HYPOFRACTIONATED RADIOTHERAPY IN CARCINOMA BREAST

PROF S.N.SENAPATI

DEPT.OF RADIOTHARAPY,

AH REGIONAL CANCER CENTRE,

CUTTACK,ODISSA

TNM Grouping and Staging

EBC

Stage I

T1*, N0, M0

Stage IIA

T0, N1, M0

T1*, N1, M0

T2, N0, M0

Stage IIB

T2, N1, M0

T3, N0, M0

LABC

- ***Stage IIIA***

  T0, N2, M0

  T1*, N2, M0

  T2, N2, M0

  T3, N1, M0

  T3, N2, M0

- ***Stage IIIB***

  T4, N0, M0

  T4, N1, M0

  T4, N2, M0

- ***Stage IIIC*****

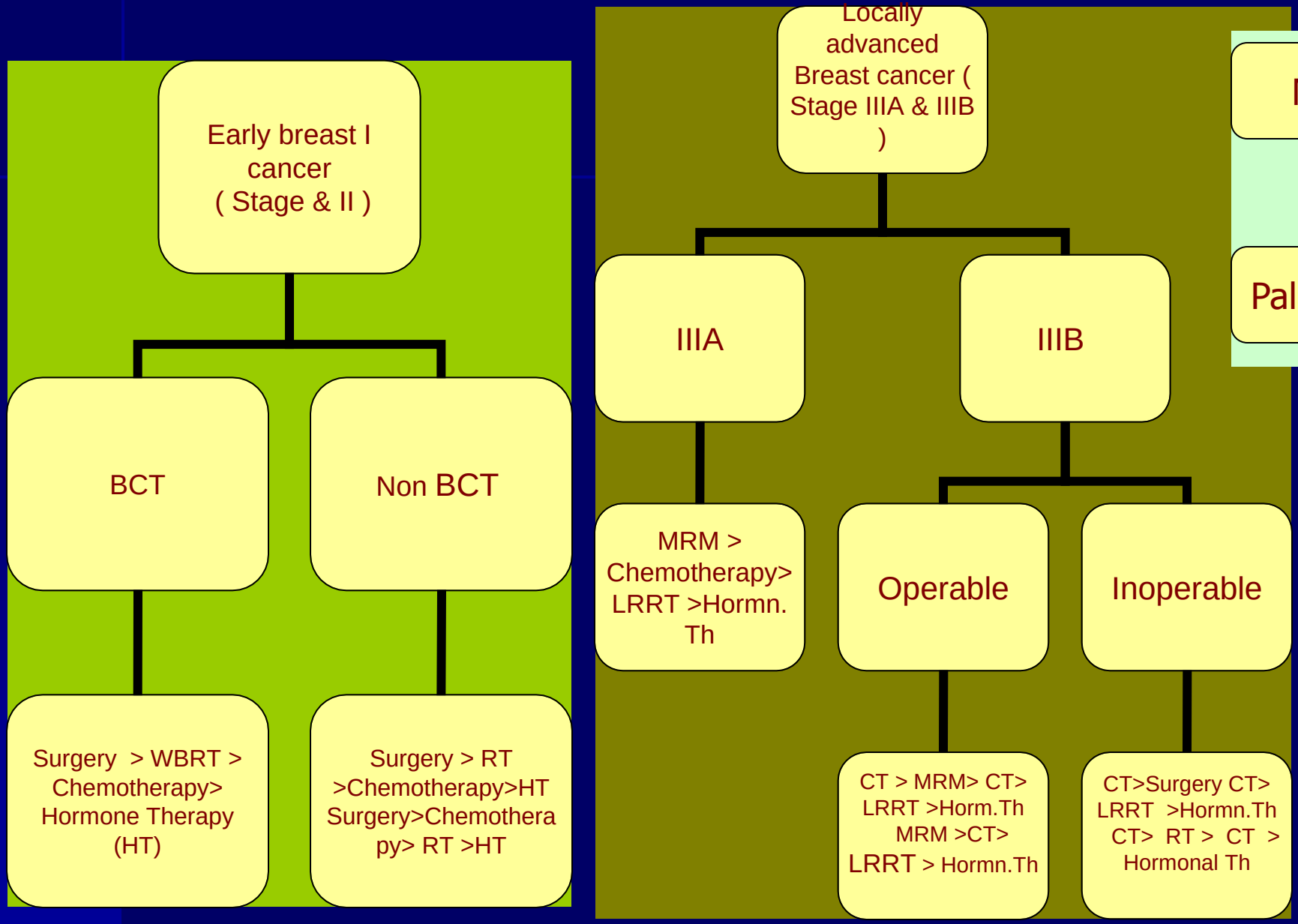
  Any T, N3, M0

MBC

Stage IV

Any T, Any N, M1

COMMON TREATMENT PROTOCOLS



ADJUVANT RT IN BREAST CANCER

In high-risk patients, rate of local relapse reduced from 35% to 10%.

NSABP-06 Study, Fisher B, NEJM 1995

In early stage patients, rate of local relapse reduced from 24% to 8.5% in BCS

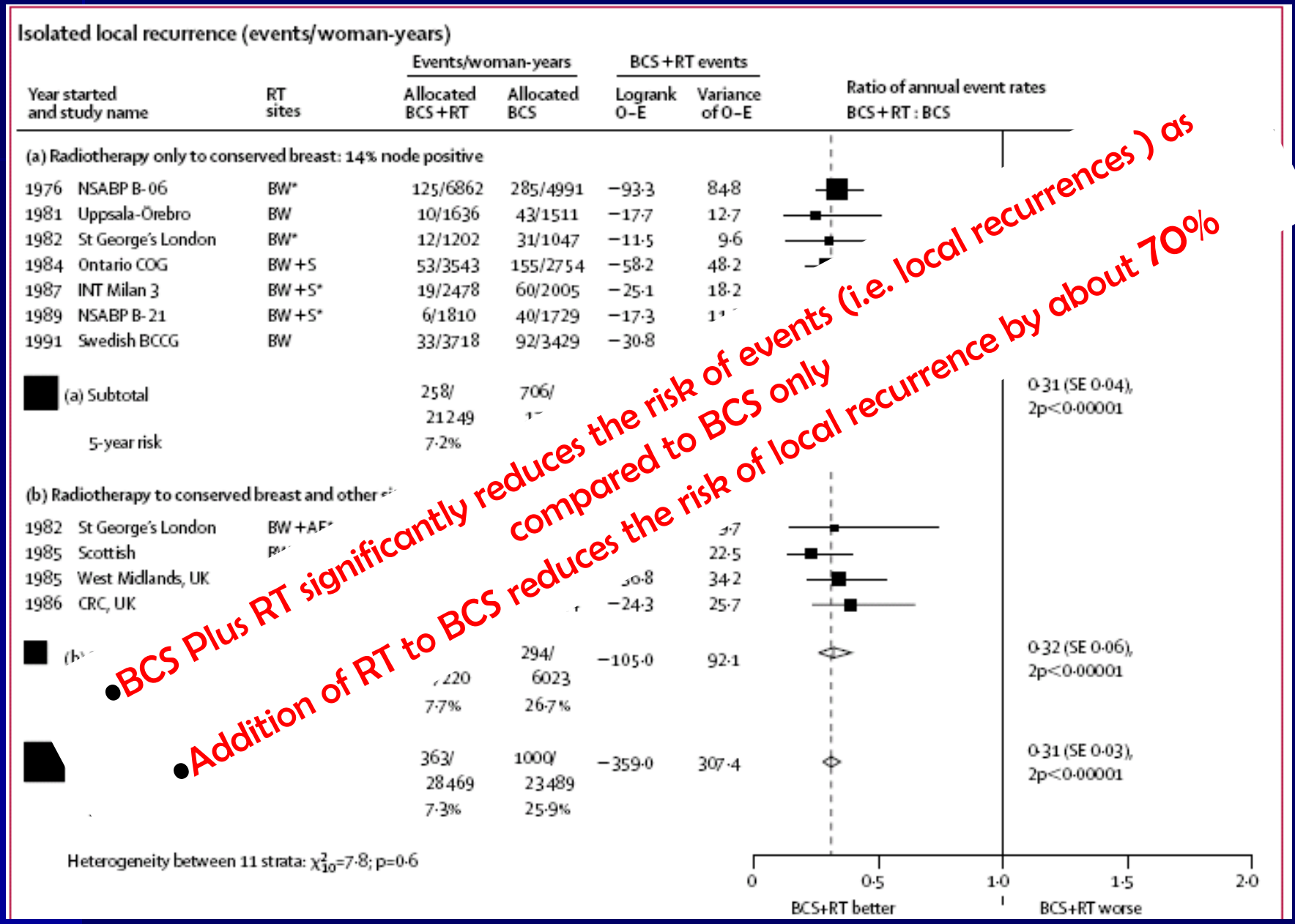
Liljegren G, JCO 1999

Early Breast Cancer Trialists' Collaborative Group (EBCTCG)

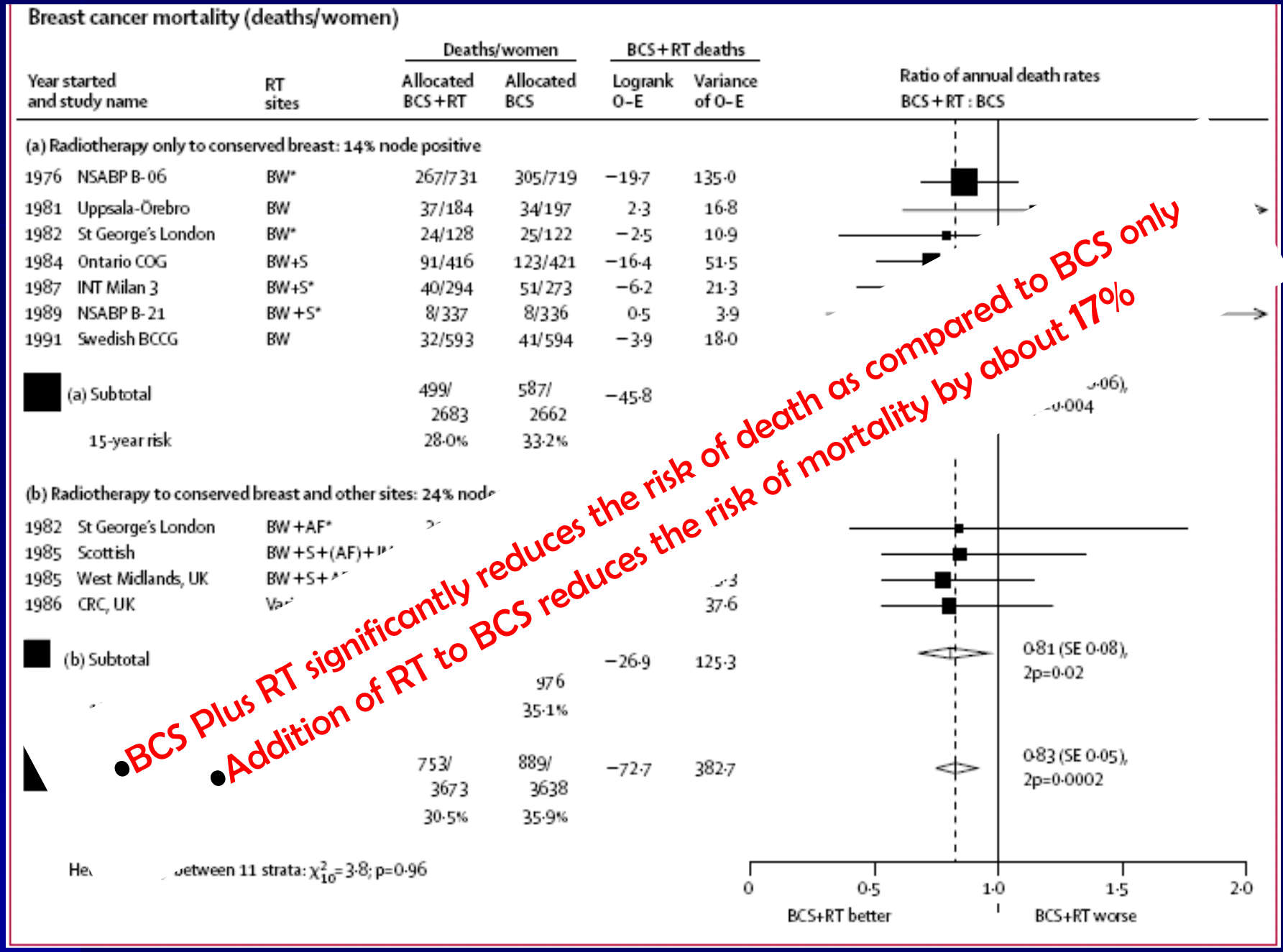
Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials

