Evolution of Hypofractionation for Breast Cancer

Dr Beela Sarah Mathew
Professor, Dept of Radiation Oncology
Regional Cancer Centre
Thiruvananthapuram

Rationale

Radiotherapy reduces local relapse and breast cancer mortality

Historical assumption: Breast cancer is less sensitive to dose per fraction

45-50Gy/25Fr/1.8-2.0Gy per Fr/5times a week

Recurrent /inoperable breast cancer α/β: 4-5Gy

Breast/chest wall RT targets microscopic cells – lower total dose

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
HD Thames et al. Time-dose factors in radiotherapy: a review of the human data . Radiotherapy and Oncology, 19 (1990) 219-235
Bentzen, S. M et al. Some methodological problems in estimating radiobiological parameters from clinical data. Alpha/beta ratios and electron RBE for cutaneous reactions in patients treated with postmastectomy radiotherapy. Acta Oncol. 27: 105-l 16, 1988.

Clinical trials

- Hypothesis: Breast cancer is similarly sensitive to fraction size as surrounding normal breast tissue.
- 1986- RMH-GOC trial (START pilot)
- 1993- Canadian (Ontario) Trial
- 1999-START A & B
- 2004- FAST
- 2011 - FAST forward

RMH-GOC Trial (START–PILOT)

- Aim: fractionation sensitivity
- 1410 patients, post BCS (1986-98)
- 50 Gy/25Fr *vs* 39Gy/13Fr *vs* 42.9Gy/13Fr
- 5 weeks
- Primary endpoint-late change in breast appearance
- Sec endpoints- breast induration, ipsilateral tumor recurrence

Yarnold J et al. Fractionation sensitivity and dose response of late adverse effects in the breast after radiotherapy for early breast cancer: long-term results of a randomised trial. Radiotherapy and Oncology 75 (2005) 9–17
Owen JR et al. Effect of radiotherapy fraction size on tumour control in patients with early-stage breast cancer after local tumour excision: long-term results of a randomised trial. Lancet Oncol. 2006;7(6):467–71.

RMH-GOC - Results

Estimates of alpha-beta ratios for each normal tissue endpoint, obtained from Cox proportional hazards regression analysis

Endpoint	α/β (95%CI), in Gy
Photographic assessment	
Any change in breast appearance	3.6 (1.8-5.4)
Marked change in breast appearance	2.9 (1.0-4.8)
Clinical assessment	
Cosmesis (fair/poor)	3.8 (1.4-6.3)
Breast shrinkage (moderate/marked)	4.7 (1.0-8.6)
Breast distortion (moderate/marked)	3.1 (1.0-5.8)
Breast oedema (moderate/marked)	2.3 (1.0-4.5)
Induration (moderate/marked)	3.1 (1.8-4.4)
Telangiectasia (moderate/marked)	5.1 (1.0-9.5)
Arm oedema (moderate/marked)	2.2 (1.0-7.9)
Shoulder stiffness (moderate/marked)	1.8 (1.0-3.6)

Breast Cancer **4.0Gy (1.0-7.8)**

RMH-GOC Results

α/β	Total dose	EQD2	50Gy/25# iso-effective
3Gy	39Gy/13Fr	46.7Gy	40.8Gy/13Fr (3.14Gy)
	42.9 Gy/13Fr	53.9Gy	
4Gy	39Gy/13Fr	45.5Gy	41.6Gy/13Fr (3.2Gy)
	42.9 Gy/13Fr	52.2Gy	

Canadian (Ontario) 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

Journal of the National Cancer Institute, Vol. 94, No. 15, August 7, 2002

Long-Term Results of Hypofractionated Radiation Therapy for Breast Cancer

Timothy J. Whelan, B.M., B.Ch., Jean-Philippe Pignol, M.D., Mark N. Levine, M.D., Jim A. Julian, Ph.D., Robert MacKenzie, M.D., Sameer Parpia, M.Sc., Wendy Shelley, M.D., Laval Grimard, M.D., Julie Bowen, M.D., Himu Lukka, M.D., Francisco Perera, M.D., Anthony Fyles, M.D., Ken Schneider, M.D., Sunil Gulavita, M.D., and Carolyn Freeman, M.D.

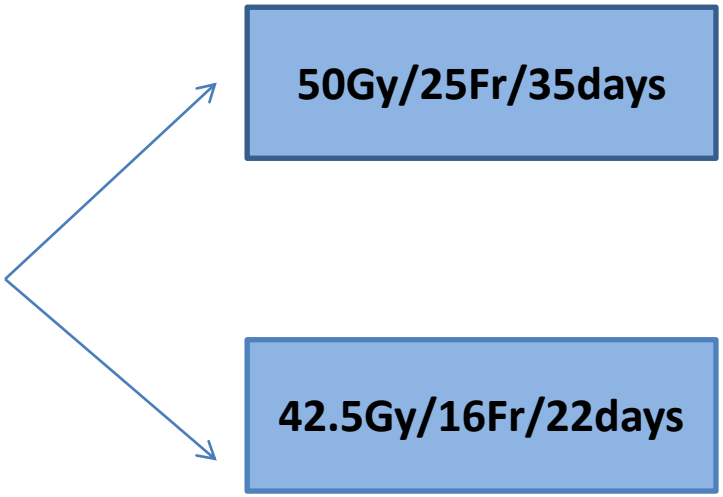
N Engl J Med 2010;362:513-20.

Canadian (Ontario) Trial

Design: Non-inferiority

Eligibility:

- Invasive carcinoma
- ≤5cm
- Node negative
- Post -lumpectomy
- margin negative



Endpoints:

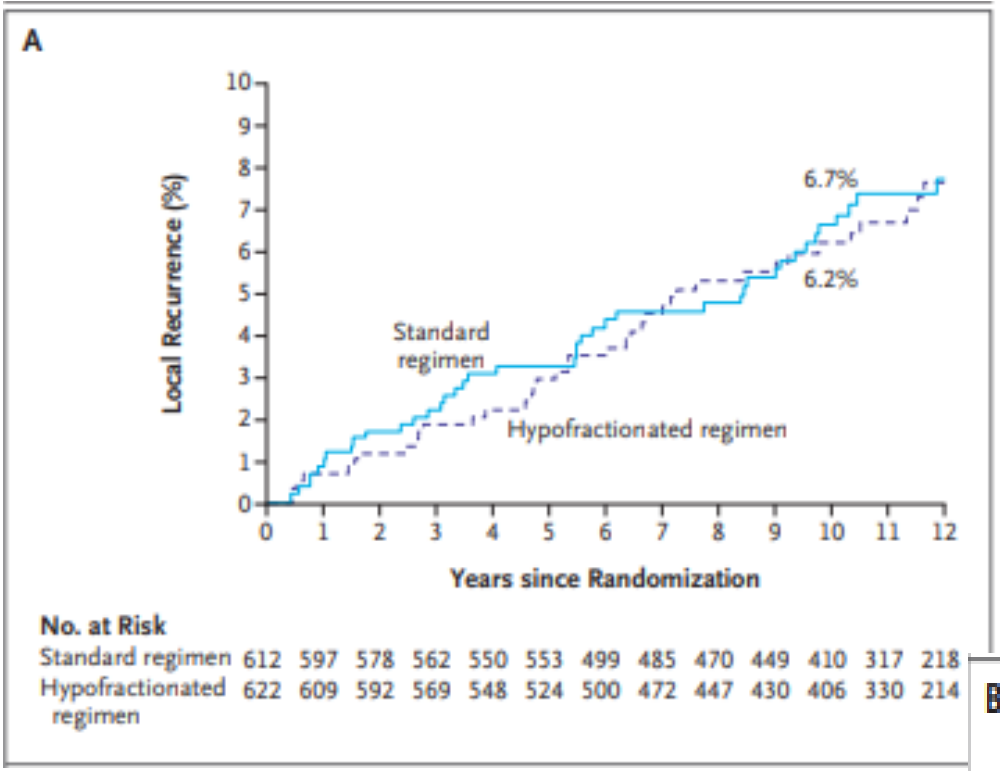
Primary : ipsilateral invasive cancer recurrence

