MRO. ART
INNOVATIVE TREATMENTS AND PATIENTS COMPLIANCE
31° RESIDENTIAL COURSE

Breast cancer innovation and compliance

CONSTRAINTS AND TOXICITY IN STANDARD TREATMENTS

Dott. Fabio Marazzi
UOC Radioterapia
Fondazione Policlinico Gemelli IRCCS - Roma

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- **Introduction**
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- **Standard moderate hypofractionation**:
  - dose constraints and breast radiotherapy tolerance
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- **Conclusions**

INTRODUCTION

- ✓ The main role of radiotherapy is the eradication of residual subclinical disease after mastectomy or breast-conservation surgery; only in a limited experimental case series breast tumour response was directly observed
- ✓ Since 1970s, we know that a total dose of 45-50 Gy (1.8-2 Gy fr) is sufficient to eradicate microscopic residual after breast conserving surgery
- ✓ A dose higher than 60 Gy is required to obtain local control when the tumor is not totally excised

Tutt A, Yarnold J. Radiobiology of breast
Arriagada R, et al Radiotherapy alone in breast can

INTRODUCTION

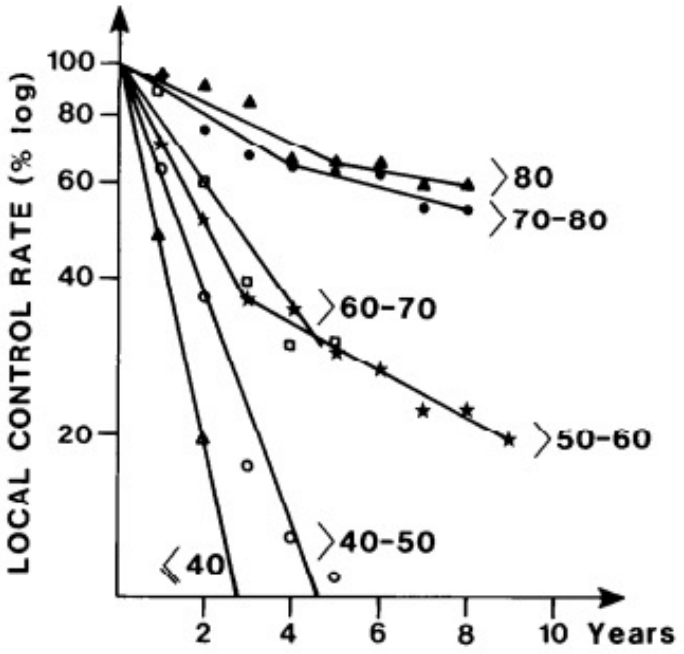


Fig. 3. Local control according to 6 groups of tumor dose (Gy). ▲ = >80 Gy; ⋆ = >50–60 Gy; ● = >70–80 Gy; ○ = >40–50 Gy; □ = >60–70 Gy; △ = ≤40 Gy.

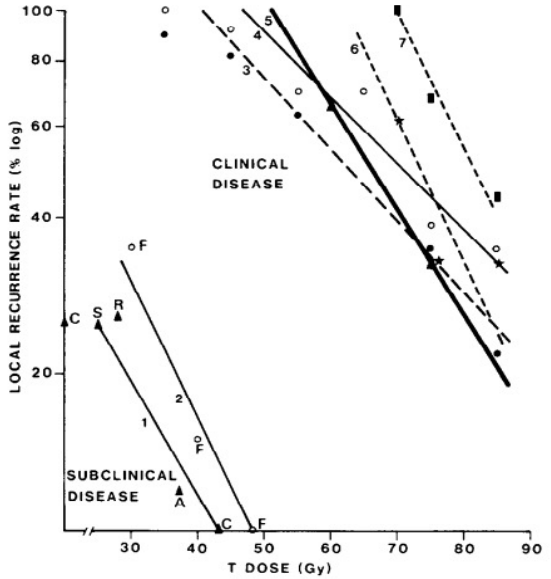


Fig. 8. Tumor (T) dose and local recurrence rate curves: Subclinical disease: 1) After lumpectomy (▲): C: Clark[7]; S: Simon *et al.*[24]; R: Rissanen[19]; A: Atkins *et al.*[2] In fact, Sarrazin *et al.*[21] and Pierquin *et al.*[12,18] report local recurrence rates at 5 years of 4% and 3%, delivering doses of 66 Gy and 70 Gy, respectively. 2) F (○): Fletcher data.[11] Clinical disease: IGR-PMH data: 3) (●): recurrence at 3 years; 4) (○): recurrence at 5 years; and 5) (▲) local recurrence and tumor dose relationship according to the multivariate analysis for a tumor larger than 5 cm, T3bN2 (see text). Calle *et al.*[5,6]: 6) (⋆) Local recurrence at 5 years for tumors ≤ 5 cm; 7) (■) Local recurrence at 5 years for tumors > 5 cm.

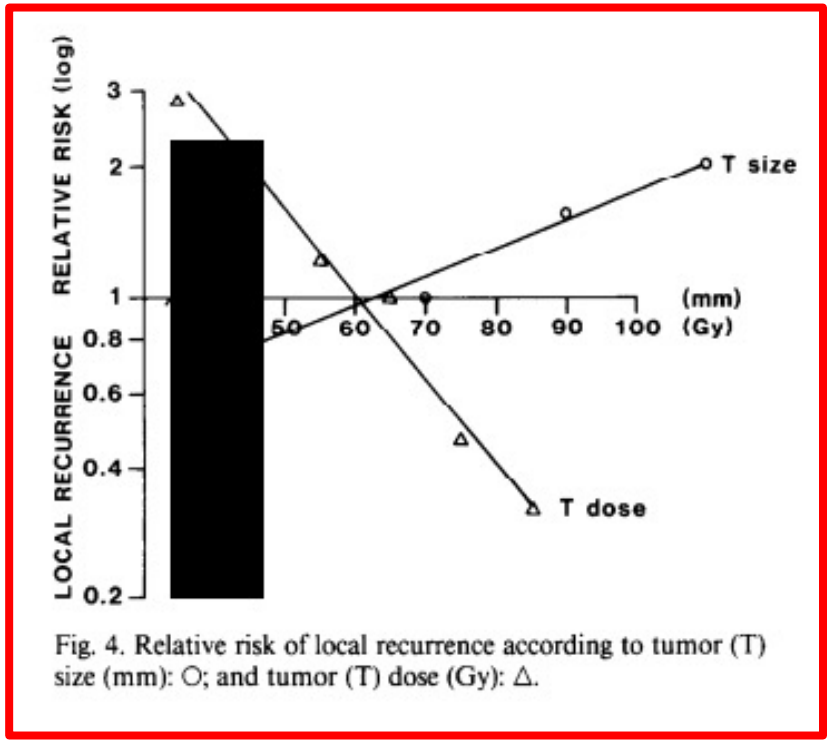


Fig. 4. Relative risk of local recurrence according to tumor (T) size (mm): ○; and tumor (T) dose (Gy): △.

- cT3cN2 60Gy risk of PD at 3 yrs 66% 75Gy risk of PD a 3 yrs 33%
- Microscopic disease after lumpectomy 60Gy risk LR 7% and 75Gy risk LR 3.5%
- 15Gy halve the risk of local relapse

Tutt A, Yarnold J. Radiobiology of breast
Douglas BG, Castro JR. Novel fractionation schemes and high linear ene

INTRODUCTION

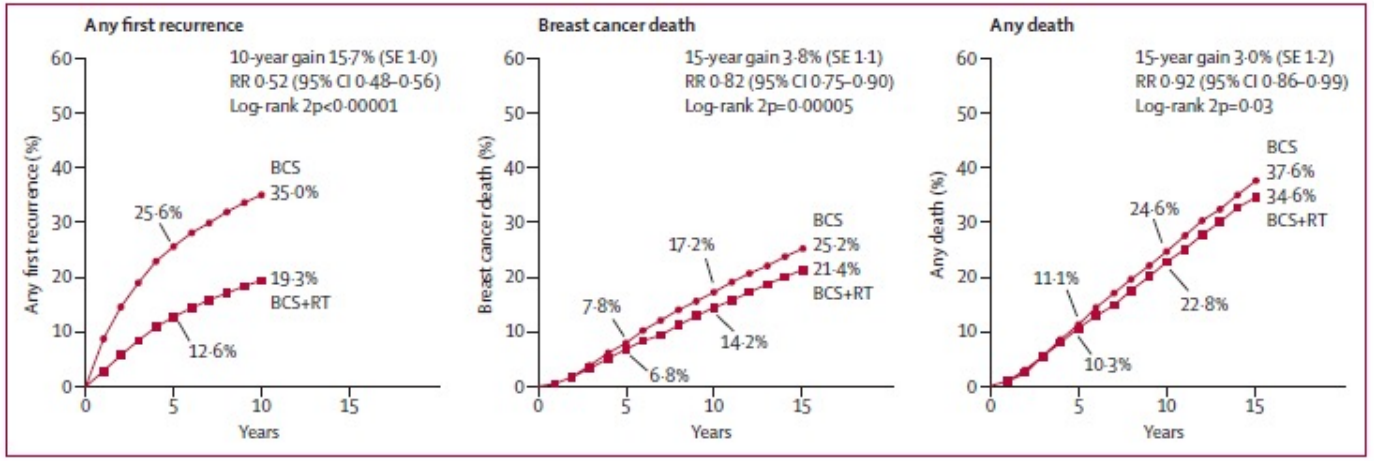
Which is the best treatment for my patient?

