e-session 575

Hypofractionation in breast cancer RT

Expert: **Prof Philip Poortmans**, GZA Ziekenhuizen Campus Sint-Augustinus and Antwerp University, Antwerp, Belgium

Discussant: **Prof Pierfrancesco Franco**, University of Eastern Piedmont, Novara, Italy

Discussant: **Prof Icro Meattini**, Florence University, Florence, Italy

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Hypofractionation for breast cancer RT.

Current trends

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Iridium Netwerk & Antwerp University, Antwerpen (B)

Former President
ESTRO European Society for RADIOTHERAPY & ONCOLOGY
ECCO European CanCer Organisation

Disclosures:

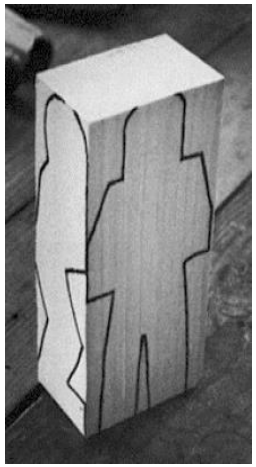
Medical advisor of Sordina IORT Technologies spa

Hypofractionation in breast RT

1. Introduction
2. Evidence
3. Discussion
4. Conclusions

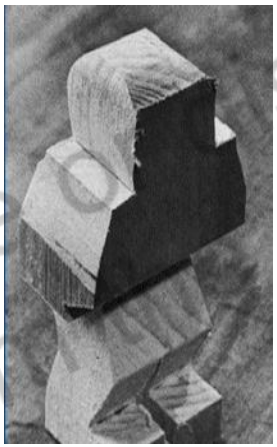
Hypofractionation in breast RT: *Introduction*

RT



3D-RT

IMRT



IG-RT

IG-IMRT

3D-IG-IMRT

SRS

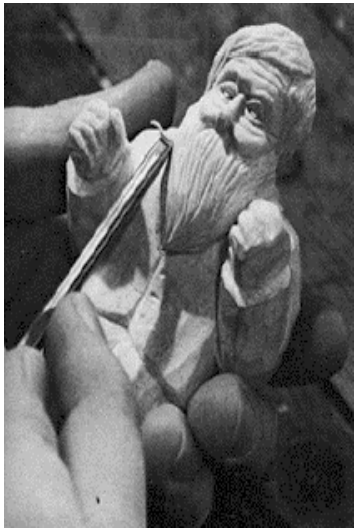
S-RT

S-IMRT

S-hRT

S-IG-IMRT

S-h-IG-IMRT



Courtesy Vincent Grégoire

Hypofractionation in breast RT: *Introduction*

20th century: Field-based RT

RT 2D; 3D; ... static IMRT

21st century: Volume-based RT

IMRT; VMAT

Evolution → RT adaptive: Volumes

Movements

Functional/biology

Medical Radiology Diagnostic Imaging

Seymour H. Levitt
James A. Purdy
Carlos A. Perez
Philip Poortmans
Editors

Technical Basis of Radiation Therapy
Practical Clinical Applications
Fifth Edition

This well-received book, now in its fifth edition, is unique in providing a detailed description of the technological basis of radiation therapy. Another novel feature is the collaborative writing of the chapters by North American and European authors. This considerably broadens the book's perspective and increases its applicability in daily practice throughout the world. The book is divided into two sections. The first covers basic concepts in treatment planning, including essential physics and biological principles related to time-dosefractionation, and explains the various technological approaches to radiation therapy, s
as intensity-modulated radiation therapy, tomotherapy, stereota
radiotherapy, and high and low dose rate brachytherapy. Is
to quality assurance, technology assessment, and cost
also reviewed. The second part of the book discu
tical clinical applications of the different radi
in a wide range of cancer sites. All of th
leaders in the field. This book will
ers, students, and practitione
basic technological facto

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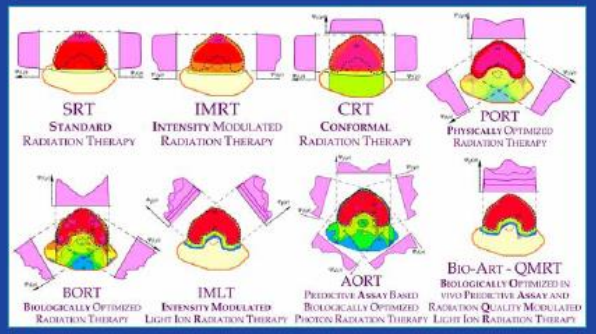


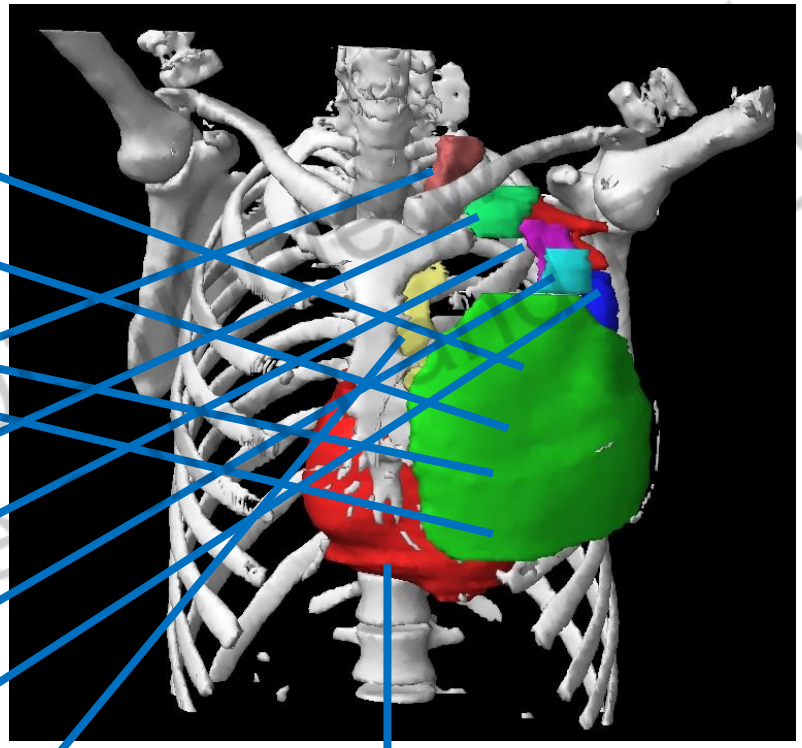
Technique serve the goal – not the other way around!

Hypofractionation in breast RT: *Introduction*

Contemporary radiation therapy

Hypofractionation in breast RT: *Introduction*

- Breast
- Boost
- PBI
- Thoracic wall
- LN supraclavicular
- LN axilla level III
- LN axilla level II
- LN axilla Rotter
- LN axilla level I
- LN internal mammary



Offersen BV, et al. Radiother Oncol 2015;114:3-10 & 2016;118:205-8.

Hypofractionation in breast RT: *Intro tion*

- Breast
- Boost
- PBI
- Thoracic wall
- LN supraclavicul
- LN axilla
- LN
- mammary

