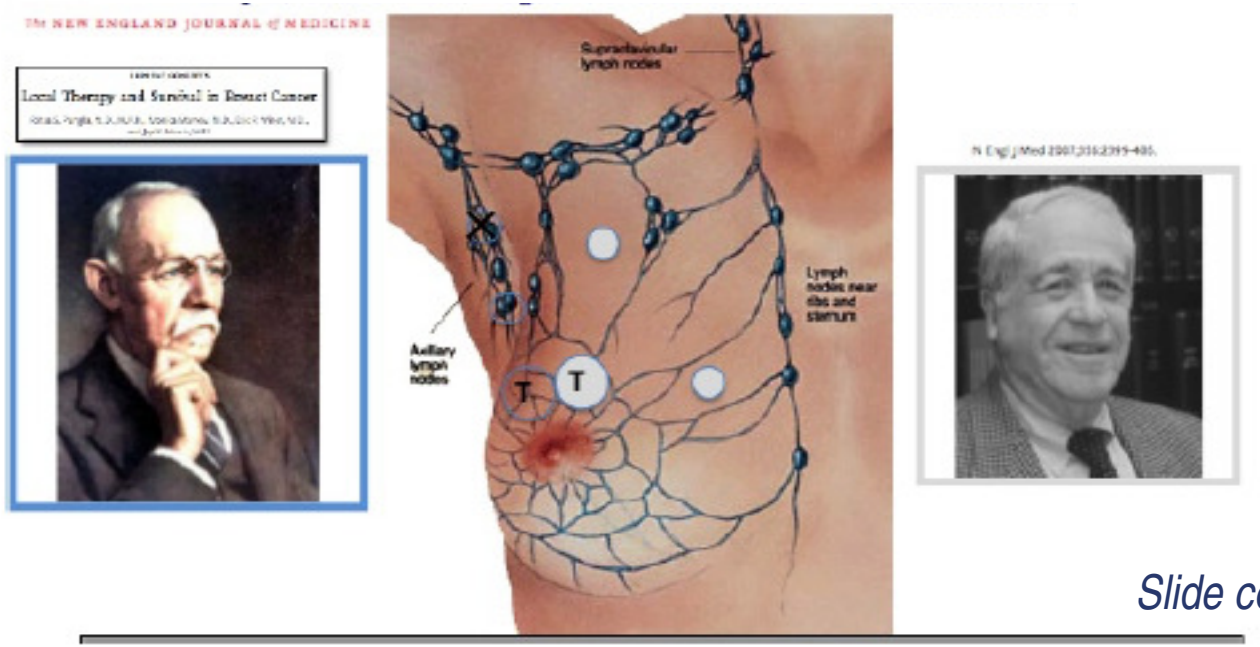


JW Denham, R & O 1986

RT to reduce local recurrences, or to improve survival ?

1980-1990

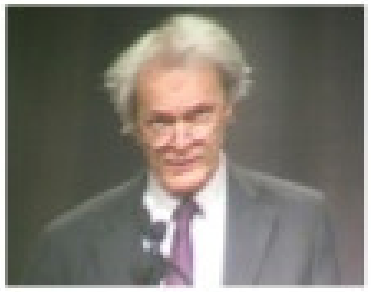
Halsted vs Fisher:
Is breast cancer a locoregional disease or
a systemic disease ?



Slide courtesy Struikmans

EBCTCG analyses / Peto analyses
Early Breast Cancer Trialists' Collaborative Group

- Every 5 yrs, the university of Oxford brings together updated data on each woman randomised into all trials of the treatment of operable breast cancer.
- The EBCTCG process was initiated in 1983, and extended in the 1990s to all aspects of early breast cancer management.
- Its results informed the year 2000 NIH consenus development conference on the treatment of early breast cancer.
- First analyses by Sir Richard Peto:



- Followed by Sarah Darby (ESTRO teacher):

EBCTCG analyses 1995

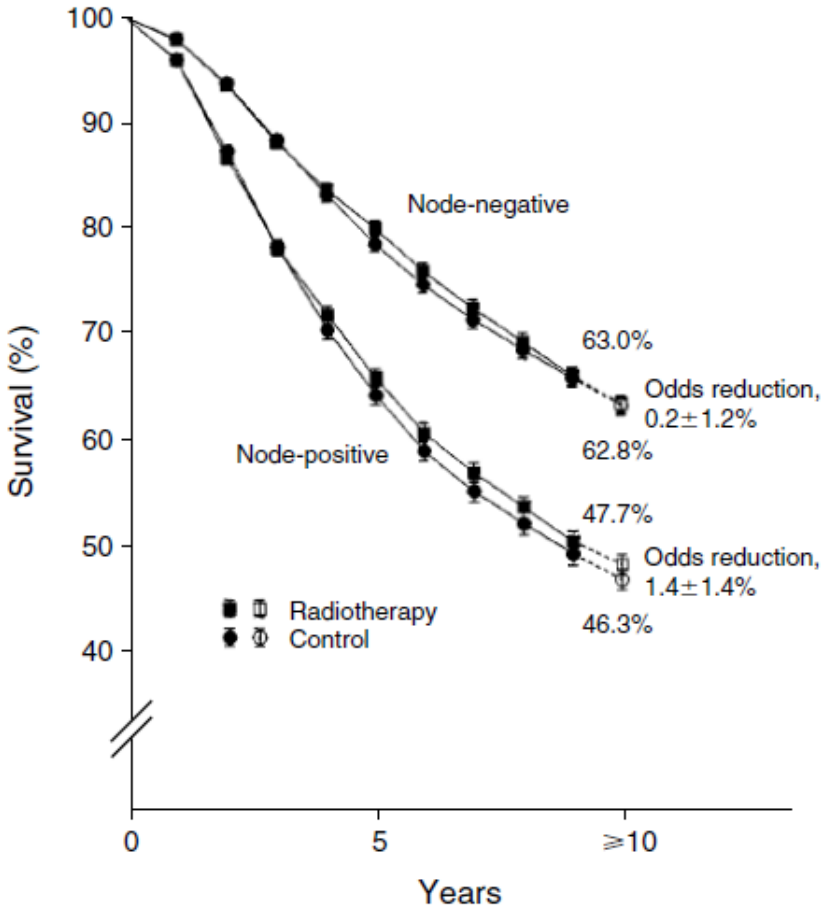


Figure 2. Ten-Year Survival among Approximately 16,000 Women in 35 Randomized Trials Comparing Surgery plus Radiotherapy with Surgery Alone.

- Trials started < 1985
- Data on app 16.000 patients in trials comparing surgery +/- RT

RT reduced LR with factor 3
RT had no effect on 10 yr OS

EBCTCG analyses, NEJM 1995

1997: Canadian Trial: RT does influence OS !

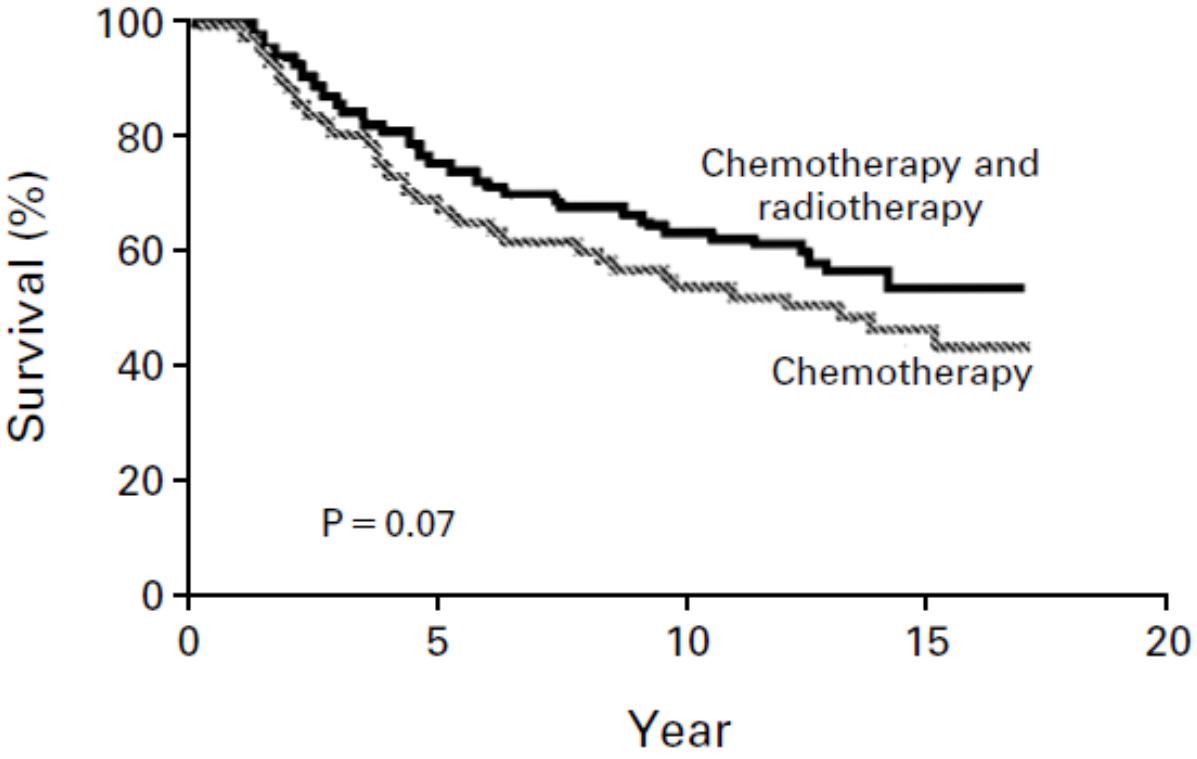


Figure 4. Overall Survival in the Study Groups.

- N = 318
- pN+
- All adjuvant CMF

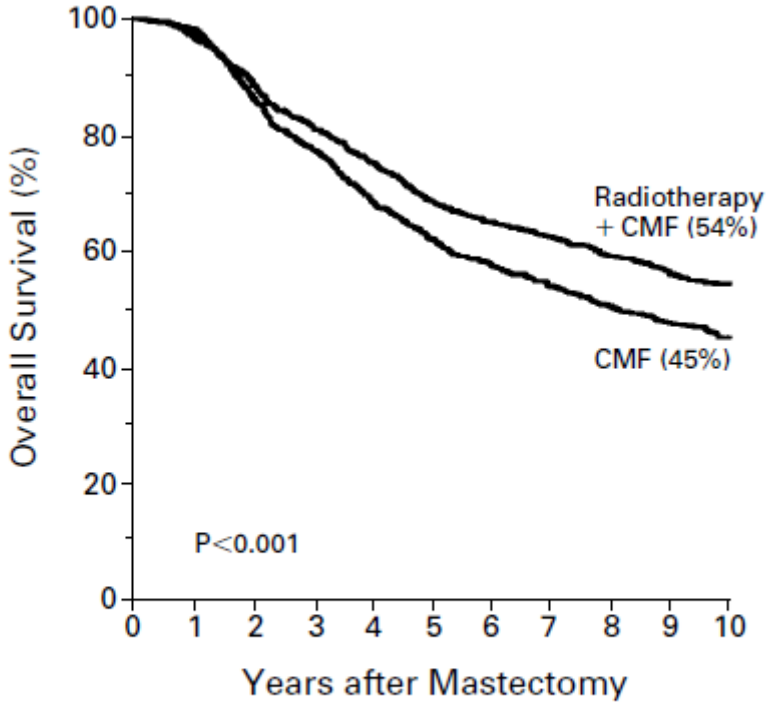
- LRRT (including IMN) vs no RT

Ragaz et al, British Columbia Trial, NEJM 1997

Danish trials - Overgaard NEJM 1997 & Lancet 1999: RT does influence OS !