EBCTCG Lancet 2005; 366: 2087-2106

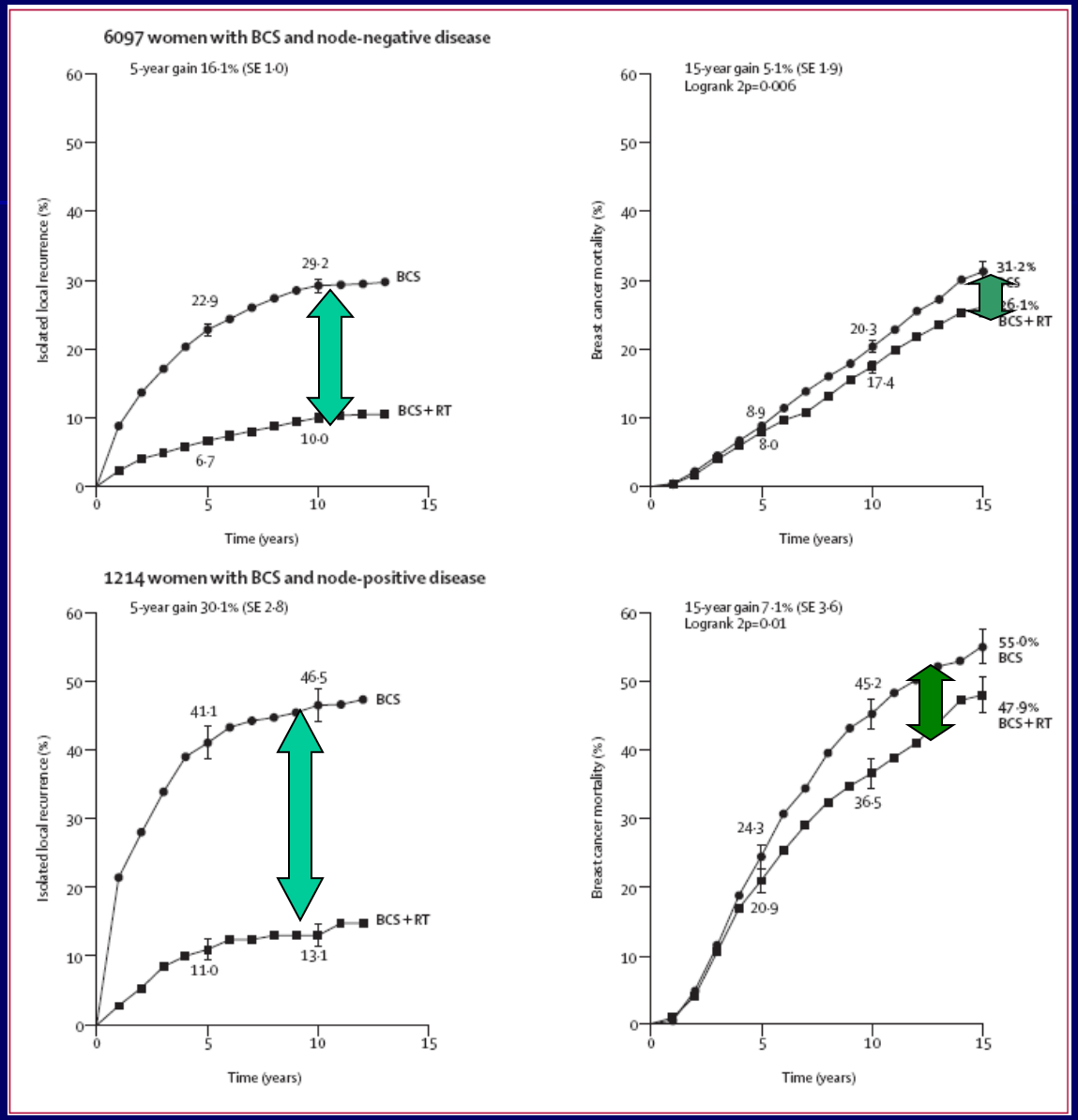
EBCTCG RESULTS



- BCS Plus RT significantly reduces the risk of events (i.e. local recurrences) as compared to BCS only
- Addition of RT to BCS reduces the risk of local recurrence by about 70%


Breast cancer mortality (deaths/women)
Deaths/women
BCS+RT deaths
Year started and study name
RT sites
Allocated BCS+RT
Allocated BCS
Logrank O–E
Variance of O–E
Ratio of annual death rates BCS+RT : BCS
(a) Radiotherapy only to conserved breast: 14% node positive
1976 NSABP B-06 BW* 267/731 305/719 −19·7 135·0
1981 Uppsala-Örebro BW 37/184 34/197 2·3 16·8
1982 St George's London BW* 24/128 25/122 −2·5 10·9
1984 Ontario COG BW+S 91/416 123/421 −16·4 51·5
1987 INT Milan 3 BW+S* 40/294 51/273 −6·2 21·3
1989 NSABP B-21 BW+S* 8/337 8/336 0·5 3·9
1991 Swedish BCCG BW 32/593 41/594 −3·9 18·0
(a) Subtotal 499/2683 587/2662 −45·8
15-year risk 28·0% 33·2%
(b) Radiotherapy to conserved breast and other sites: 24% nod
1982 St George's London BW+AF*
1985 Scottish BW+S+(AF)+
1985 West Midlands, UK BW+S+
1986 CRC, UK
37·6
(b) Subtotal −26·9 125·3
976
35·1%
753/3673 889/3638 −72·7 382·7
30·5% 35·9%
between 11 strata: χ^2_{10}=3·8; p=0·96
·06),
·004
0·81 (SE 0·08), 2p=0·02
0·83 (SE 0·05), 2p=0·0002
0
0·5
1·0
1·5
2·0
BCS+RT better
BCS+RT worse
•BCS Plus RT significantly reduces the risk of death as compared to BCS only
•Addition of RT to BCS reduces the risk of mortality by about 17%

Effect of RT after BCS on local recurrence and on breast cancer mortality—15-year probabilities. EBCTCG Meta-analysis



Lancet 2005;366:2087–2106,

POST OPERATIVE RT

Fletcher showed the benefits of postoperative LRRT in reducing the nodal recurrence from 20% to <5%, and the chest wall recurrence from 30% to <10%.

ECOG group also had shown the benefit of adjuvant postoperative RT for reducing the local and regional recurrence.

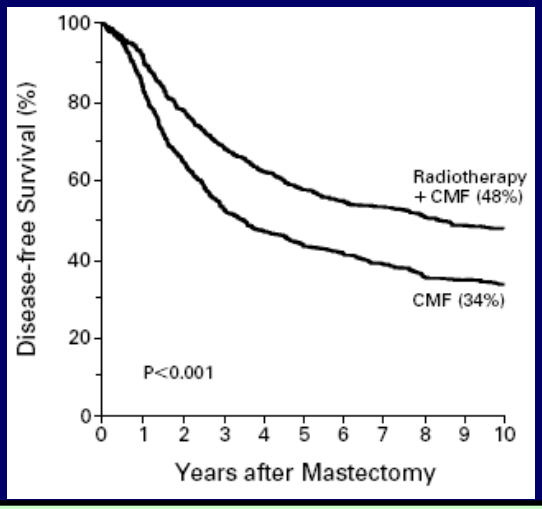
The NEW ENGLAND JOURNAL of MEDICINE

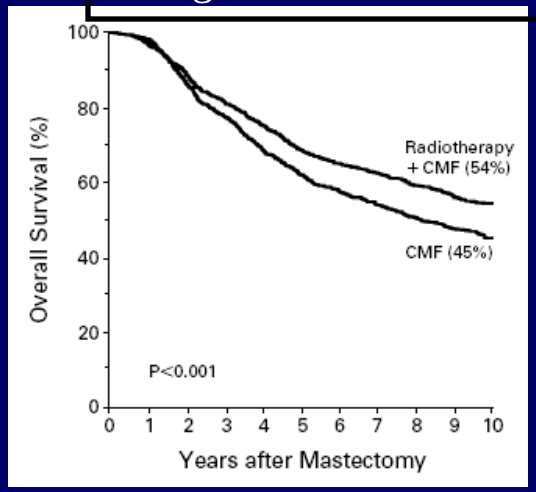
Volume 337:949-955 October 2, 1997 Number 14

PORT in High-Risk Premenopausal Women with Breast Cancer Who Receive Adjuvant

Overgaard et al. NEJM 1997 337:949

Chemotherapy





1789 patients, 1982 – 1989, premenopausal, node + or Tumor > 5cm, M0

Total mastectomy, level I + II (partly) + CMF +/- 50Gy/25fx (electrons + photons)

Sx in 79 departments, RT in mainly 6 centres

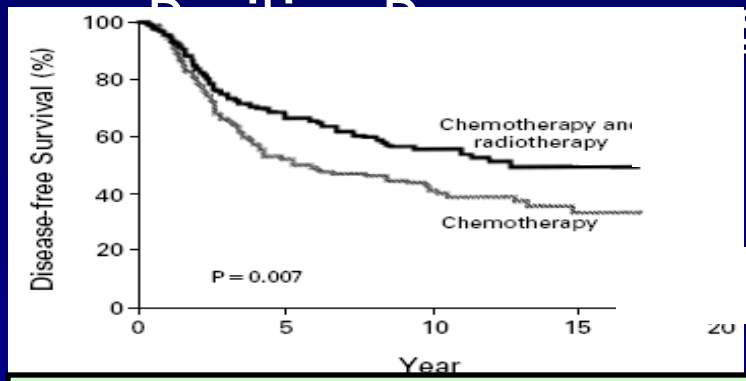
Conclusions: The addition of postoperative irradiation to mastectomy and adjuvant chemotherapy reduces locoregional recurrences and prolongs survival in high-risk premenopausal women with breast cancer.

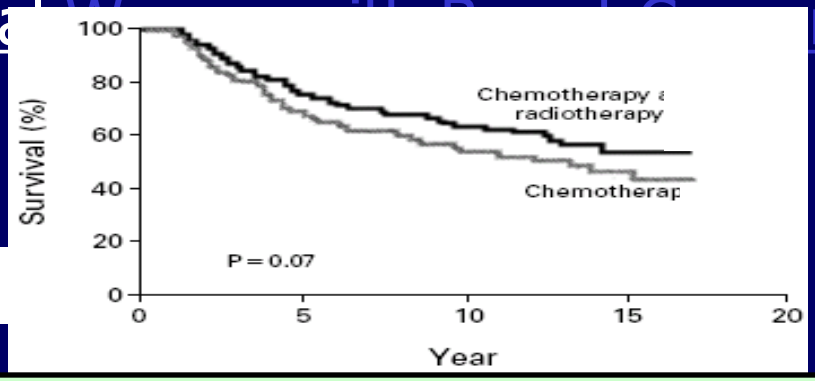
Ragaz et al. NEJM 1997 337:956

The NEW ENGLAND JOURNAL of MEDICINE

Volume 337:956-962 October 2, 1997 Number 14

Adjuvant Radiotherapy and Chemotherapy in Node-



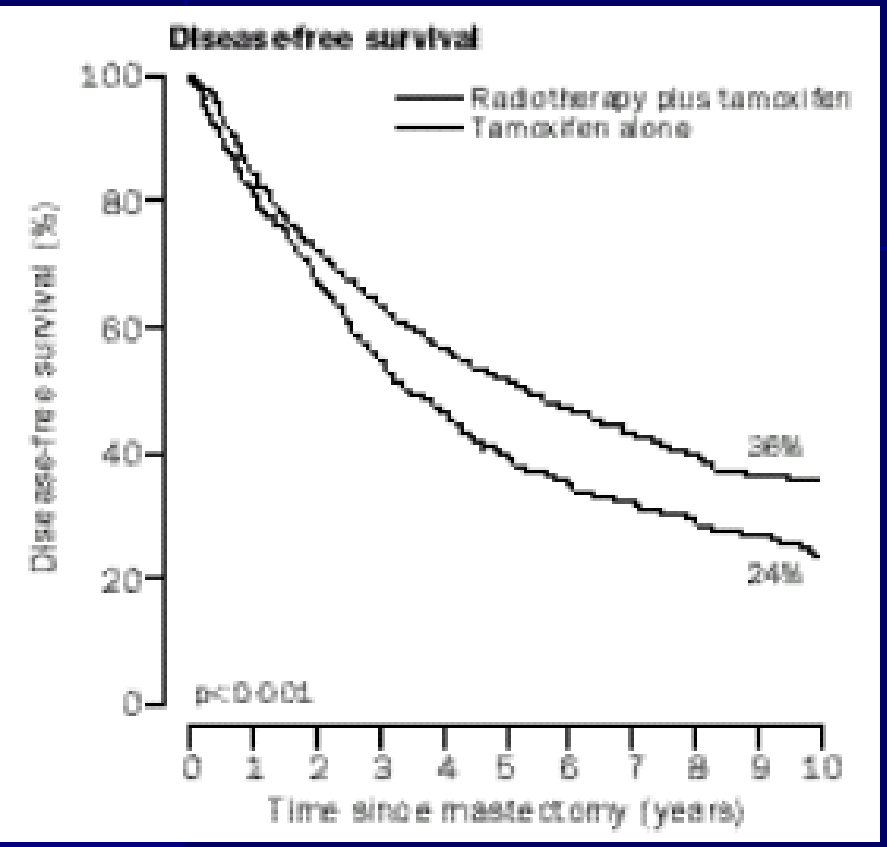


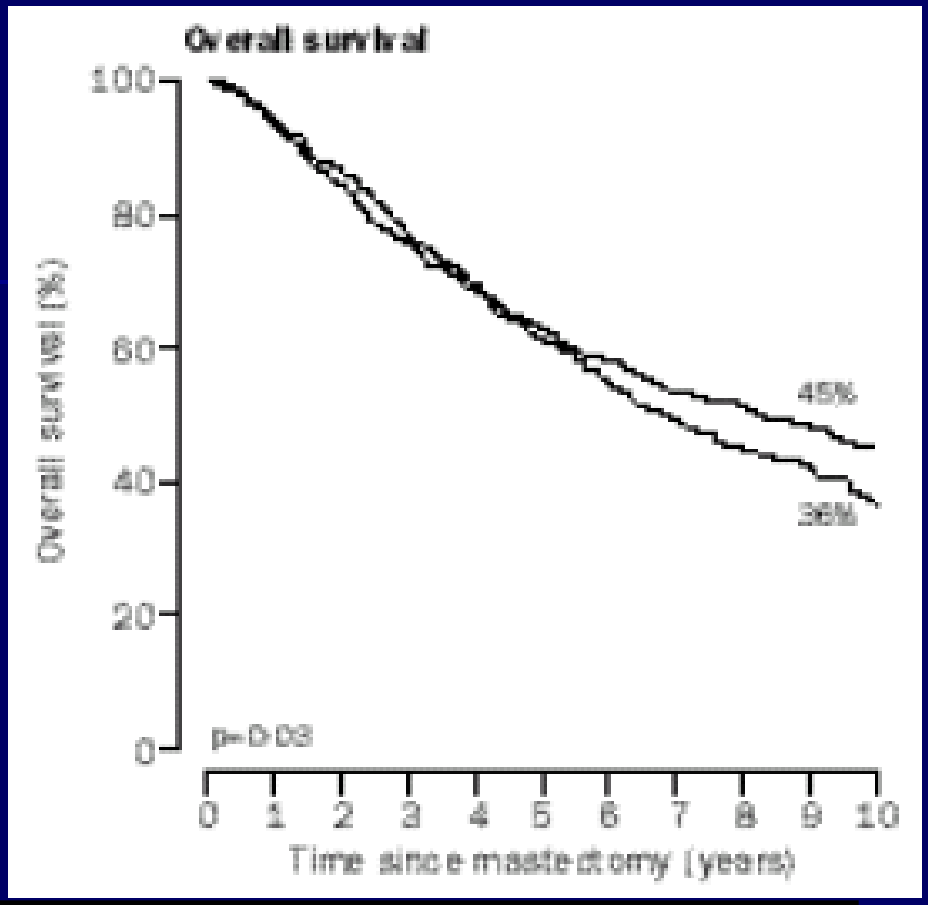
318 patients, 1979 – 1986, premenopausal, node +, any T, M0

MRM + CMF +/- 37.5Gy/16fx RT (photons) Sx by 'specialists', CT & RT in one centre

Conclusions: Radiotherapy combined with chemotherapy after modified radical mastectomy decreases rates of locoregional and systemic relapse and reduces mortality from breast cancer.