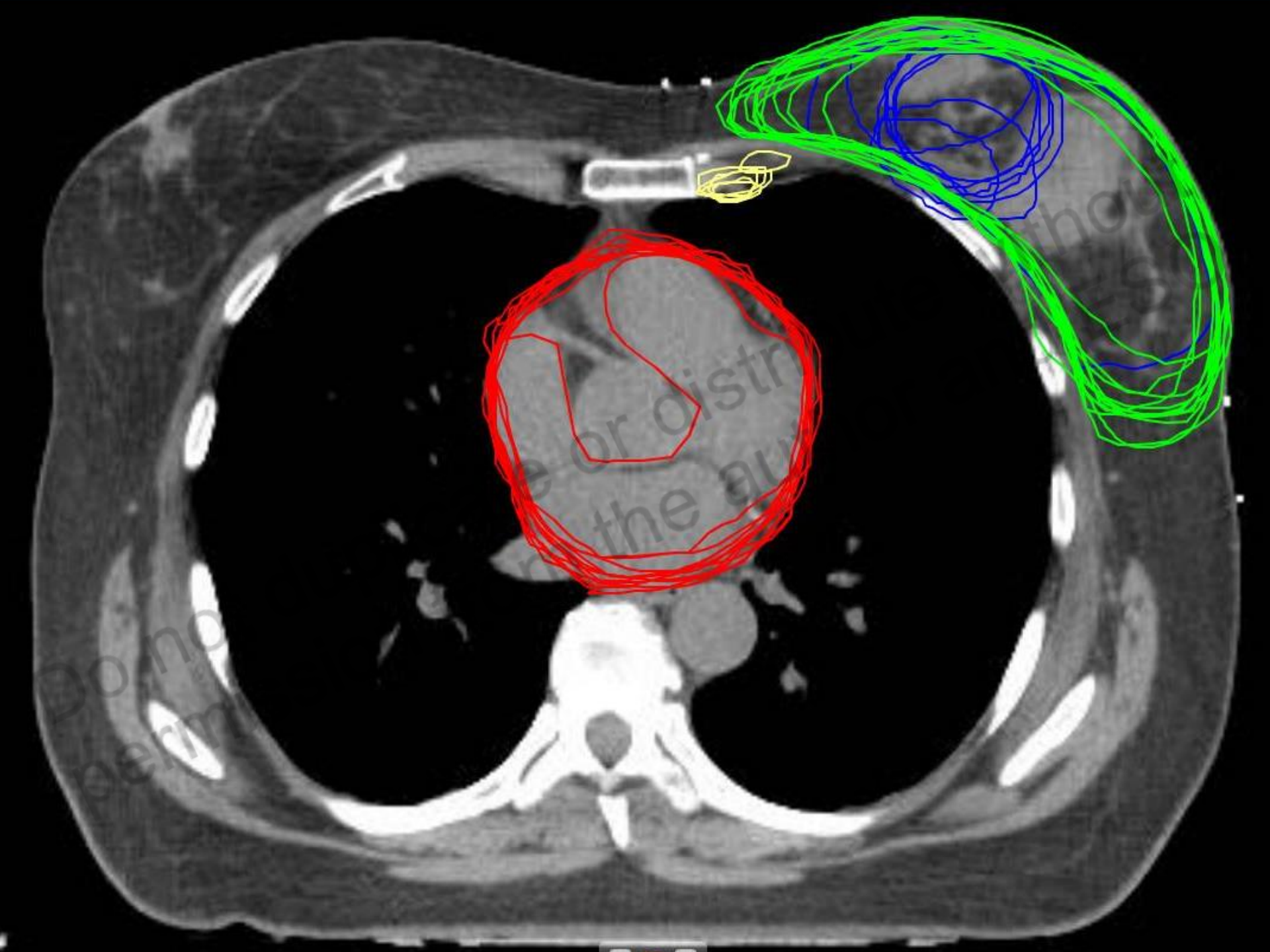
It's all about volumes
Forget the fields!!!!

Heart

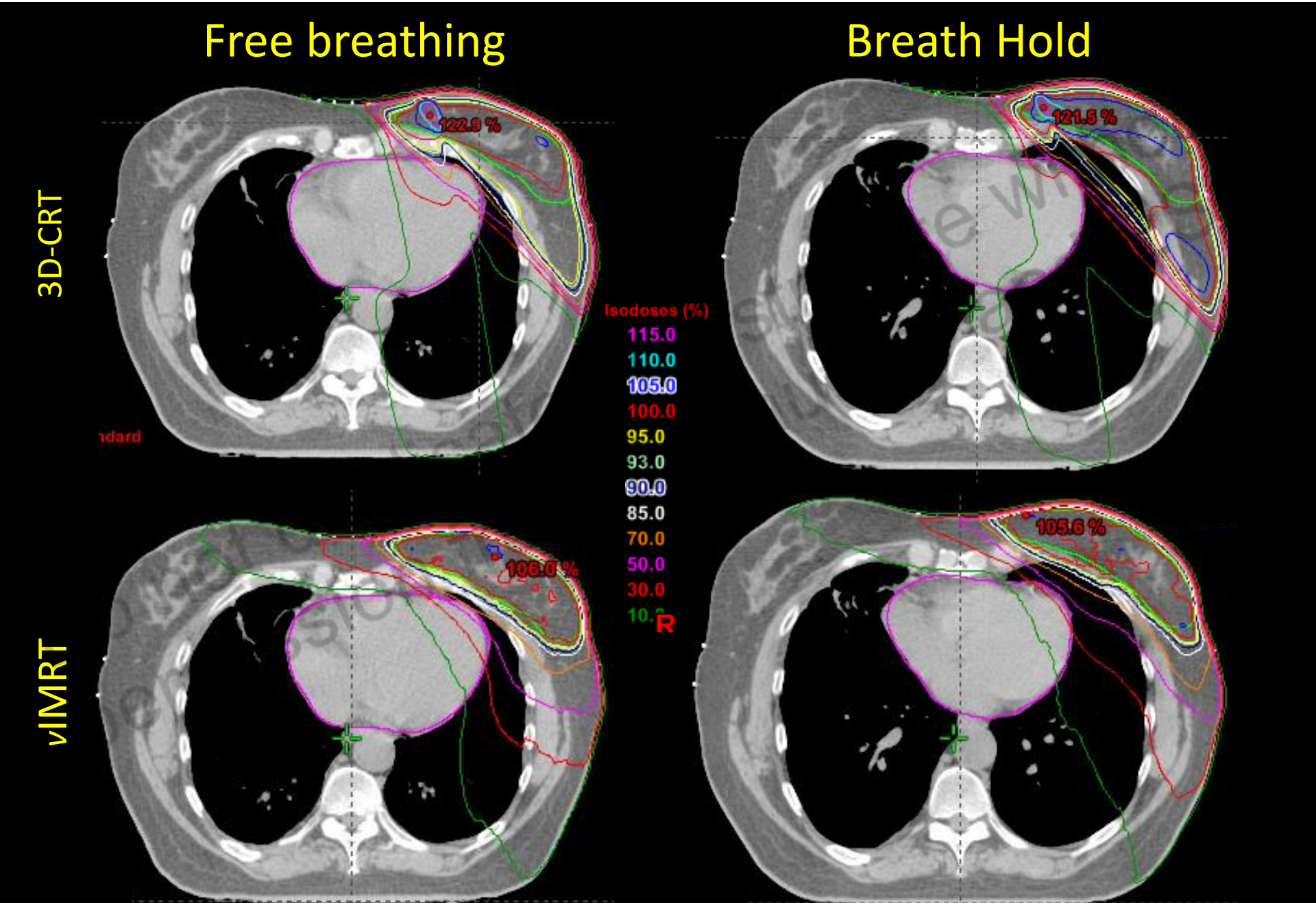
Hypofractionation in breast RT: *Introduction*