DBCG 82b, pre-menopausal

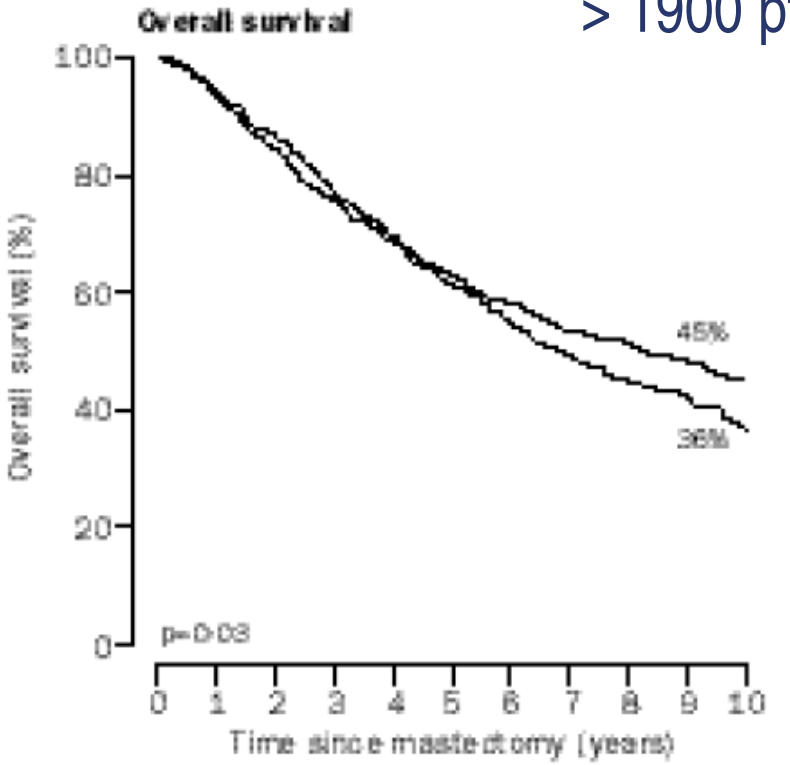
> 1700 pts



Radiotherapy + CMF	852	755	641	555	392	188
CMF	856	738	587	494	329	163

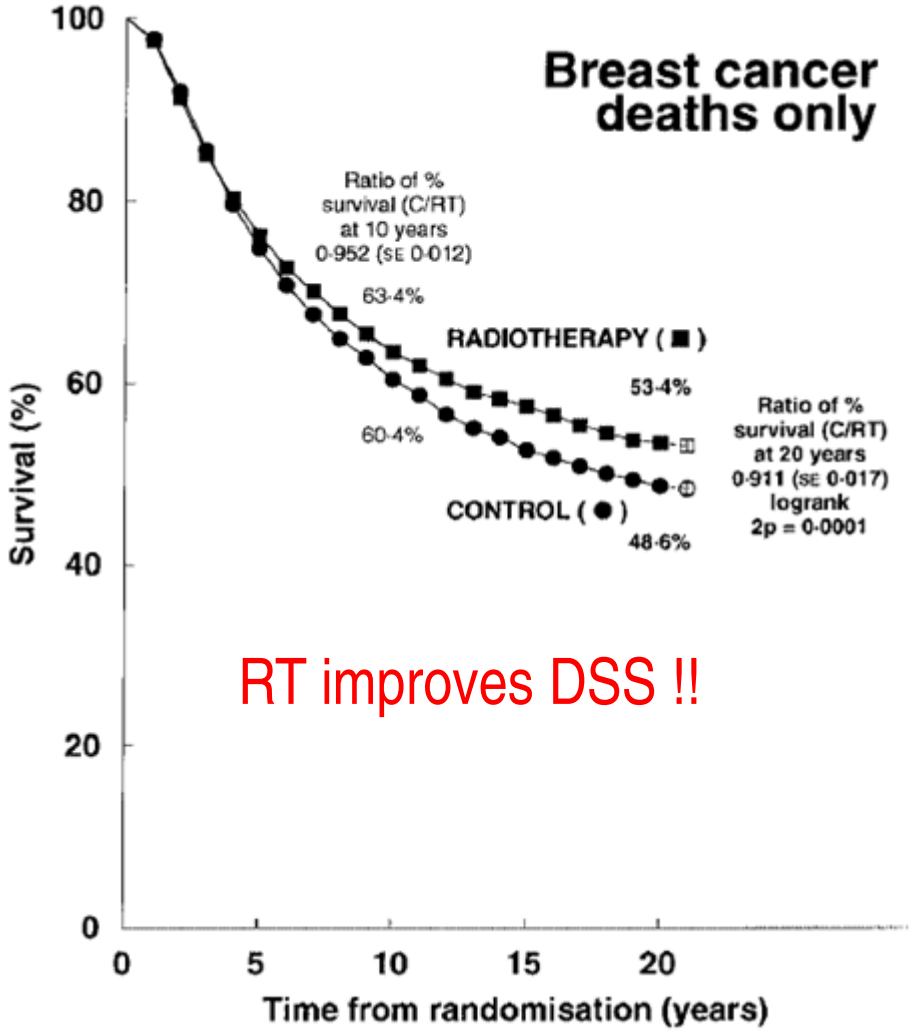
DBCG 82c, post- menopausal

> 1900 pts

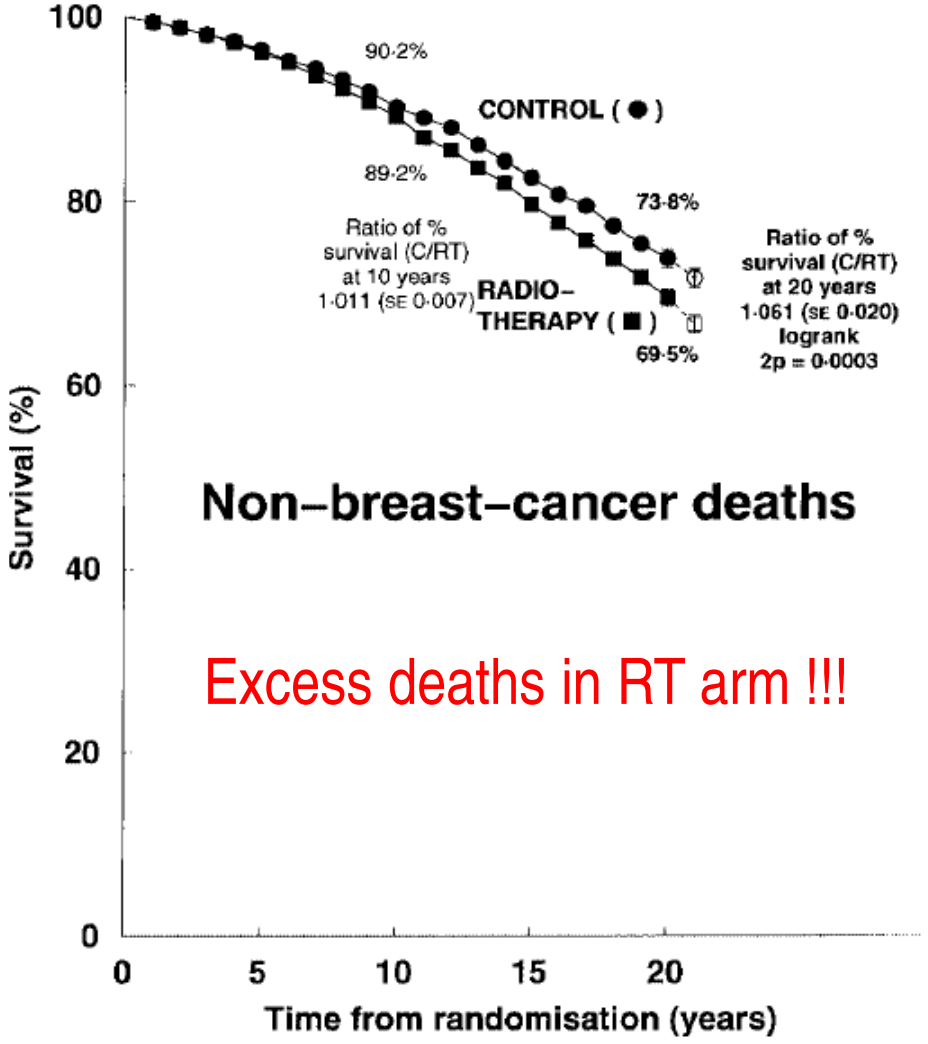


Patients at risk						
Radiotherapy plus tamoxifen	686	580	469	398	285	175
Tamoxifen only	689	598	479	378	251	136

EBCTCG, Lancet 2000

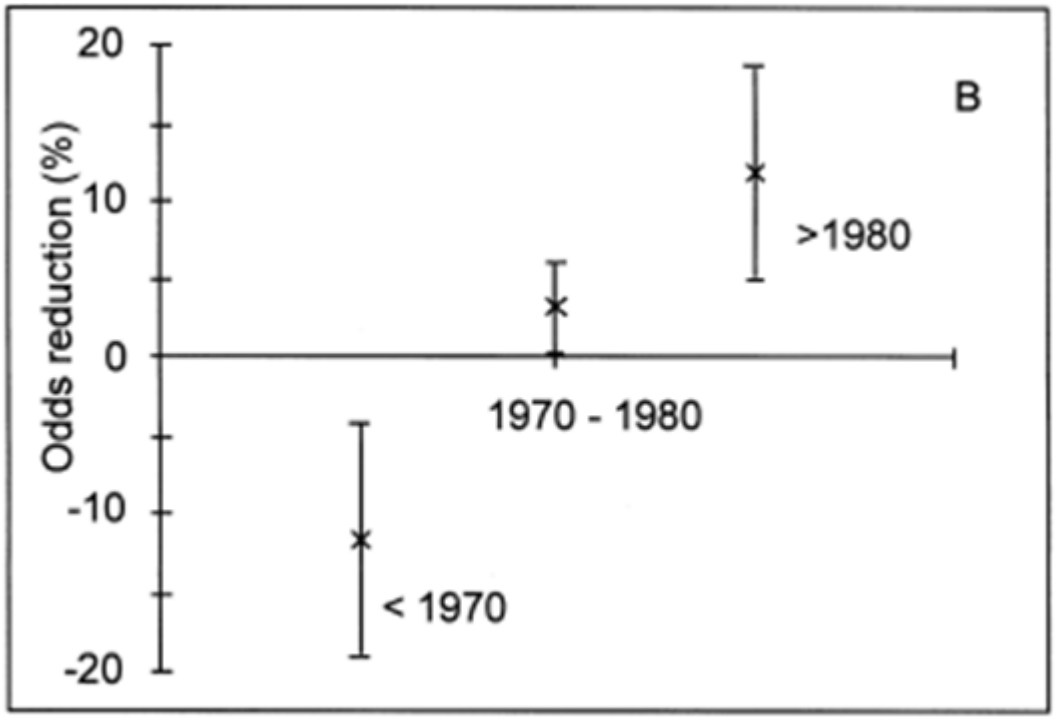


RT improves DSS !!