Secondary : distant recurrence

death

breast cosmesis

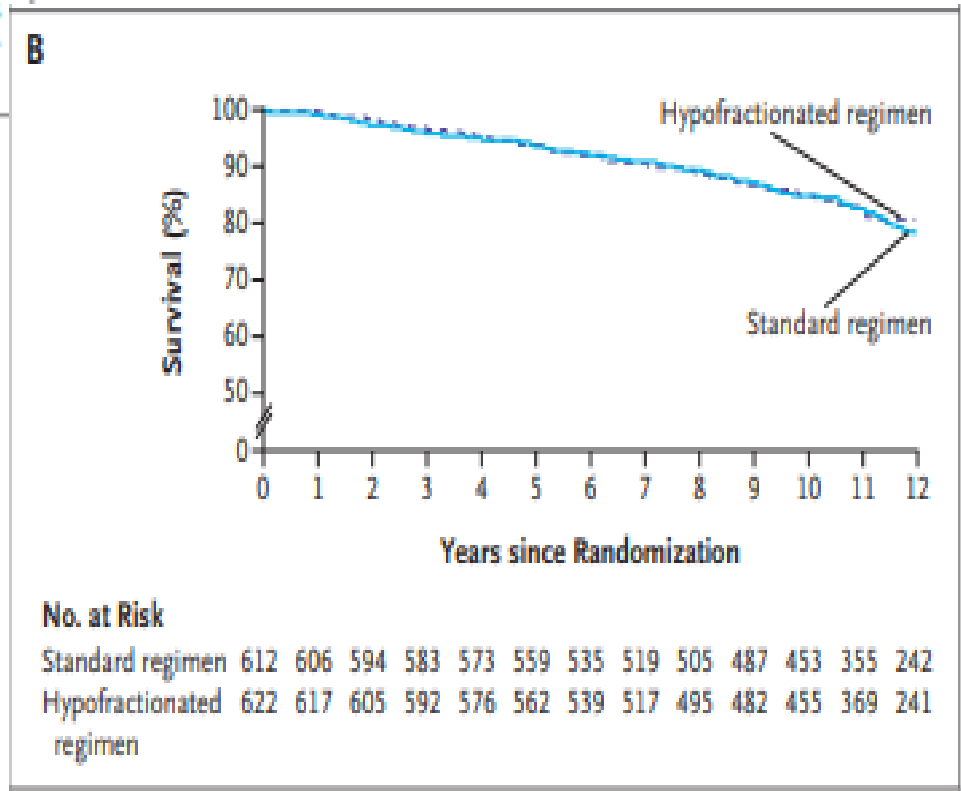
late radiation toxicity



Apr 1993 –Sep 1996
1234 patients
10 year update

LR (n=83) : 6.7% vs 6.2% ;
95% CI −2.5 to 3.5

OS (n=248): 84.4% vs 84.6%;
95% CI CI, −4.3 to 4.0



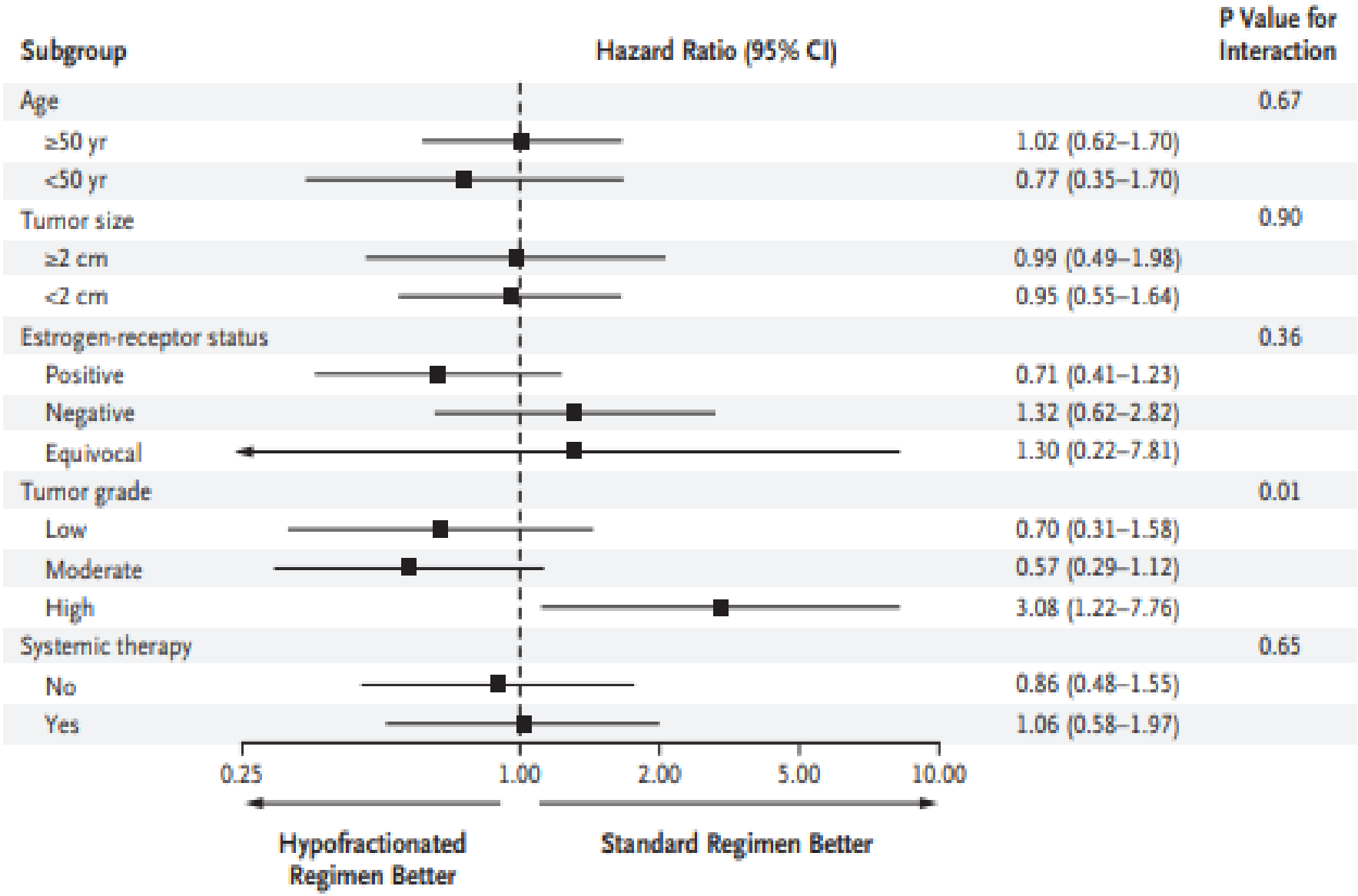


Figure 2. Hazard Ratios for Ipsilateral Recurrence of Breast Cancer in Subgroups of Patients.