ESTRO
European SocieTy for
RADIOTHERAPY
& ONCOLOGY

FALCON
Fellowship in Anatomic deLineation & CONtouring



Hypofractionation in breast RT: *Introduction*



Hypofractionation in breast RT

1. Introduction

2. Evidence

3. Discussion

4. Conclusions

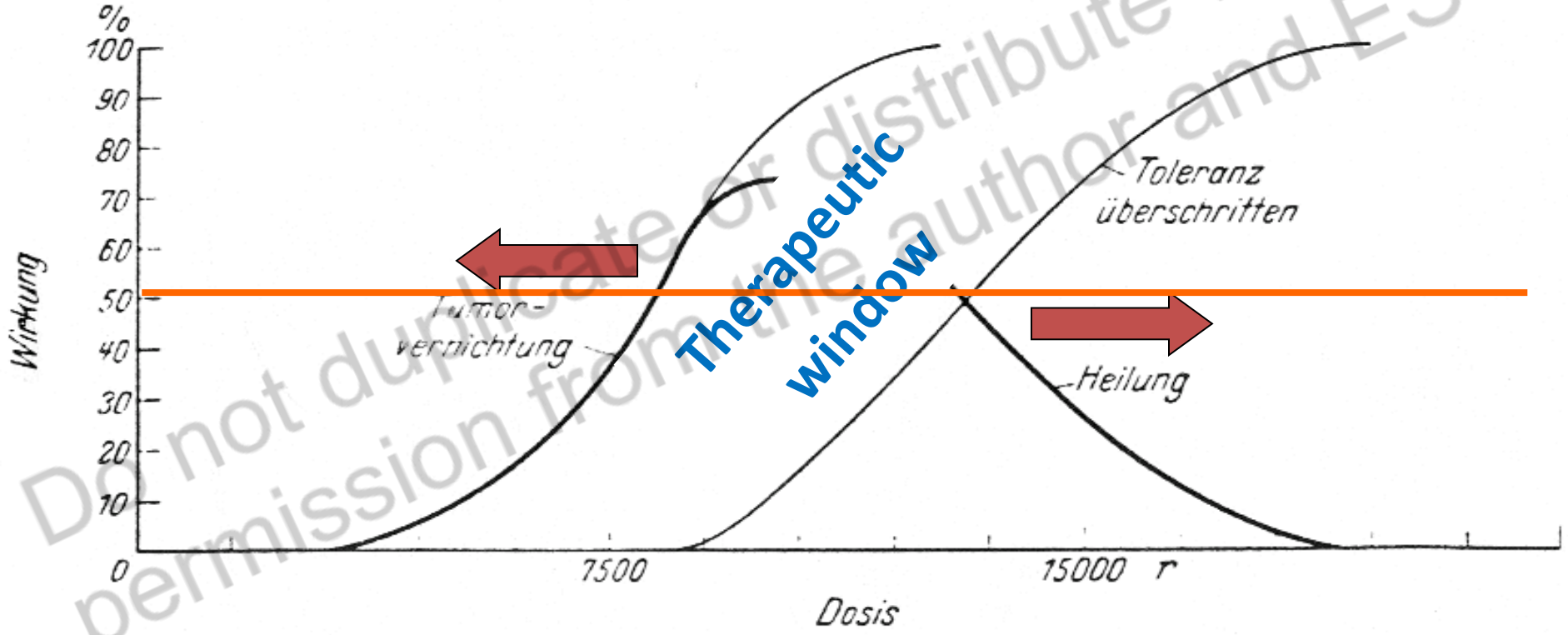
Hypofractionation in breast RT: *Evidence*

Erfahrungen über die Verträglichkeitsgrenze für Röntgenstrahlen und deren Nutzanwendung zur Verhütung von Schäden*).

Von

H. Holthusen, Hamburg.

Hypofractionation ?



*) Vortrag vor der Deutschen Röntgengesellschaft am 24. April 1936

Hypofractionation in breast RT: *Evidence*

- Total dose
- Dose per fraction
- Overall treatment time
- Time interval between fractions
- Volume

Hypofractionation in breast RT: *Evidence*

1 x 10 Newton	≠	10 x 1 Newton
1 x 20 Gy	≠	10 x 2 Gy

Kellerer & Rossi, 1973; Hall, 2000

Hypofractionation in breast RT: *Evidence*

Ellis' NSD

DOSE, TIME AND FRACTIONATION: A CLINICAL HYPOTHESIS

FRANK ELLIS

From the Radiotherapy Department, The Churchill Hospital, Oxford

Based on published clinical results of radiotherapy, a formula is suggested which relates total dose, number of fractions and overall treatment time to a quantity termed 'Nominal Standard Dose'. This quantity represents the biological effect of a given treatment regime. Using this concept it is possible to compare various treatment schedules that involve different fractionation patterns and various overall treatment times. The evidence upon which the idea is based, and also its use in routine clinical practice, are discussed.

Ellis F. Clin. Rad. 1969, 1-7

Hypofractionation in breast RT: *Evidence*

Ellis' NSD - Late effects

Innstilling fra sosialkomiteen om erstatning ved stråleskader etter brystkreftbehandling ved Radiumhospitalet i årene 1975-86.

Innst. S. nr. 41 (1998-99)

Kjeldedokument: St.prp. nr. 3 (1998-99)
Dato: 26.11.1998
Utgivar: Sosialkomiteen

Norway: 43 Gy / 10 fr:

85 x 10^6 NKr (12 x 10^6 euro)

Strålskadade får dela på 30 miljoner

SVT Nyheter | Publicerad 10 november 2005 - 17:55
Uppdaterad 20 juni 2006 - 11:26

De strålskadade kvinnor som Aktuellt har berättat om i flera reportage får nu ersättning från landstingen. De får dela på sammanlagt 30 miljoner kronor.

Sweden:

30 x 10^6 NKr (4 x 10^6 euro)

Hypofractionation in breast RT: *Evidence*

The LQ model (α/β)

The Effect of Multiple Small Doses of X Rays on Skin Reactions in the Mouse and a Basic Interpretation

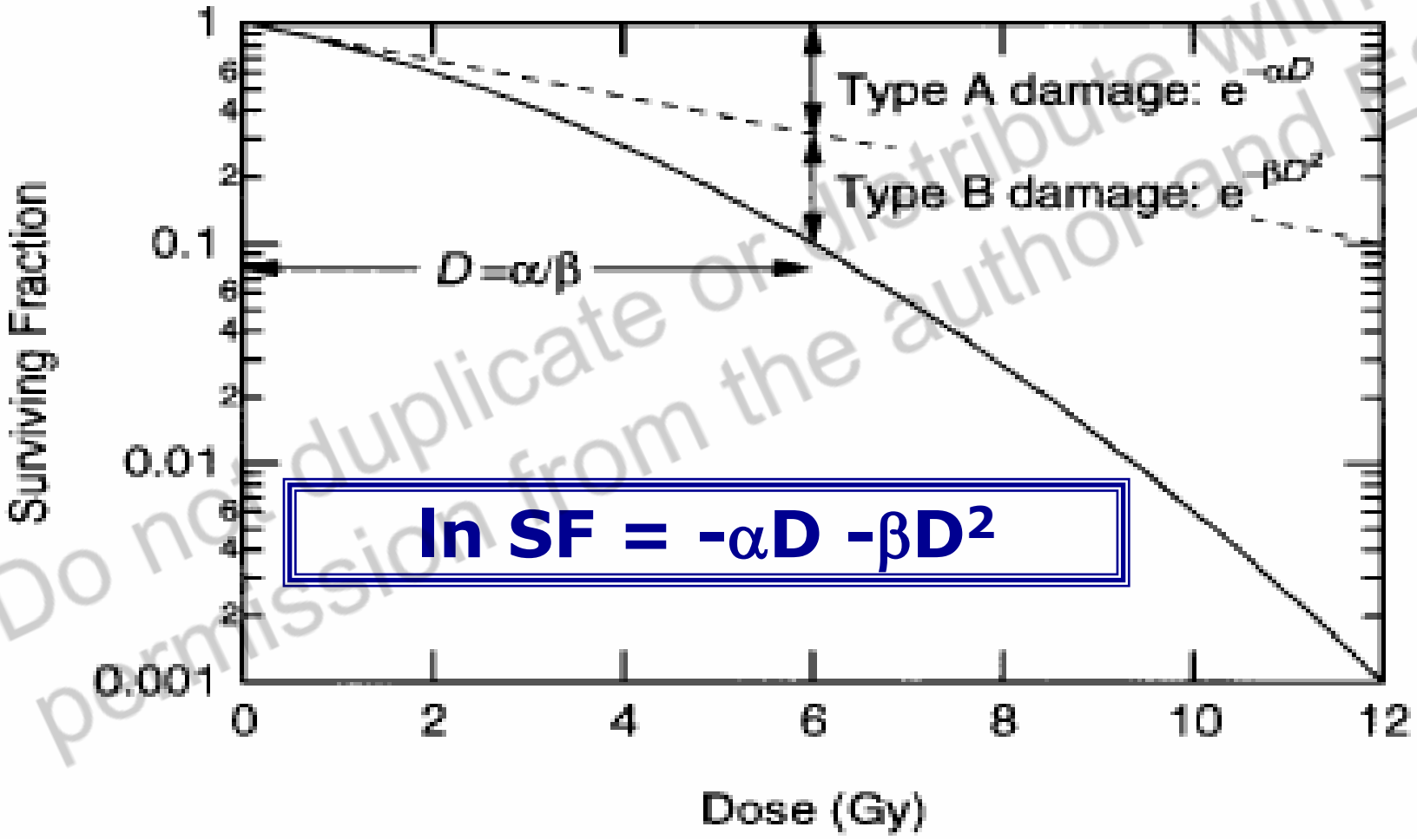
B. G. Douglas[1] and J. F. Fowler

Gray Laboratory of the Cancer Research Campaign, Mount Vernon Hospital, Northwood, Middlesex, HA6 2RN, England

Douglas and Fowler. Rad Res 1976;66: 401-426.