Excess deaths in RT arm !!!

Re-analysis EBCTCG data NEJM 1995
More recent trials: clear OS benefit



vd Steene et al, R & O 2000

Cause of excess deaths in RT arms ?
EBCTCG 2005

Mortality before recurrence, from causes other than breast cancer					
By cause					
Circulatory disease	1510	77·6	345·4	1·25 (0·06)	0·00003
Heart disease, etc§	1106	60·7	252·7	1·27 (0·07)	0·0001
Stroke	345	9·1	80·9	1·12 (0·12)	0·3
Pulmonary embolism	59	7·8	11·8	1·94 (0·41)	0·02
Other specified cause	1455	6·4	335·8	1·02 (0·06)	0·7
Lung cancer	156	21·7	37·5	1·78 (0·22)	0·0004
Oesophagus cancer	23	4·9	5·6	2·40 (0·68)	0·04
Leukaemia	31	2·4	7·0	1·40 (0·45)	0·4
Soft-tissue sarcoma	7	1·3	1·7	2·13 (1·14)	0·3
Respiratory disease (460–519, 786)	241	−1·0	55·5	0·98 (0·13)	0·9
Other known cause	997	−22·9	228·5	0·90 (0·06)	0·1
Unspecified cause, not breast cancer	701	7·8	159·4	1·05 (0·08)	0·5
By years since randomisation (and, for deaths, mean year of randomisation)					
0–4 (1976)	756	7·4	176·4	1·04 (0·08)	0·6
5–14 (1975)	1513	37·7	348·4	1·11 (0·06)	0·05
≥15 (1970)	1397	46·9	304·8	1·17 (0·06)	0·01
By age at randomisation					
<50 years	554	27·4	129·6	1·24 (0·10)	0·02
≥50 years	3112	64·4	699·8	1·10 (0·04)	0·02
Total non-breast-cancer deaths¶	3666	91·8	829·4	1·12 (0·04)	0·001

Clarke et al, Lancet 2005

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

*Early Breast Cancer Trialists' Collaborative Group (EBCTCG)**

- Data on 42.000 patients:

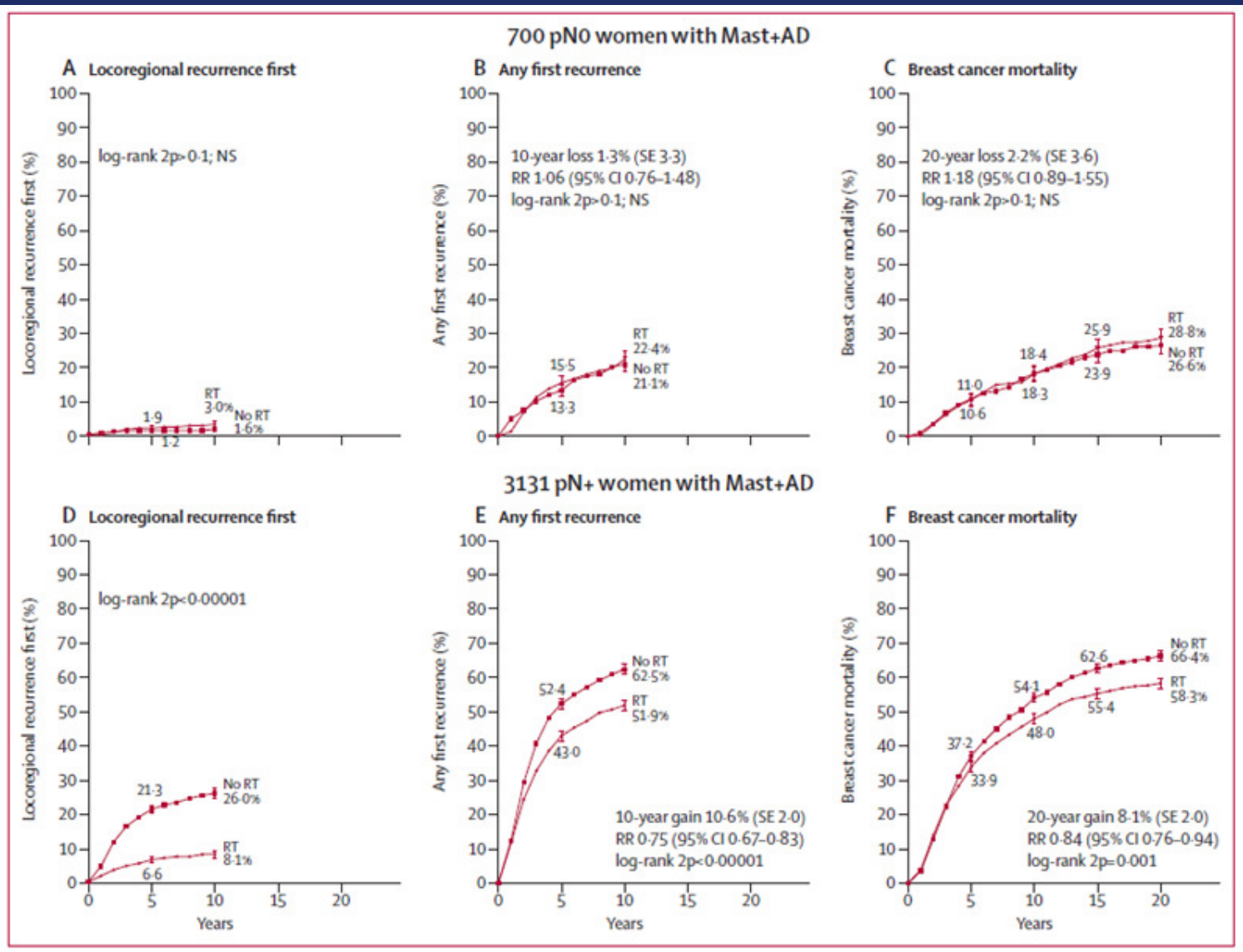
- RT *vs* no RT: 23.500;
- More *vs* less surgery: 9300;
- More surgery *vs* RT: 9300.

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.

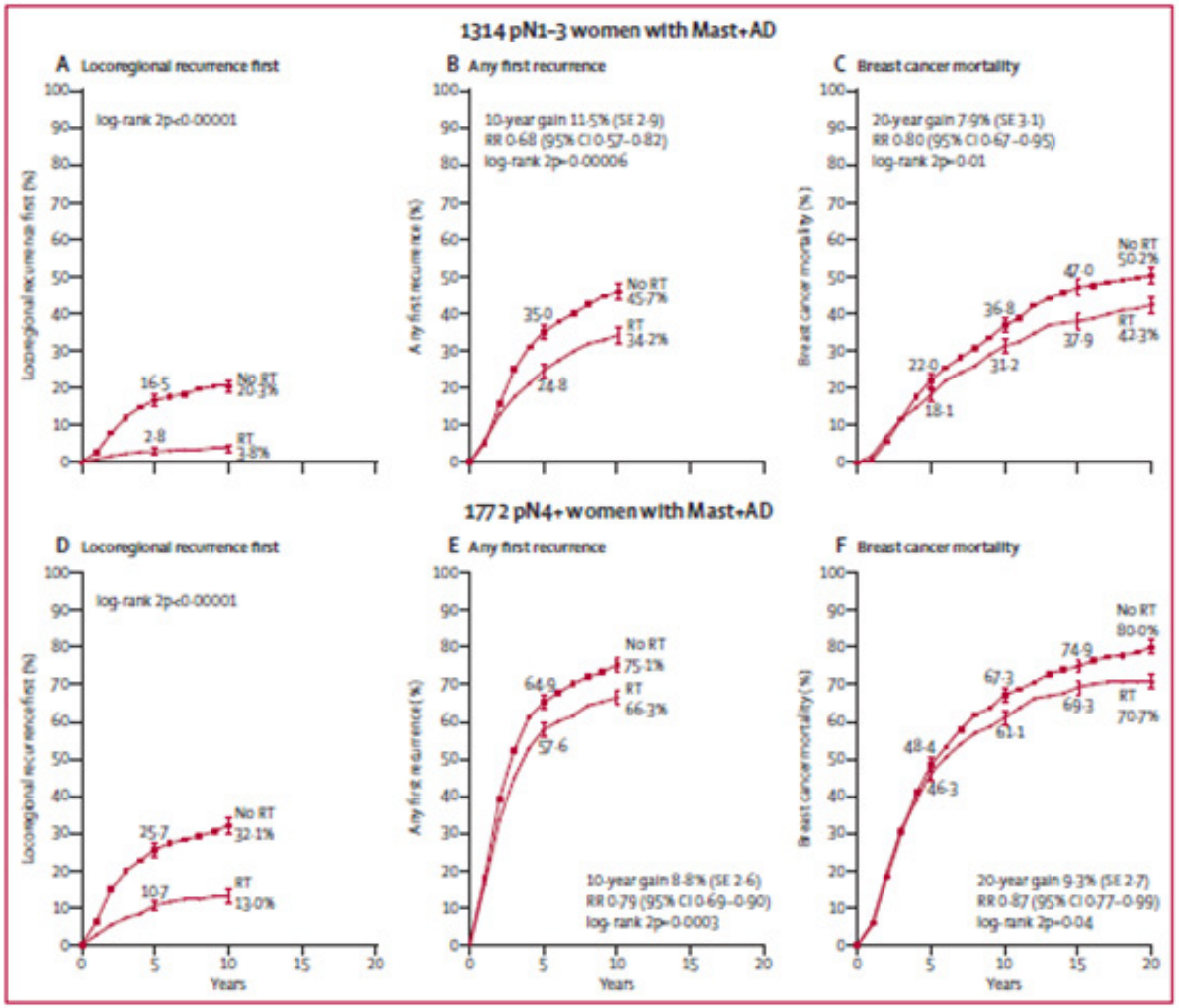
Also known as: the 1 in 4 rule

Clarke et al, Lancet 2005

EBCTCG, Lancet 2014: PMRT improves survival in pN+ patients



EBCTCG, Lancet 2014: PMRT improves DSS in both pN1 and pN2 patients



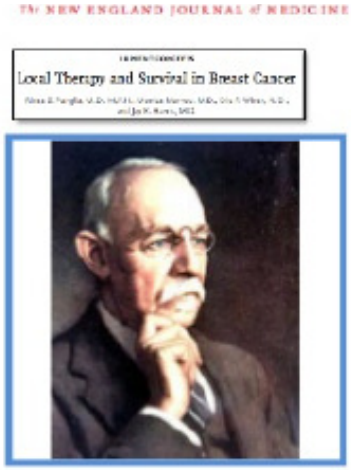
LRR:
pN1: RR 0.68;
pN2: RR 0.79

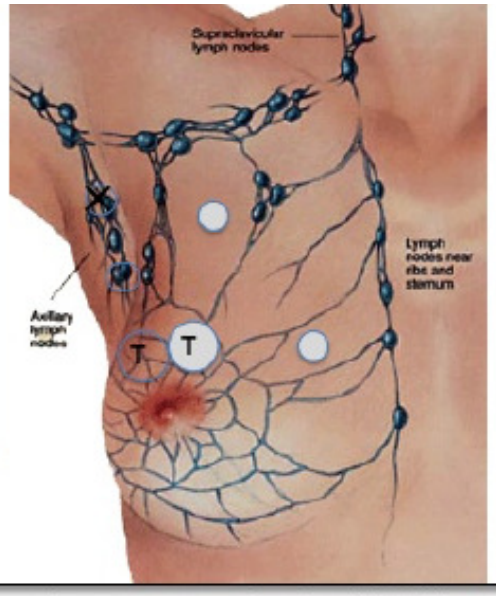
DSS:
pN1: RR 0.80;
pN2: RR 0.87

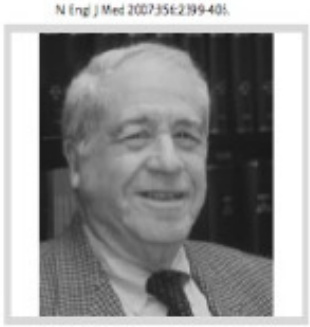
OS:
pN1: RR 0.89 (NS);
pN2: RR 0.78

1994

Halsted vs Fisher:
Is breast cancer a locoregional disease or a systemic disease ?