- **Best oncological results** (target volume, total dose, fractionation)
- **Lowering side effects** (heart, lung, brachial plexus neoropathy, rib fracture, cosmetic results - *fibrosis*, *edema*, *shrinkage*, *teleangectasie*- arm Lynphedema, shoulder stifness,….)
  (total dose, technology used, radiotherapy techniques)
- **Total time of the treatment**

STANDARD FRACTIONATION:
dose constraints and breast radiotherapy tolerance

Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10 801 women in 17 randomised trials

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



20 y of follow up of standard RT fractionation 50 Gy/2 Gy

Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Effect of radiotherap

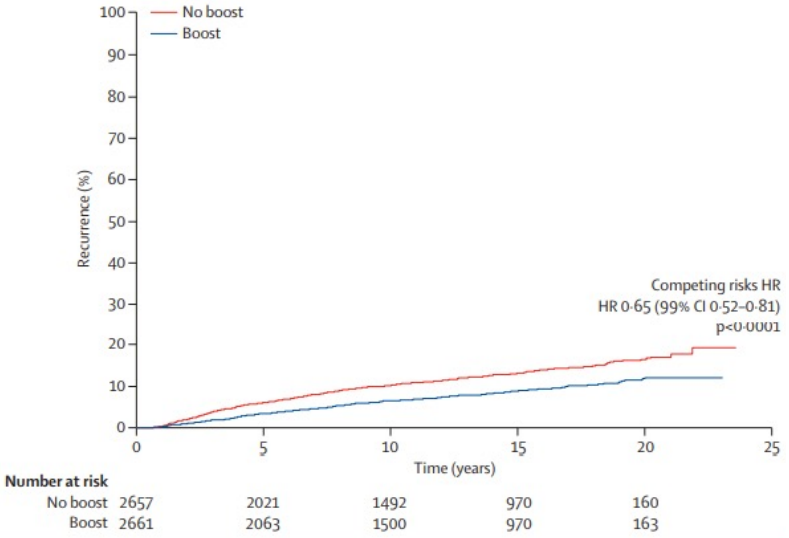
STANDARD FRACTIONATION:
dose constraints and breast radiotherapy tolerance

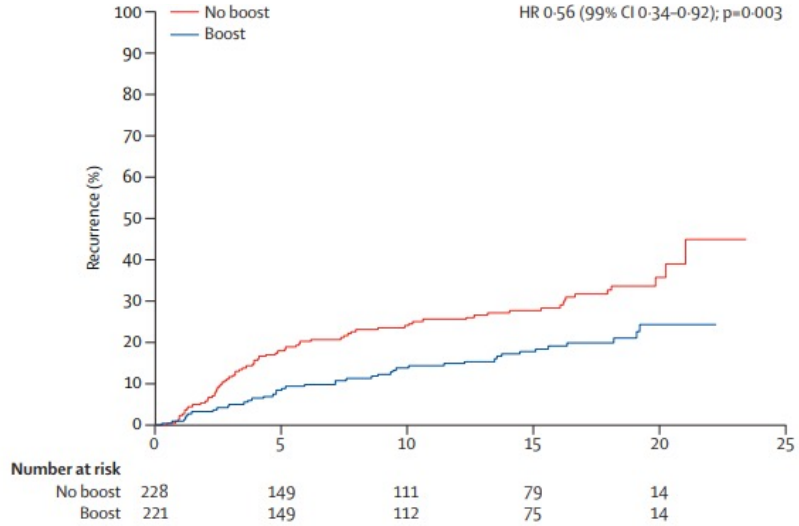
Whole-breast irradiation with or without a boost for patients treated with breast-conserving surgery for early breast cancer: 20-year follow-up of a randomised phase 3 trial

Harry Bartelink, Philippe Maingon, Philip Poortmans, Caroline Weltens, Alain Fourquet, Jos Jager, Dominic Schinagl, Bing Oei, Carla Rodenhuis, Jean-Claude Horiot, Henk Struikmans, Erik Van Limbergen, Youlia Kirova, Paula Elkhuizen, Rudolf Bongartz, Raymond Miralbell, David Morgan, Jean-Bernard Dubois, Vincent Remouchamps, René-Olivier Mirimanoff, Sandra Collette, Laurence Collette; on behalf of the European Organisation for Research and Treatment of Cancer Radiation Oncology and Breast Cancer Groups

Cosmetic issue

Local control





Local Recurrence 16,4% No-boost 12.0% Boost (16Gy)

Significant relative reduction of risk for w

20 yrs cumulative risk of fibrosis is 5,2% in the boost group versus 1,8% in no boost grou

Bartelink H, et al, Whole-breast irradiation with or without a

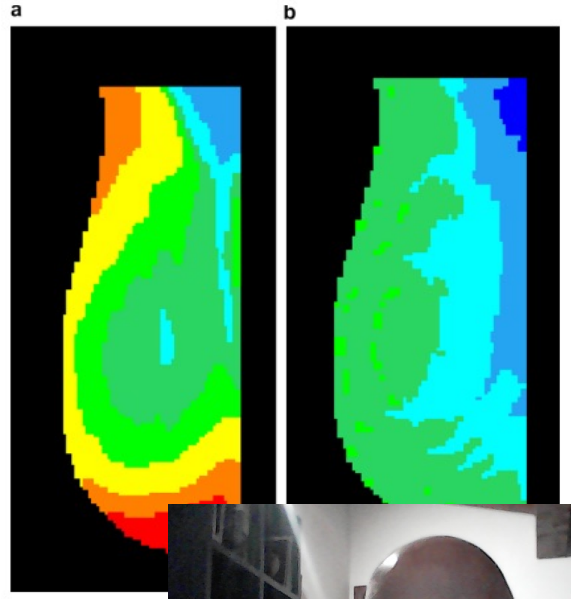
STANDARD FRACTIONATION:
dose constraints and breast radiotherapy tolerance

Cosmetic issue

Randomised trial of standard 2D radiotherapy (RT) versus intensity modulated radiotherapy (IMRT) in patients prescribed breast radiotherapy

Ellen Donovan[a], Natalie Bleakley[a], Erica Denholm[b], Phil Evans[a], Lone Gothard[c], Jane Hanson[c], Clare Peckitt[b], Stephanie Reise[a], Gill Ross[d], Grace Sharp[c], Richard Symonds-Tayler[a], Diana Tait[c], John Yarnold[c,*], on behalf of the Breast Technology Group

- 306 women randomised to 3D IMRT or 2D RT delivered using standard wedge compensators
- All patients were treated with 50 Gy in 25 fractions followed by an electron boost to the tumour bed of 11.1 Gy in 5 fractions
- PRIMARY ENDPOINT: Change in breast appearance since to 5 y of follow up
- 2D RT control arm patients were 1.7 times more likely to have a change in breast appearance than the IMRT arm patients after adjustment for year of photographic assessment (95% confidence interval 1.2–2.5, p = 0.008)



Donovan E, et al. Randomised trial of standard 2D radiotherapy (RT) versus intensity modulated radio

STANDARD FRACTIONATION:
dose constraints and breast radiotherapy tolerance

Risk of Ischemic Heart Disease in Women after Radiotherapy for Breast Cancer

Sarah C. Darby, Ph.D., Marianne Ewertz, D.M.Sc., Paul McGale, Ph.D., Anna M. Bennet, Ph.D., Ulla Blom-Goldman, M.D., Dorthe Brønnum, R.N., Candace Correa, M.D., David Cutter, F.R.C.R., Giovanna Gagliardi, Ph.D., Bruna Gigante, Ph.D., Maj-Britt Jensen, M.Sc., Andrew Nisbet, Ph.D., Richard Peto, F.R.S., Kazem Rahimi, D.M., Carolyn Taylor, D.Phil., and Per Hall, Ph.D.