Adjuvant Radiotherapy and Chemotherapy in Node-Positive Postmenopausal Women with Breast Cancer





1460 patients, 1982 – 1990, postmenopausal, node +, any T, M0

MRM + Tamoxifen +/- 50Gy/25fx RT (electrons + photons)

Sx in 79 departments, RT in mainly 6 centres

Overgaard et al. 1999, 353:1641

VOLUME 22 · NUMBER 21 · NOVEMBER 1 2004

JOURNAL OF CLINICAL ONCOLOGY

EDITORIAL

Postmastectomy Radiation Therapy: Who Needs It?

Ivo A. Olivotto and Pauline T. Truong, *British Columbia Cancer Agency–Vancouver Island Centre and University of British Columbia, Victoria, British Columbia Canada;* Boon Chua, *Peter MacCallum Cancer Centre and University of Melbourne, Melbourne, Australia*

- LOCO-REGIONAL FAILURE (LRF) IS ≈ 25% FOR >4 NODES; T >5 CM; < 6 NODES AT AXILLARY DISSECTION; PATIENT YOUNGER THAN 40
- PMRT REDUCES THIS RISK TO 6 – 8% (ABSOLUTE BENEFIT OF 17-19 WOMEN FOR EACH 100 TREATED)
- IN THE SUBGROUP OF 1-3 NODES, LRF IS 13%; PMRT REDUCES THIS TO 3-4% (ABSOLUTE BENEFIT OF 9-10 WOMEN FOR EVERY 100 TREATED)
- FOR A LRF REDUCTION OF 20%, CANCER SPECIFIC SURVIVAL IMPROVES BY 4-5%
- A NORTH-AMERICAN TRIAL ON PMRT FOR 1-3 NODES WAS CLOSED DUE TO INSUFFICIENT INTERESTH

INDICATION OF RADIATION IN CARCINOMA BREAST

- EARLY BREAST CANCER:- BCT
- POST MRM
  - TUMOR SIZE:- =/> 5CM
  - MARGIN +VE
  - L.N.INVOLVEMENT
  - EXTRACAPSULAR INV
  - LEFT OVER DISEASE AT AXILLA
- APBI
- PALLIATIVE RT

Recommended Selection Criteria for APBI

Criteria	American Brachytherapy Society	American Society of Breast Surgeons
Patient age	45 years or more	50 years or more
Tumour size	Up to 3cm	Up to 2cm
Node	Negative	Negative
Histology	IDC	IDC or DCIS
Margins	Microscopically negative	Microscopically -ve (>2mm)

Several ongoing RCTs are also including ILC, EIC

At TMH we are now also excluding women with hereditary breast cancer

Accelerated Dose

The smaller tissue volume allows larger fraction sizes and thereby shorter overall treatment time

Hypo-fractionation schedule decrease the time period

Radiobiological modeling predicted safety of various dose fractionation schedule

34Gy/10 fr/5 days BD equivalent to 50 Gy

20Gy to 22 Gy Single fraction = 55Gy to 60 Gy

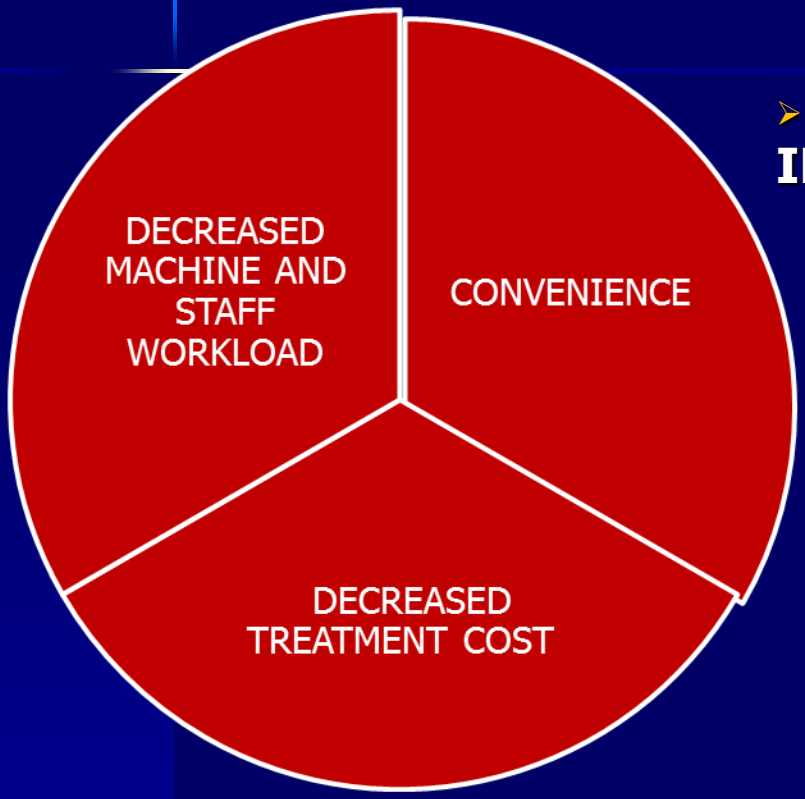
DOSE OF RADIATION

INDICATION	TOTA DOSE	DOSE/#	DURATION
BCT	WHOLE BREAST:- 45-50 Gy + BOOST 10-15Gy	180 TO 200 cGy	6WkS
POST MRM	50 Gy	180 TO 200 cGy	5 WkS
APBI	34Gy 20Gy to 22 Gy	3.4 Gy	2#/Day x 5 Dys SINGLE #
PALLIATIVE RT	30Gy	180 TO 200 cGy	2Wks

HYPOFRACTIONATION - DEFINED

- ***LARGER DOSES*** OF RADIATION PER TREATMENT FRACTION DELIVERING A FULL COURSE OF TREATMENT OVER A ***SHORTER PERIOD OF TIME*** COMPARED TO CONVENTIONAL FRACTIONATION
- TYPICAL CONVENTIONAL FRACTION SIZES: 1.8 – 2.0 GY PER DAY
- HYPOFRACTIONATION: 2.25 - >20 GY PER DAY

HYPOFRACTIONATION:-LOGISTIC



- **REDUCED COST (FEWER FRACTIONS, INCREASED THROUGHPUT)**

- INCREASED CONVENIENCE (1-3 WEEKS VS 6-7)
  - DECREASED PATIENT TRAVEL AND LODGING
  - INCREASED TREATMENT COMPLIANCE AND ACCEPTANCE OF THERAPY

started as an empirical practice in government run health care systems of UK and Canada

RADIOBIOLGY EVIDENCE

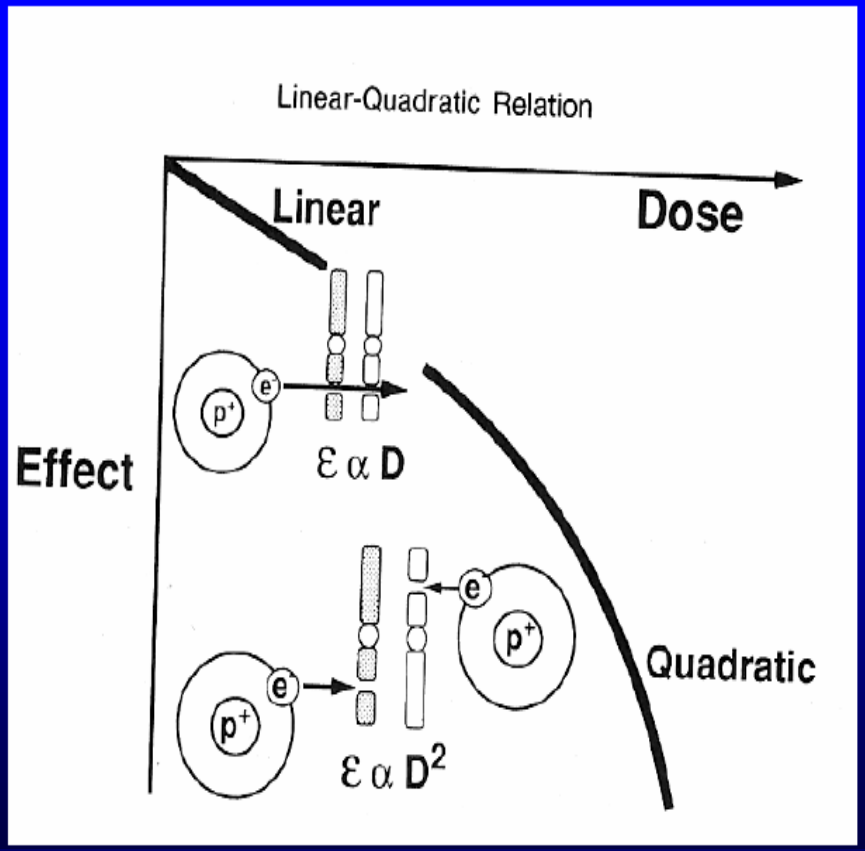
LINEAR QUaDRATIC MODEL

- A lethal event is supposed to be caused by one hit due to one particle track (the linear component αD)

  or

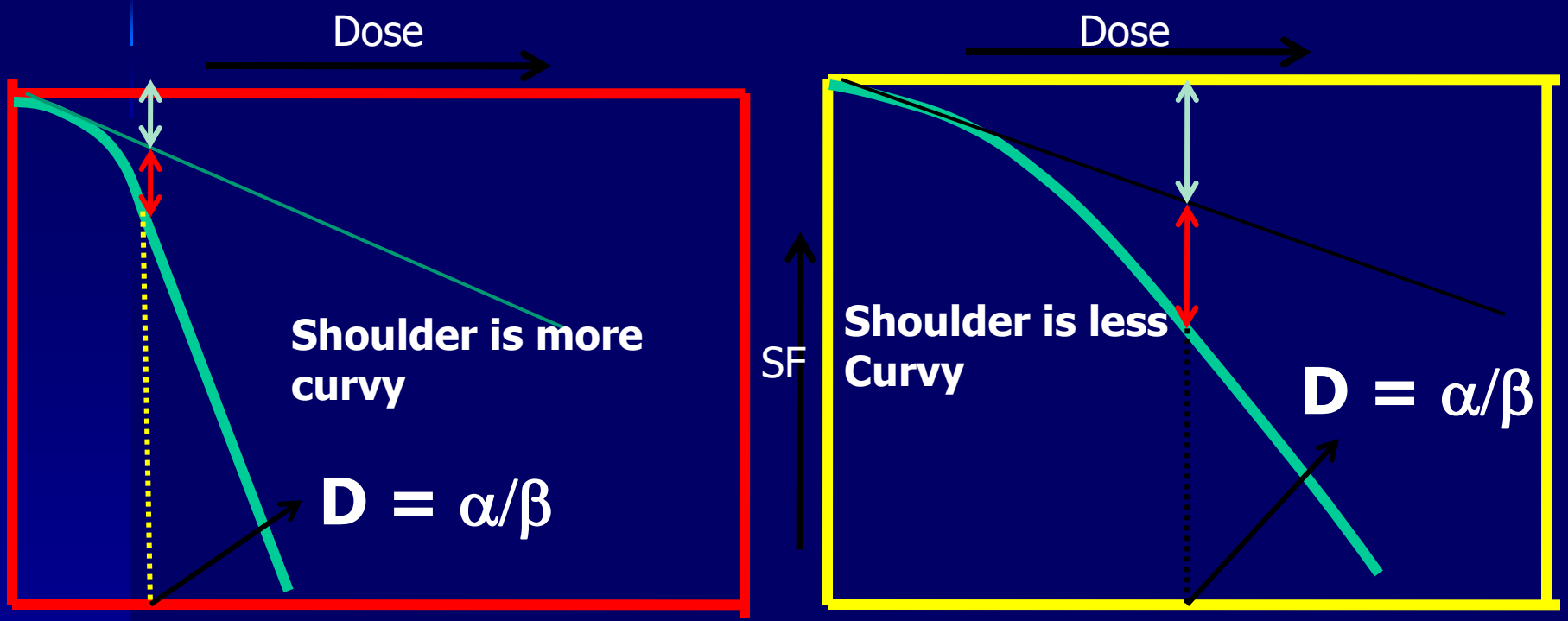
- Two particle tracks (the quadratic component βD2)
- Dual radiation action
- First component - cell killing is proportional to dose
- Second component - cell killing is proportional to dose squared