Canadian Trial - Cosmesis

- No grade 4 skin or subcutaneous toxicity
- Grade 3 toxicity ≤ 4%
- Grade 0 skin toxicity: 70.5% *vs* 66.8% (95% CI −4.9 to 12.1)
- Grade 0 subcutaneous toxicity: 45.3% vs 48.1% (95% CI −11.7 to 6.5)

- Good or excellent cosmetic outcome:

  71.3% vs 69.8% (95% CI, −6.9 to 9.8)

START A & B Trials

1999-2002; 35 UK centres

Eligibility:

- pT1-3, pN0-1, M0
- Post BCS/mastectomy
- 10Gy/5# sequential boost allowed

Endpoints:

Principal**:** loco-regional tumour relapse, normal tissue effects, quality of life

Others: DFS, OS, second primary cancers, health economic consequences

The START Trialists' Group
The UK Standardisation of Breast Radiotherapy (START) Trial A of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial Lancet Oncol 2008;9:331-341. The UK Standardisation of Breast Radiotherapy (START) Trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. Lancet 2008; 371(9618): 1098–1107.
Haviland JS et al. 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. Lancet Oncol 2013; 14: 1086–94

START A & B Trials

START A

- 80% power to detect 5% difference in loco-regional recurrence

50 Gy /25Fr

41.6 Gy/13Fr

39Gy/13Fr

START B

95% power to exclude 5% increase in loco-regional recurrence

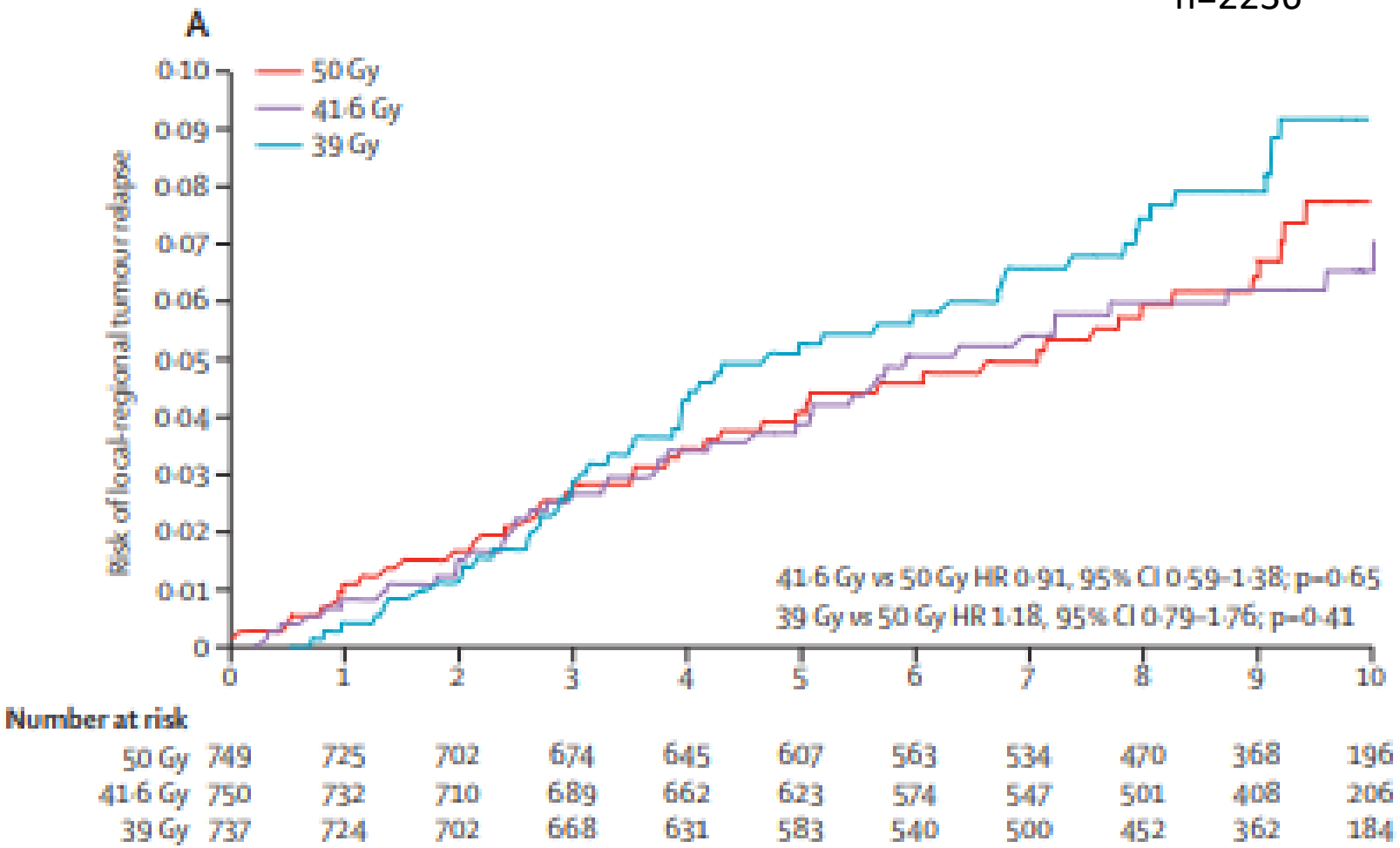
50 Gy /25Fr/5 weeks

40Gy/15Fr/3 weeks

Overall treatment time: 5 weeks

START A – locoregional relapse

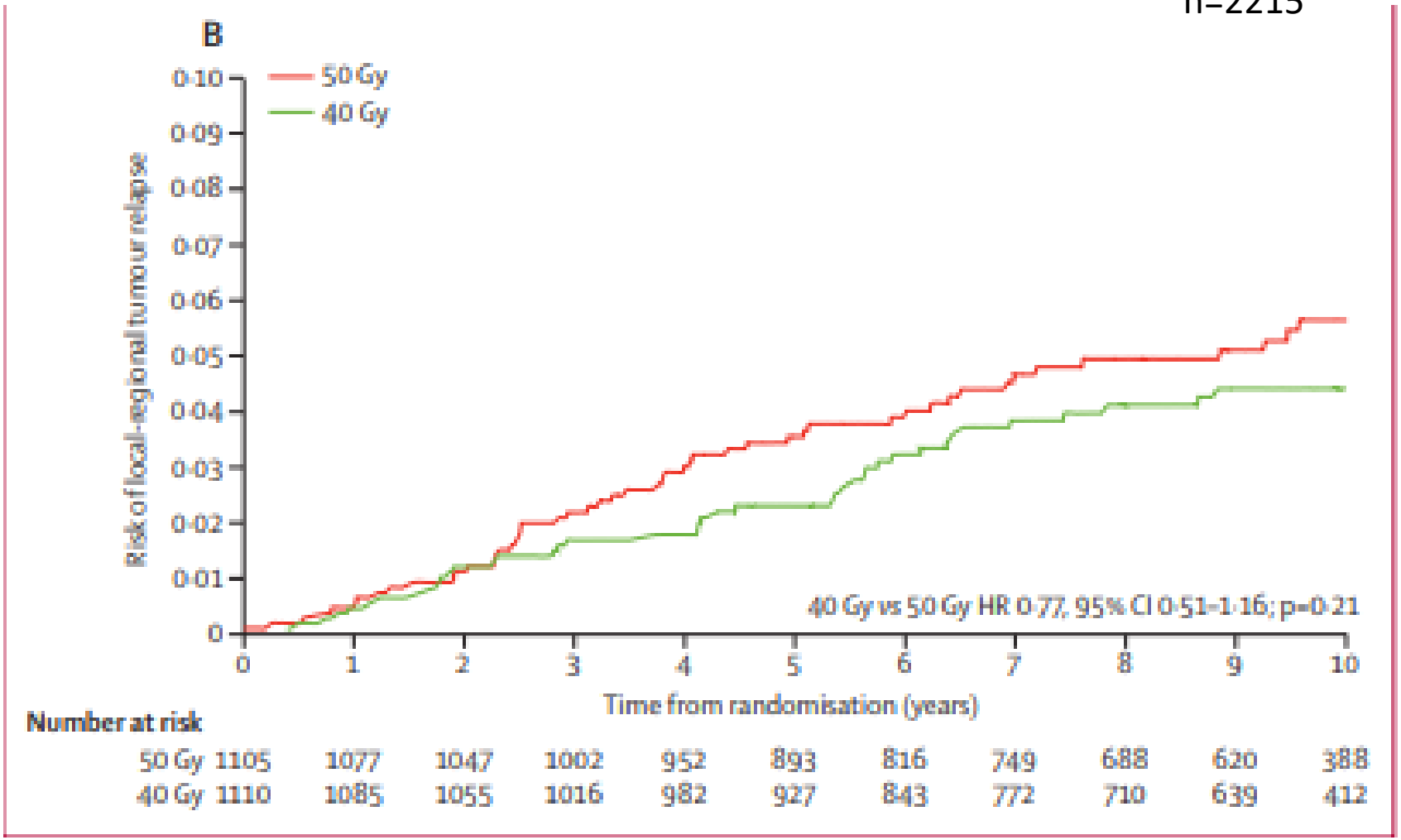
n=2236



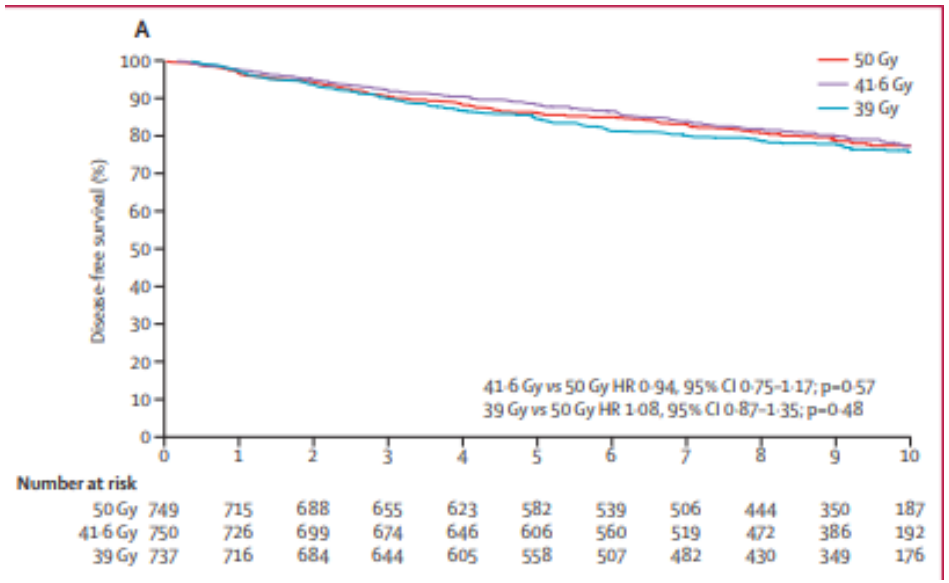
Haviland JS et al. The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials. Lancet Oncol 2013; 14: 1086–94