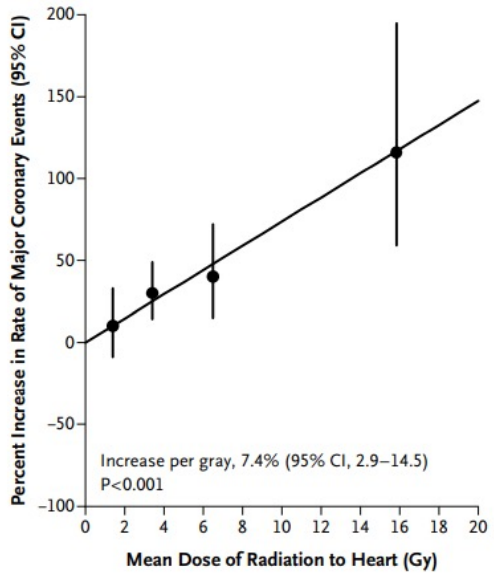
Cardiac issue

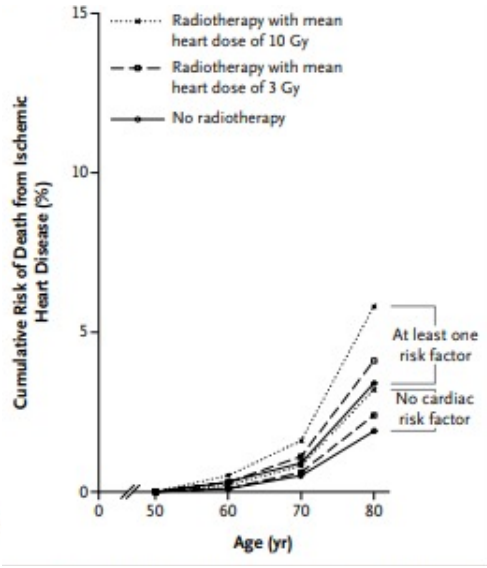
Table 3. Percentage Increase in the Rate of Major Coronary Events per Gray, According to Time since Radiotherapy.

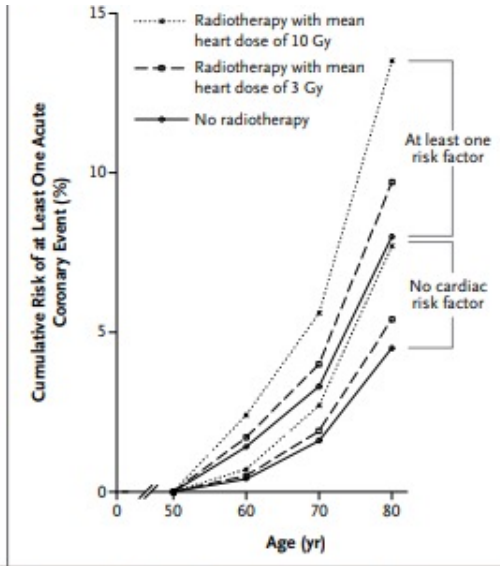
Time since Radiotherapy*	No. of Case Patients	No. of Controls	Increase in Rate of Major Coronary Events (95% CI)†
			% increase/Gy
0 to 4 yr	206	328	16.3 (3.0 to 64.3)
5 to 9 yr	216	296	15.5 (2.5 to 63.3)
10 to 19 yr	323	388	1.2 (–2.2 to 8.5)
≥20 yr	218	193	8.2 (0.4 to 26.6)
0 to ≥20 yr	963	1205	7.4 (2.9 to 14.5)

* The values shown are the numbers of years since the breast-cancer diagnosis. The median time from the breast-cancer diagnosis to the start of radiotherapy was 42 days.

† The percentage increase was estimated after stratification according to country, age at breast-cancer diagnosis, year of breast-cancer diagnosis, years from breast-cancer diagnosis to first major coronary event (for case patients) or index date (for controls), and the presence or absence of a cardiac risk factor. Chi-square for heterogeneity=5.2 with 3 df, P=0.16; chi-square for trend=1.2 with 1 df, P=0.26.







Rates of major coronary events increased linearly with the mean dos
gray (95% confidence interval, 2.9 to 14.5; P<0.001), with no apparen

Darby SC, et Al. Risk of ischemic heart disease in women after radiotherapy

STANDARD FRACTIONATION:
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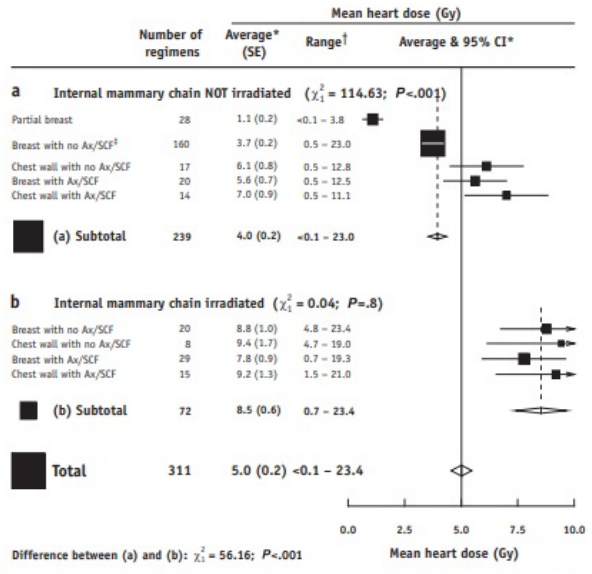
Cardiac issue

A SEER study showed a progressive reduction in cardiac mortality in left breast cancer, decreasing from 13% (1973-1979) to 9.5% (1980-1984) and 5.8% (1985-1989).

Comparison of percent ischemic heart disease mortality (with 95% confidence intervals) at 15 years of follow-up between women with left-sided and right-sided breast cancers, stratified by stage of disease at time of diagnosis

	All patients			Patients with in situ/localized disease			Patients with regional disease		
Cohort by year of diagnosis	Left-sided, %	Right-sided, %	*P*	Left-sided, %	Right-sided, %	*P*	Left-sided, %	Right-sided, %	*P*
Overall	8.7 (8.0 to 9.3)	7.5 (6.9 to 8.2)	.07	7.6 (6.7 to 8.4)	6.7 (5.9 to 7.5)	.40	10.2 (9.1 to 11.3)	8.6 (7.6 to 9.6)	.09
1973–1979	13.1 (11.6 to 14.6)	10.2 (8.9 to 11.5)	.02	12.7 (10.3 to 15.2)	9.6 (7.5 to 11.8)	.14	13.3 (11.5 to 15.1)	10.6 (8.9 to 12.3)	.06
1980–1984	9.4 (8.1 to 10.6)	8.7 (7.4 to 10.0)	.64	8.9 (7.2 to 10.5)	8.7 (7.1 to 10.4)	.87	10.0 (7.9 to 12.1)	8.8 (6.8 to 10.9)	.38
1985–1989	5.8 (4.8 to 6.7)	5.2 (4.4 to 5.9)	.98	5.7 (4.5 to 6.8)	4.9 (4.0 to 5.8)	.79	6.0 (4.4 to 7.6)	5.7 (4.1 to 7.2)	.76



- Taylor's Review NEJM 2015: 357 trials from 2003 to 2013
- Mean Dose to the heart 4 Gy without Internal Mammary Chain (IMC)
- Mean Dose to the heart 8 Gy with IMC
- Without previously cardiac risk factors the clinical benefit supports the cardiac toxicity risk

- Acute and chronic pericarditis ⇓⇓⇓
- Radiation-induced cardiomyopathy ⇓⇓⇓
- Valvular heart disease ⇓⇓⇓
- Radiation-induced coronary heart disease ⇓⇓⇓

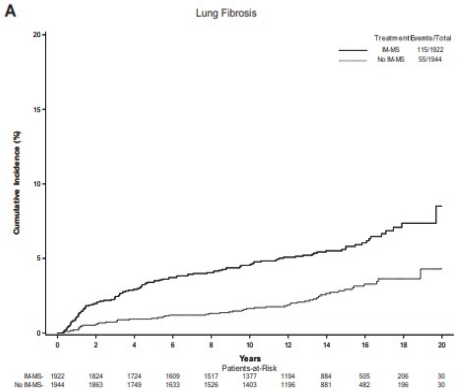
Table 1
The 20 year cardiac risks of breast cancer radiotherapy modelled for a typical 50-year-old woman