Fig.3-5: DNA strand break follow L-Q model



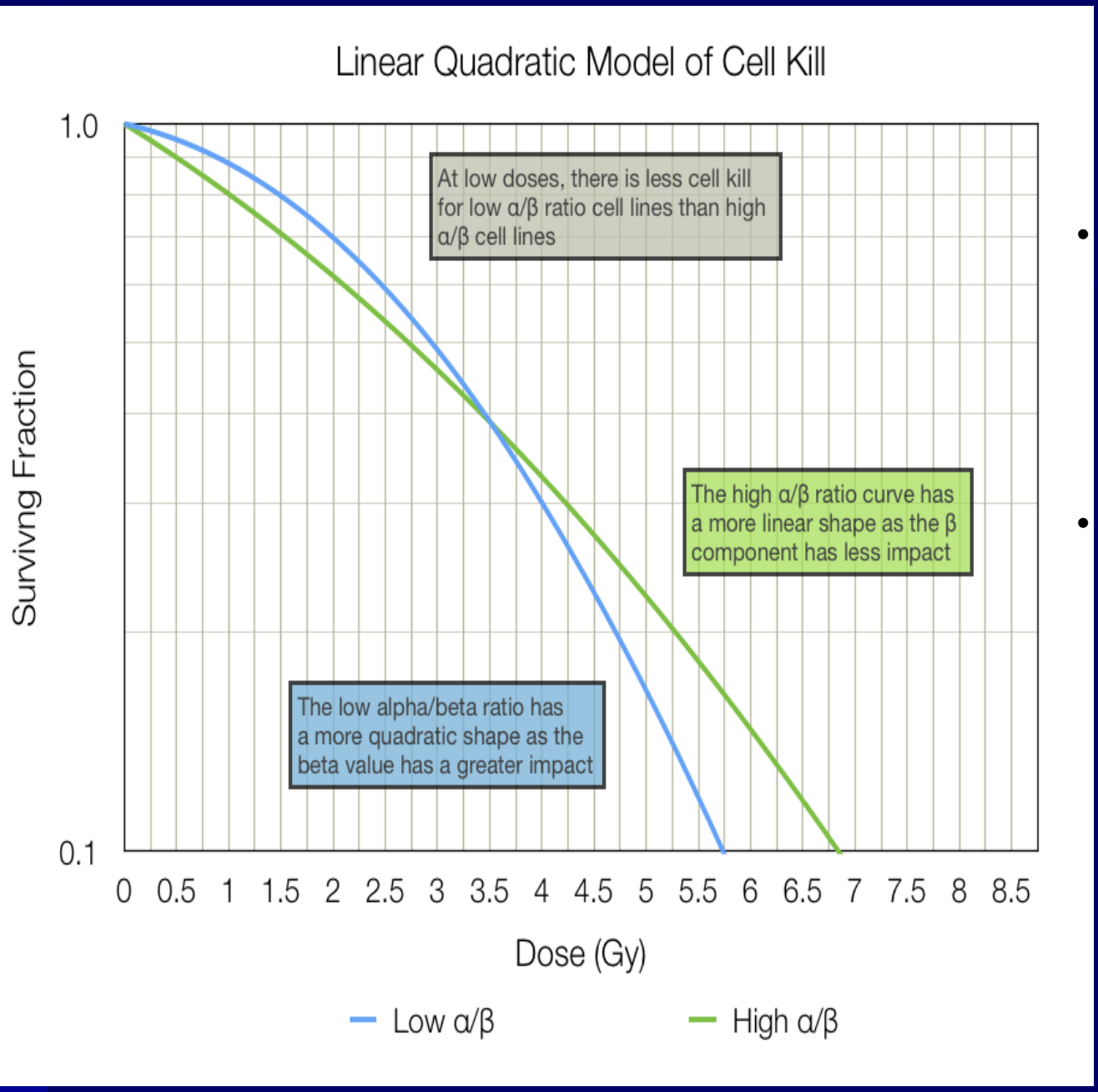
SMALL α/β RATIO INDICATE MORE CURVY NATURE OF LARGE A/B RATIO INDICATE LESS CURVY

Late Reacting Tissue ***Early Reacting Tissue***



α/β = 1Gy to 7 Gy (3Gy)
late effect of radiation
Eg. Spinal cord, urinary bladder, kidney, liver etc and HYPOFRACTIONATION

α/β = 6Gy to 15 Gy (10Gy)
Responsible for acute effect of radiation
Eg, skin, mucosa, lining of intestine, bone marrow etc.



- Carcinomas of the head and neck and lung, it is higher
- Melanomas, sarcomas, prostate cancers etc it's low

Choise of Fractionation – Therapeutic Ratio

- If α/β ratio of tumor is the same or less than that of the critical normal tissue, then a larger dose per fraction *(hypofractionation)* is preferred.
  i.e., prostate cancer, breast cancer

Brenner D., IJROBP 57: 912-914, 2003

- If α/β ratio of tumor is high (often 10 or greater) and > α/β ratio of normal tissue (often < 5) a lower dose per fraction *(hyperfractionation)* is preferred.
  i.e., squamous cancer of head and neck

Horiot J., Radiother Oncol 25: 231-241, 1992

Tissue/organ	Endpoint	α/β (Gy)	95% CL (Gy)	Source
Early reactions				
Skin	Erythema	8.8	6.9; 11.6	Turesson and Thames (1989)
	Erythema	12.3	1.8; 22.8	Bentzen *et al.* (1988)
	Dry desquamation	~8	N/A	Chogule and Supe (1993)
	Desquamation	11.2	8.5; 17.6	Turesson and Thames (1989)
Oral mucosa	Mucositis	9.3	5.8; 17.9	Denham *et al.* (1995)
	Mucositis	15	−15; 45	Rezvani *et al.* (1991)
	Mucositis	~8	N/A	Chogule and Supe (1993)
Late reactions				
Skin/vasculature	Telangiectasia	2.8	1.7; 3.8	Turesson and Thames (1989)
	Telangiectasia	2.6	2.2; 3.3	Bentzen *et al.* (1990)
	Telangiectasia	2.8	−0.1; 8.1	Bentzen and Overgaard (1991)
Subcutis	Fibrosis	1.7	0.6; 2.6	Bentzen and Overgaard (1991)
Breast	Cosmetic change in appearance	3.4	2.3; 4.5	START Trialists Group (2008)
	Induration (fibrosis)	3.1	1.8; 4.4	Yarnold *et al.* (2005)
Muscle/vasculature/ cartilage	Impaired shoulder movement	3.5	0.7; 6.2	Bentzen *et al.* (1989)
Nerve	Brachial plexopathy	<3.5*	N/A	Olsen *et al.* (1990)
	Brachial plexopathy	~2	N/A	Powell *et al.* (1990)
	Optic neuropathy	1.6	−7; 10	Jiang *et al.* (1994)
Spinal cord	Myelopathy	<3.3	N/A	Dische *et al.* (1981)
Eye	Corneal injury	2.9	−4; 10	Jiang *et al.* (1994)
Bowel	Stricture/perforation	3.9	2.5; 5.3	Deore *et al.* (1993)
Bowel	Various late effects	4.3	2.2; 9.6	Dische *et al.* (1999)
Lung	Pneumonitis	4.0	2.2; 5.8	Bentzen *et al.* (2000)
	Lung fibrosis (radiological)	3.1	−0.2; 8.5	Dubray *et al.* (1995)
Head and neck	Various late effects	3.5	1.1; 5.9	Rezvani *et al.* (1991)
Head and neck	Various late effects	4.0	3.3; 5.0	Stuschke and Thames (1999)
Supraglottic larynx	Various late effects	3.8	0.8; 14	Maciejewski *et al.* (1986)
Oral cavity + oropharynx	Various late effects	0.8	−0.6; 2.5	Maciejewski *et al.* (1990)
Tumours				
Head and neck				
Various		10.5	6.5; 29	Stuschke and Thames (1999)
Larynx		14.5*	4.9; 24	Rezvani *et al.* (1993)
Vocal cord		~13	'wide'	Robertson *et al.* (1993)
Buccal mucosa		6.6	2.9; ∞	Maciejewski *et al.* (1989)
Tonsil		7.2	3.6; ∞	Maciejewski *et al.* (1989)
Nasopharynx		16	−11; 43	Lee *et al.* (1995)
Skin		8.5*	4.5; 11.3	Trott *et al.* (1984)
Prostate†		1.1	−3.3; 5.6	Bentzen and Ritter (2005)
Breast		4.6	1.1; 8.1	START Trialists Group (2008)
Oesophagus		4.9	1.5; 17	Geh *et al.* (2006)

IS THERE ANY EVIDENCE

FIVE RANDOMISED TRIALS

RMH/GOC

CANADIAN

SPOONER

START A

START B

ROYAL MARSDEN HOSPITAL/GLOUCESTER ONCOLOGY CENTRE TRIAL (RMH/GOC)

(T1–3, N0–1, M0)
<75 years of age,
BCS

(N=1,410)

50 Gy in 25 fractions
5 WKS
N=348

39 Gy in 13 fractions
5 WKS
N=348

42.9 Gy in 13 fractions
5 WKS
N=351

CANADIAN TRIAL

BREAST CONSERVING SURGERY
AXILLARY:- -VE
(N=1,234)

50 Gy in 25 fractions over 35 days
N=612

42.5 Gy
in 16 fractions over 22 days
N=622

SPOONER ET AL

STAGE 1 AND 2 DISEASE (N=707)

50 GY IN 25 DAILY FRACTIONS).

40 GY IN 15 DAILY FRACTIONS

STANDARDISATION OF BREAST RADIOTHERAPY TRIAL A (START A)
(17 centres)

T1-3a, N0-1 M0
BCS/MASTECTOMY,
clear tumour margins ≥1 mm
(N=2,236)

50 GY IN 25 FRACTIONS
N= 749

41.6 GY IN 13 FRACTIONS
N=750

39 GY IN 13 FRACTIONS
N=737

STANDARDISATION OF BREAST RADIOTHERAPY TRIAL B (START B)

T1-3a, N0-1 M0
BCS/MASTECTOMY
N=2,215

50 GY IN 25 FRACTIONS
FIVE WEEKS
N=1105

40 GY IN 15 FRACTIONS
THREE WEEKS
N=1110

Table 17 Key characteristics of included studies

Study ID	Study type Quality	Population, median follow-up Country	Intervention	Comparator	Outcomes
Post breast conserving surgery					
RMH/GOC[1, 8]	RCT Fair	T1-3, N0-1, M0, <75years N=1,410 9.7 years (range 7.8-11.8 years) UK	39 Gy in 13 fractions over 5 weeks (N=474) 42.9 Gy in 13 fractions over 5 weeks (N=466)	50 Gy in 25 fractions over 5 weeks (N=470)	Local recurrence Cosmetic outcomes
Canadian[2, 7]	RCT Fair	Invasive carcinoma with negative axillary nodes, N=1,234 12 years (range not reported) Canada	42.5 Gy in 16 fractions over 22 days (N=622)	50 Gy in 25 fractions over 35 days (N=612)	Local recurrence (including subgroup analysis) Overall survival Adverse events and toxicity Cosmetic outcome
Post breast conserving surgery or mastectomy					
START A[4, 6]	RCT Fair	T1-3a, N0-1, M0 N=2,236 5.1 years (range 4.4-6.0) UK	39 Gy in 13 fractions over 5 weeks (N=737) 41.6 Gy in 13 fractions over 5 weeks (N=750)	50 Gy in 25 fractions over 5 weeks (N=749)	Local recurrence Overall survival Adverse events and toxicity Cosmetic outcome (including subgroup analysis) Quality of life (including subgroup analysis)
START B[5, 6]	RCT Fair	T1-3a, N0-1, M0 N=2,215 6 years (range 5.0-6.2) UK	40 Gy in 15 fractions over 3 weeks (N=1,110)	50 Gy in 25 fractions over 5 weeks (N=1,105)	Local recurrence Overall survival Adverse events and toxicity Cosmetic outcome (including subgroup analysis) Quality of life (including subgroup analysis)
Spooner[3]	RCT (conference abstract) Poor[a]	Stage 1 or 2, median tumour size 2cm N=707 16.9 years (range 15.4-18.8 years) UK	40 Gy in 15 daily fractions (N=NR) 50 Gy in 25 daily fractions (N=NR)	Delayed salvage treatment	Time to first relapse

Abbreviations: NR=not reported, RCT=randomised controlled trial

a The conference abstract provided insufficient study detail to rate it as either fair or good. It is unclear from the abstract whether allocation was concealed from those responsible for recruiting subjects, whether outcome assessment was blinded, and whether there was loss to follow up,

WHAT IS OUR AIM

- LOCAL RECURRENCE
- LOCOREGIONAL RECURRENCE
- DISTANCE DISEASE
- OVER ALL SURVIVAL
- ADVERSE EVENT AND TOXICITY
- COSMESIS
- QUALITY OF LIFE

WHAT IS THE EVIDENCE

	TOTAL DOSE	DOSE/#	NO OF #	DURATION
RMH/GOC				
	39Gy	300 cGy	13 #	5 WKS
	42.5Gy	326 cGy	13#	5 WKS
	50Gy	200 cGy	25#	5 WKS
CANADIAN				
	42.5Gy	2.65	16 #	22 days
	50Gy	200 cGy	25#	5WKS
SPOONER				
	40Gy	266 cGy	15#	5 WKS
	50Gy	200 cGy	25#	5 Wks
START A				
	39Gy/13 #,5 WKS	300cGy	13 #	5 WKS
	41.6 Gy/13 #,5 WKS	320cGy	13 #	5 WKS
	50Gy	200cGy	25#	5WKS
START B				
	40Gy	266cGy	15#	3 WKS