A third hypothesis « the spectrum thesis » (1994) considers breast cancer to be a heterogeneous disease that can be thought of as a spectrum of proclivities (tendencies) extending from a disease that remains local throughout its course to one that is systemic when first detectable

Slide courtesy Struikmans

Interaction systemic and locoregional treatments

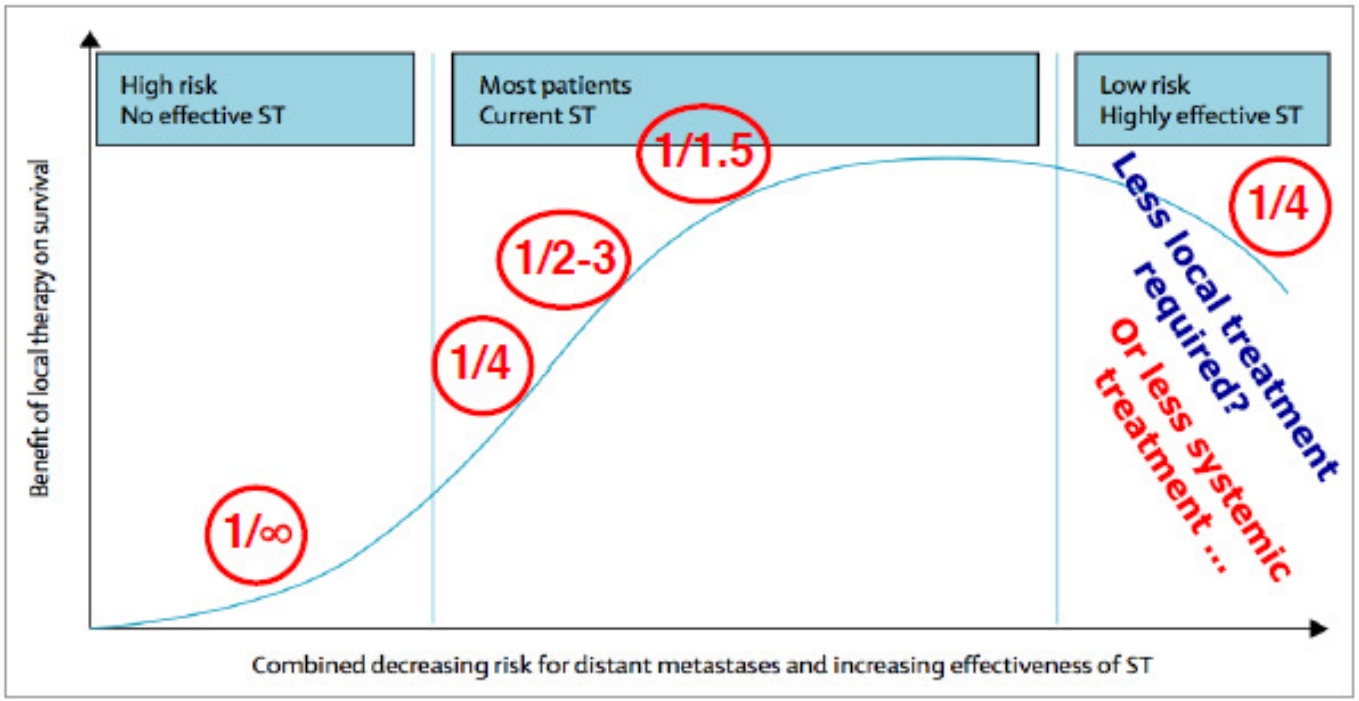


***Figure*: Combined hypothetical benefit of local tumour control on survival with increasing effectiveness of systemic therapy (ST) and decreasing risk of distant metastases of the primary tumour**

Poortmans P. Lancet. 2014 Jun 21;383(9935):2104-6.

Modified from Punglia et al, NEJM 2007

Summary on effect of PMRT on LR and OS

- EBCTCG analyses 1995:
  - RT reduces LR rate with factor 3; No effect on Overall Survival
- 1997 – 1999: Danish and Canadian trials:
  - OS benefit seen !
- EBCTCG 2000:
  - RT reduces LR rate with factor 3-4; No effect in OS, but effect on DSS. More non-breast cancer deaths in RT arm
- EBCTCG 2005:
  - 1 in 4 rule: prevention of 4 LR, prevents 1 death. Excess deaths largely due to heart toxicity & lung cancer !
- EBCTCG 2014:
  - OS benefit in case of RT after MRM in pN+ disease

Indications for PMRT i.e. thoracic wall and periclavicular region

- pT3N1, pT4N*any*
- pN2
- Irradically removed tumor
- Discussion on:
  - pT1-2N1
  - pT1-2N0
  - Pro: small OS benefit in EBCTCG analyses, and 3 recent trials analyzing regional RT (see further)
  - Contra: absolute OS benefit probably small with contemporary chemotherapy; wait for results of SUPREMO trial

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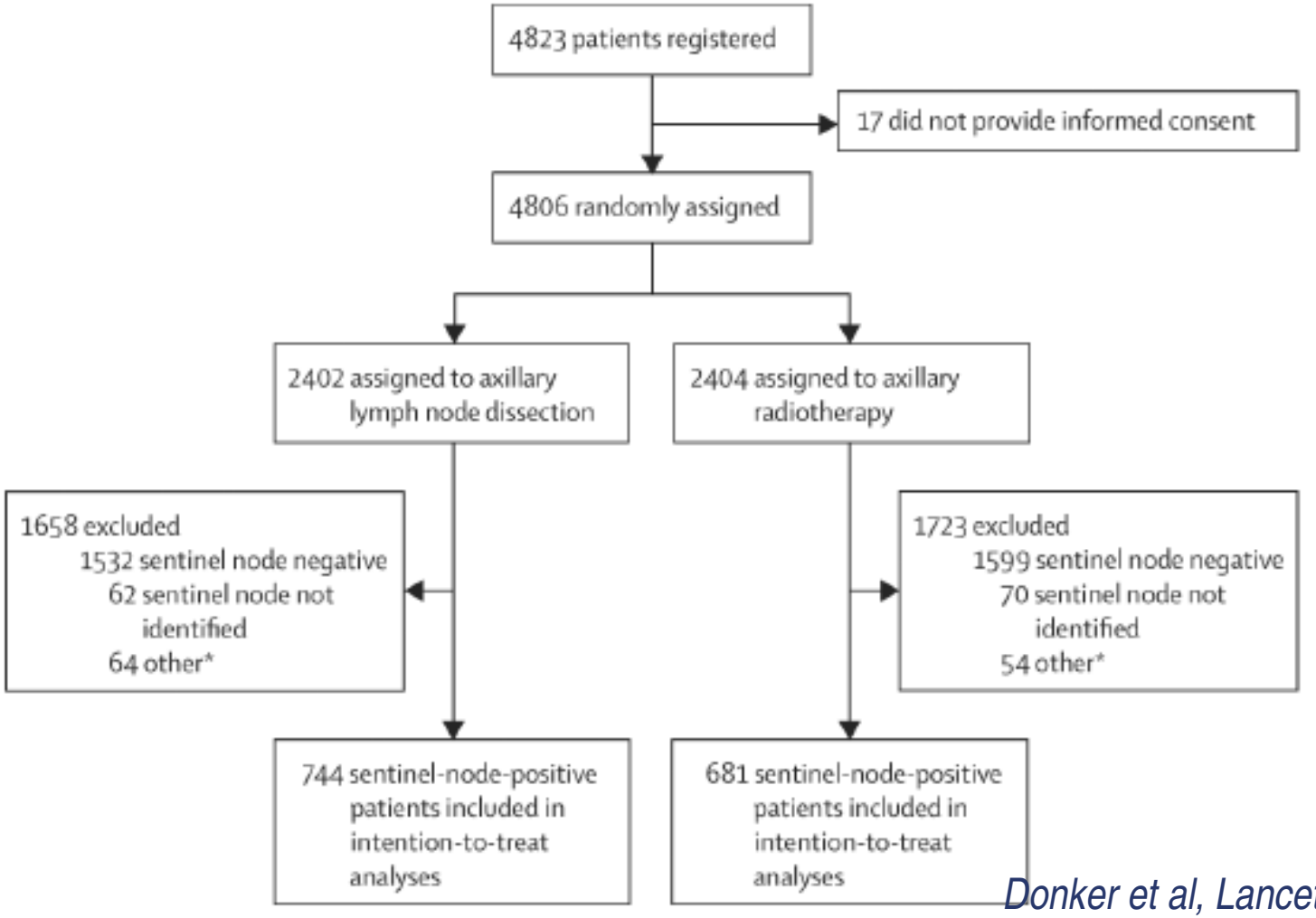
History of axillary treatment

- Until late nineties:
  - ALND was considered to be standard part of therapy in invasive breast carcinoma
- Late nineties: introduction of SN procedure:
  - ALND limited to patients with a positive SN
- Last decade: does axillary treatment influence OS ?
  - RT equally effective as ALND (AMAROS trial)
  - Is axillary treatment (ALND or RT) always necessary in case of a positive SN ?