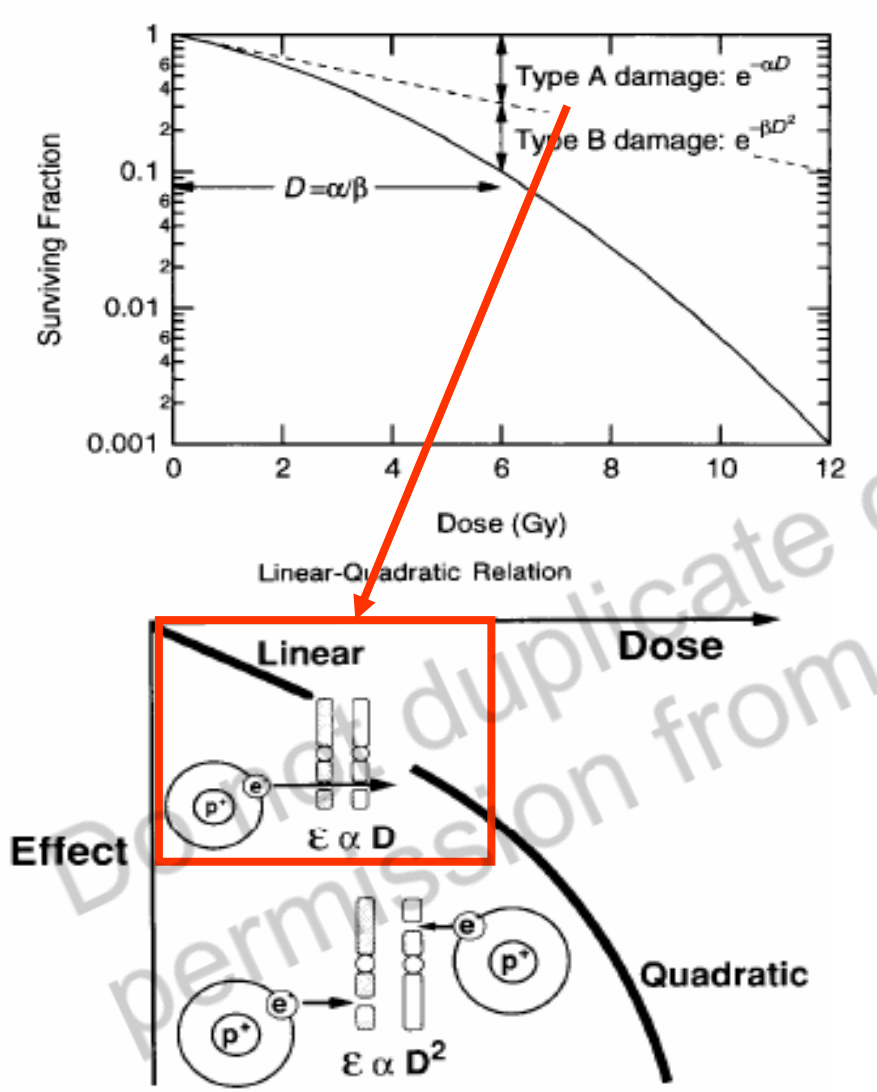
Hypofractionation in breast RT: *Evidence*

The LQ model (α/β)



Kellerer & Rossi, 1973; Hall, 2000

Hypofractionation in breast RT: *Evidence*



$\ln SF = -\alpha D - \beta D^2$

αD:

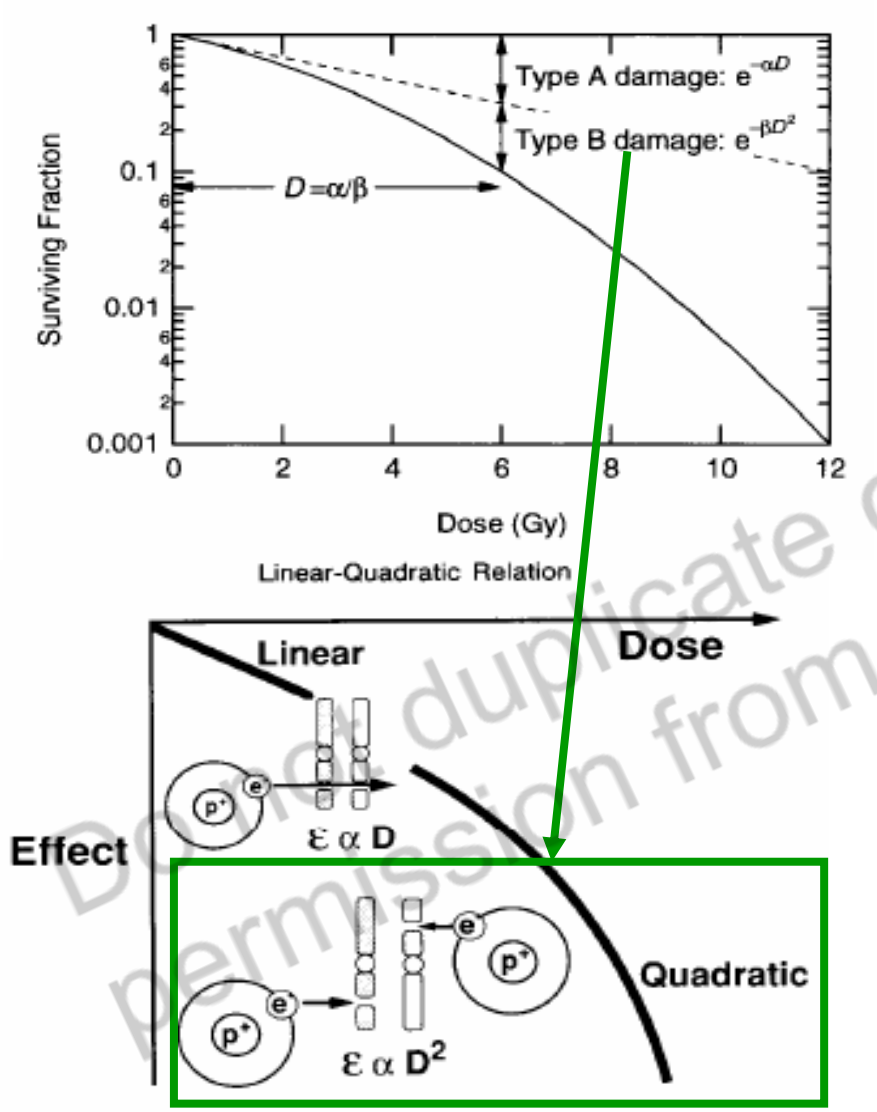
- linear component

  (start of the cell survival curve)

- ionizing radiation event simultaneously damaging two individual targets
- non-repairable damage

Kellerer & Rossi, 1973; Hall, 2000

Hypofractionation in breast RT: *Evidence*



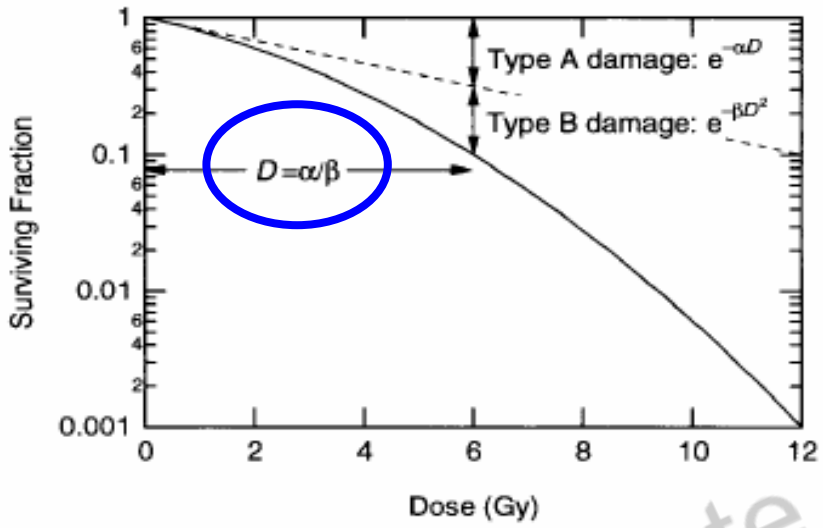
$\ln SF = -\alpha D - \beta D^2$

βD^2:

- quadratic component
  (final bending of the curve)
- two ionizing events that damage two targets separately
- sublethal damage

Kellerer & Rossi, 1973; Hall, 2000

Hypofractionation in breast RT: *Evidence*

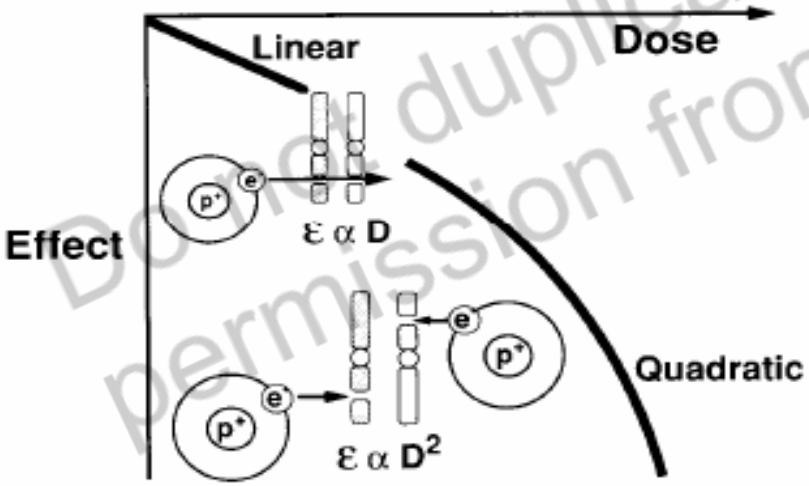


$\ln SF = -\alpha D - \beta D^2$

When

$e^{-\alpha D} = e^{-\beta D2}$

$D = \alpha/\beta$!



Kellerer & Rossi, 1973; Hall, 2000

Hypofractionation in breast RT: *Evidence*

The α/β relationship shows how tissues react to changes in fractionation: "sensitivity to fractionation"

Hypofractionation in breast RT: *Evidence*

It is important to recognize that the α/β ratio is not constant and that its value should be chosen carefully to match the specific tissue in question

Hypofractionation in breast RT: *Evidence*

α/β

Tissue/organ	End-point	α/β (Gy)	95% conf. lim. (Gy)	Reference
Early reactions				
Skin	Erythema	8.8		
	Erythema	12.3		
	Desquamation	11.2		
Oral mucosa	Mucositis	9.3		
	Mucositis	15		
	Mucositis	~8		
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		
Muscle/vasculature/ cartilage	Impaired shoulder movement	3.5		
Nerve	Brachial plexopathy	<3.5*		
	Brachial plexopathy	~2		
	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	±0.7	Deore *et al*, 1993
Lung	Pneumonitis	3.3	±1.5	van Dyk *et al*, 1989
	Fibrosis (radiological)	3.1	[-0.2; 8.5]	Dubray *et al*, 1995
Head and neck	Various late effects	3.5	±1.2	Rezvani *et al*, 1991
Supraglottic larynx	Various late effects	3.8	[0.8; 14]	Maciejewski *et al*, 1986
Oral cavity + oroph.	Various late effects	0.8	[–0.6;2.5]	Maciejewski *et al*, 1990
Tumours				
Head and neck		14.5*	±4.9	Rezvani *et al*, 1993
Larynx		~13	wide	Robertson *et al*, 1993
Vocal cord		~16*	N/A	Horiot *et al*, 1992
Oropharynx		6.6		
Buccal mucosa		7.2		
Tonsil		16		
Nasopharynx		8.5*		
Skin		0.6		
Melanoma		0.4	[–1.4; 5.4]	Thames and Suit 1986
Liposarcoma				

High ~ 10

Low ~ 1 – 3.5

High ~ 10

Hypofractionation in breast RT: *Evidence*

Clinical data from multiple institutions support that breast and prostate cancer have a low ratio (≤ 3-4) of α/β, favouring hypofractionation.

Hypofractionation in breast RT: *Evidence*

Everything depends on the assumption that the α / β of the tumour is very low

Trials START ➔ α/β of tumour ~ 4-5 Gy

α/β	39/13	40/15	50/25
1.8	**49.3**	**47.1**	**50**
2	**48.8**	**46.7**	**50**
3	**46.8**	**45.4**	**50**
4	**45.5**	**44.7**	**50**
6	**43.9**	**43.4**	**50**
8	**42.9**	**42.7**	**50**
10	**42.3**	**42.2**	**50**

Yarnold et al., Radiother Oncol 2005;75:9-17

Hypofractionation in breast RT: *Evidence*

The LQ model (α/β)

If the α/β of the tumour > α/β of late side effects

+

treatment prescription adapted to late side effects

⇓

we must accept to under-dose the tumour!

Conclusion:

Even using hypofraction safely, the therapeutic ratio always drops

Hypofractionation in breast RT: *Evidence*

The LQ model (α/β)

If the α/β of the tumour > α/β of late side eff

+

treatment prescription ad[illegible]rects

we m[illegible]er-dose the tumour!

But is this true????

Conclusion:

Even using hypofraction safely, the therapeutic ratio always drops

Hypofractionation in breast RT: *Evidence*

Is the α/β for breast cancer really low?

Data from:	α/β (Gy)
Whelan 2002	3.21
Owen 2006	4.39
Shelly 2000	2.21
Start A 2008	3.91
Start B 2008	2.49
Clark 1996	1.44
Arriagada 1985	3.89

95% CL:

0.75-5.01

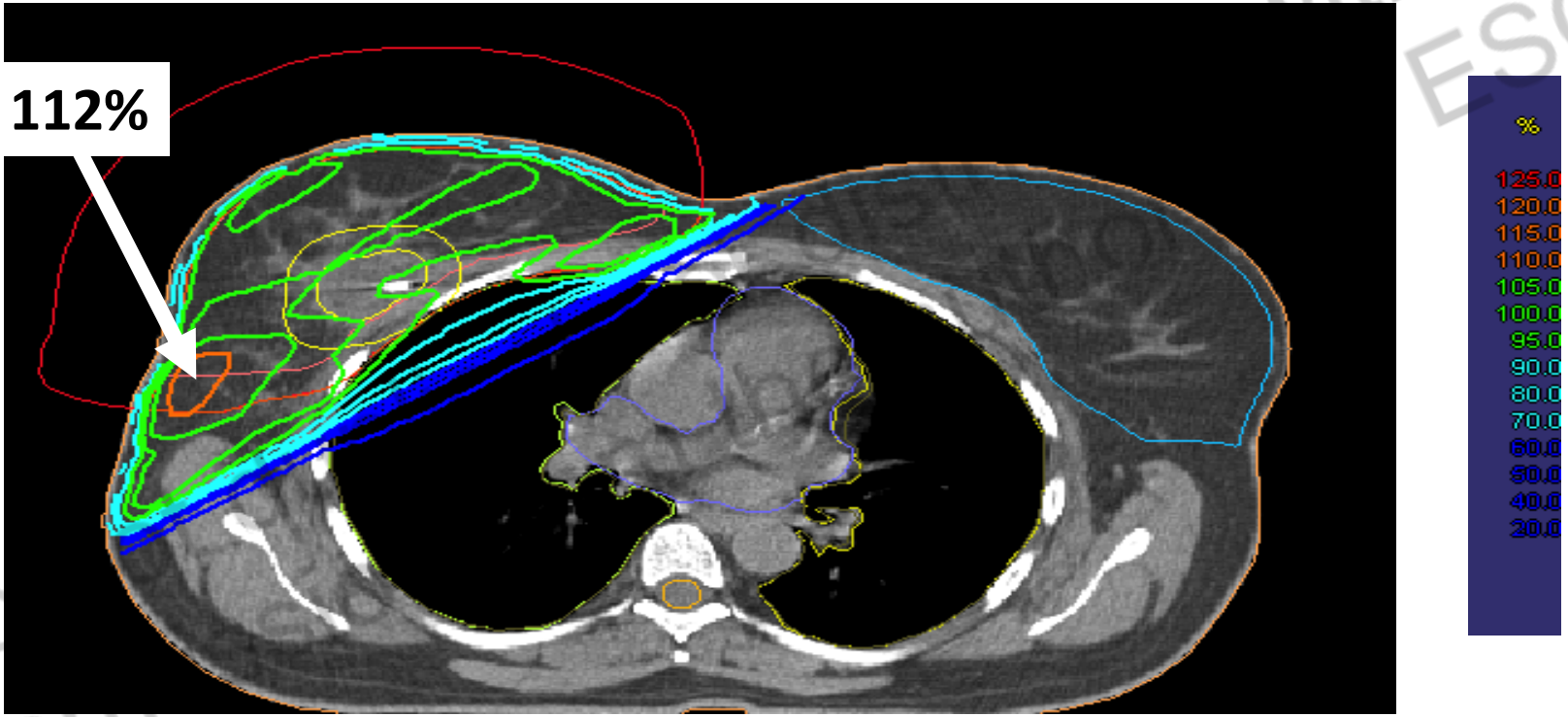
➔ *Many clinical data support that breast cancer has a low α/β ratio, thereby supporting the use of HipoF*