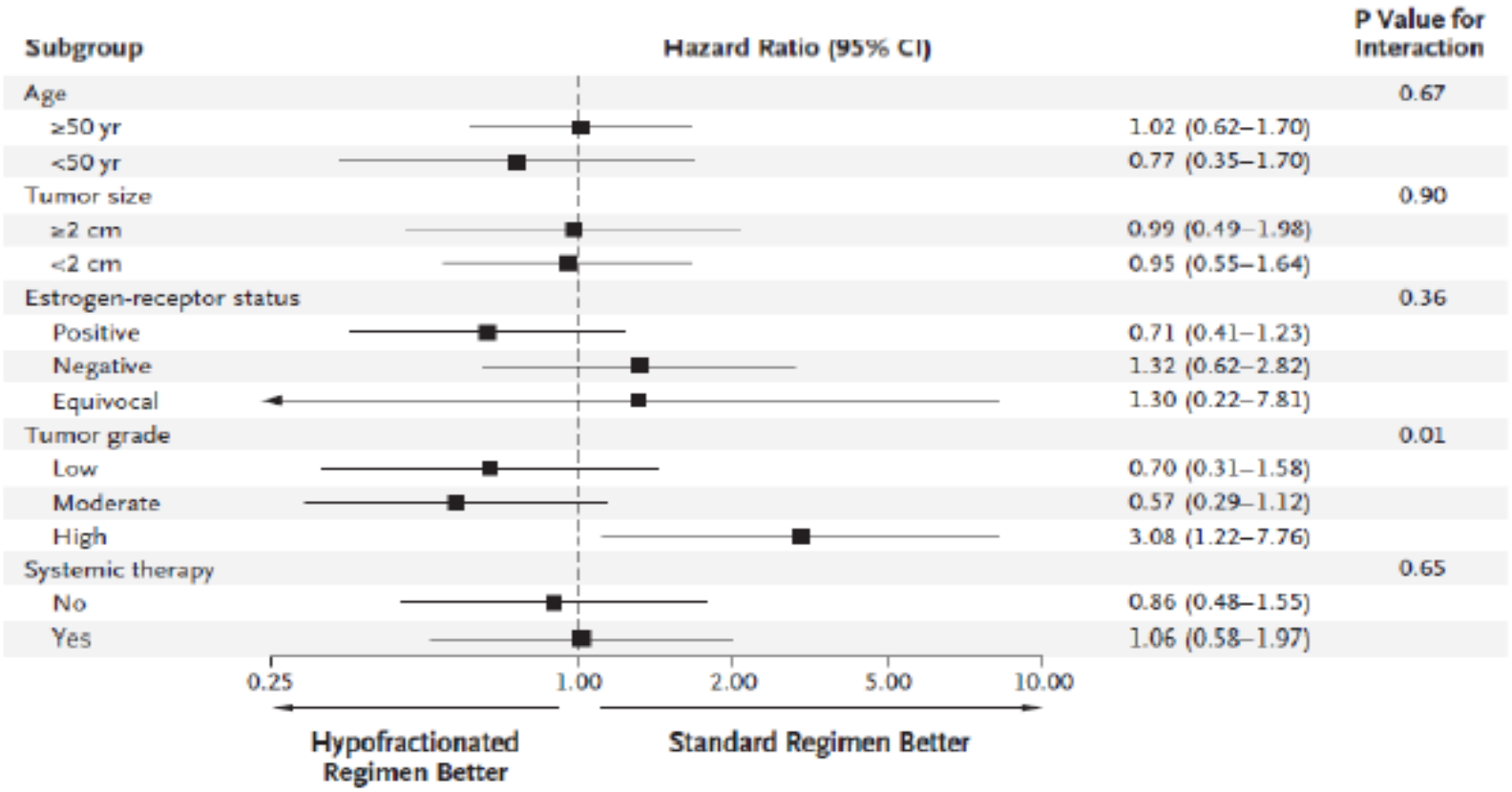
LOCAL RECURRENCE

TRIAL	5YRS	10 YRS	P-Value
RMH/GOC			
39Gy/13 #,5 WKS	**9.1%**	**14.8%**	**0.027**
42.5Gy/13 #,5 WKS	**7.1%**	**9.6%**	**N.S**
50Gy/25#,5WKS	**7.9%**	**12.1%**	**N.S**
CANADIAN			
42.5Gy/16 #,22 days		**6.2%**	**N.S**
50Gy/25#,5WKS		**6.7%**	**GRADE =0.01**
SPOONER			
40Gy/15 #,5 WKS			**17 YRS NO FDIFF**
50Gy/25#,5WKS			
START A			
39Gy/13 #,5 WKS	**4.6%**		**N.R**
41.6 Gy/13 #,5 WKS	**3.2%**		**N.R**
50Gy/25#,5WKS	**3.2%**		**N.R**
START B			
40Gy/15#/3 WKS	2%		**N.R**
50Gy/25#/5 WKS	**3.3%**		**N.R**

CANADIAN:- HYPOFRACTIONATED REGIMEN LESS EFFECTIVE IN PREVENTING LOCAL RECURRENCE IN PATIENTS WITH HIGH-GRADE TUMOURS (P=0.01).

CANADIAN TRIAL:-LOCAL RECURRENCE

Figure 3 Canadian trial: Hazard ratios for Ipsilateral recurrence of breast cancer in subgroups of patients[2]



Source: Whelan 2010[2] Figure 2 page 517

LOCO REGIONAL RECURRENCE

TRIAL	5YRS	10 YRS	P-Value
START A			
39Gy/13 #,5 WKS	5.2%		N.R
41.6 Gy/13 #,5 WKS	3.5%		N.R
50Gy/25#,5WKS	3.6%		N.R
START B			
40Gy/15#/3 WKS	2.2%		N.R
50Gy/25#/5 WKS	3.3%		N.R

no evidence that any hypofractionated radiotherapy regimen was associated with a statistically significant difference in local recurrence rate

DISTANT RELAPSE

TRIAL	5YRS	10 YRS	P-Value
START A			
39Gy/13 #,5 WKS	11.9%		N.R
41.6 Gy/13 #,5 WKS	9.5%		N.R
50Gy/25#,5WKS	9.8%		N.R
START B			
40Gy/15#/3 WKS	7.6%		N.R
50Gy/25#/5 WKS	10.2%		N.R

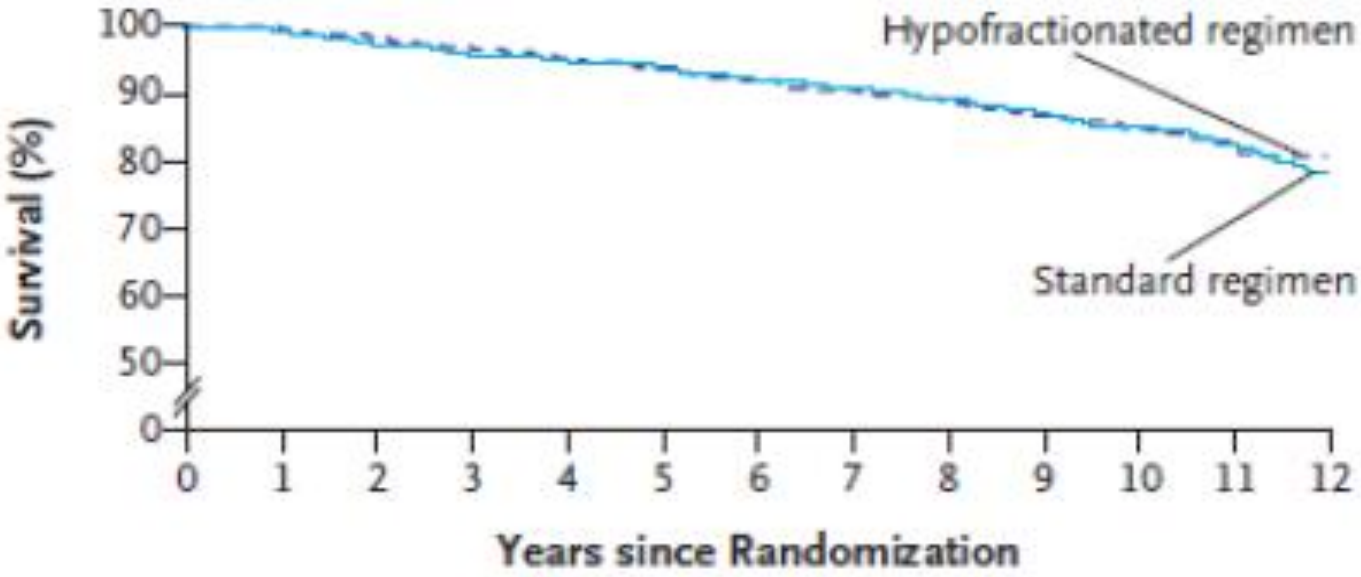
OVERALL SURVIVAL

TRIAL	5YRS	10 YRS	P-Value
Canadian			
42.5Gy/16 #,22 days		**84.6%**	**0.79**
50Gy/25#,35 days		**84.4%**	
SPOONER			
40Gy/15 #,5 WKS		**17 year survival**	
50Gy/25#,5WKS		**No difference**	
START A			
39Gy/13 #,5 WKS	ALL CAUSE MORTALITY		**0.99**
41.6 Gy/13 #,5 WKS			**0.81**
50Gy/25#,5WKS			
START B			
40Gy/15#/3 WKS	All cause mortality		**0.03**
50Gy/25#/5 WKS			

there was no evidence that any hypofractionated radiotherapy regimen was associated with a worse overall survival rate

OVERALL SURVIVAL

Figure 4 Canadian trial: Kaplan-Meier estimate for overall survival[2]



No. at Risk

Standard regimen	612	606	594	583	573	559	535	519	505	487	453	355	242
Hypofractionated regimen	622	617	605	592	576	562	539	517	495	482	455	369	241

Source: Whelan 2010[2] Figure 1b page 516
p=0.79

CANADIAN TRIAL:-CAUSE OF DEATH

Table 32 Canadian trial: Cause of deaths[2]

Arm	50 Gy n (%)	42.5 Gy n (%)	P value
Deaths related to cancer	82 (13.4)	82 (13.2)	NS
Deaths related to cardiac disease	9 (1.5)	12 (1.9)	NS
Deaths related to other causes	35 (5.7)	28 (4.5)	NS

Source: Whelan 2010[2] page 517
Abbreviations: NS=not significant

START A:
SURVIVAL ANALYSES OF RELAPSE AND MORTALITY

Table 33 START A: Survival analyses of relapse and mortality according to fractionation schedule (All-cause mortality)[4]

Arm	Events/total (%)	Estimated % with event by 5 years (95% CI)	Crude hazard ratio (95% CI)	P value
50 Gy	84/749 (11.2)	11.1 (8.7, 13.4)	1	–
41.6 Gy	89/750 (11.9)	11.3 (8.9, 13.7)	1.04 (0.77, 1.40)	0.81
39 Gy	83/737 (11.3)	10.7 (8.3, 13.1)	1.00 (0.74, 1.36)	0.99

Source: Bentzen *et al* 2008[4] Table 2 page 335
Abbreviations: CI=confidence interval

START B:
SURVIVAL ANALYSES OF RELAPSE AND MORTALITY

Arm	Events/total (%)	Estimated % with event by 5 years (95% CI)	Crude hazard ratio (95% CI)	P value
50 Gy	138/1105 (12.5)	11.0 (9.1, 12.9)	1	–
40 Gy	107/1110 (9.6)	8.0 (6.4, 9.7)	0.76 (0.59, 0.98)	0.03

THERE WAS NO EVIDENCE THAT HYPOFRACTIONATED RADIOTHERAPY WAS ASSOCIATED WITH A STATISTICALLY SIGNIFICANTLY DIFFERENCE IN OVERALL SURVIVAL

ADVERSE EVENT AND TOXICITY

TRIAL	RESULTS
CANADIAN	Late toxic radiation effects,NS
42.5Gy/16 #,22 days	
50Gy/25#,5WKS	
START A	
39Gy/13 #,5 WKS	Ischemic heart disease, symptomatic rib fracture, symptomatic lung fibrosis, contra lateral breast cancer, other secondary primary cancers: NS
41.6 Gy/13#,5 WKS	
50Gy/25#,5WKS	
START B	
40Gy/15#/3 WKS 50Gy/25#/5 WKS	Ischemic heart disease, symptomatic rib fracture, symptomatic lung fibrosis, contra lateral breast cancer, other secondary primary cancers: NS

Skin appearance: 39 Gy HR 0.63 (95% CI 0.47, 0.84), p=0.0019
40 Gy HR 0.76 (95% CI 0.60, 0.97), p=0.0262

LATE TOXIC EFFECTS OF RADIATION, ASSESSED ACCORDING TO THE RTOG-EORTC LATE RADIATION MORBIDITY

Table 36 Canadian trial: Late toxic effects of radiation, assessed according to the RTOG-EORTC late radiation morbidity scoring scheme[a2]

Site and Grade	5 year follow-up		10 year follow-up	
	50 Gy n=424 %	42.5 Gy n=449 %	50 Gy n=220 %	42.5 Gy n=235 %
Skin				
0[b]	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[c]	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

START A: INCIDENCE OF ISCHEMIC HEART DISEASE, SYMPTOMATIC RIB FRACTURE, AND SYMPTOMATIC LUNG FIBROSIS

Outcome	Arm	Reported n, (%)	Confirmed n, (%) [a]
Ischemic heart disease [b]	50 Gy	12 (1.6)	3 (0.4) [1][c]
	41.6 Gy	7 (0.9)	2 (0.3) [0][c]
	39 Gy	8 (1.1)	5 (0.7) [4][c]
	Total	27(1.2)	10 (0.4) [5][c]
Symptomatic rib fractures [d]	50 Gy	8 (1.1)	1 (0.1)
	41.6 Gy	9 (1.2)	2 (0.3)
	39 Gy	10 (1.4)	1 (0.1)
	Total	27 (1.2)	4 (0.2)
Symptomatic lung fibrosis	50 Gy	5 (0.7)	0 (0)
	41.6 Gy	6 (0.8)	2 (0.3)
	39 Gy	7 (0.9)	1 (0.1)
	Total	18 (0.8)	3 (0.1)

START B: INCIDENCE OF ISCHEMIC HEART DISEASE, SYMPTOMATIC RIB FRACTURE, AND SYMPTOMATIC LUNG FIBROSIS

Outcome	Arm	Reported (%)	Confirmed (%) [a]
Ischemic heart disease [b]	50 Gy	19 (1.7)	12 (1.1) [4][c]
	40 Gy	15 (1.3)	7 (0.6) [3][c]
	Total	34 (1.5)	19 (0.9) [7] [c]
Symptomatic rib fractures [d]	50 Gy	17 (1.5)	2 (0.2)
	40 Gy	16 (1.4)	2 (0.2)
	Total	33 (1.5)	4 (0.2)
Symptomatic lung fibrosis	50 Gy	15 (1.4)	1 (0.1)
	40 Gy	16 (1.4)	3 (0.3)
	Total	31 (1.4)	4 (0.2)

Change in breast appearance since radiotherapy*	41·0 (35·0–46·9)	41·9 (36·1–47·8)	1·05 (0·82–1·35)	0·6781
Breast hardness since radiotherapy*	43·2 (37·2–49·2)	45·0 (39·1–50·8)	1·09 (0·85–1·39)	0·5073
Breast shrinkage since radiotherapy*	22·6 (17·5–27·7)	24·4 (19·3–29·5)	1·09 (0·80–1·47)	0·5841
Change in skin appearance since radiotherapy	31·6 (26·6–36·6)	25·3 (20·7–29·8)	0·83 (0·63–1·08)	0·1663
Skin problems on or in area of affected breast	16·9 (12·8–20·9)	16·6 (12·7–20·6)	1·01 (0·71–1·43)	0·9468
Pain in area of affected breast	21·4 (17·0–25·8)	23·9 (19·4–28·3)	1·17 (0·86–1·58)	0·3175
Oversensitivity in area of affected breast	23·3 (18·7–27·8)	22·1 (17·7–26·4)	1·09 (0·81–1·47)	0·5668
Swelling in area of affected breast	15·5 (11·7–19·4)	12·2 (8·8–15·6)	0·81 (0·55–1·20)	0·2933
Arm or shoulder symptoms				
Pain in arm or shoulder	30·9 (25·9–35·9)	30·2 (25·3–35·0)	1·00 (0·77–1·29)	0·9967
Shoulder stiffness	19·8 (15·5–24·1)	16·0 (12·2–19·9)	0·80 (0·64–1·23)	0·4726
Difficulty in raising or moving arm sideways	15·0 (11·1–18·9)	14·1 (10·4–17·7)	0·97 (0·67–1·39)	0·8576
Swelling in arm or hand	14·5 (10·7–18·3)	11·8 (8·3–15·3)	0·84 (0·57–1·22)	0·3742