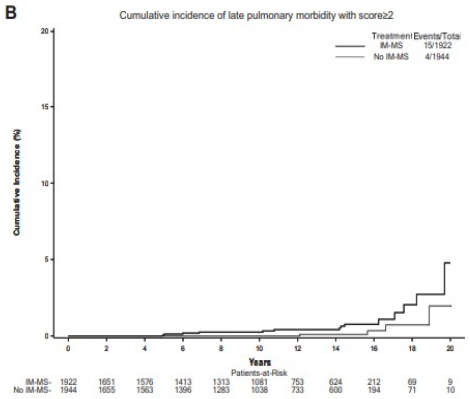
Cardiac risk factor(s) before radiotherapy	Mean heart dose (Gy)	20 year risk of death from ischaemic heart disease (%)*		
		Without radiotherapy	With radiotherapy	Absolute difference in risk: radiotherapy versus not
No	2	0.5	0.5	<0.1
No	10	0.5	0.8	0.3
Yes†	2	0.9	1.1	0.2
Yes†	10	0.9	1.6	0.7

Taylor CW, et al. Exposure of the Heart in Breast Cancer Radiation Therapy: A Systematic Re
Giordano SH,et al. Risk of cardiac death after adjuvant radiotherapy for

STANDARD FRACTIONATION:
dose constraints and breast radiotherapy tolerance

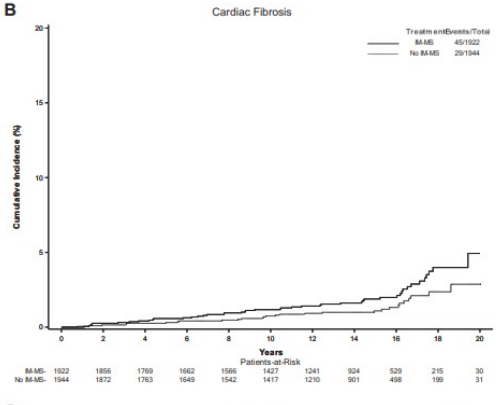
Side Effects 15 Years After Lymph Node Irradiation in Breast Cancer: Randomized EORTC Trial 22922/10925

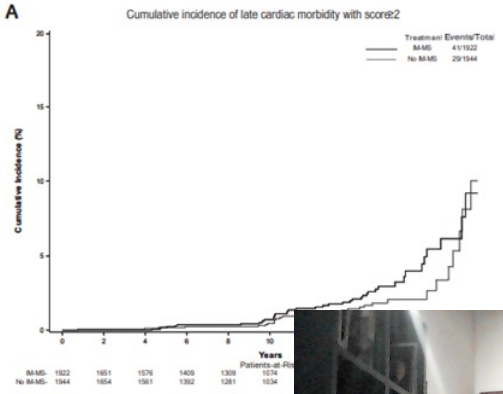




Late side effect	Rate (95% CI), %	
	No IM-MS (n = 1944)	IM-MS (n = 1922)
Cardiac late RT morbidity score		
≥ 1	3.9 (2.9 to 5.1)	4.5 (3.4 to 5.8)
≥ 2	1.8 (1.1 to 2.8)	2.6 (1.8 to 3.7)
≥ 3	1.1 (0.6 to 1.8)	1.0 (0.5 to 1.7)
≥ 4	0.3 (0.1 to 0.7)	0.1 (0.0 to 0.5)
Lung late RT morbidity score		
≥ 1	2.5 (1.7 to 3.6)	3.7 (2.8 to 4.9)
≥ 2	0.1 (0.0 to 0.5)	0.8 (0.4 to 1.4)
≥ 3	0.0 (NE-NE)	0.2 (0.0 to 0.7)
≥ 4	0.0 (NE-NE)	0.1 (0.0 to 0.7)
Esophageal late RT morbidity		
≥ 1	0.7 (0.4 to 1.3)	1.1 (0.7 to 1.8)
≥ 2	0	0.1 (0.0 to 0.4)
≥ 3	0	0.1 (0.0 to 0.4)
≥ 4	0	0

[a]CI = confidence interval; IM-MS = internal mammary–medial supraclavicular irradiation; NE = Not Evaluated; RT = Radiation Therapy.





Poortmans PM, et al. EORTC Radiation Oncology and Breast Cancer Groups. Side Ef

STANDARD FRACTIONATION:
dose constraints and breast radiotherapy tolerance

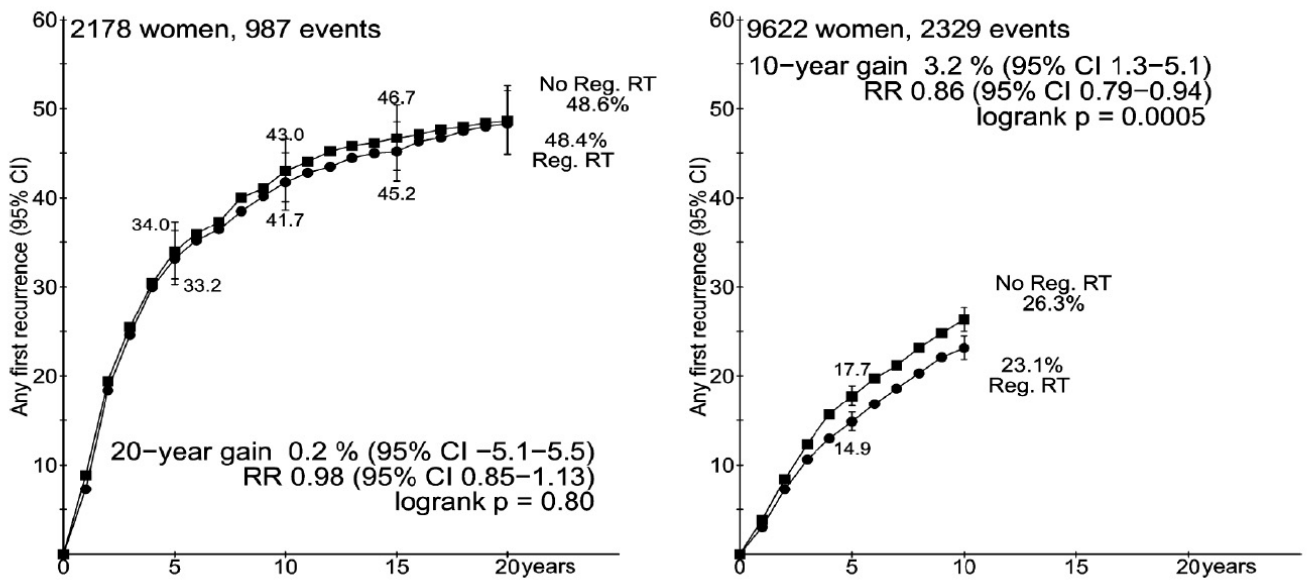
Regional node irradiation:

Meta-analysis of 13,500 women in 14 trials

Early Breast Cancer Trialists' Collaborative Group (EBCTCG)

Writing Committee: David Dodwell (presenter), Carolyn Taylor, Paul McGale, Charlotte Coles, Fran Duane, Richard Gray, Thorsten Kühn, Christophe Hennequin, Robert Hills, Sileida Oliveros, Yaochen Wang, Jonas Bergh, Kathy Pritchard, Sandra Swain, Jens Overgaard, Philip Poortmans, Tim Whelan

Any recurrence



Dodwell D, et al. Regional lymph node irradiation in early stage breast cancer: An EBCTCG meta-analysis of

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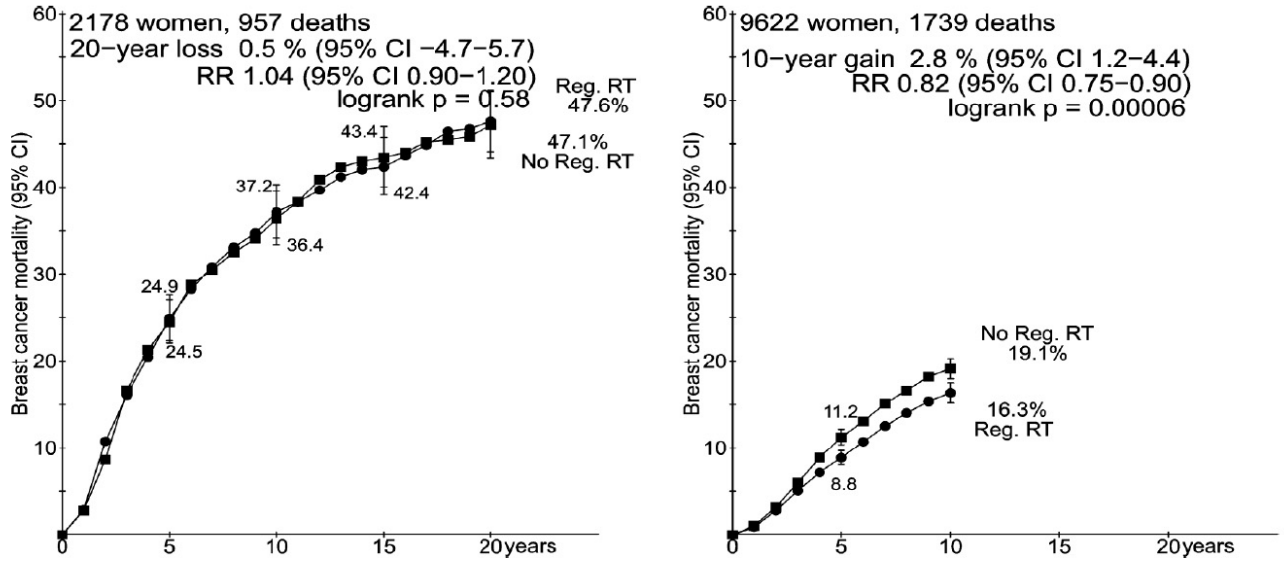
Breast cancer mortality