AMAROS trial (EORTC 10981- 22023)



Donker et al, Lancet Oncol 2014

AMAROS trial (EORTC 10981- 22023)

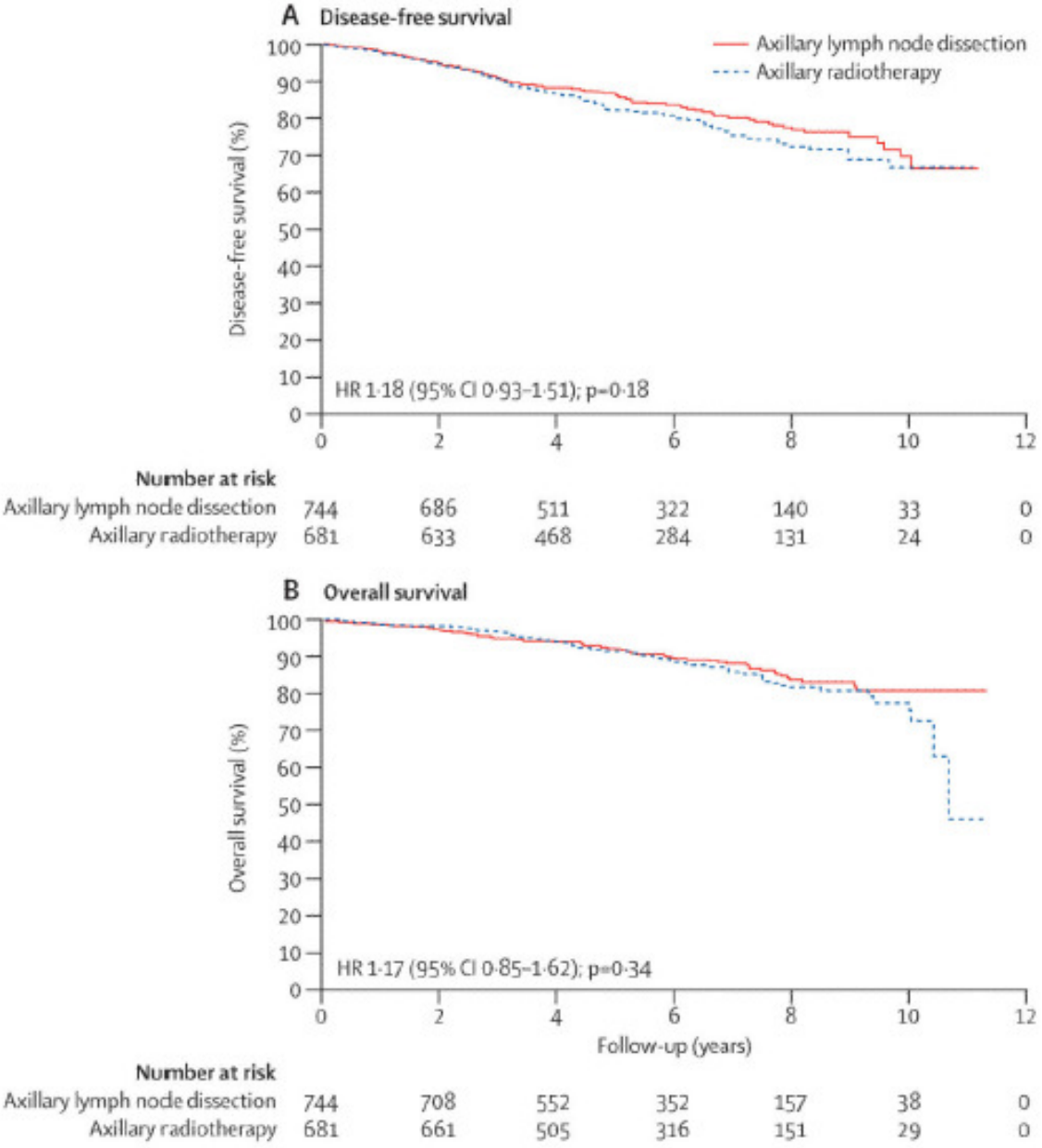
Lymphoedema

	Axillary lymph node dissection	Axillary radiotherapy	p value
Clinical sign of lymphoedema in the ipsilateral arm			
Baseline	3/655 (<1%)	0/586 (0%)	0.25
1 year	114/410 (28%)	62/410 (15%)	<0.0001
3 years	84/373 (23%)	47/341 (14%)	0.003
5 years	76/328 (23%)	31/286 (11%)	<0.0001
Arm circumference increase >10% of the ipsilateral upper or lower arm, or both			
Baseline	33/655 (5%)	24/586 (4%)	0.497
1 year	32/410 (8%)	24/410 (6%)	0.332
3 years	38/373 (10%)	22/341 (6%)	0.080
5 years	43/328 (13%)	16/286 (5%)	0.0009

Data are n/N (%), unless otherwise specified.

Donker et al, Lancet Oncol 2014

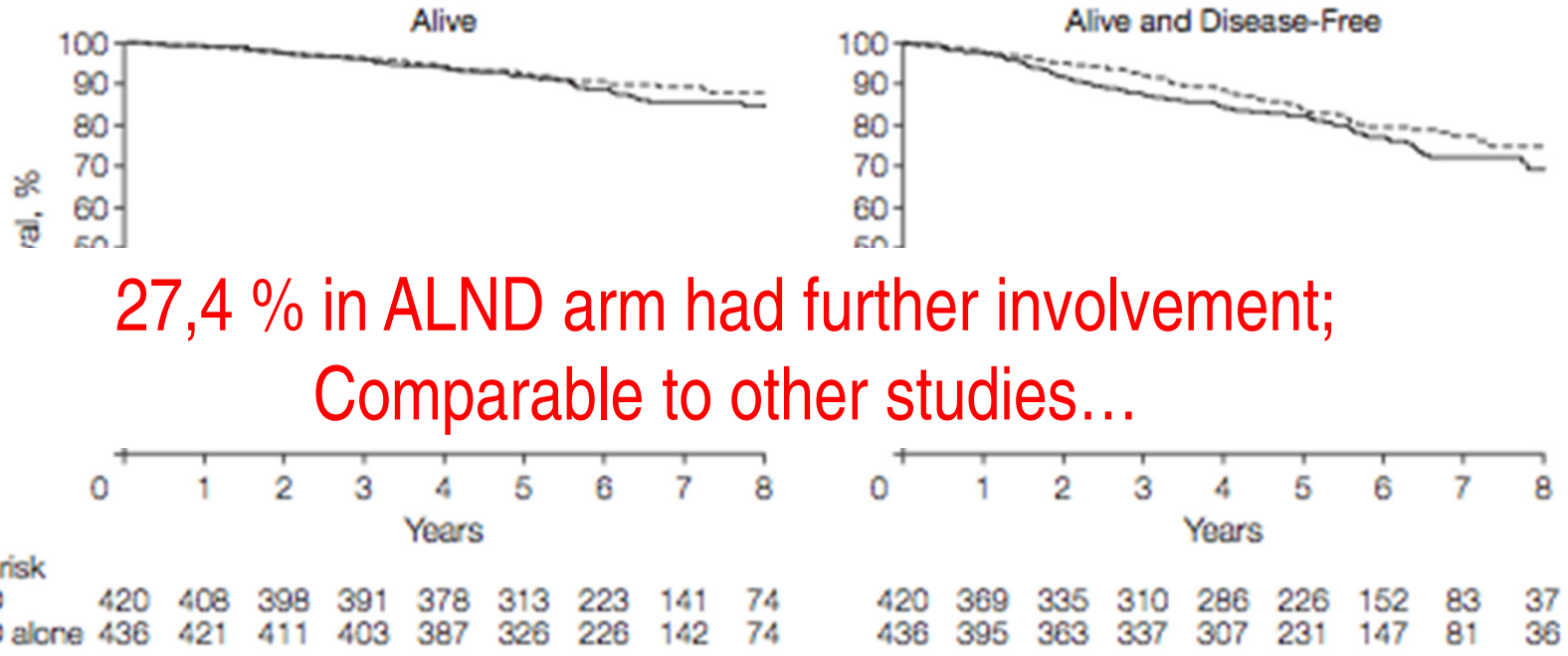
AMAROS trial



Donker et al, Lancet Oncol 2014

Surgical trials ACOSOG Z11: DFS and OS

Figure 2. Survival of the ALND Group Compared With SLND-Alone Group



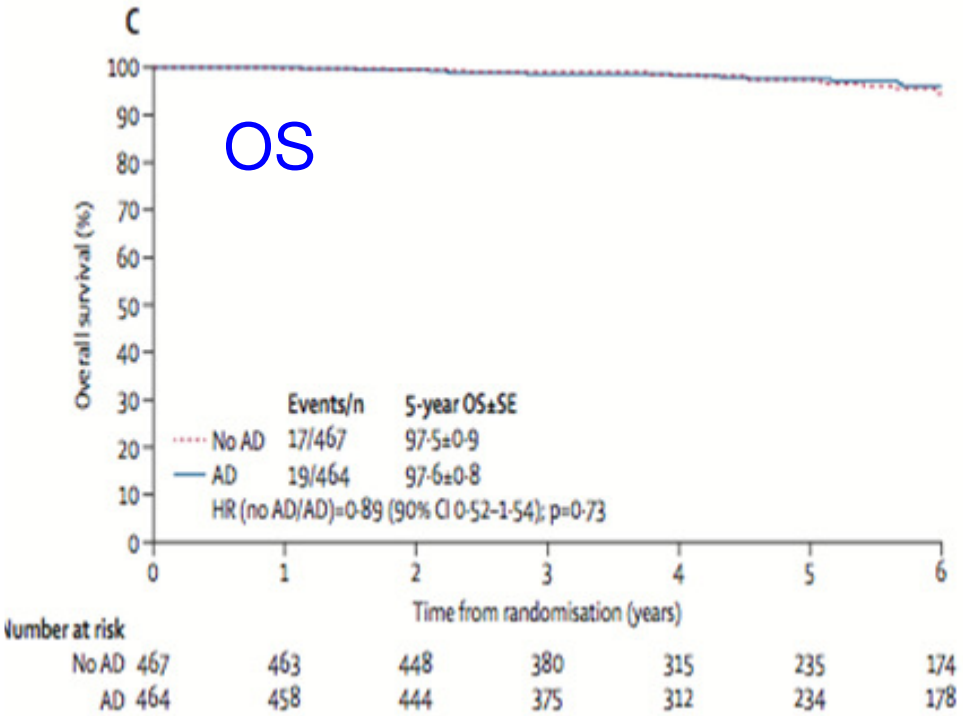
27,4 % in ALND arm had further involvement;
Comparable to other studies…

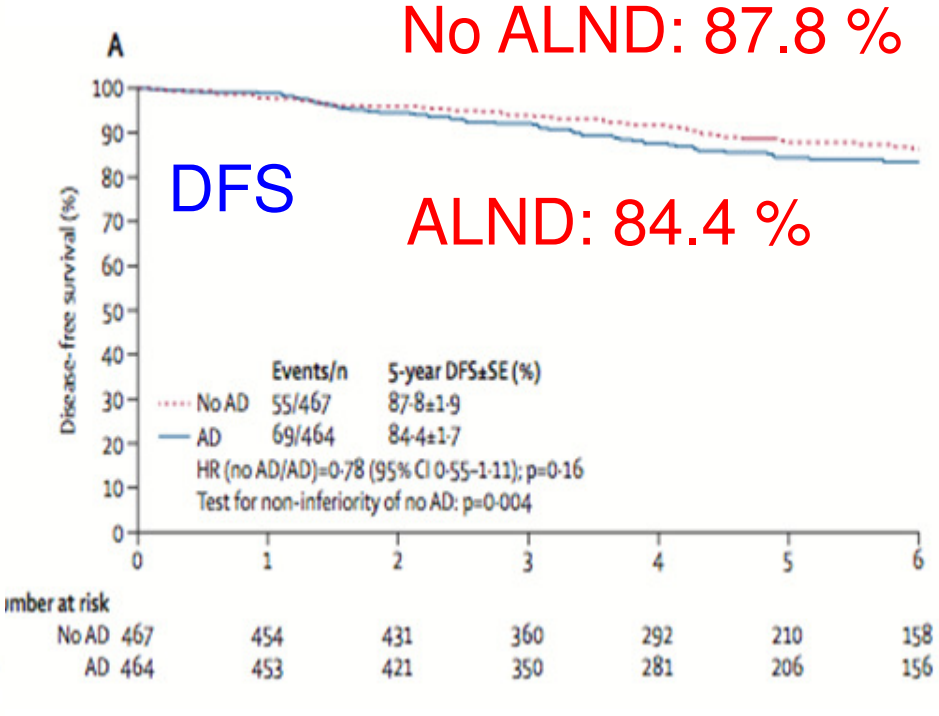
ALND indicates axillary lymph node dissection; SLND, sentinel lymph node dissection.