Favours 41·6 Gy | Favours 50 Gy

B START trial A, 39 Gy vs 50 Gy

	50 Gy	39 Gy		
Breast symptoms				
Change in breast appearance since radiotherapy*	41·0 (35·0–46·9)	34·1 (28·4–39·8)	0·84 (0·65–1·08)	0·1775
Breast hardness since radiotherapy*	43·2 (37·2–49·2)	35·0 (29·3–40·7)	0·79 (0·61–1·04)	0·0894
Breast shrinkage since radiotherapy*	22·6 (17·5–27·7)	22·9 (17·8–28·0)	1·00 (0·73–1·37)	0·9823
Change in skin appearance since radiotherapy	31·6 (26·6–36·6)	21·7 (17·3–26·1)	0·63 (0·47–0·84)	0·0019
Skin problems on or in area of affected breast	16·9 (12·8–20·9)	16·5 (12·4–20·5)	0·90 (0·63–1·28)	0·5539
Pain in area of affected breast	21·4 (17·0–25·8)	20·1 (15·8–24·4)	0·97 (0·70–1·32)	0·8311
Oversensitivity in area of affected breast	23·3 (18·7–27·8)	18·1 (14·9–23·3)	0·79 (0·58–1·05)	0·1541
Swelling in area of affected breast	15·5 (11·7–19·4)	12·0 (8·6–15·5)	0·73 (0·49–1·08)	0·1182
Arm or shoulder symptoms				
Pain in arm or shoulder	30·9 (25·9–35·9)	32·5 (27·5–37·5)	1·07 (0·82–1·38)	0·6252
Shoulder stiffness	19·8 (15·5–24·1)	18·1 (13·9–22·2)	0·84 (0·60–1·17)	0·3015
Difficulty in raising or moving arm sideways	15·0 (11·1–18·9)	13·9 (10·2–17·7)	0·97 (0·68–1·38)	0·8586
Swelling in arm or hand	14·5 (10·7–18·3)	14·8 (10·9–18·7)	0·90 (0·62–1·33)	0·6030

Favours 39 Gy | Favours 50 Gy

C START trial B, 40 Gy vs 50 Gy

	50 Gy	40 Gy		
Breast symptoms				
Change in breast appearance since radiotherapy*	41·2 (36·6–45·9)	35·5 (30·9–40·0)	0·84 (0·69–1·03)	0·0956
Breast hardness since radiotherapy*	42·8 (38·2–47·5)	38·4 (33·8–42·9)	0·88 (0·72–1·08)	0·2142
Breast shrinkage since radiotherapy*	26·3 (22·1–30·5)	23·8 (19·8–27·8)	0·86 (0·68–1·09)	0·2176
Change in skin appearance since radiotherapy	28·3 (24·3–32·3)	23·0 (19·4–26·7)	0·76 (0·60–0·97)	0·0262
Skin problems on or in area of affected breast	18·7 (15·3–22·1)	17·0 (13·7–20·2)	0·88 (0·67–1·17)	0·3820
Pain in area of affected breast	22·7 (18·9–26·4)	20·7 (17·2–24·2)	0·94 (0·73–1·22)	0·6532
Oversensitivity in area of affected breast	23·0 (19·3–26·8)	23·7 (20·0–27·4)	1·11 (0·86–1·42)	0·4193
Swelling in area of affected breast	12·4 (9·5–15·3)	10·6 (7·9–13·2)	0·91 (0·64–1·30)	0·6112
Arm or shoulder symptoms				
Pain in arm or shoulder	32·0 (27·9–36·2)	32·0 (27·9–36·1)	1·02 (0·82–1·25)	0·8746
Shoulder stiffness	19·3 (15·8–22·8)	18·3 (14·9–21·7)	0·95 (0·73–1·25)	0·7308
Difficulty in raising or moving arm sideways	17·0 (13·6–20·3)	15·9 (12·7–19·1)	0·97 (0·72–1·29)	0·8154
Swelling in arm or hand	12·9 (9·9–15·9)	12·2 (9·2–15·1)	1·05 (0·75–1·48)	0·7658

0·4 | 0·6 | 0·8 | 1·0 | 1·2 | 1·4 | 1·6

Favours 40 Gy | Favours 50 Gy

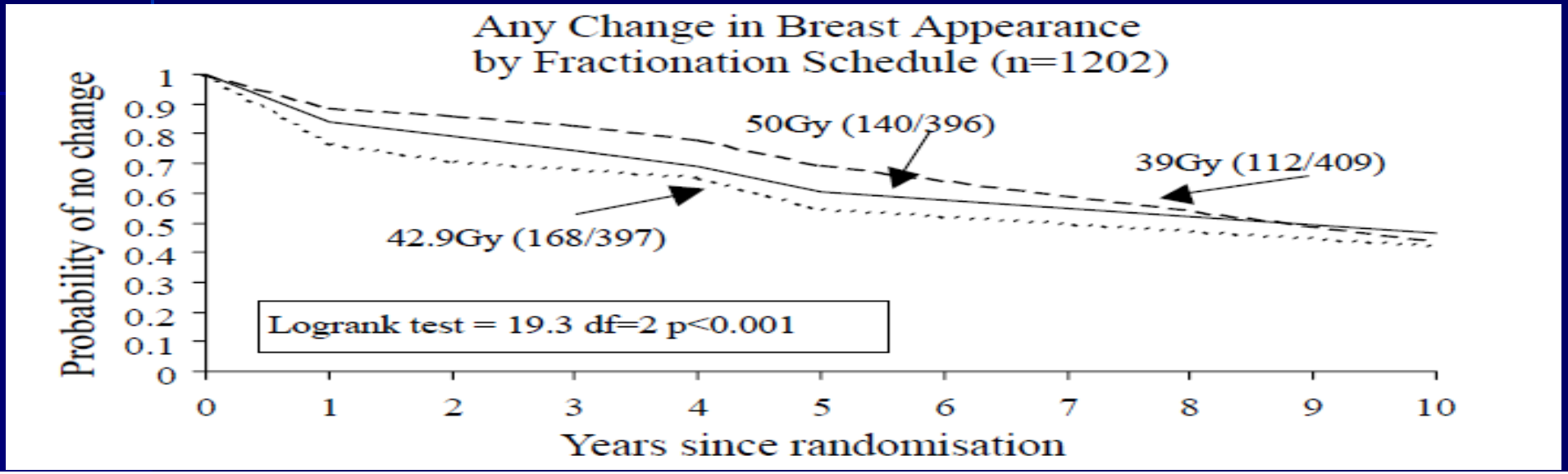
MOST TRIALS REPORTED THAT THERE WAS NO DIFFERENCE IN ADVERSE EVENTS AND TOXICITY. COMBINED RESULTS FROM THE START A AND START B TRIALS FOUND THAT A CHANGE IN SKIN APPEARANCE OCCURRED SIGNIFICANTLY LESS OFTEN IN THE 39 GY AND 40 GY ARMS WHEN COMPARED WITH THE CONTROL ARM

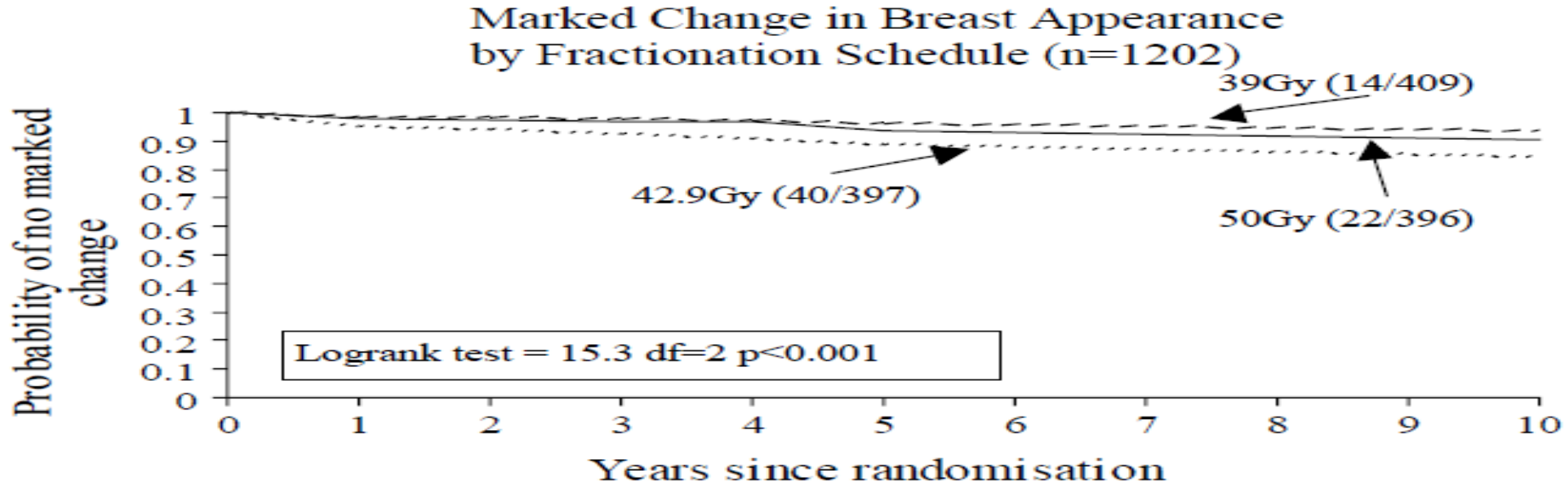
COSMETIC OUTCOME

TRIAL	RESULTS	p-Value
RMH/GOC		
39Gy/13 #,5 WKS	39 GY: ADVERSE COSMETIC OUTCOMES WERE REPORTED LESS FREQUENTLY WHEN COMPARED TO THE 50 GY ARM	0.01
42.9Gy/13 #,5 WKS	42.9 GY: COSMETIC OUTCOMES WERE REPORTED MORE FREQUENTLY WHEN COMPARED TO THE 50 GY ARM	0.05
50Gy/25#,5WKS		
CANADIAN		
42.5Gy/16 #,22D	NO STATISTICALLY SIGNIFICANT DIFFERENCES IN ANY COSMETIC OUTCOME.	
50Gy/25#,5WKS		
As for START A and START B	CHANGE IN SKIN APPEARANCE 39 GY: HR 0.63 (95% CI 0.47, 0.84), P=0.0019 40 GY: HR 0.76 (95% CI 0.60, 0.97), P=0.0262	

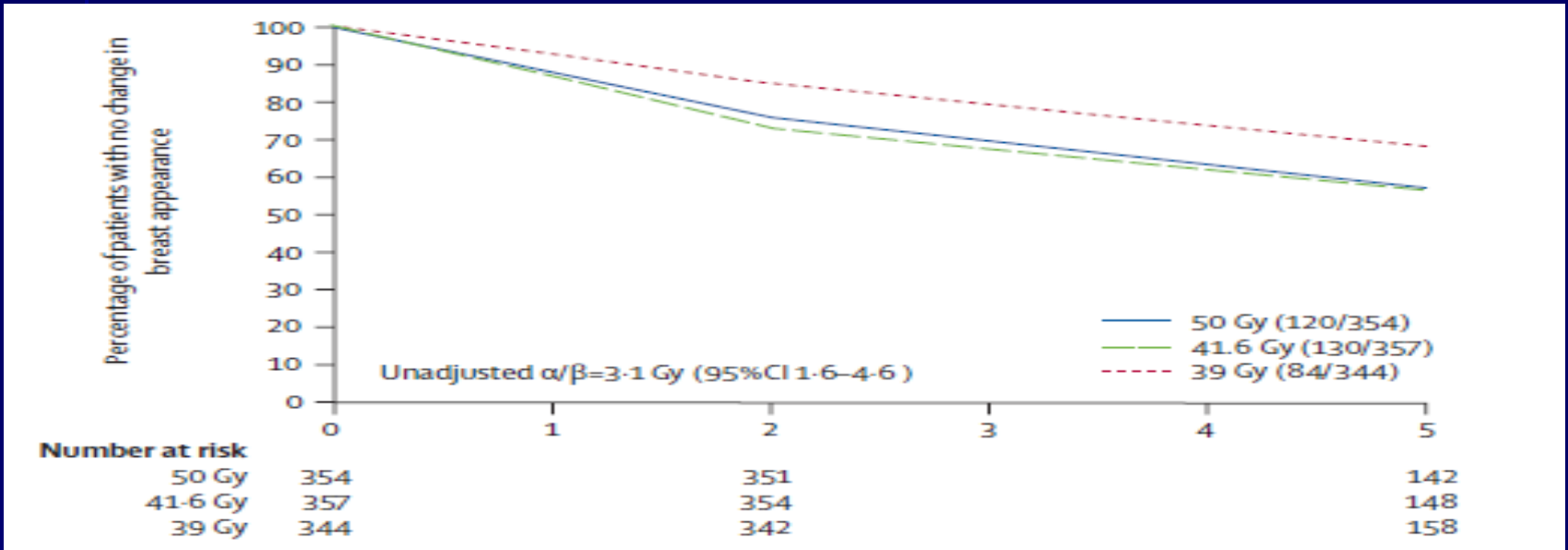
THE RISK OF DEVELOPING ANY LATE RADIATION EFFECT WAS STATISTICALLY SIGNIFICANTLY LOWER FOR PATIENTS IN THE 39 GY ARM COMPARED TO THE 50 GY ARM (P=0.01)

RMH/GOC TRIAL:
PROBABILITY OF MARKED CHANGE IN BREAST APPEARANCE LATE RADIATION EFFECT TEN YEARS AFTER RADIOTHERAPY BY FRACTIONATION