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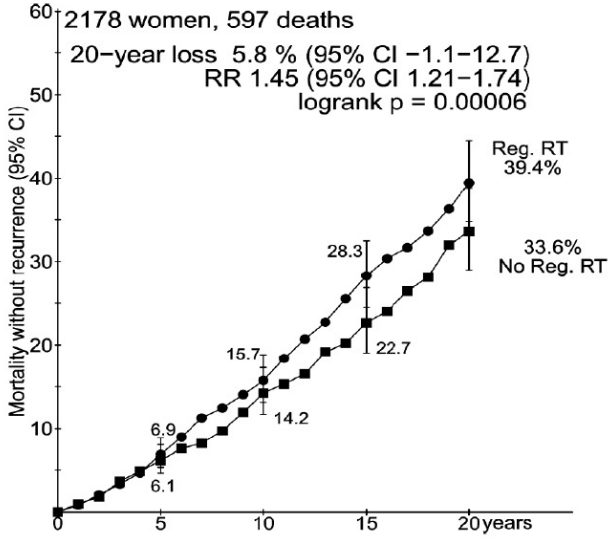
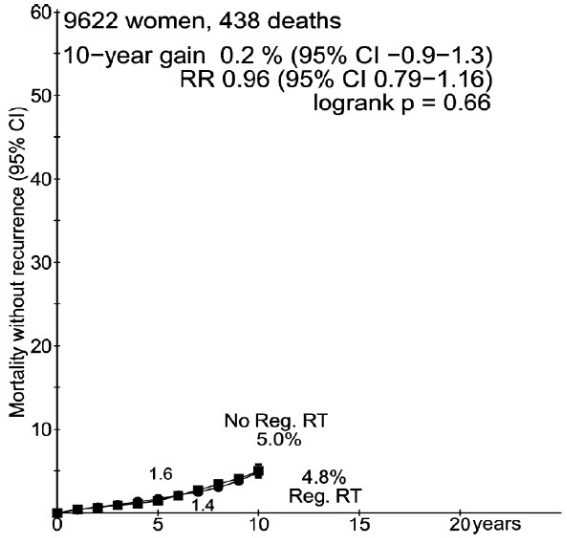
Non-breast-cancer mortality

Older trials



Newer trials



Dodwell D, et al. Regional lymph node irradiation in early stage breast cancer: An EBCTCG meta-analysis of

STANDARD FRACTIONATION:
dose constraints and breast radiotherapy tolerance

TOLERANCE OF NORMAL TISSUE TO THERAPEUTIC IRRADIATION

B. Emami, M.D.,[1] J. Lyman, Ph.D.,[5] A. Brown, M.D.,[4] L. Coia, M.D.,[3] M. Goitein, Ph.D.,[4] J. E. Munzenrider, M.D.,[4] B. Shank, M.D.,[2] L. J. Solin, M.D.[3] and M. Wesson, M.D.[2]

[1]Mallinckrodt Institute of Radiology, Washington University School of Medicine, St. Louis, MO 63110; [2]Memorial Sloan-Kettering Cancer Center, New York, NY 10021; [3]Department of Radiation Therapy, University of Pennsylvania School of Medicine and the Fox Chase Cancer Center, Philadelphia, PA 19111; [4]Massachusetts General Hospital, Department of Radiation Medicine, Boston, MA 02114 and Harvard Medical School; and [5]University of California-Lawrence Berkeley Laboratory, Research Medicine and Radiation Biophysics Division, Berkeley, CA 94720

Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC): An Introduction to the Scientific Issues

Søren M. Bentzen, Ph.D., D.Sc.[a], Louis S. Constine, M.D.[b], Joseph O. Deasy, Ph.D.[c], Avi Eisbruch, M.D.[d], Andrew Jackson, Ph.D.[e], Lawrence B. Marks, M.D.[f], Randall K. Ten Haken, Ph.D.[d], and Ellen D. Yorke, Ph.D.[e]

Delineation of target volumes and organs at risk in adjuvant radiotherapy of early breast cancer: National guidelines and contouring atlas by the Danish Breast Cancer Cooperative Group

METTE H. NIELSEN[1], MARTIN BERG[2], ANDERS N. PEDERSEN[3], KAREN ANDERSEN[4], VLADIMIR GLAVICIC[5], ERIK H. JAKOBSEN[6], INGELISE JENSEN[7], MIRJANA JOSIPOVIC[8], EBBE L. LORENZEN[9], HANNE M. NIELSEN[10], LARS STENBYGAARD[11], METTE S. THOMSEN[12], SUSANNE VALLENTIN[13], SUNE ZIMMERMANN[9], BIRGITTE V. OFFERSEN[10] & ON BEHALF OF THE DANISH BREAST CANCER COOPERATIVE GROUP RADIOTHERAPY COMMITTEE

Table II. Constraints for organs at risk in adjuvant radiotherapy of early breast cancer.

Organ at risk	Normofractionation 2 Gy per fraction/ 5 fractions/week
LADCA	$V_{20Gy} = 0\%$
Heart	$V_{20Gy} = 10\%, V_{40Gy} = 5\%$
Ipsilateral lung	$V_{20Gy} = 25\%$ (exclusive periclavicular LN) $V_{20Gy} = 35\%$ (inclusive periclavicular LN) Mean dose < 18 Gy
Spinal cord	Max. 45 Gy
Plexus brachialis	Max. 54 Gy
Maximal dose of CTV	107% = 53.5 Gy
Maximal dose outside PTV	54 Gy

CTV, clinical target volume; LADCA, left anterior descending coronary artery; LN, lymph nodes; PTV, planning tumor volume.

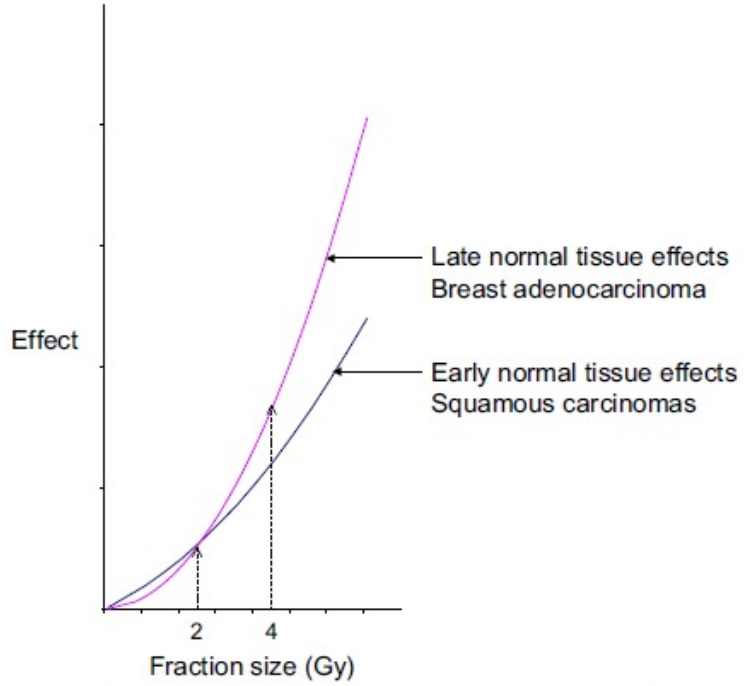
- Long-term Follow up in 2D and 3D techniques allowed us to get reliable costraints to reduce toxicites
- New techniques such as Breath HOLD, IMRT, VMAT, MRI-RT, Proton therapy allowed to reduce the administered doses to OARs but at the same time it will be necessary to have new costrains, which will require a long follow up for a clinical validation
- Changes in target volume delineation will allow us to better further the patient's compliance (new ESTRO guidelines in the setting of postmaste

Emami B,et al. Tolerance of normal tissue to therapeutic irradi
Bentzen SM, et al Quantitative Analyses of Normal Tissue Effects in the Clinic (QUAN
Nielsen et al. Delineation of target volum