Giuliano AE. JAMA 2011;305:569-75

Axillary dissection versus no axillary dissection in patients with sentinel-node micrometastases (IBCSG 23–01): a phase 3 randomised controlled trial

Galimberti et al, Lancet Oncology 2013 Apr;14(4):297-305





No effect on axillary recurrences; What about effect of regional RT on overall survival ?

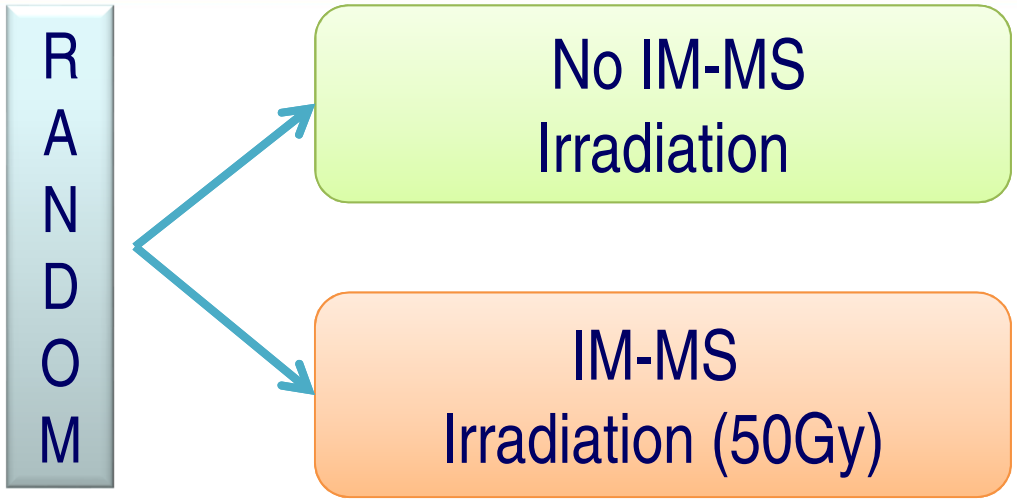
- Several recent studies comparing local RT only vs local AND regional RT:
  - MA 20 trial
  - Studies on RT of Internal Mammary Chain
    - EORTC RCT
    - French RCT
    - Danish study
  - EBCTCG meta analysis

MA -20 trial, ASCO 2011, Whelan et al.

- 1832 pts with high risk node negative or node positive breast cancer, randomized between breast RT only or full locoregional RT, 2000-2007.
- Majority pN1, majority received adjuvant systemic treatment
- Median f-up 62 months
- DFS: 89.7% vs 84.0% , p = 0.003
- OS: 92.3% vs 90.7%, p = 0.07

EORTC phase III trial 22922/10925: (NCT number NCT00002851) Study Design

pN+ axillary nodes
or pN- central
or medial tumour



- July 1996 – January 2004, 4004 patients randomized
- 46 institutions, 13 countries
- Median follow-up: 10.9 years

Poortmans, Struikmans et al, EBCC 2014, Glasgow

Most important findings EORTC - IMC trial

Primary endpoint = Overall Survival at 10 yr:

- Increased with IM-MS RT from 80.7% to 82.3%
- HR 0.87; p=0.056; after correction of stratification factors: p=0.0496

Secondary endpoints = MFS; cause of death at 10 yr:

- MFS: increased from 75.0% to 78.0% (HR 0.86; p=0.02)
- Cause of death: just reduction of breast cancer related deaths; no increased lethal toxicity (L=R)

EBCC 9 European Breast Cancer Conference

19-21 March 2014 GLASGOW, SCOTLAND

DBCG-IMN

Effect of radiotherapy to the internal mammary nodes in patients treated for early node-positive breast cancer:

Results from the DBCG-IMN study

Lise B J Thorsen, M Berg, H J Brodersen, H Danø, I Jensen,

J Overgaard, M Overgaard, A N Pedersen, S J Zimmermann,
B V Offersen

On behalf of the DBCG Radiotherapy Committee

CIRRO

DBCG

EORTC

www.ecco-org.eu

Results Danish study

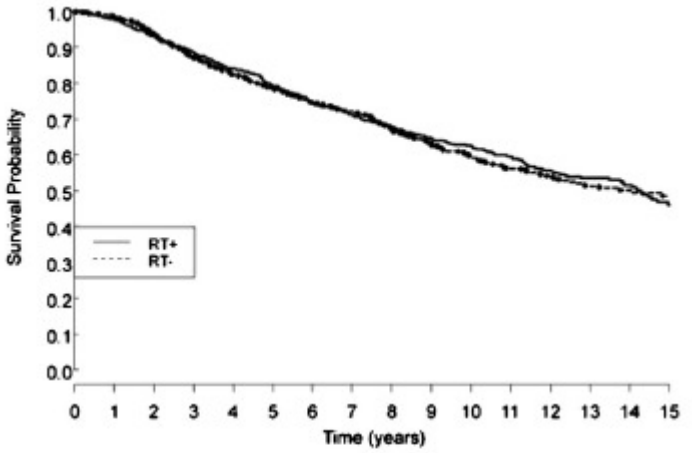
- Prospective study 2003-2007; pN1, < 70 yr.
  - 1485 patients with right sided breast cancer **with IMC RT**
  - 1586 patients with left sided breast cancer **without IMC RT**
  - 100 % RT axilla level 2-4; of whom 20% also RT axilla level 1.

- Results comparable to EORTC IMC trial:
  - Small benefit in 10 yr OS: 67.8% -> 72.2%, p = 0.03
  - Small benefit in 10 yr DMF : 71.3% -> 73.1; NS

- Difference: EORTC trial: benefit mainly in pN0 patients; Danish study: benefit mainly in pN2 patients

French trial IMC RT

- 1334 pts pN+ or medially located breast cancer
- RT thoracic wall and supraclavicular nodes, randomisation between RT IMC yes/ no
- 10 yr OS 59.3% vs. 62.6%, however NS



At Risk																
RT +	672	650	598	544	501	459	416	379	352	332	304	263	196	140	101	49
RT -	662	635	589	523	483	444	408	380	346	314	276	222	168	116	72	48
Events																
RT +	-	14	45	73	101	130	157	174	192	209	219	233	249	256	260	269
RT -	-	10	40	81	109	131	152	166	191	214	231	245	253	260	262	264

Fig. 2. Overall 10-year survival according to the treatment group.

Hennequin et al: Int J Radiat Oncol Biol Phys 2013

Studies on regional RT

- These studies:
  - 3 studies IMC RT yes/no (EORTC, French, Danish)
  - 1 RCT local RT vs locoregional RT (MA 20, Whelan)
  - Meta-analysis locoregional RT vs no RT (Darby, EBCTCG)

  ….are in line with the hypothesis that microscopic regional disease might be a source for distant metastases

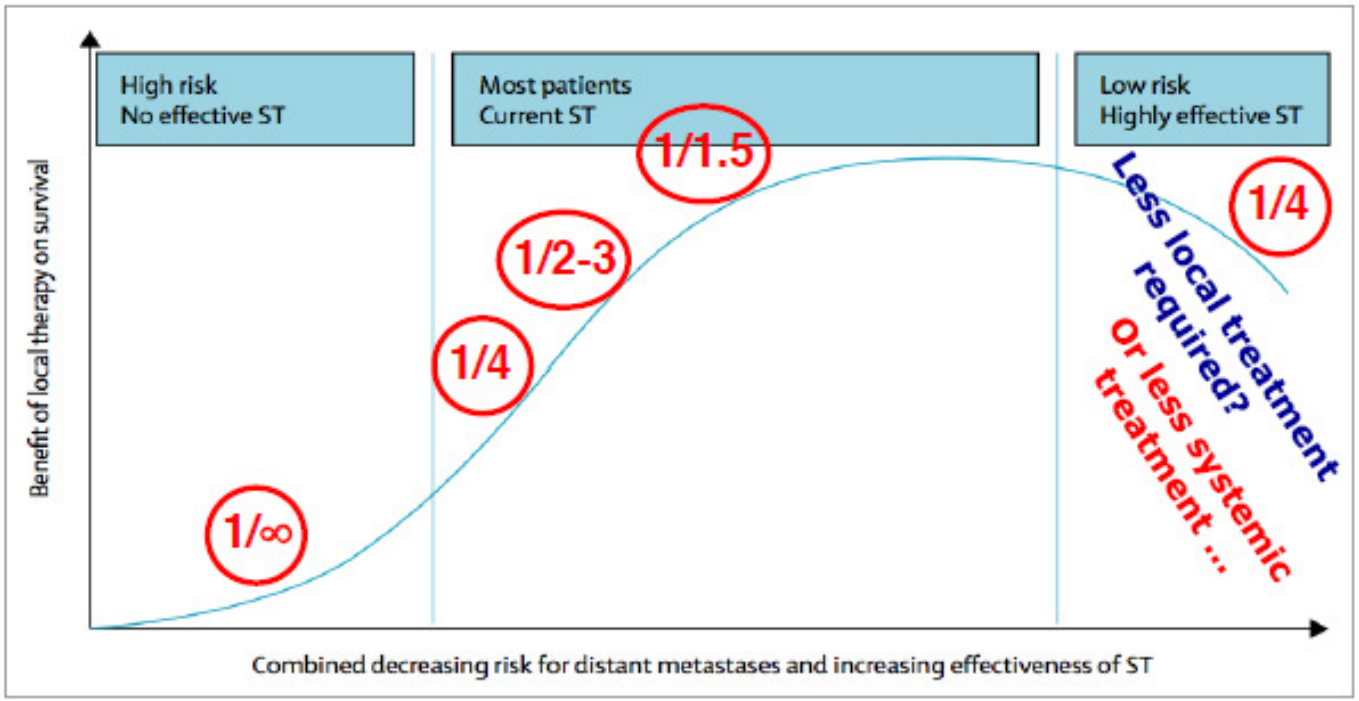
- Effect of RT:
  - Small benefit with respect to DM
  - Small benefit with respect to OS
  - However, we cannot discriminate between the effect of RT axilla, periclav or IMC.

Considerations pro and con regional RT

- Against regional RT in case of pN1:
  - In general, the recurrence rates are probably lower nowadays, leading to a smaller absolute benefit
  - F-up of IMC trial too short for cardiac toxicity
  - No discrimination possible between effect of RT axilla, periclav or IMC

- In favour of regional RT in case of pN1:
  - It is likely that effect RT is underestimated, since nowadays we use improved techniques: less geographic miss, less toxicity
  - Due to better systemic treatment more effect on OS expected

Interaction systemic and locoregional treatments



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Breast conserving therapy

- First report 1924 – Keynes: Can't we avoid mutilation ?