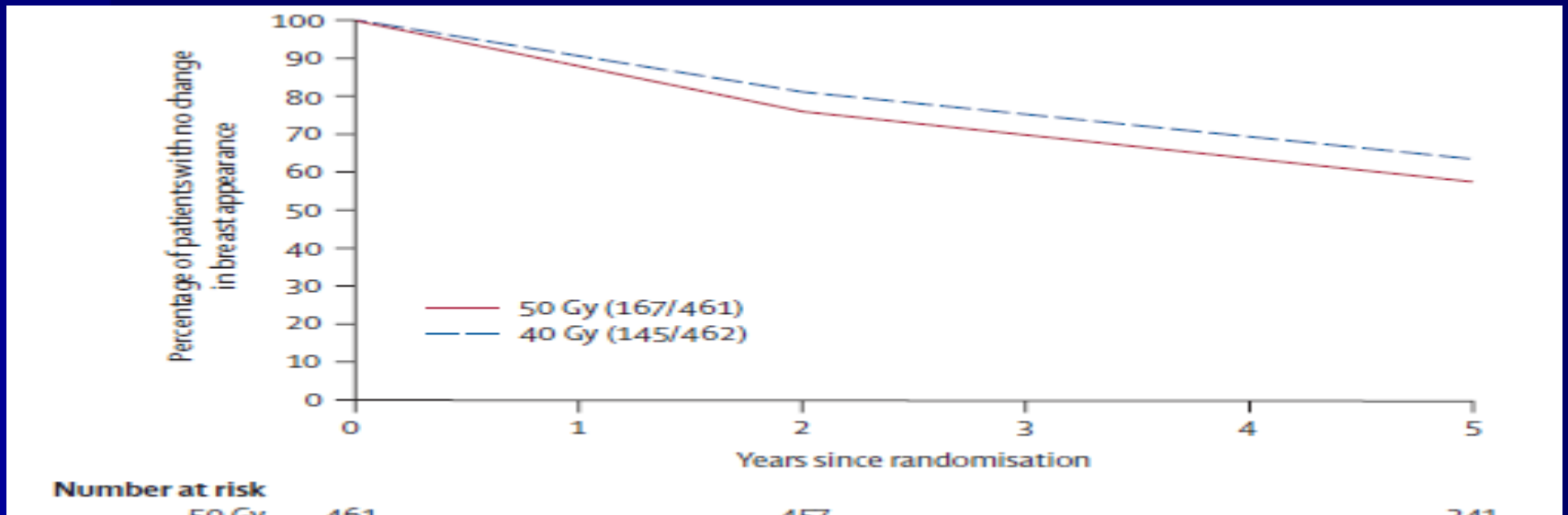




START A: Kaplan-Meier plot of mild/marked change in breast appearance (photographic) in 1055 patients with breast conserving surgery4



START B: Kaplan-Meier plot of mild/marked change in breast appearance (photographic) in 923 patients with bcs



RMH/GOC

REPORTED THE RISK OF DEVELOPING ANY LATE RADIATION EFFECT WAS STATISTICALLY SIGNIFICANTLY LOWER FOR PATIENTS IN THE 39 GY ARM COMPARED TO THE 50 GY ARM (P=0.01). FOR MOST CLINICALLYASSESSED BREAST AND ARM OUTCOMES ESTIMATED AT 10 YEARS, :- 39Gy < 50Gy < 42.9 Gy

THE START A :-
39 GY ARM WAS ASSOCIATED WITH SIGNIFICANTLY LESS MILD OR MARKED CHANGE IN PHOTOGRAPHIC BREAST APPEARANCE AND CHANGE IN SKIN APPEARANCE

START B :-
THE 40 GY ARM WAS ASSOCIATED WITH SIGNIFICANTLY LESS CHANGE IN SKIN APPEARANCE

Figure 3 Canadian trial: Hazard ratios for Ipsilateral recurrence of breast cancer in subgroups of patients[2]

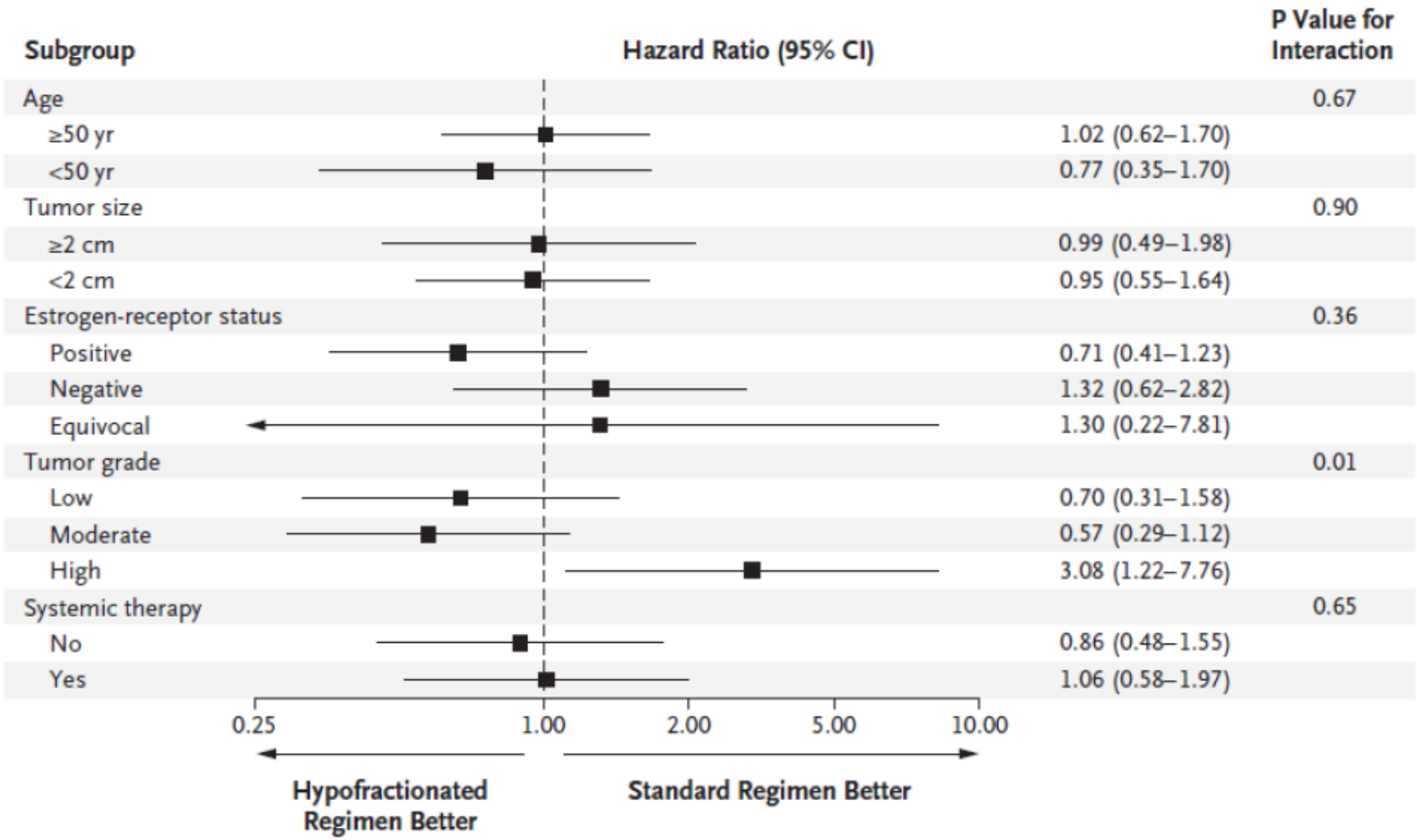


Figure 5 START A AND B: Forest plots of normal tissue effects assessed as moderate or marked by patients, according to radiotherapy regimens[6]

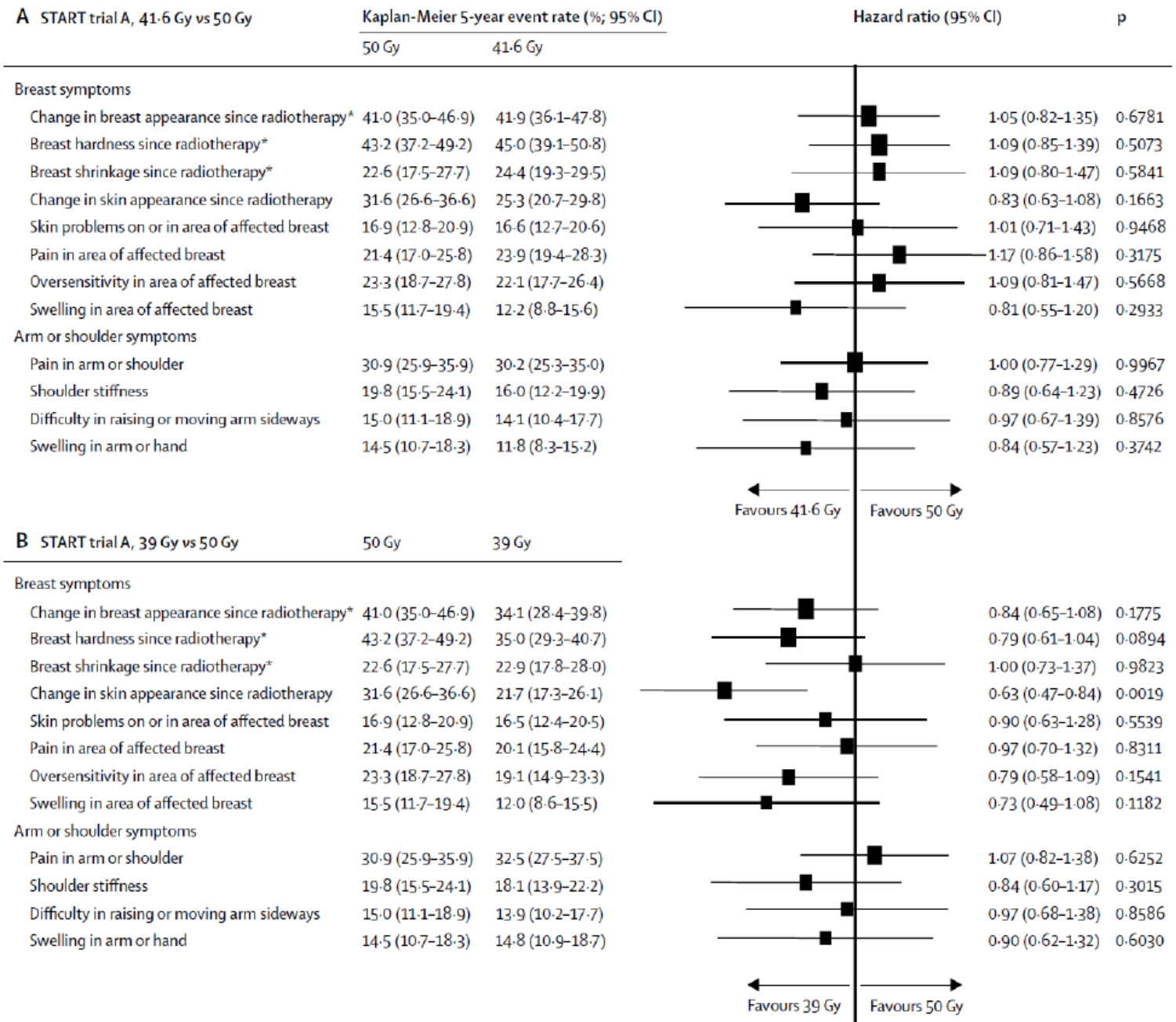


Figure 5 START A AND B: Forest plots of normal tissue effects assessed as moderate or marked by patients, according to radiotherapy regimens[6]

C START trial B, 40 Gy *vs* 50 Gy	50 Gy	40 Gy		
Breast symptoms				
Change in breast appearance since radiotherapy*	41·2 (36·6–45·9)	35·5 (30·9–40·0)	0·84 (0·69–1·03)	0·0956
Breast hardness since radiotherapy*	42·8 (38·2–47·5)	38·4 (33·8–42·9)	0·88 (0·72–1·08)	0·2142
Breast shrinkage since radiotherapy*	26·3 (22·1–30·5)	23·8 (19·8–27·8)	0·86 (0·68–1·09)	0·2176
Change in skin appearance since radiotherapy	28·3 (24·3–32·3)	23·0 (19·4–26·7)	0·76 (0·60–0·97)	0·0262
Skin problems on or in area of affected breast	18·7 (15·3–22·1)	17·0 (13·7–20·2)	0·88 (0·67–1·17)	0·3820
Pain in area of affected breast	22·7 (19·0–26·4)	20·7 (17·2–24·2)	0·94 (0·73–1·22)	0·6532
Oversensitivity in area of affected breast	23·0 (19·3–26·8)	23·7 (20·0–27·4)	1·11 (0·86–1·42)	0·4193
Swelling in area of affected breast	12·4 (9·5–15·3)	10·6 (7·9–13·2)	0·91 (0·64–1·30)	0·6112
Arm or shoulder symptoms				
Pain in arm or shoulder	32·0 (27·9–36·2)	32·0 (27·9–36·1)	1·02 (0·82–1·25)	0·8746
Shoulder stiffness	19·3 (15·8–22·8)	18·3 (14·9–21·7)	0·95 (0·73–1·25)	0·7308
Difficulty in raising or moving arm sideways	17·0 (13·6–20·3)	15·9 (12·7–19·1)	0·97 (0·72–1·29)	0·8154
Swelling in arm or hand	12·9 (9·9–15·9)	12·2 (9·2–15·1)	1·05 (0·75–1·48)	0·7658

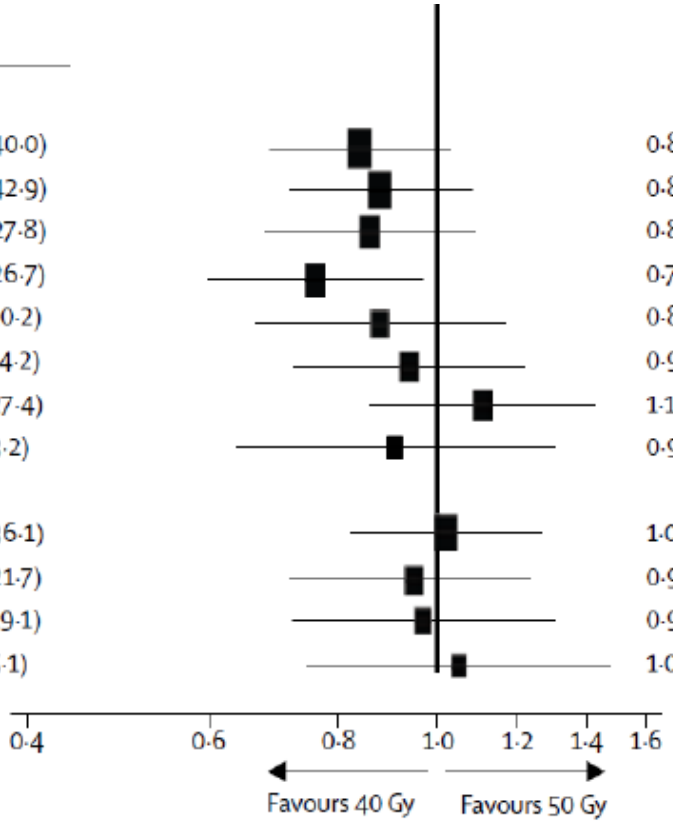


Figure 11 START A AND B: Forest plots of normal tissue effects assessed as moderate or marked by patients, according to radiotherapy regimen[6]