Qi et al. Radiother. Oncol 2011

Hypofractionation in breast RT: *Evidence*

Physics aspects related to HF:

HipoF: be careful with treatment planning



➔ Subdoses and overdoses are more important for late effects with hypofractionation

Yarnold et al., Breast 2010;19:176-79

Hypofractionation in breast RT: *Evidence*

Physics aspects related to HF:

HipoF: be careful with treatment planning

If we increase the fraction size:

➔ *we must lower the total dose.....*

Importance of high dose points in a treatment plan:

➔ *higher dose + higher fractional dose*

„Double trouble“ (Withers 1992)

High dose points in HypoF RT:

➔ *penalized with greater severity: higher dose + high dose points = 2x higher dose per fraction*

➔ TRIPLE TROUBLE

Hypofractionation in breast RT: *Evidence*

Physics aspects related to HF:

HipoF: be careful with treatment planning

If we increase the fraction size:

➔ *we must lower the total dose..*

Importance of high d… …eatment plan:

➔ *higher dos… …l dose*

…ble“ (Withers 1992)

…points in HypoF RT:

…penalized with greater severity: higher dose + high dose points = 2x higher dose per fraction

➔ TRIPLE TROUBLE

But is this true????

Hypofractionation in breast RT: *Evidence*

Inhomogeneity of the dose in the breast	Equivalent total dose (Gy) if α/β=3 Gy, using fractions of….		
	2Gy	4Gy	6Gy
100 %	50.0	50.0	50.0
105 %	53.6 →	54.0 →	54.3

'double trouble'

'triple trouble'

Adapted from Yarnold, IJROBP, 2011, 79; 1-9

Hypofractionation in breast RT: *Evidence*

Inhomogeneity of the dose in the breast	Equivalent total dose α/β=3 Gy

The "triple trouble" is also not a concern in patients with large breasts

50.0 → 54.0 → 54.3

'double trouble'

'triple trouble'