  High dose RT after wide excision, using internal RT techniques

- Early sixties:
- 3 French groups focused on BCT
- In 1960: first prospective trial in London (Hayward et al)
- Publication in JAMA 1967, Vera Peters (Canada): "wedge resection and irradiation, an effective treatment in early breast cancer".
- Seventies: IGR, Paris (Sarrazin) and Milano (Veronesi)

- Eigthies: 3 big trials started: NSABP-06 & EORTC 10801 & DBCG 82TM

TWENTY-YEAR FOLLOW-UP OF A RANDOMIZED TRIAL COMPARING TOTAL MASTECTOMY, LUMPECTOMY, AND LUMPECTOMY PLUS IRRADIATION FOR THE TREATMENT OF INVASIVE BREAST CANCER

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

N Engl J Med, Vol. 347, No. 16 · October 17, 2002 ·

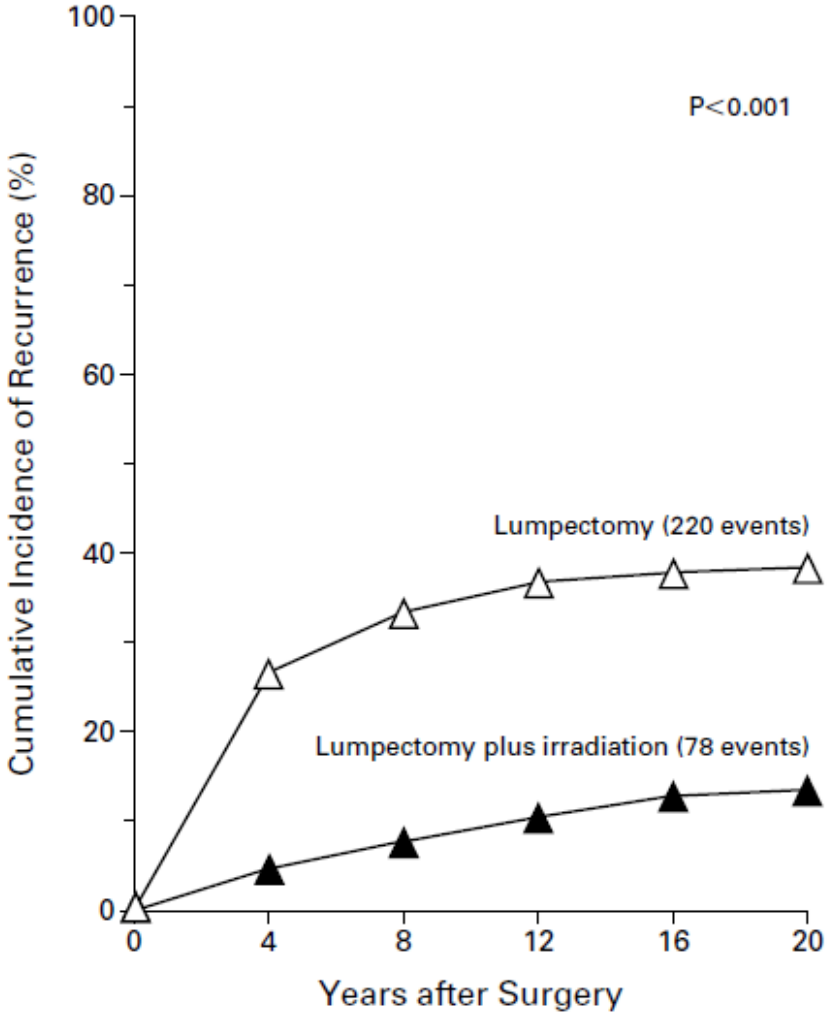
TABLE 1. DISTRIBUTION OF PATIENTS AND DURATION OF FOLLOW-UP AMONG THE TREATMENT GROUPS.*

VARIABLE	TOTAL MASTECTOMY	LUMPECTOMY ALONE	LUMPECTOMY PLUS IRRADIATION
Enrolled (no.)	713	719	731
No follow-up data	21	20	17
Excluded (no.)	103	65	86
Refused assigned treatment	76	34	55
Ineligible	26	28	27
Unknown nodal status	1	3	4
Included in analysis of total mastectomy vs. lumpectomy with or without irradiation (no.)	589	634	628
Included in analysis of lumpectomy alone vs. lumpectomy plus irradiation (no.)	—	570	567
Time in study (yr)			
Mean	20.8	20.6	20.7
Range	17.9–25.6	17.9–25.6	17.9–25.7

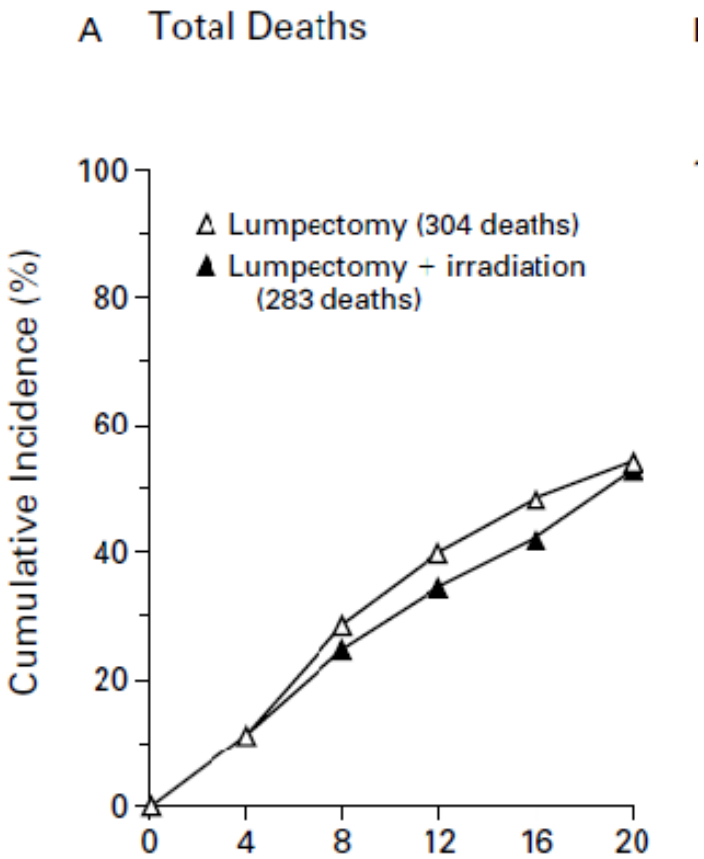
*Of the 1262 women who underwent lumpectomy with or without irradiation, 125 were not included because of the presence of tumor at the margins of the resected specimen.

- RCT started in 1976
- Inclusion of 1851 patients

Again:
RT reduces LR with factor 3-4



Again:
No OS benefit in this early trial

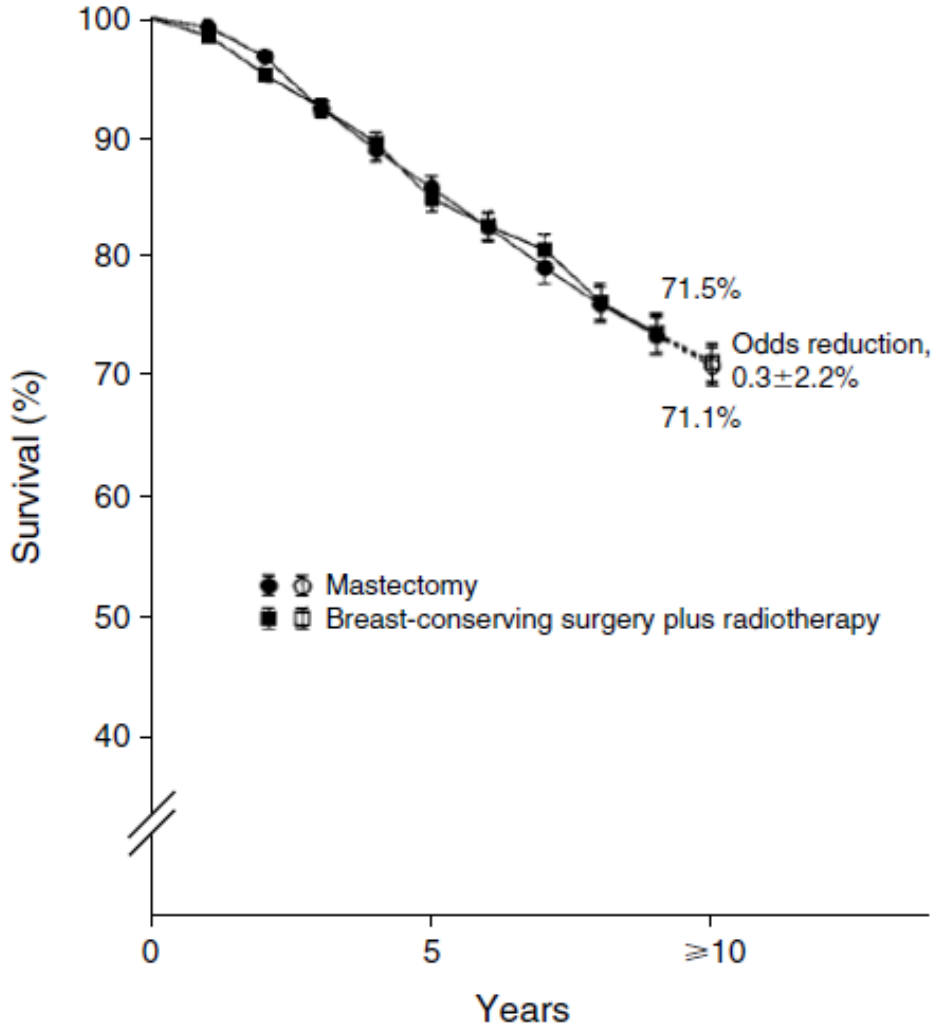


Fisher et al, NEJM 2002

Percentage breast recurrences with or without whole breast irradiation

	Years follow-up	Without RT*	With RT*	Hazard Ratio
NSABP B-06 Fisher et al 1995; geen boost	12	35%	9%	4.1
Scottish Cancer Trials : met boost Forrest et al 1996	6	24%	6%	4.2
Uppsala-Orebro Geen boost; liljegren et al 1999	10	24%	8.5%	3.1
Ontario: boost ? Clark et al 1996	8	35%	11%	4.0
Milan 3 Met Boost Veronesi et al 2001	9	24%	6%	4.5

OS of Lumpectomy + RT (BCT) equals MRM



EBCTCG analyses, NEJM 1995

MRM vs BCT

10-year results EORTC 10801 and DBCG 82 TM

	Treatment in fact given		
End-point	BCT	MRM	p-value
	% (95% confidence intervals)		
Overall survival	67 (64-71)	67 (64-70)	0.96
Distant recurrence-free	66 (62-69)	68 (65-71)	0.38
Local recurrence	10 (8-13)	9 (8-12)	0.96