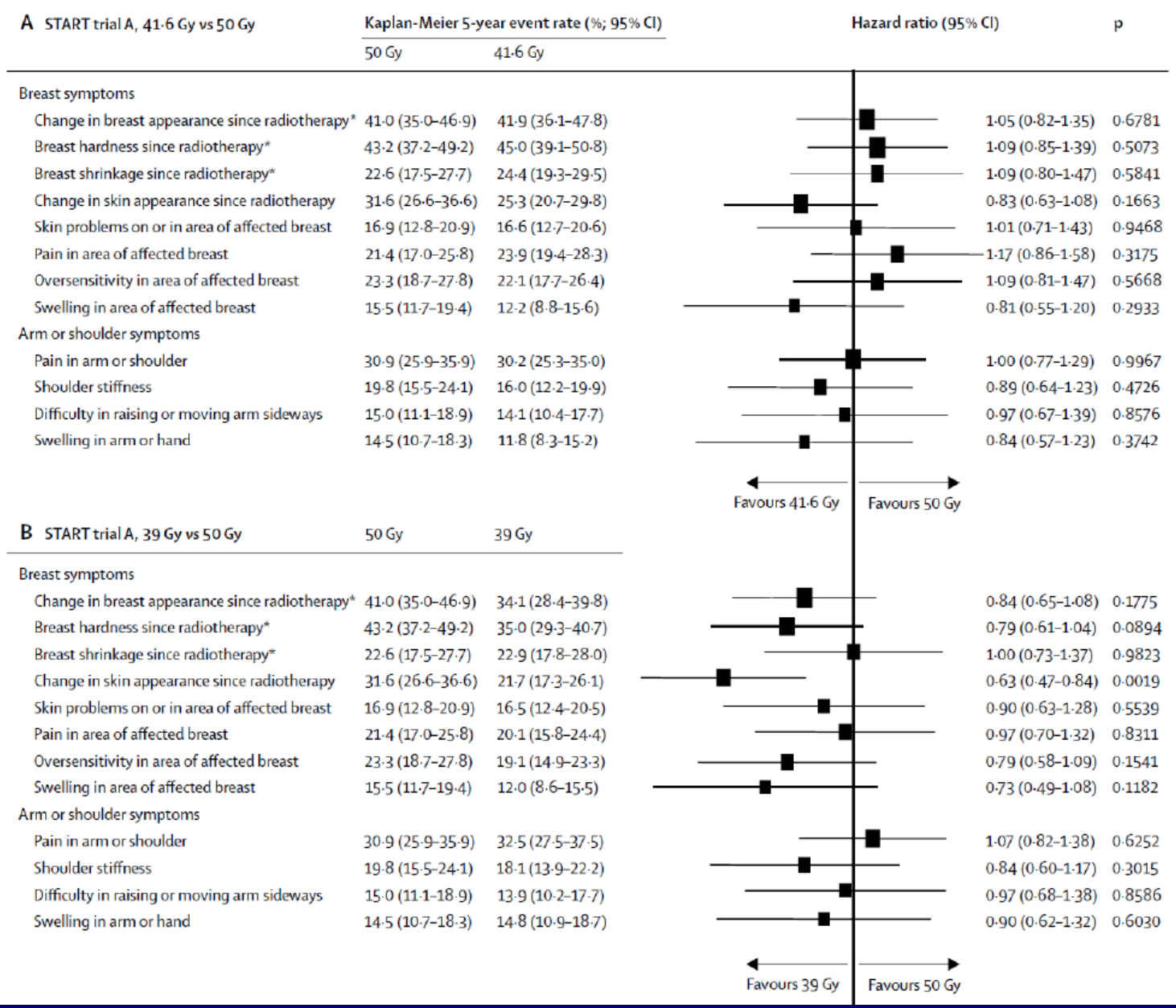
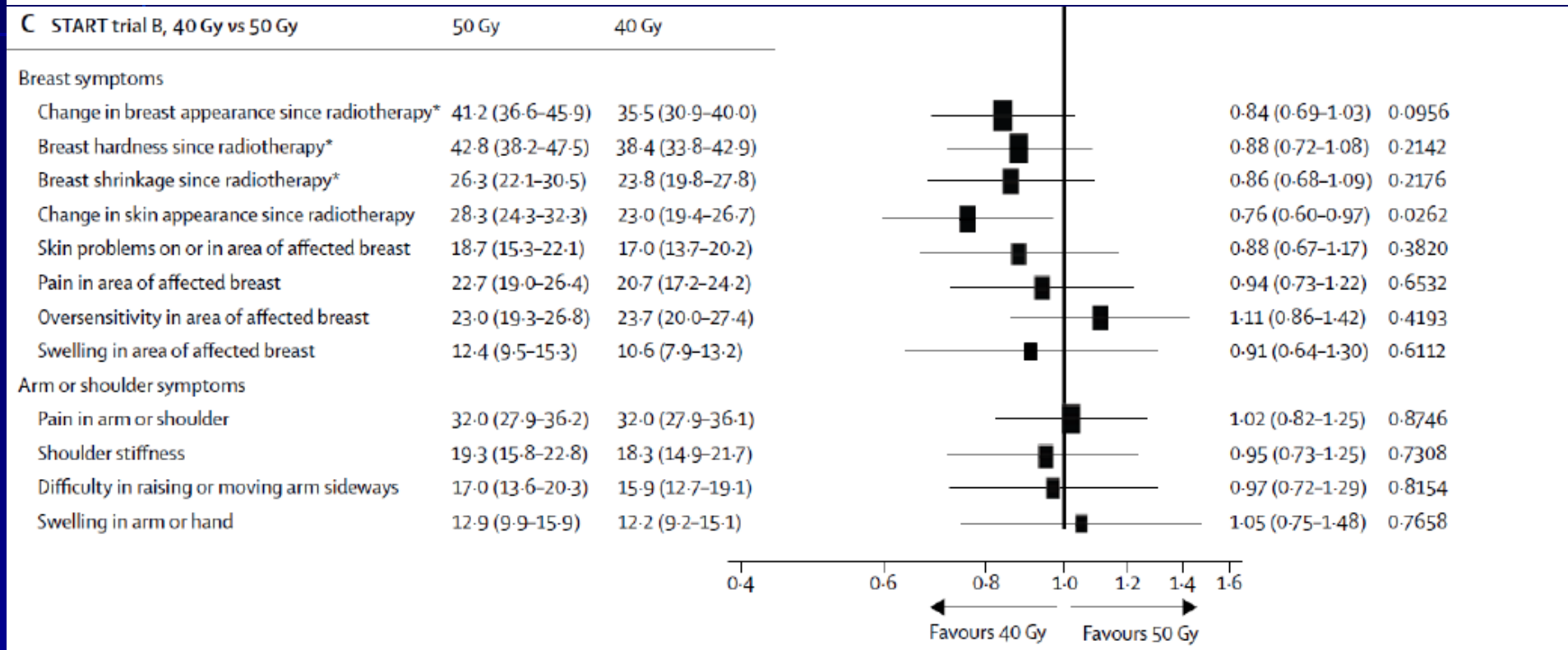


Figure 11 START A AND B: Forest plots of normal tissue effects assessed as moderate or marked by patients, according to radiotherapy regimen[6]



COSMETIC OUTCOME

START A	Results	P value
39Gy/13 #,5 WKS	39 Gy: No statistically significant differences in cosmetic outcome, with the exception of mild or marked change in breast appearance	0.01
41.6 Gy/13 #,5 WKS	No statistically significant differences in any cosmetic outcome	
50Gy/25#,5WKS		
START B		
40Gy/15#/3 WKS	0.77 (95% CI 0.61-0.98)	0.02
50Gy/25#/5 WKS		

ASTRO RECOMMENDATION

- AGE:- 50/>50 Yrs
- T1-2,NO WITH BCT
- NOT TREATED WITH CHEMOTHERAPY
- DOSE:- MIN 93% TO MAXM 107%

PATIENTS NOT RECEIVING A TUMOUR-BED BOOST, THE TASK FORCE FAVOURED A DOSE OF 42.5 GY IN 16 FRACTIONS OVER APPROXIMATELY 22 DAYS WHEN HYPOFRACTIONATED RADIOTHERAPY WAS PLANNED

NEW ZEALAND MINISTRY OF HEALTH GUIDELINES

50 GY IN 25 FRACTIONS OVER 5 WEEKS (GRADE A†),

42.5 GY IN 16 FRACTIONS OVER 3.5 WEEKS FOR THOSE WITH SMALL OR MEDIUM BREASTS, NOT REQUIRING BOOST OR NODAL RADIATION (GRADE B†),

IF BOOST :- 2 GY PER FRACTION

LARGE BREASTS AND THOSE WITH SIGNIFICANT POSTOPERATIVE INDURATION, OEDEMA,ERYTHEMA, HAEMATOMA OR INFECTION:- BE CONSIDERED FOR EXTENDED FRACTIONATION, WITH SMALLER DAILY DOSES OVER 5–6 WEEKS

NICE 2009 GUIDELINES

EXTERNAL BEAM RADIOTHERAPY :- 40 GY IN 15 FRACTIONS AS STANDARD PRACTICE FOR PATIENTS WITH EARLY INVASIVE BREAST CANCER AFTER BREAST CONSERVING SURGERY OR MASTECTOMY.

BOOST GUIDELINE

TO MINIMISE LATE TISSUE DAMAGE WHILST MAXIMISING TUMOUR CONTROL,BOOST DOSE RADIOTHERAPY AT 2GY PER FRACTION WHERE INDICATED FOLLOWING A HYPOFRACTIONATED REGIMEN

HYPOFRACTIONATION:- NOT RECOMMENDED

LARGE BREASTS
AND THOSE WITH SIGNIFICANT POSTOPERATIVE INDURATION, OEDEMA,ERYTHEMA, HAEMATOMA OR INFECTION

NODAL RT

POST OP CA BREAST

CURRENT EVIDENCE IS NOT ABLE TO IDENTIFY AN OPTIMAL DOSE/FRACTIONATION FOR POST-OPERATIVE RADIOTHERAPY.

IT IS THEREFORE REASONABLE TO TREAT PATIENTS WITH CURRENTLY ACCEPTED REGIMENS SUCH AS 50 GY IN 25 DAILY FRACTIONS OVER FIVE WEEKS, 45 GY IN 20 FRACTIONS, OR 40 GY IN 15 OR 16 FRACTIONS.

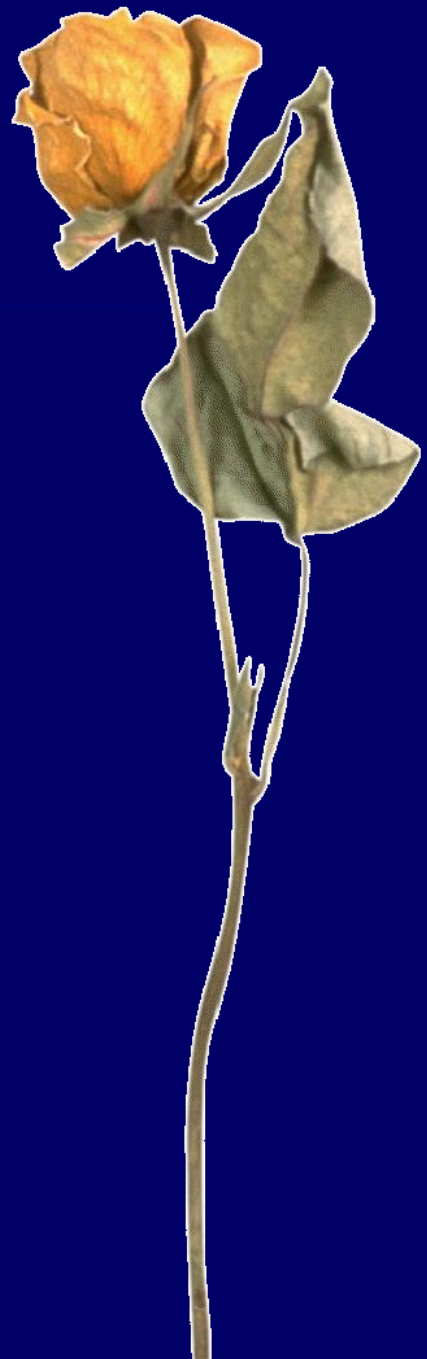
RESULTS OF ONGOING TRIALS INVESTIGATING FRACTIONATED ARE AWAITED

TAKE HOME MESSAGE

- LOCAL RECURRENCE :- NO DIFFERENCE MORE SO IN HIGH GRADE (CANADIAN)
- LOCO REGIONAL RECURRENCE :- NO DIFFERENCE(START A,START-B):-
- DISTANT RELAPSE :- NO STATISTICALLY DIFFERENCE IN START A BUT STATISTICALLY DIFFERENCE IN START-B)
- OVERALL SURVIVAL:- NO DIFFERENCE IN OVER ALL SURVIVAL STITISTICALLY EXCEPT 40Gy ARM IN START B HAVING LESS MORTALITY.
- ADVERSE EVENT AND TOXICITY:- NO DIFFERENCE.SKIN TOXICITY IN START A AND START B WAS LESS IN 39Gy ARM THAN 50Gy ARM
- COSMETICOUTCOME:- 39Gy > 40 Gy >50Gy>42.9 Gy

TAKE HOME MESSAGE

- Recent randomized trials justify the routine use of HF for adjuvant radiotherapy in women with breast cancer.
- Hypofractionated radiation therapy resulted in OAS rate comparable to that of CF (50 Gy/25 fractions/5weeks) without evidence of inferior local tumor control or higher adverse effects.
- Hypofractionated radiation therapy can be recommended as safe and effective alternatives to CF for whole-breast or postmastectomy chest wall radiotherapy.



THANK YOU