Adapted from Yarnold, IJROBP, 2011, 79; 1-9

Hypofractionation in breast RT: *Evidence*

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

The NEW ENGLAND JOURNAL of MEDICINE

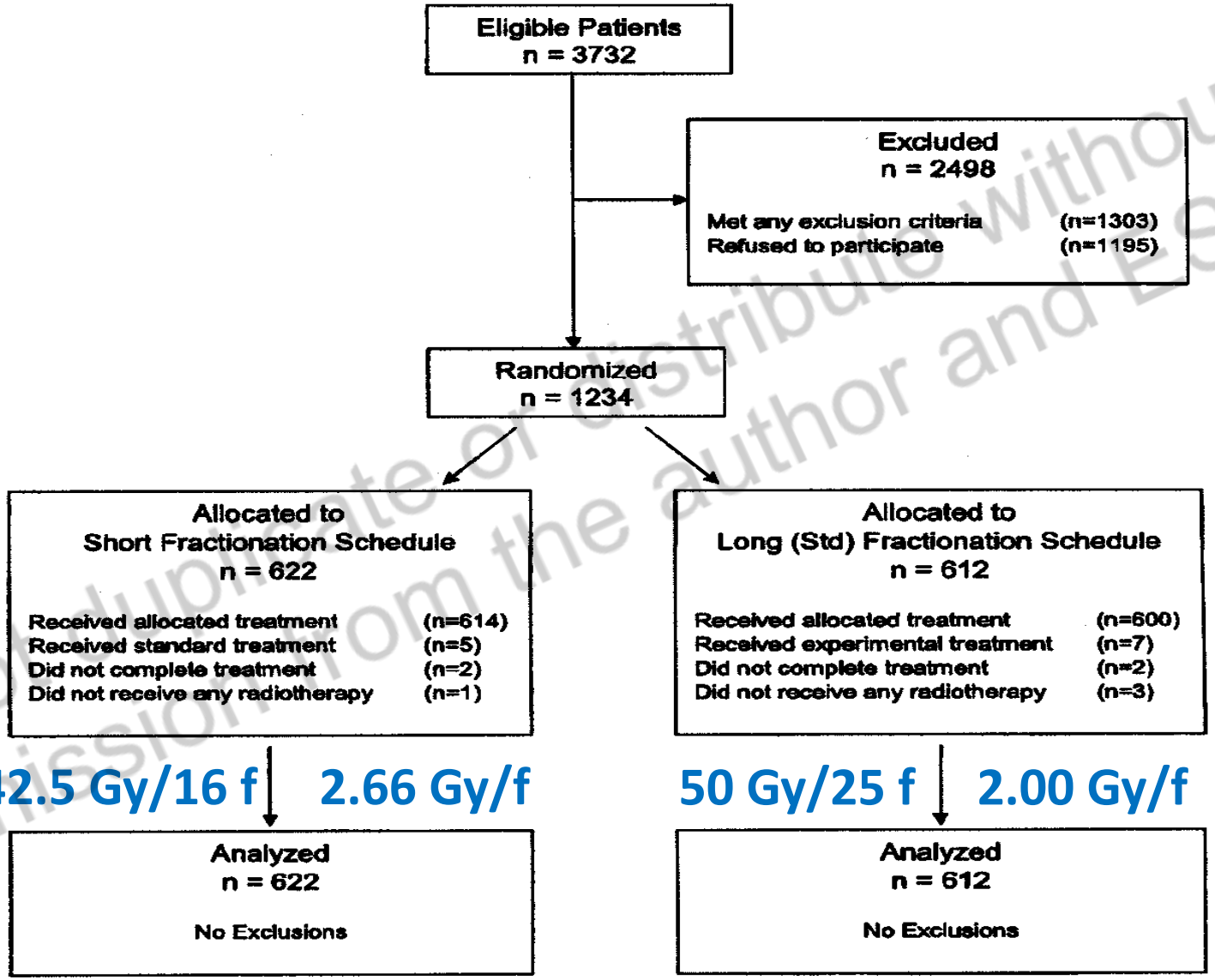
ORIGINAL ARTICLE

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.,

Whelan et al. JNCI 2002;94:1143-50 & NEJM 2010;362:513-20

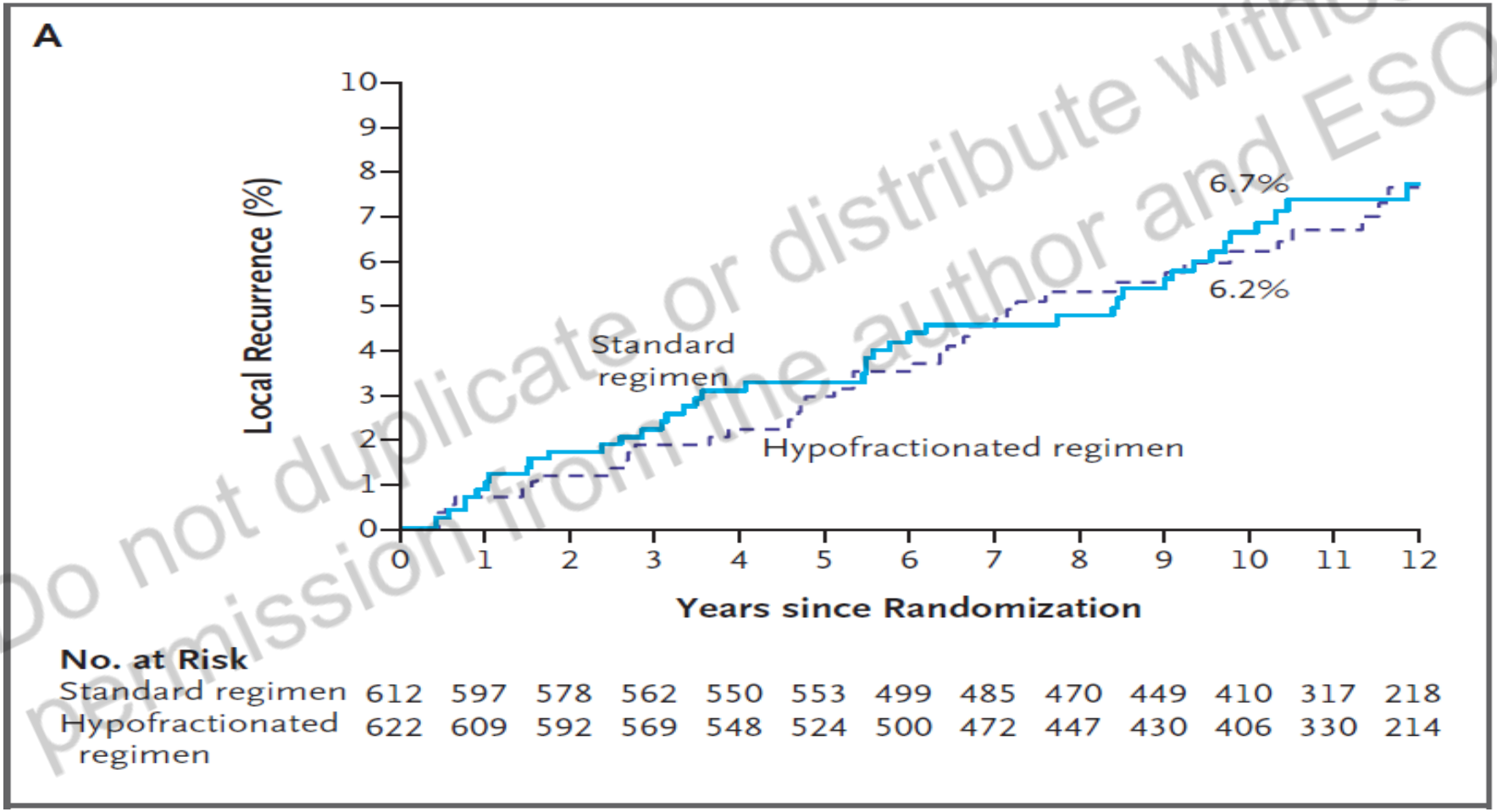
Hypofractionation in breast RT: *Evidence*



Whelan et al. JNCI 2002;94:1143-50 & NEJM 2010;362:513-20

Hypofractionation in breast RT: *Evidence*

Local control



Whelan et al. JNCI 2002;94:1143-50 & NEJM 2010;362:513-20

Hypofractionation in breast RT: *Evidence*

Table 1. Late Toxic Effects of Radiation, Assessed According to the RTOG–EORTC Late Radiation Morbidity Scoring Scheme.*

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

Multivariate analysis on cosmetic outcome: time since treatment, age, tumour size, NOT fractionation

Whelan et al. JNCI 2002;94:1143-50 & NEJM 2010;362:513-20

Hypofractionation in breast RT: *Evidence*

The UK Standardisation of Breast Radiotherapy (START) Trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial

Inclusion 1999-2001, 23 centres in UK
Tumour < 5 cm and N0-1a
(92% lumpectomy, 74% pN0, 64% T<2 cm,
72% Tam, 15% Tam+CT)

2215 pts

- **40 Gy / 15 fractions, 2.67 Gy / fr**
- **50 Gy / 25 fractions, 2.0 Gy / fr**

Endpoints: local control and morbidity
Median follow-up 6.0 years

Yarnold et al. Lancet 2008;371:1098-107.

Hypofractionation in breast RT: *Evidence*

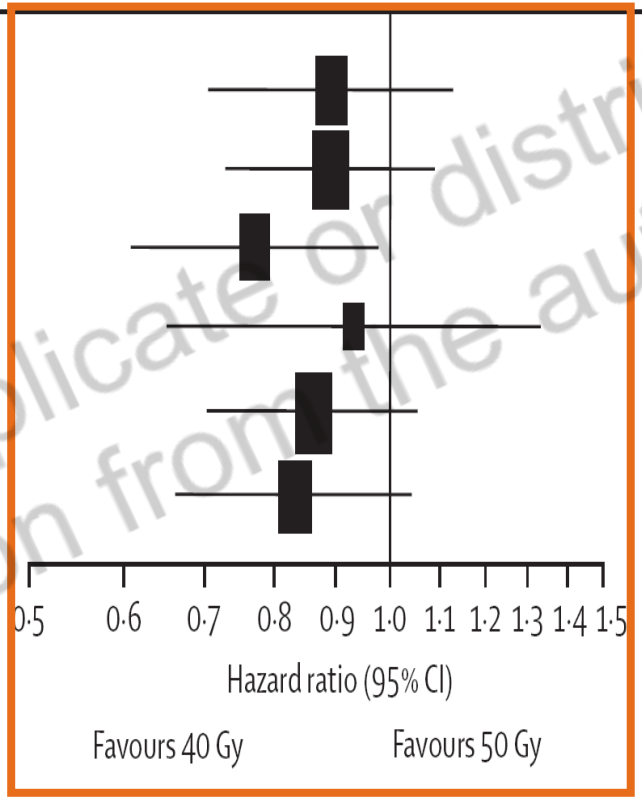
	Events/total (%)	Estimated % with event by 5 years (95% CI)	Crude hazard ratio (95% CI)	Log-rank test p value
Local relapse*				
50 Gy	34/1105 (3·1)	3·3 (2·2–4·4)	1	
40 Gy	25/1110 (2·2)	2·0 (1·1–2·8)	0·72 (0·43–1·21)	0·21
Local-regional relapse				
50 Gy	36/1105 (3·2)	3·3 (2·2–4·5)	1	
40 Gy	29/1110 (2·6)	2·2 (1·3–3·1)	0·79 (0·48–1·29)	0·35
Distant relapse				
50 Gy	122/1105 (11·0)	10·2 (8·4–12·1)	1	
40 Gy	87/1110 (7·8)	7·6 (6·0–9·2)	0·69 (0·53–0·91)	0·01
Any breast cancer-related event†				
50 Gy	164/1105 (14·8)	14·1 (12·0–16·2)	1	
40 Gy	127/1110 (11·4)	10·6 (8·7–12·4)	0·75 (0·60–0·95)	0·02
All-cause mortality				
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

Yarnold et al. Lancet 2008;371:1098-107.