STANDARD MODERATE HYPOFRACTIONATION:
dose constraints and breast radiotherapy tolerance

Linear quadratic model on breast cancer

- After the first clinical evidences, in the 1980s linear-quadratic model was applied to clinical data
- The point estimate for human breast cancer was in the range 3-5 Gy
- Sensitivity similar to *late responding tissues*



Tutt A. et al. Radiobiolog

Douglas BG, Castro JR. Novel fractionation schemes and high linear ene

STANDARD MODERATE HYPOFRACTIONATION:
dose constraints and breast radiotherapy tolerance

FROM STANDARD TO MODERATE HYPOFRACTIONATION

- **Breast tumor α/β = 3 Gy**
- **Reduction of overall treatment time**
- **Sparing of organ at risks**

START A TRIAL -> 41.6 Gy in 13 fractions (EQD2 = 51.58 Gy), or HF-WBI 39 Gy in 13 fractions (EQD2 = 46.80)
START B TRIAL -> 40.05 Gy in 15 daily fractions over 3 weeks 40.05 Gy in 15 daily fractions over 3 weeks(EQD2 = 45.42 Gy)
ONTARIO TRIAL -> 42.56 Gy in 16 fractions (EQD2 47.24 Gy)

Marta GN, et al. The use of moderately hypofractionated post-operative radiation therapy fo
Haviland JS et al. START Trialists' Group. The UK Standardisation of Breast Radiotherapy (START) tri

STANDARD MODERATE HYPOFRACTIONATION:
dose constraints and breast radiotherapy tolerance

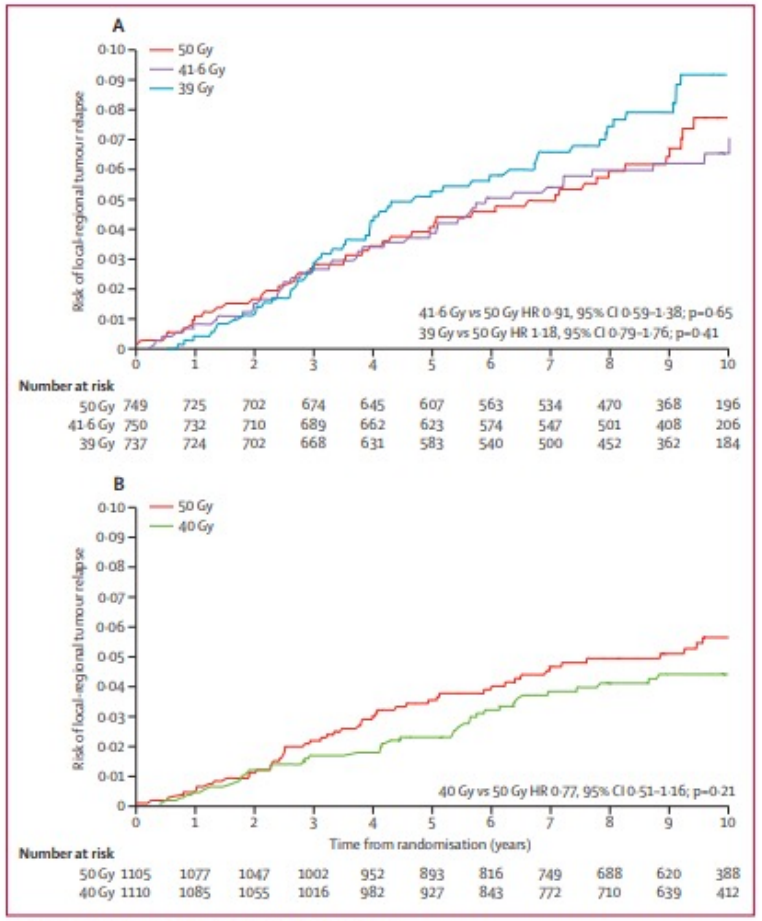


Figure 1: Cumulative risk of local-regional tumour relapse
In START-A (A) and START-B (B).

The additional 0.6 Gy/die may balance out the lower total dose acting on **cell Repopulation!** (in the STARTB setting)

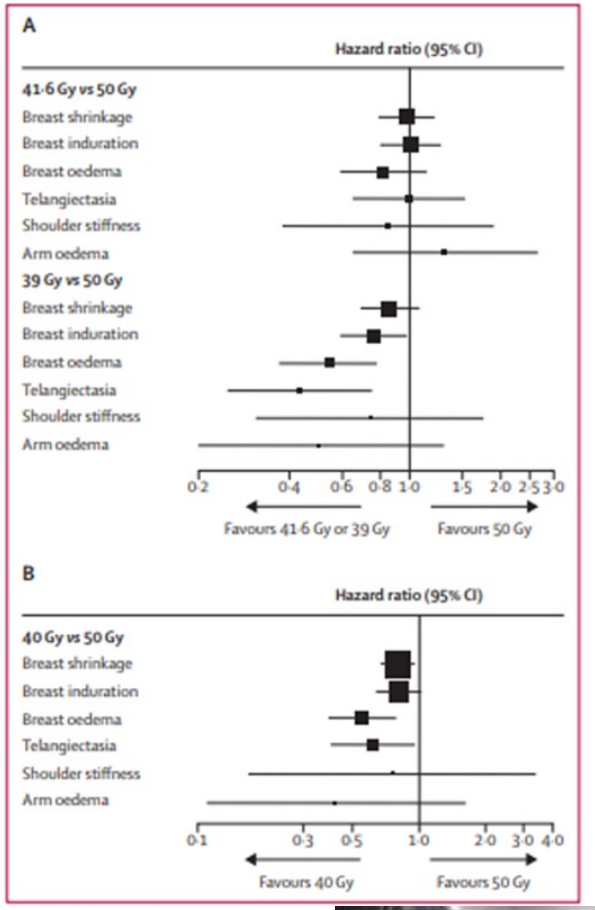
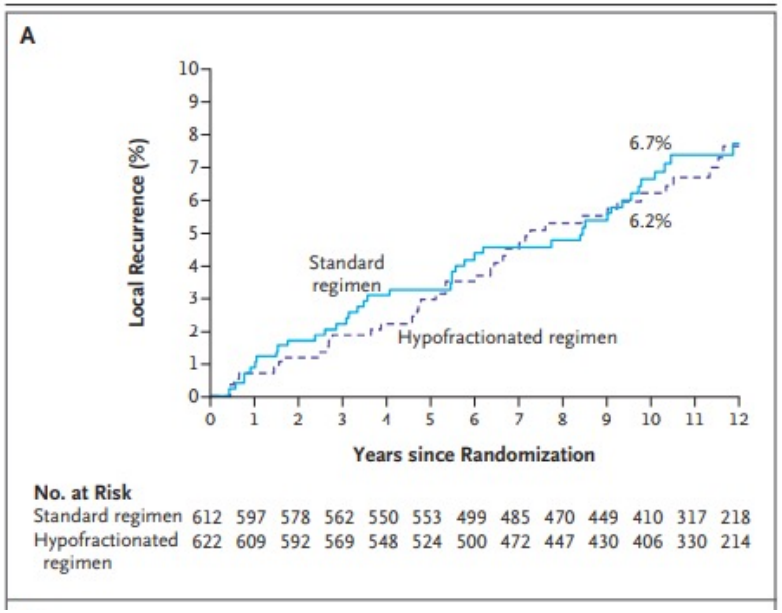


Figure 3: Late normal tissue effects
In START-A (A) and START-B (B). Assessed as
physicians.

Marta GN, et al. The use of moderately hypofractionated post-operative radiation therapy fo
Haviland JS et al. START Trialists' Group. The UK Standardisation of Breast Radiotherapy (START) tri

STANDARD MODERATE HYPOFRACTIONATION:
dose constraints and breast radiotherapy tolerance

ONTARIO TRIAL



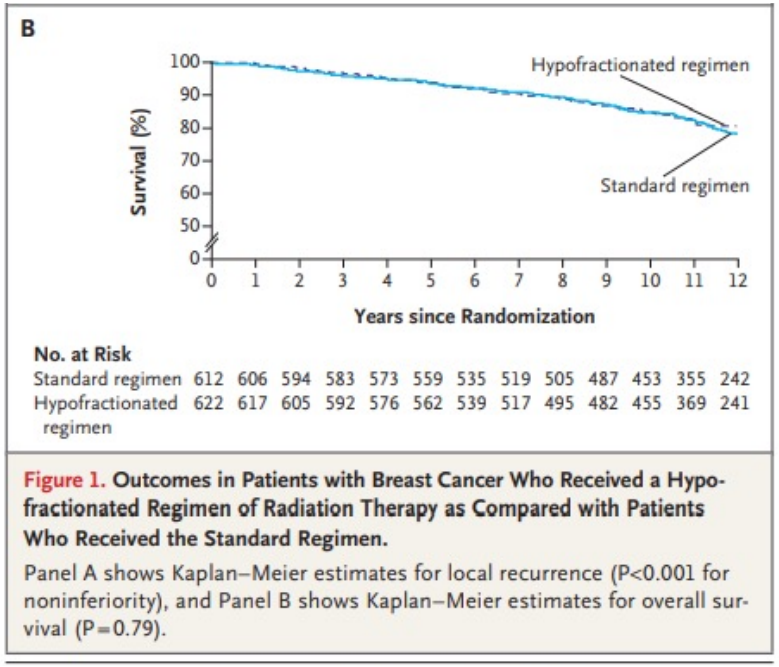


Figure 1. Outcomes in Patients with Breast Cancer Who Received a Hypofractionated Regimen of Radiation Therapy as Compared with Patients Who Received the Standard Regimen.