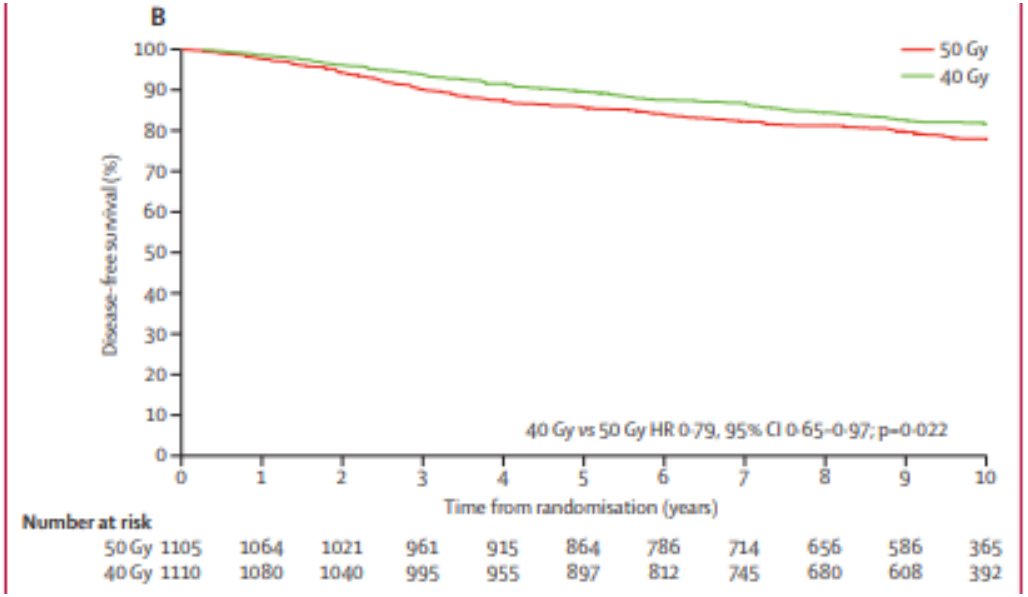
START B – locoregional relapse

n=2215

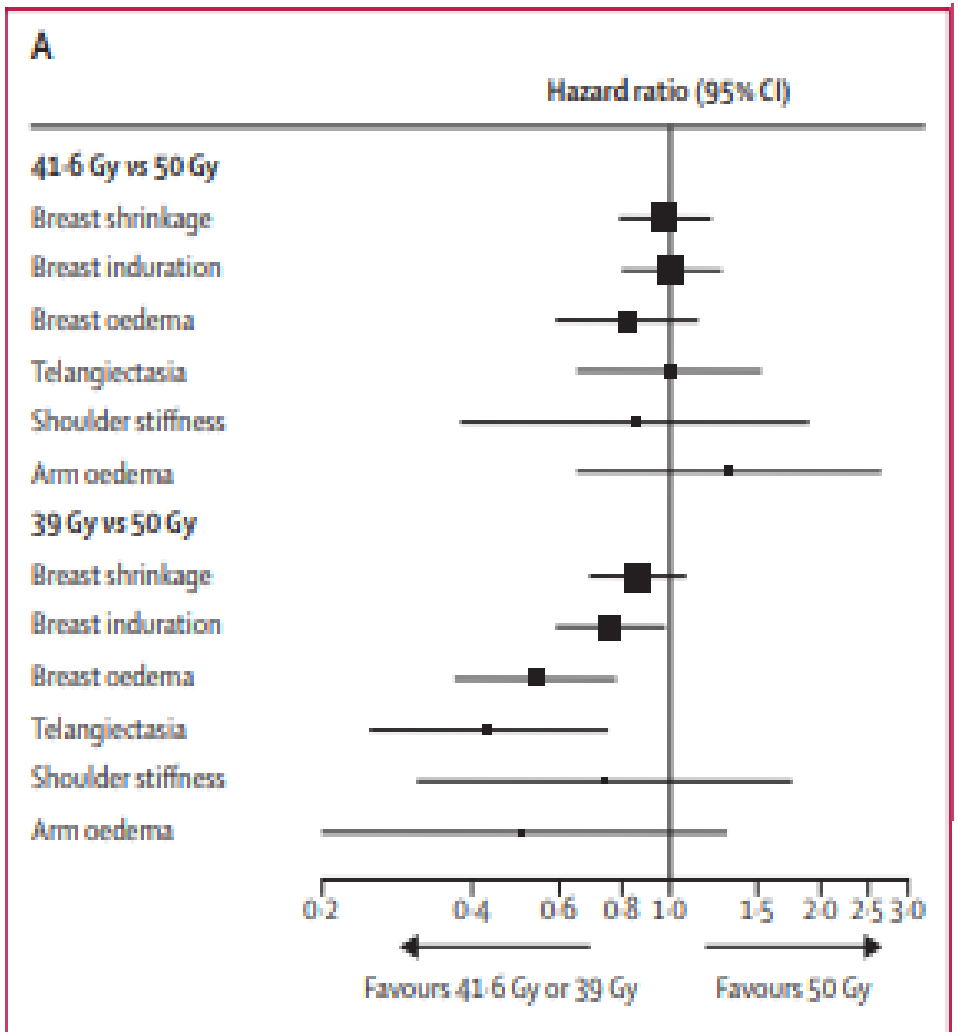


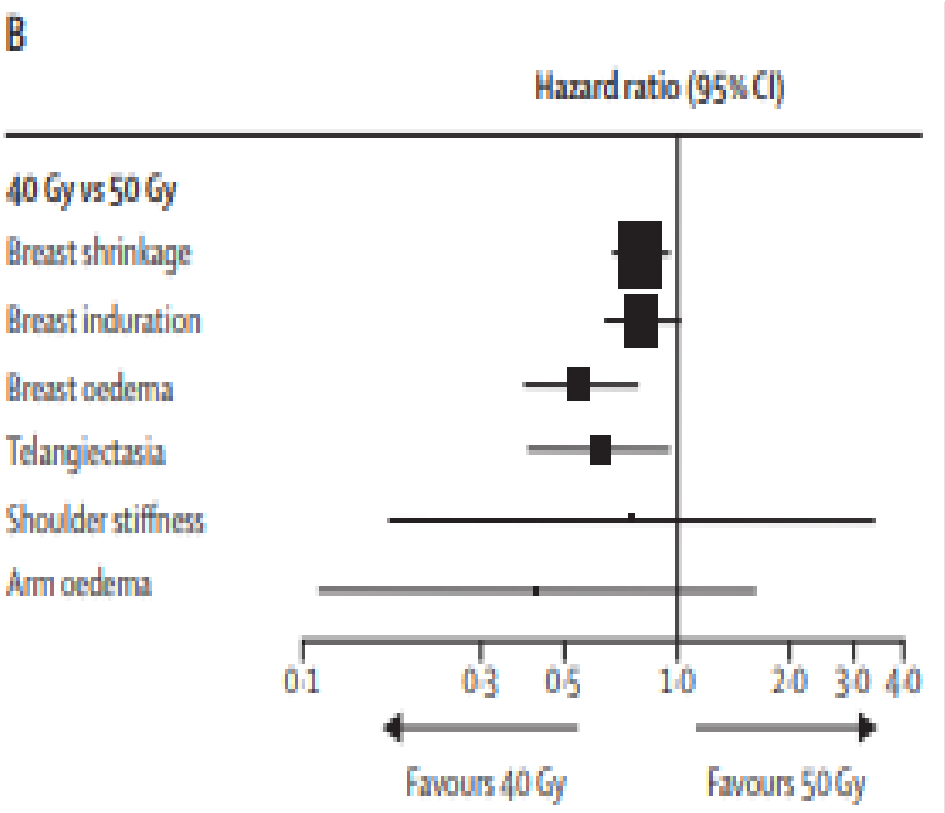
START A & B Trials – Disease free survival