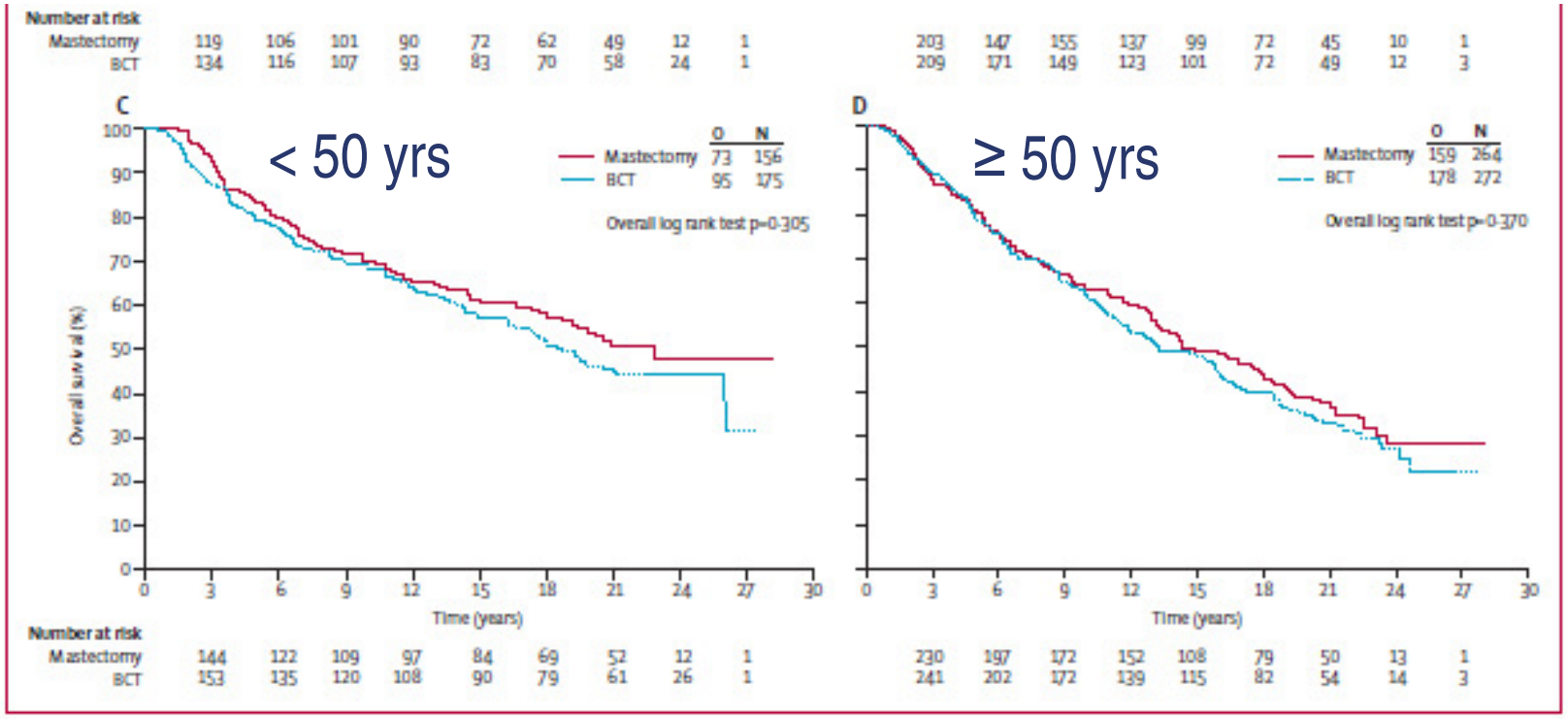
Voogd et al, J Clin Oncol 2001

Breast conserving therapy versus mastectomy for stage I–II breast cancer: 20 year follow-up of the EORTC 10801 phase 3 randomised trial

Saskia Litière, Gustavo Werutsky, Ian S Fentiman, Emiel Rutgers, Marie-Rose Christiaens, Erik Van Limbergen, Margreet H A Baaijens, Jan Bogaerts, Harry Bartelink

Lancet Oncol 2012; 13: 412–19

No difference in OS



Accrual 1980-1986

N = 850

Boost no boost trial- EORTC-22881-10882
RCT: after 50 Gy WBRT: no boost vs 16 Gy boost

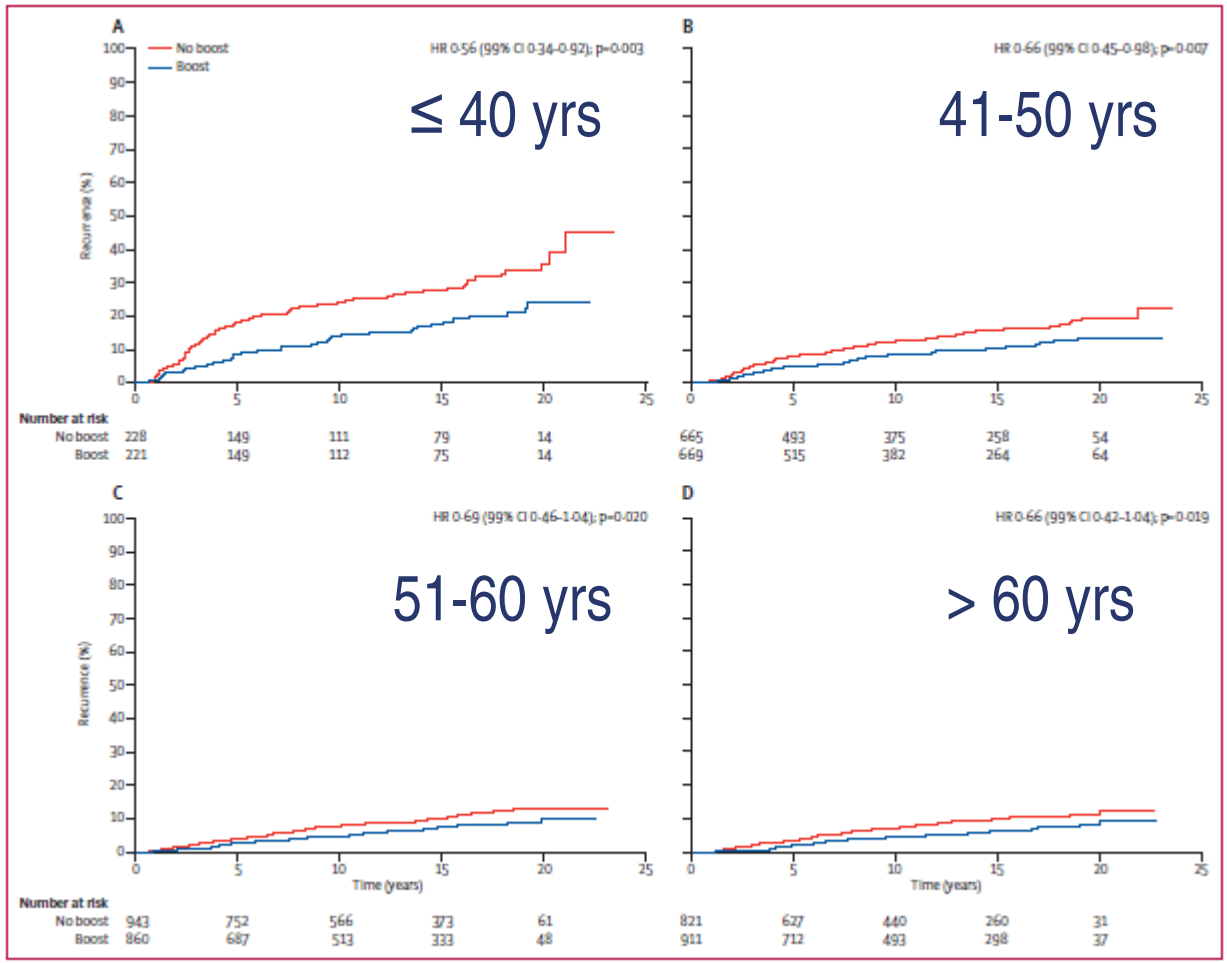


Figure 4: Cumulative incidence of ipsilateral breast tumour recurrence by age
For patients aged ≤40 years, 71 patients in the no boost group versus 42 in the boost group had recurrence (A); for patients aged 41–50 years, 108 versus 74 had recurrence (B); for patients aged 51–60 years, 100 versus 64 had recurrence (C); and for patients aged >60 years, 75 versus 57 had recurrence (D). HR=hazard ratio.

Accrual
1989-1996

N > 5000 pts

Bartelink et al, Lancet Oncol 2015

No effect on OS ?!?
Due to adequate salvage mastectomy ?

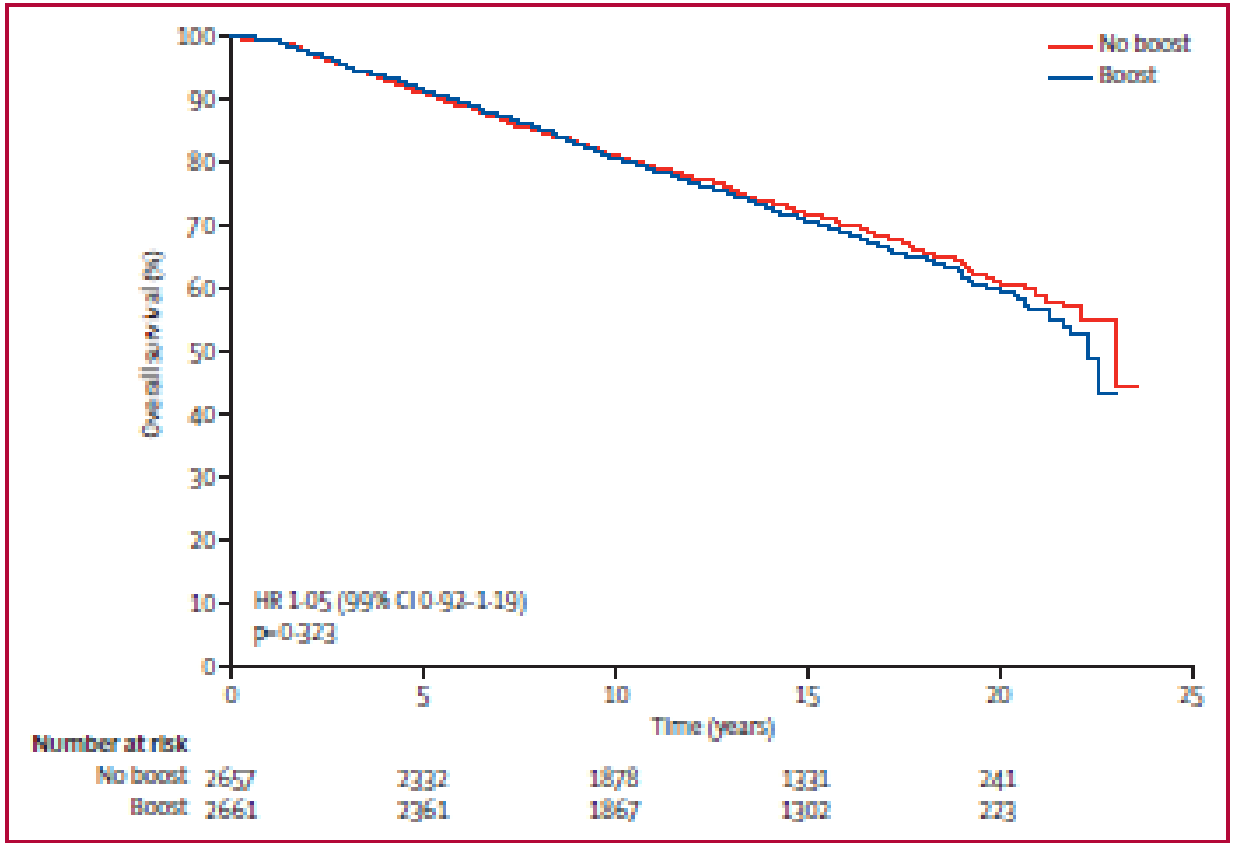


Figure 2: Overall survival
HR=hazard ratio.

Bartelink et al, Lancet Oncol 2015