Panel A shows Kaplan–Meier estimates for local recurrence (P<0.001 for noninferiority), and Panel B shows Kaplan–Meier estimates for overall survival (P=0.79).

Table 3. Predictors of an Excellent or Good EORTC Global Cosmetic Rating.*

Variable	Odds Ratio (95% CI)	P Value
Treatment (hypofractionated regimen vs. standard regimen)†	1.00 (0.81–1.25)	0.94
Time from randomization (per yr)	0.93 (0.90–0.95)	<0.001
Age (<50 yr vs. ≥50 yr)	1.64 (1.26–21.5)	<0.001
Tumor size (<2 cm vs. ≥2 cm)	1.26 (0.99–1.62)	0.07
Systemic therapy (yes vs. no)	0.89 (0.70–1.12)	0.30

* Data are based on a repeated-measures logistic-regression analysis. EORTC denotes European Organization for Research and Treatment of Cancer.
† There were no first-order interactions of treatment with time from randomization, age, tumor size, or systemic therapy.

Whelan TJ,et al. Long-term results of hypofractionated radiation therap

STANDARD MODERATE HYPOFRACTIONATION:
dose constraints and lymph nodes radiotherapy tolerance

Late normal tissue effects in the arm and shoulder following lymphatic radiotherapy: Results from the UK START (Standardisation of Breast Radiotherapy) trials

Joanne S Haviland [a,*], Mariella Mannino [b], Clare Griffin [a], Nuria Porta [a], Mark Syde
Judith M. Bliss [a,1], John R. Yarnold [c,1], on behalf of the START Trialists' Group

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10 yrs FUP

START studies (*the Royal Marsden Hospital study, as well as both START A and START B*) showed that 14.7 % (n = 864) of the patients received lymphatic radiation on **axillary chain** and/or the **supraclavicular nodes**

- ! No statistical differences were found in arm stiffness and arm oedema in START groups compared to standard group
- ! Very low rate of brachial plexopathy in patients who received regional nodal radiation
- ! The results were the same in both **patient and physician assesments**

Table 2
Patient-assessed moderate/marked normal tissue effects in the arm or shoulder following lymphatic radiotherapy in START-A and START-B.

Schedule	Total moderate/ marked events (n/total, %)	Estimated cumulative incidence by 5 years, % (95%CI)	Hazard ratio (95% CI)[1]	P-value[2]	Prevalence of moderate/ marked events at 5 years, n/total (%)	P-value[3]
m/shoulder pain						
T-A						
Gy	30/95 (31.6)	32.3 (23.3-43.7)	1		12/65 (18.5)	
	24/78 (30.8)	31.4 (22.1-43.6)	1.03 (0.60-1.77)	0.92	5/58 (8.6)	0.13
	23/77 (29.9)	30.8 (21.4-43.0)	0.96 (0.56-1.66)	0.89	7/58 (12.1)	0.45
Gy	13/46 (28.3)	29.7 (18.0-46.6)	1		2/28 (7.1)	
40 Gy	15/52 (28.9)	23.6 (14.1-37.9)	0.94 (0.44-2.00)	0.87	4/35 (11.4)	0.68
Swelling in arm or hand						
START-A						
50 Gy	15/95 (15.8)	14.2 (8.3-23.8)	1		6/65 (9.2)	
41.6 Gy	13/78 (16.7)	18.2 (11.0-29.3)	1.01 (0.46-2.18)	0.99	1/58 (1.7)	0.12
39 Gy	13/77 (16.9)	16.1 (9.2-27.3)	1.15 (0.54-2.47)	0.72	6/58 (10.3)	>0.99
START-B						
50 Gy	5/46 (10.9)	9.5 (3.7-23.3)	1		1/28 (3.6)	
40 Gy	3/51 (5.9)	6.0 (2.0-17.4)	0.55 (0.13-2.36)	0.42	0/36 (0)	0.44
Difficulty in raising arm						
START-A						
50 Gy	17/95 (17.9)	18.8 (11.9-29.0)	1		3/65 (4.6)	
41.6 Gy	9/78 (11.5)	9.5 (4.7-19.0)	0.63 (0.28-1.43)	0.27	2/58 (3.4)	>0.99
39 Gy	11/77 (14.3)	15.4 (8.8-26.1)	0.83 (0.39-1.80)	0.64	2/58 (3.4)	>0.99
START-B						
50 Gy	8/46 (17.4)	18.6 (9.2-35.4)	1		3/28 (10.7)	
40 Gy	7/51 (13.7)	10.1 (4.3-22.6)	0.64 (0.23-1.78)	0.40	3/36 (8.3)	>0.99
Shoulder stiffness						
START-A						
50 Gy	25/96 (26.0)	27.5 (19.0-38.7)	1		8/65 (12.3)	
41.6 Gy	15/78 (19.2)	17.7 (10.6-28.5)	0.75 (0.39-1.43)	0.39	4/58 (6.9)	0.37
39 Gy	10/77 (13.0)	14.0 (7.8-24.4)	0.52 (0.25-1.11)	0.09	2/58 (3.4)	0.10
START-B						
50 Gy	5/46 (10.9)	12.0 (5.2-26.5)	1			
40 Gy	7/52 (13.5)	14.2 (7.0-27.6)	0.88 (0.26-			

[1]Results adjusted for baseline; P-values represent comparison of each test

Haviland JS, et al. START Trialists' Group. Late normal tissue effects in the arm and shoulder following lymphat

STANDARD MODERATE HYPOFRACTIONATION:
dose constraints and lymph nodes radiotherapy tolerance

Hypofractionated versus conventional fractionated postmastectomy radiotherapy for patients with high-risk breast cancer: a randomised, non-inferiority, open-label, phase 3 trial

Shu-Lian Wang, Hui Fang*, Yong-Wen Song, Wei-Hu Wang, Chen Hu, Yue-Ping Liu, Jing Jin, Xin-Fan Liu, Zi-Hao Yu, Hua Ren, Ning Li, Ning-Ning Lu, Yu Tang, Yuan Tang, Shu-Nan Qi, Guang-Yi Sun, Ran Peng, Shuai Li, Bo Chen, Yong Yang, Ye-Xiong Li*

5 yrs FUP

Beijing TRIAL -> pT3-4 pN2-3 post-mastectomy 820 pts randomized to postmastectomy RT of the chest wall and select nodal irradiation (supraclavicular and level 3) of 50 Gy in 25 fractions weeks or 3-week hypofractionation 43.5 Gy in 15 fractions (EDQ2 = 50 Gy)

	Conventional fractionated radiotherapy group (n=409)	Hypofractionated radiotherapy group (n=401)	p value
Acute toxicity			
Skin toxicity	..	..	<0·0001
Grade 1–2	357 (87%)	351 (89%)	..
Grade 3	32 (8%)	14 (3%)	..
Pneumonitis	..	..	0·278
Grade 1	62 (15%)	61 (15%)	..
Grade 2	7 (2%)	14 (3%)	..
Grade 3	..	..	..
Late toxicity			
Skin toxicity	..	..	0·669
Grade 1–2	90 (22%)	86 (21%)	..
Grade 3	0	1 (<1%)	..
Lymphoedema	..	..	0·961
Grade 1–2	81 (20%)	78 (19%)	..
Grade 3	3 (1%)	3 (1%)	..
Shoulder dysfunction	..	..	0·734
Grade 1–2	13 (3%)	7 (2%)	..
Grade 3	1 (<1%)	1 (<1%)	..
Lung fibrosis	..	..	0·081
Grade 1–2	42 (10%)	62 (15%)	..
Grade 3	0	0	..
Ischaemic heart disease	..	..	0·569
Grade 1–2	1 (<1%)	3 (1%)	..
Grade 3	3 (1%)	4 (1%)	..