START A & B – normal tissue effects

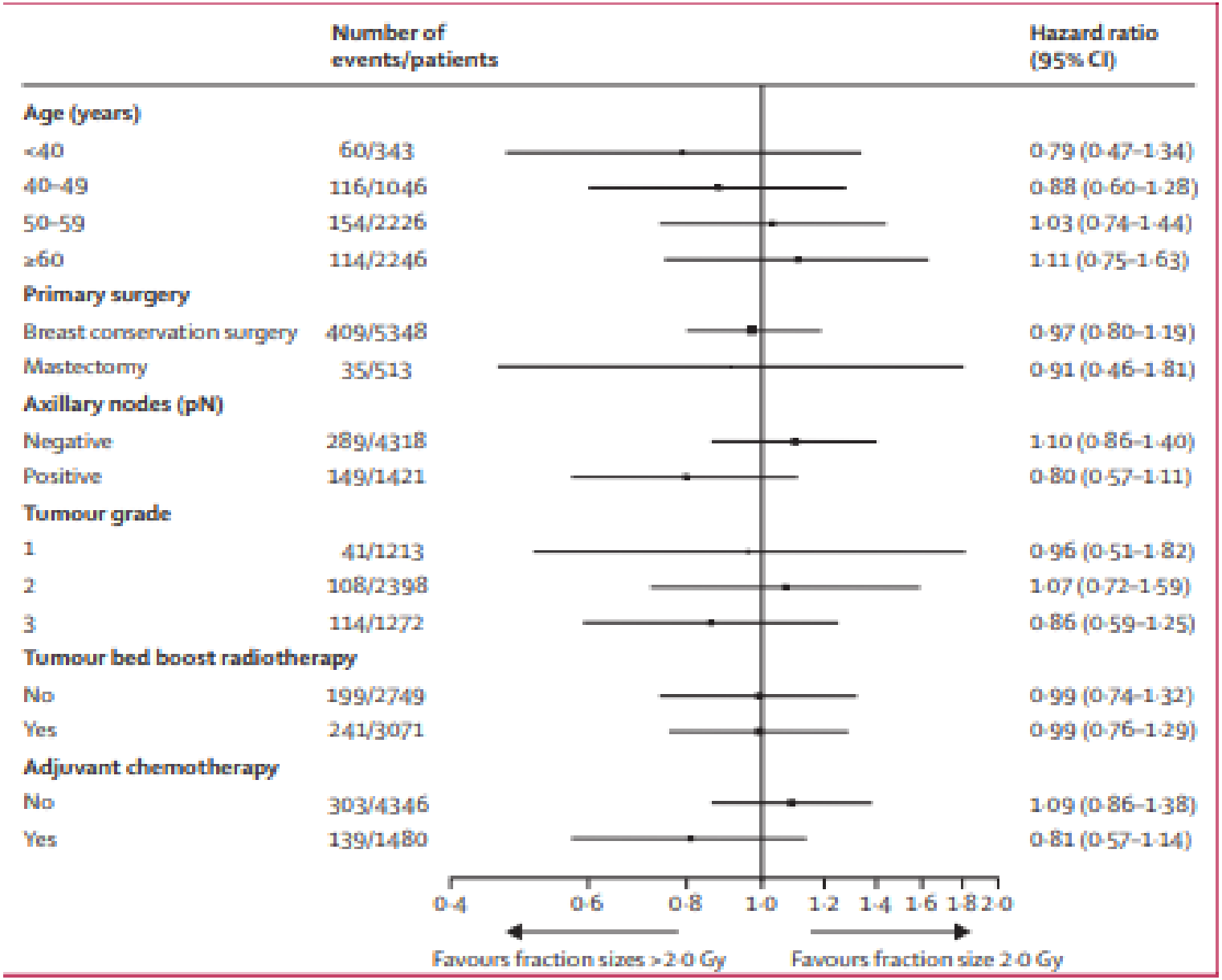




Ischemic heart disease, symptomatic rib fractures, symptomatic lung fibrosis, brachial plexopathy were rare (<2%) and similar.

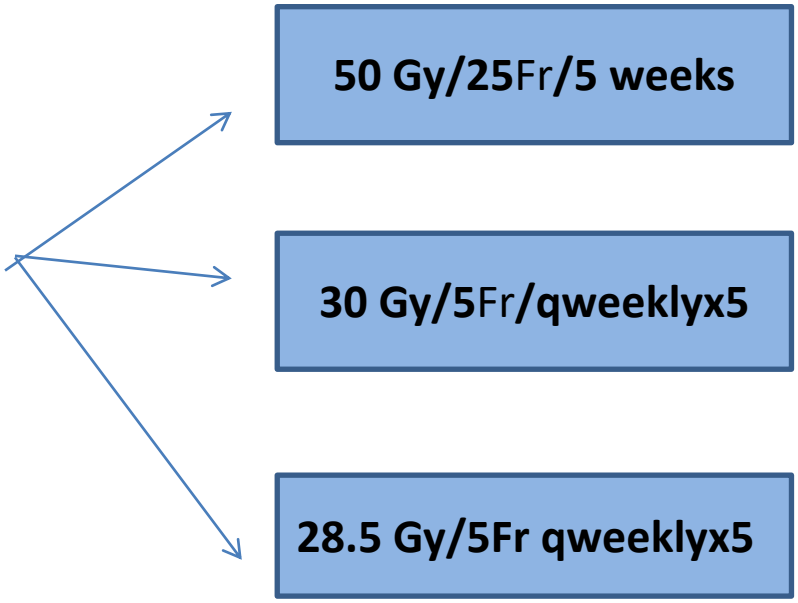
START pilot, A & B-Meta-analysis

n=5861



UK- FAST

- 2004-2007
- ≥ 50 years
- pT1-2 pN0



Primary end point- change in photographic breast appearance at 2 and 5 years

Secondary end points- normal tissue effects, local tumor control

Brunt AM et al. Ten-Year Results of FAST: A Randomized Controlled Trial of 5-Fraction Whole-Breast Radiotherapy for Early Breast Cancer. J Clin Oncol 2020 Oct 1; 38(28): 3261–3272.

UK- FAST

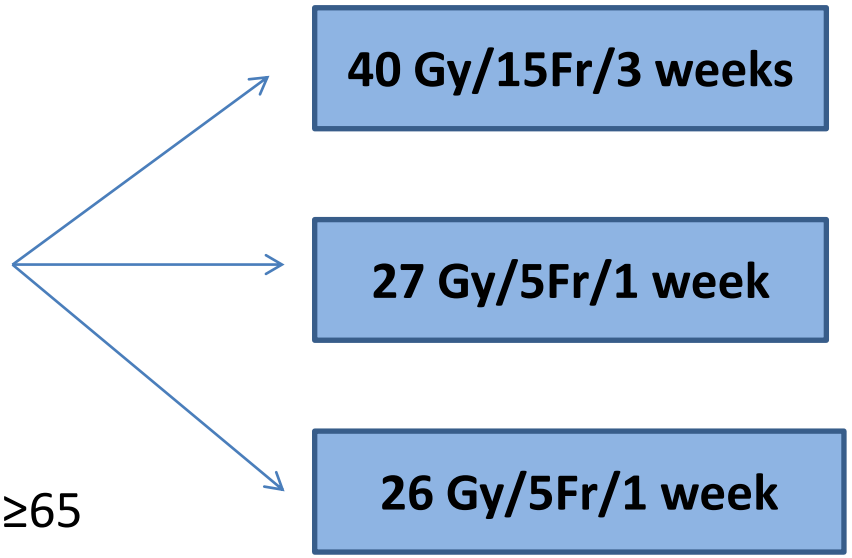
- 915 patients
- Median FU 9.9 years
- Moderate/marked NTE significantly higher for 30 Gy *vs* 50 Gy
- Moderate/marked NTE higher for 28.5 Gy *vs* 50 Gy but not significant
- Breast shrinkage, telangiectasia, and breast edema significantly higher for 30 Gy *vs* 28.5 Gy
- Prevalence of breast shrinkage and telangiectasia increased over time
- Local recurrence 1.3% (under-powered)
- 28Gy/5Fr/once weekly at 5.7Gy/Fr -potential option for convenience