Data are n (%). The χ^2 test was used to calculate p values. No grade 4 events or deaths due to adverse eff

Table 2: Adverse event

Results: **no significant differences** between groups in the incidence of other acute or late toxicities lymphoedema and shoulder dysfunction. None of the patients had brachial plexopathy or rib fractures during follow-up.

Weaknesses: 97% of pts received 2D tecnique RT with electron beams -> 8.3 vs 8.1% LR
5 years follow up!

Wang SL, et al. Hypofractionated versus conventional fractionate

STANDARD MODERATE HYPOFRACTIONATION:

dose constraints and radiotherapy tolerance after mastectomy with immediate or delate reconstruction

- Little data are available about the use of hypofractionation before or **after breast reconstruction**, which is increasingly done using implants or autologous tissue.
- RT might increase the frequency of complications including capsular contracture rates and reconstruction failures.
- It is plausible that moderate hypofractionation for patients after breast reconstruction will compare it positively to conventional fractionation, provided a homogenous dose distribution is given

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

J Roger Owen, Anita Ashton, Judith M Bliss, Janis Homewood, Caroline Harper, Jane Hanson, Joanne Haviland, Soren M Bentzen, John R Yarnold

ORIGINAL ARTICLE

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.

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†*

Hypofractionated versus conventional fractionated postmastectomy radiotherapy for patients with high-risk breast cancer: a randomised, non-inferiority, open-label, phase 3 trial

Shu-Lian Wang, Hui Fang*, Yong-Wen Song, Wei-Hu Wang, Chen Hu, Yue-Ping Liu, Jing Jin, Xin-Fan Liu, Zi-Hao Yu, Hua Ren, Ning Li, Ning-Ning Lu, Yu Tang, Yuan Tang, Shu-Nan Qi, Guang-Yi Sun, Ran Peng, Shuai Li, Bo Chen, Yong Yang, Ye-Xiong Li*

STANDARD MODERATE HYPOFRACTIONATION:

dose constraints and radiotherapy tolerance after mastectomy with immediate or delate reconstruction

Customizing local and systemic therapies for women with early breast cancer: the St. Gallen International Consensus Guidelines for treatment of early breast cancer 2021

H. J. Burstein[1*†], G. Curigliano[2*†], B. Thürlimann[3], W. P. Weber[4], P. Poortmans[5], M. M. Regan[1], H. J. Senn[6], E. P. Winer[1] & M. Gnant[7], Panelists of the St Gallen Consensus Conference[‡]

[1]Dana-Farber Cancer Institute, Harvard Medical School, Boston, USA; [2]European Institute of Oncology, University of Milan, Milan, Italy; [3]Cantonal Hospital, St. Gallen; [4]University of Basel, Basel, Switzerland; [5]University of Antwerp, Antwerp, Belgium; [6]St. Gallen Oncology Conferences (Foundation SONK), St. Gallen, Switzerland; [7]Medical University of Vienna, Vienna, Austria

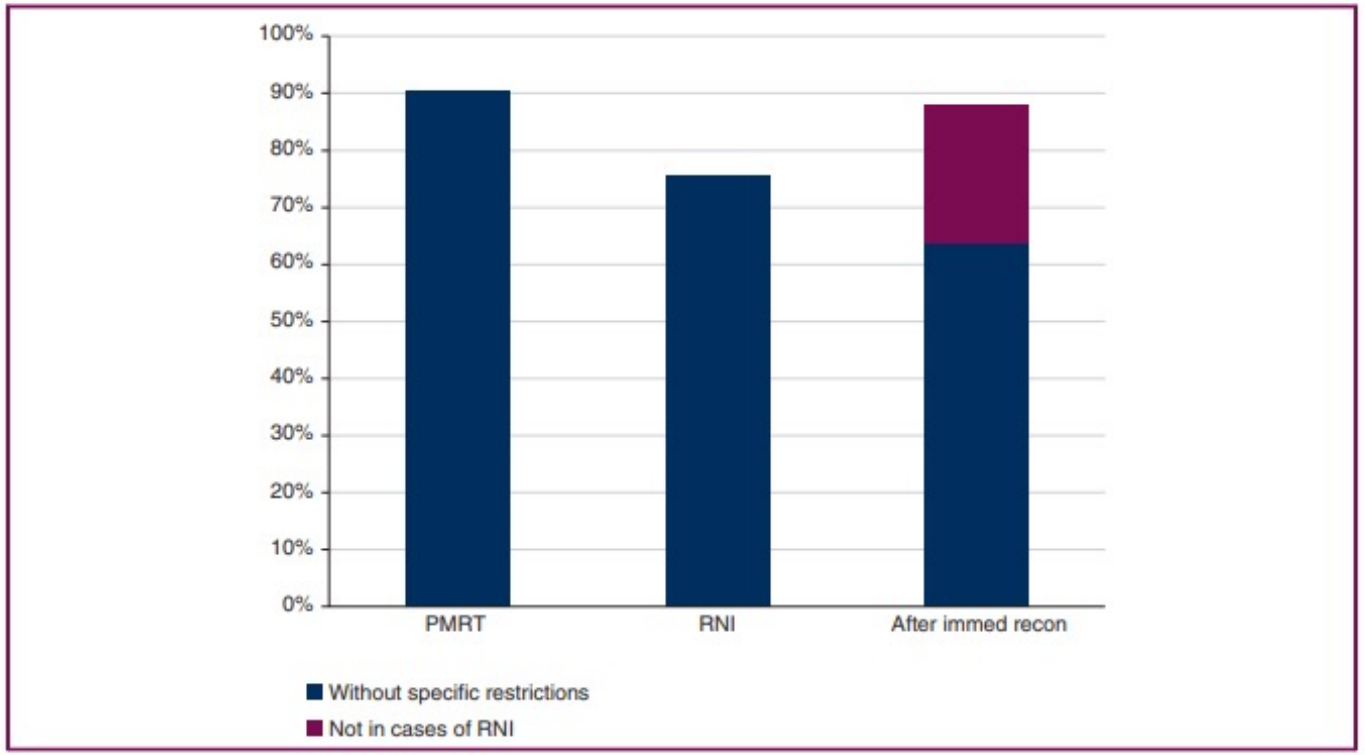

Figure 3. Moderately hypofractionated radiation therapy.
Percentage of panelists endorsing moderately hypofractionated schedules of radiation therapy.
After immed recon, after immediate reconstruction; PMRT, postmastectomy radiation therapy; RNI, regional nodal irradia

Burstein HJ,et al. Customizing local and systemic therapies for women with early breast cancer: the St. Gallen Int

STANDARD MODERATE HYPOFRACTIONATION:

dose constraints and radiotherapy tolerance after mastectomy with immediate or delate reconstruction

Which is the future?

Hypofractionated vs Standard Radiotherapy in Breast Cancer With an Indication for Regional Lymph Node Irradiation About Lymphedema Occurrence (HYPOG-01)

ClinicalTrials.gov Identifier: NCT03127995

Shorter Course Radiation for the Treatment of Breast Cancer That Has Spread to Lymph Nodes

ClinicalTrials.gov Identifier: NCT02700386

Hypofractionated Loco-regional Adjuvant Radiation Therapy of Breast Cancer Combined With a Simultaneous Integrated Boost

ClinicalTrials.gov Identifier: NCT02384733

Hypofractionated Radiation Therapy for Patients With Breast Cancer Receiving Regional Nodal Irradiation

ClinicalTrials.gov Identifier: NCT02958774

Conventional Versus Hypofractionated Radiotherapy in Node Positive Breast Cancer

ClinicalTrials.gov Identifier: NCT02690636

CONCLUSIONS

Compliance in the principal conventional fractionations in breast cancer RT

- **Standard fractionation ->** 20 yrs follow up – good compliance
- **Standard moderate hypofractionation** -> 10 yrs follow up – very good compliance
- **Standard moderate hypofractionation (lymph nodes)** -> 5-10 yrs follow up in some cohorts – good compliance (few clinical data when IMN are included)
- **Standard moderate hypofractionation (*after reconstruction*)->** few data -> promising better compliance, but more clinical evidences needed

CONCLUSIONS

Compliance in the principal conventional fractionations in breast cancer RT

- **Standard moderate hypofractionation** can be the standard even for the lymph nodes irradiation
- There are different **ongoing trials** which will better clear the role of radiotherapy in the post-reconstruction setting

CONSTRAINTS AND TOXICITY IN STANDARD TREATMENTS

Thank you for your kind attention

Dott. Fabio Marazzi
UOC Radioterapia
Fondazione Policlinico Gemelli IRCCS - Roma