FAST Forward

- Non-inferiority design
- Nov 2011-Jun 2014

- pT1-3, pN0-1, M0
- Post BCS or mastectomy

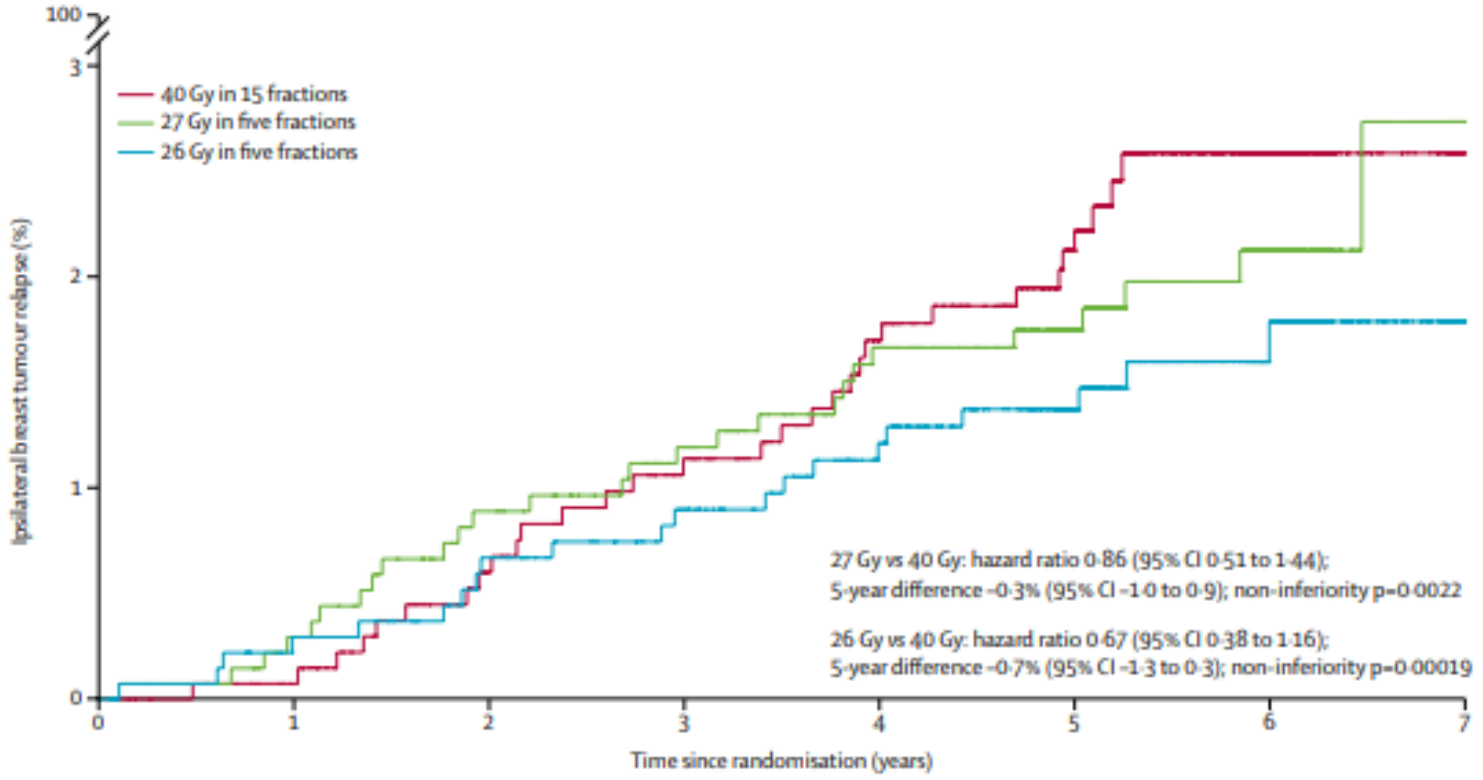
- Excluded Luminal A, stage I, age ≥65 years from 2015



Primary endpoint- ipsilateral breast tumour relapse
Secondary endpoints-Normal tissue effects assessed by clinicians, patients, and from photographs, locoregional relapse, distant relapse, disease-free survival, and overall survival.

Brunt AM et al. 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. Lancet 2020 23-29 May; 395(10237): 1613–1626.

FAST Forward



40 Gy								
Number at risk	1361	1347	1307	1281	1230	1045	486	91
Censored	0	13	46	65	109	289	844	1239
Events	0	1	8	15	22	27	31	31
27 Gy								
Number at risk	1367	1352	1328	1303	1255	1066	508	90
Censored	0	11	27	48	90	278	833	1250
Events	0	4	12	16	22	23	26	27
26 Gy								
Number at risk	1368	1347	1325	1302	1257	1070	524	89
Censored	0	17	34	54	95	280	824	1258
Events	0	4	9	12	16	18	20	21

n = 4096

Median FU=71.5 mos

FAST Forward

- Locoregional relapse, distant relapse, disease-free survival, and overall survival similar
- Clinician-assessed NTE (breast distortion, shrinkage, induration and breast or chest wall oedema):
  - significantly worse for 27Gy *vs* 40Gy/26Gy
  - Similar for 26Gy *vs* 40Gy
- Patient assessed:
  - significantly worse moderate/marked breast hardness for 27 Gy *vs* 40 Gy
  - lower risk of change in breast appearance for 26 Gy *vs* 27 Gy
  - no significant differences for other NTE
- Photographic assessments:
  - 27 Gy worse than 40Gy & 26Gy
  - 26Gy similar to 40Gy

Role of Boost?

EORTC RCT: 2657 patients – boost 16Gy in 8 Fr over 50 Gy in 25Fr improves local control but not OS, in young patients

- Canadian trial – no boost
- START trials – allowed boost
- Metanalysis of START trials: no difference (small numbers)
- Ultrahypofractionation trials – no boost

- Hypofractionated -SIB RT (RTOG 1005 and IMPORT-HIGH)
- 5-year results of IMPORT HIGH(ESTRO 2021):
- comparable ipsilateral breast recurrence and moderate/marked side effects for 48Gy/15Fr

Bartelink H et al. Whole-breast irradiation with or without a boost for patients treated with breast-conserving surgery for early breast cancer: 20-year follow-up of a randomised phase 3 trial. Lancet Oncol. 2015;16(1):47-56
Schmitt M et al. Adjuvant hypofractionated radiotherapy with simultaneous integrated boost after breast-conserving surgery: A systematic literature review. Transl Oncol 2022 Aug:22:101456.

Hypofractionated Versus Standard Fractionated Radiotherapy in Patients With Early Breast Cancer or Ductal Carcinoma In Situ in a Randomized Phase III Trial: The DBCG HYPO Trial

Birgitte V. Offersen, MD, PhD[1,2]; Jan Alsner, PhD[1]; Hanne M. Nielsen, PhD[2]; Erik H. Jakobsen, MD[3]; Mette H. Nielsen, PhD[4]; Mechthild Krause, MD, PhD[5]; Lars Stenbygaard, MD[6]; Ingvil Mjaaland, MD[7]; Andreas Schreiber, MD, PhD[8]; Unn-Miriam Kasti, MD[9]; and Jens Overgaard, MD, DMSc[1]; on behalf of the Danish Breast Cancer Group Radiation Therapy Committee

J Clin Oncol 2020 Nov 1;38(31):3615-3625.

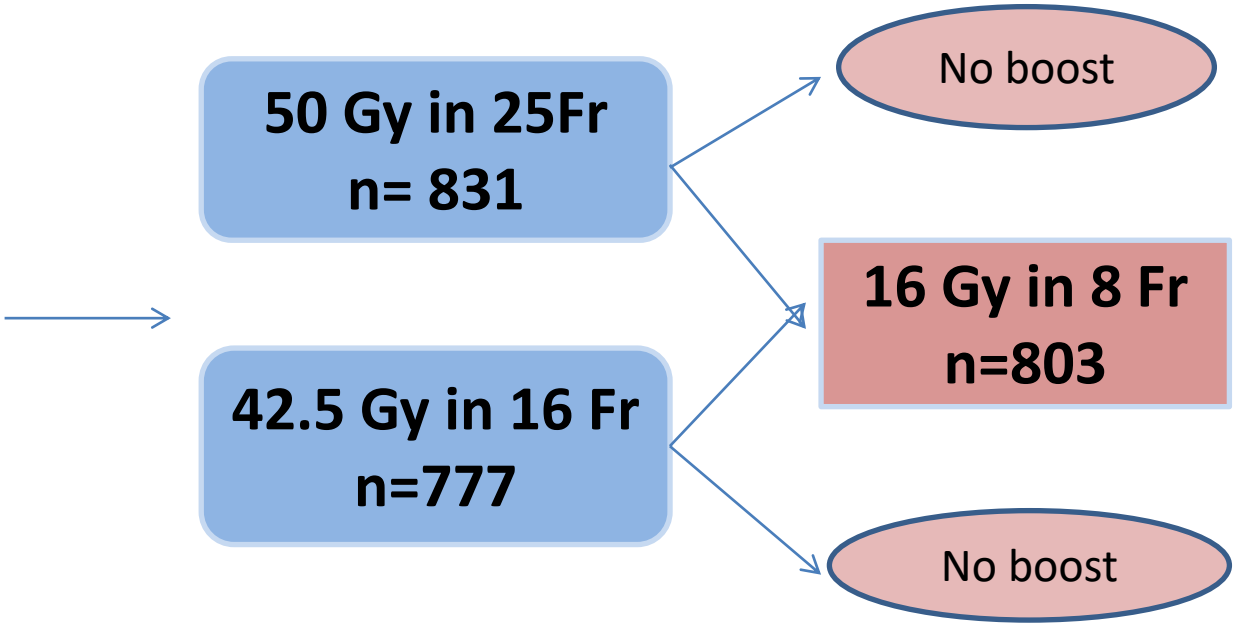
- 2009-2014; Non-inferiority
- N=1854; node negative invasive = 1608, DCIS = 246
- 50Gy in 25 Fr *vs* 40Gy in 15 Fr
- 3 year breast induration rates comparable
- Cosmesis and patient satisfaction comparable or better with 40Gy
- 9 year risk of locoregional recurrence and OS comparable
- Cardiac and lung effects rare and not influenced by fractionation

Radiation doses and fractionation schedules in non-low-risk ductal carcinoma in situ in the breast (BIG 3–07/TROG 07.01): a randomised, factorial, multicentre, open-label, phase 3 study

The Lancet 2022; 400 (10350): 431-440

2007-2014

- n=1608
- Non-low risk DCIS
- Post BCS
- 1mm margin



Median follow-up- 6.6 years

- *Hypofractionated WBI was as safe and effective in DCIS*
- *Tumour bed boost significantly reduces local recurrence with an increase in grade 2 or higher toxicity*

Cardiac Toxicity

Contents lists available at SciVerse ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

Original Article

Modern Hypofractionation Schedules for Tangential Whole Breast Irradiation Decrease the Fraction Size-corrected Dose to the Heart

A.L. Appelt *†, I.R. Vogelius ‡, S.M. Bentzen §

60 left-sided breast cancers; tangential WBI

Dose distribution corrected to EQD2 for 40Gy/15Fr, 42.5Gy/16Fr,

39Gy/13Fr and 41.6Gy/13Fr for α/β values of 0-5 Gy.

All except 41.6Gy spared the heart compared to 50Gy /25Fr.

The Breast 48 (2019) 24–31

Contents lists available at ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

Review

Meta-analysis of long-term efficacy and safety of hypofractionated radiotherapy in the treatment of early breast cancer

Teresa R.M. Andrade [a], Marcelo C.M. Fonseca [a, *], Helena R.C. Segreto [b], Roberto A. Segreto [b], Eduardo Martella [c], Afonso C.P. Nazário [d]

Purpose: To evaluate the efficacy and safety of hypofractionated radiotherapy in women with early stage breast cancer after breast conservative surgery.

Methods: We performed a search for randomized controlled trials (RCTs) that compare conventional fractioning and hypofractioned radiotherapy. The studied outcomes were local and loco-regional recurrence, disease-free survival, mortality, cardiac ischemia, rib fracture and pulmonary fibrosis up to 5 years and 5 years after treatment. Shrinkage of the breast, breast tightening, telangiectasia, breast edema, shoulder stiffness and arm edema were evaluated within 10 years. Cosmesis and acute skin radiation toxicity were evaluated.

Results: Ten publications of six RCTs were included. No statistical difference in local and loco-regional recurrence, disease-free survival, mortality, cardiac ischemia, ribs fracture and pulmonary fibrosis, shrinkage of the breast, breast tightening, shoulder stiffness, arm edema and cosmesis was found. However, there was a significant difference in favor of hypofractionated for breast edema (RR 0.68, 95% CI 0.53 to 0.88, p = 0.003, 4675 patients), telangiectasia (RR 0.41, 95% CI 0.19 a 0.87, p = 0.02, 5167 patients), and acute skin radiation toxicity (RR 0.34, 95% CI 0.19 to 0.61, p = 0.0003, 347 patients).

Conclusion: There is no difference between conventional fractionation and hypofractionated in terms of efficacy when we evaluate local recurrence, loco-regional recurrence, distance recurrence, disease-free survival and mortality. There is also no difference concerning safety when we assess the occurrence of fibrosis, ischemia and ribs fractures. Hypofractionated showed better results in relation to breast edema, telangiectasia, and acute skin radiation toxicity.

Hypofractionation

- Improves therapeutic index for breast cancer
- Maintains dose equivalence of TCP
- Decreases total normal tissue dose
- 3DCRT, DIBH, prone, IMRT improves NTCP
- Patient convenience
- Decreases costs on resources

Current Recommendations

ESTRO Advisory Committee in Radiation Oncology Practice consensus

- Moderately hypofractionated radiotherapy can be offered to any patient for whole breast, chest wall (with or without reconstruction), and nodal volumes.

- Ultrafractionation (five fractions) can also be offered for non-nodal breast or chest wall (without reconstruction) radiotherapy either as standard of care or within a randomised trial or prospective cohort.

Meattini I et al. European Society for Radiotherapy and Oncology Advisory Committee in Radiation Oncology Practice consensus recommendations on patient selection and dose and fractionation for external beam radiotherapy in early breast cancer. Lancet Oncol 2022; 23: e21–31

Ongoing studies

- Hyport-Adjuvant trial –multicentre, phase III trial
  - RT to breast or chest wall (with/without RNI)
  - 40 Gy/15 fr/3 weeks vs 26 Gy/5 fr/1 week
  - SIB of 8 Gy and 6 Gy allowed

- FLASH radiotherapy

Contents lists available at ScienceDirect

Clinical and Translational Radiation Oncology

journal homepage: www.sciencedirect.com/journal/clinical-and-translational-radiation-oncology

Comparison of intratumor and local immune response between MV X-ray FLASH and conventional radiotherapies

Hongyu Zhu [a,1], Dehuan Xie [b,1], Ying Wang [a], Runda Huang [a], Xi Chen [c], Yiwei Yang [d], Bin Wang [a], Yinglin Peng [a], Jianxin Wang [d], Dexin Xiao [d], Dai Wu [d], Chao-Nan Qian [e,*], Xiaowu Deng [a,*]

Pencil Beam Scanning Bragg Peak FLASH Technique for Ultra-High Dose Rate Intensity-Modulated Proton Therapy in Early-Stage Breast Cancer Treatment

Grant Lattery [1,†], Tyler Kaulfers [1,†], Chingyun Cheng [2], Xingyi Zhao [3,4], Balaji Selvaraj [4], Haibo Lin [4], Charles B. Simone II [4], J. Isabelle Choi [4,‡], Jenghwa Chang [1,5,*,‡] and Minglei Kang [4,*]

" Half of cancer patients who need radiotherapy in low and middle income countries do not have access to it. This is a sobering statistic. And it is unacceptable"

Rafael Grossi

IAEA Director General