Hypofractionation in breast RT: *Evidence*

Morbidity

	Kaplan-Meier 5 year event rate (95% CI), %		Hazard ratio (95% CI)
	50 Gy	40 Gy	
Breast shrinkage since radiotherapy*	24·4 (20·3–28·4)	23·2 (19·3–27·2)	0·89 (0·70–1·12)
Breast hardness since radiotherapy*	42·3 (37·6–46·9)	38·2 (33·6–42·7)	0·89 (0·73–1·09)
Change in skin appearance since radiotherapy	27·8 (23·8–31·8)	22·9 (19·3–26·6)	0·77 (0·61–0·98)
Swelling in area of affected breast	12·4 (9·5–15·2)	10·5 (7·9–13·2)	0·93 (0·65–1·33)
Change in breast appearance since radiotherapy*	39·4 (34·8–44·0)	34·4 (30·0–38·9)	0·86 (0·70–1·05)
Change in breast appearance (photographic)*	42·2 (37·3–47·4)	36·5 (31·8–41·6)	0·83 (0·66–1·04)



*Breast conserving patients only

Yarnold et al. Lancet 2008;371:1098-107.

Hypofractionation in breast RT: *Evidence*

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*

Inclusion 2008-2016, 1 centre in China
T3-4 / N2

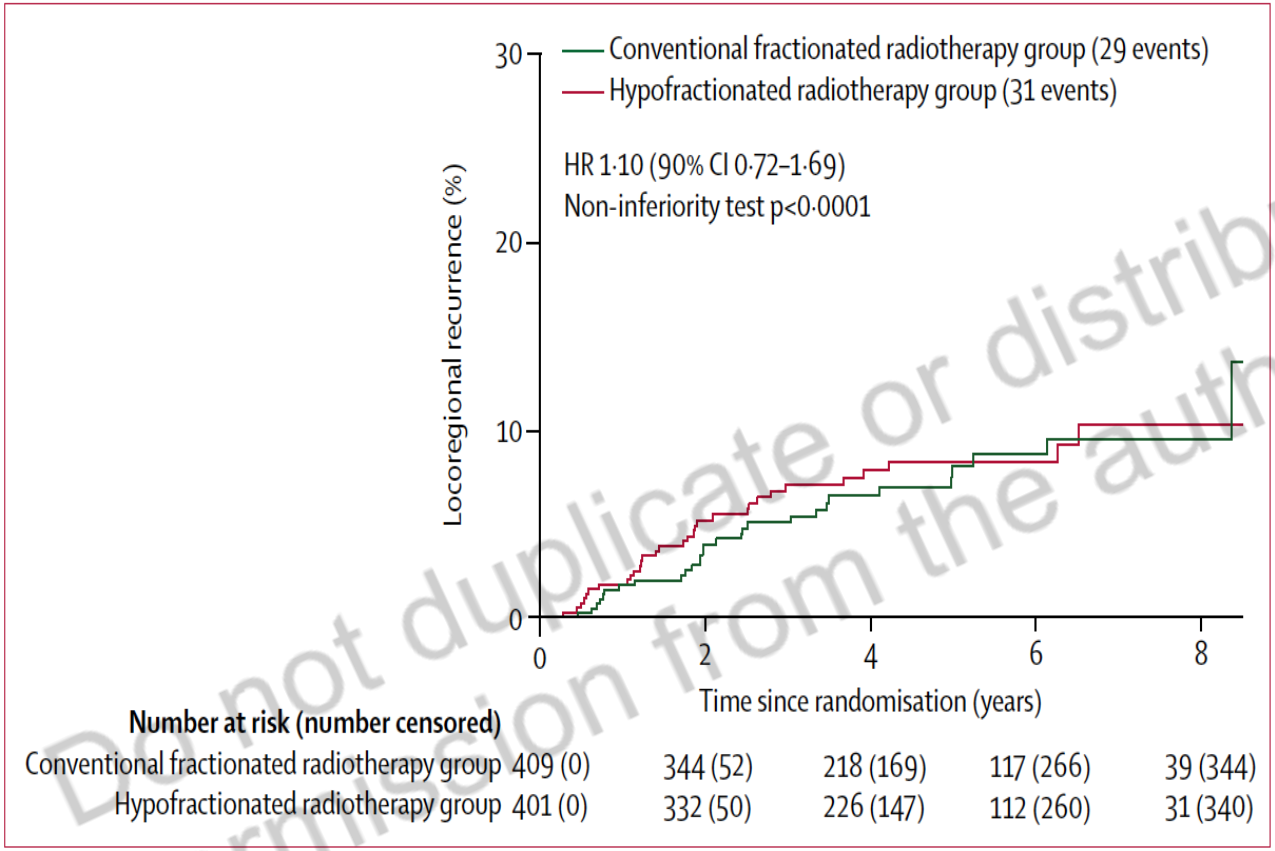
820 pts

- **43.5 Gy / 15 fractions, 2.9 Gy / fr**
- **50.0 Gy / 25 fractions, 2.0 Gy / fr**

Endpoints: loc0-regional control
Median follow-up 58.5 months

Wang SL, et al. Lancet Oncol 20019;e-pub.

Hypofractionation in breast RT: *Evidence*



	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 effects were reported.

Table 2: **Adverse events**

Wang SL, et al. Lancet Oncol 20019;e-pub.

Hypofractionation in breast RT: *Evidence*

Reshma Jagsi
Department of Radiation Oncology, University of Michigan,
Ann Arbor, MI 48109-5010, USA
rjagsi@med.umich.edu

Comment

Hypofractionated radiotherapy after mastectomy: a new frontier

Trials specifically focused on reconstruction outcomes after moderate hypofractionation are underway in the USA (Alliance 221505 [NCT03414970] and FABREC [NCT03422003]). Together with other ongoing trials, this research will hopefully advance our understanding in the near future, and one day, hypofractionated regional nodal irradiation might be considered a standard approach worldwide. For now, we owe our gratitude to Wang and colleagues for their illuminating work in an area of great ongoing interest and investigation.

Hypofractionation in breast RT: *Evidence*

Where is the limit? ➔ FAST

Ten-Year Results of FAST: A Randomized Controlled Trial of 5-Fraction Whole-Breast Radiotherapy for Early Breast Cancer

Adrian Murray Brunt, FRCR[1]; Joanne S. Haviland, MSc[2]; Mark Sydenham, BSc Hons[2]; Rajiv K. Agrawal, FRCR[3]; Hafiz Algurafi, FRCR[4]; Abdulla Alhasso, FRCR[5]; Peter Barrett-Lee, FRCR[6]; Peter Bliss, FRCR[7]; David Bloomfield, FRCR[8]; Joanna Bowen, FRCR[9]; Ellen Donovan, PhD[10]; Andy Goodman, FRCR[11]; Adrian Harnett, FRCR[12]; Martin Hogg, FRCR[13]; Sri Kumar, FRCR[14]; Helen Passant, FRCR[6]; Mary Quigley, FRCR[15]; Liz Sherwin, FRCR[16]; Alan Stewart, FRCR[17]; Isabel Syndikus, FRCR[18]; Jean Tremlett, MSc[8]; Yat Tsang, PhD[19]; Karen Venables, PhD[19]; Duncan Wheatley, FRCR[20]; Judith M. Bliss, MSc[2]; and John R. Yarnold, FRCR[21]

Brunt AM, et al. J Clin Oncol. 2020 Oct 1;38(28):3261-3272.

Hypofractionation in breast RT: *Evidence*

Where is the limit? ➔ FAST

<u>Patient selection :</u>

- ≥ 50 years
- < 3 cm
- N0

N = 915; median FU 3 years

Brunt AM, et al. J Clin Oncol. 2020 Oct 1;38(28):3261-3272.

Hypofractionation in breast RT: *Evidence*

Where is the limit? ➔ FAST

Table 2
Schema of the UK FAST trial testing two dose levels of a 5-fraction regimen delivered as one fraction per week versus 50 Gy in 25 fractions over 5 weeks to the whole breast after local tumour excision of early breast cancer.

Group	Total dose (Gy)	Fraction size (Gy)	Number of fractions	Fractions per week
Control	50.0	2.0	25	5
Test 1[a]	30.0	6.0	5	1
Test 2[b]	28.5	5.7	5	1

[a] Iso-effective with Control if $\alpha/\beta = 4.0$ Gy.
[b] Iso-effective with Control if $\alpha/\beta = 3.0$ Gy.

Yarnold & Haviland. The Breast 2010

Hypofractionation in breast RT: *Evidence*

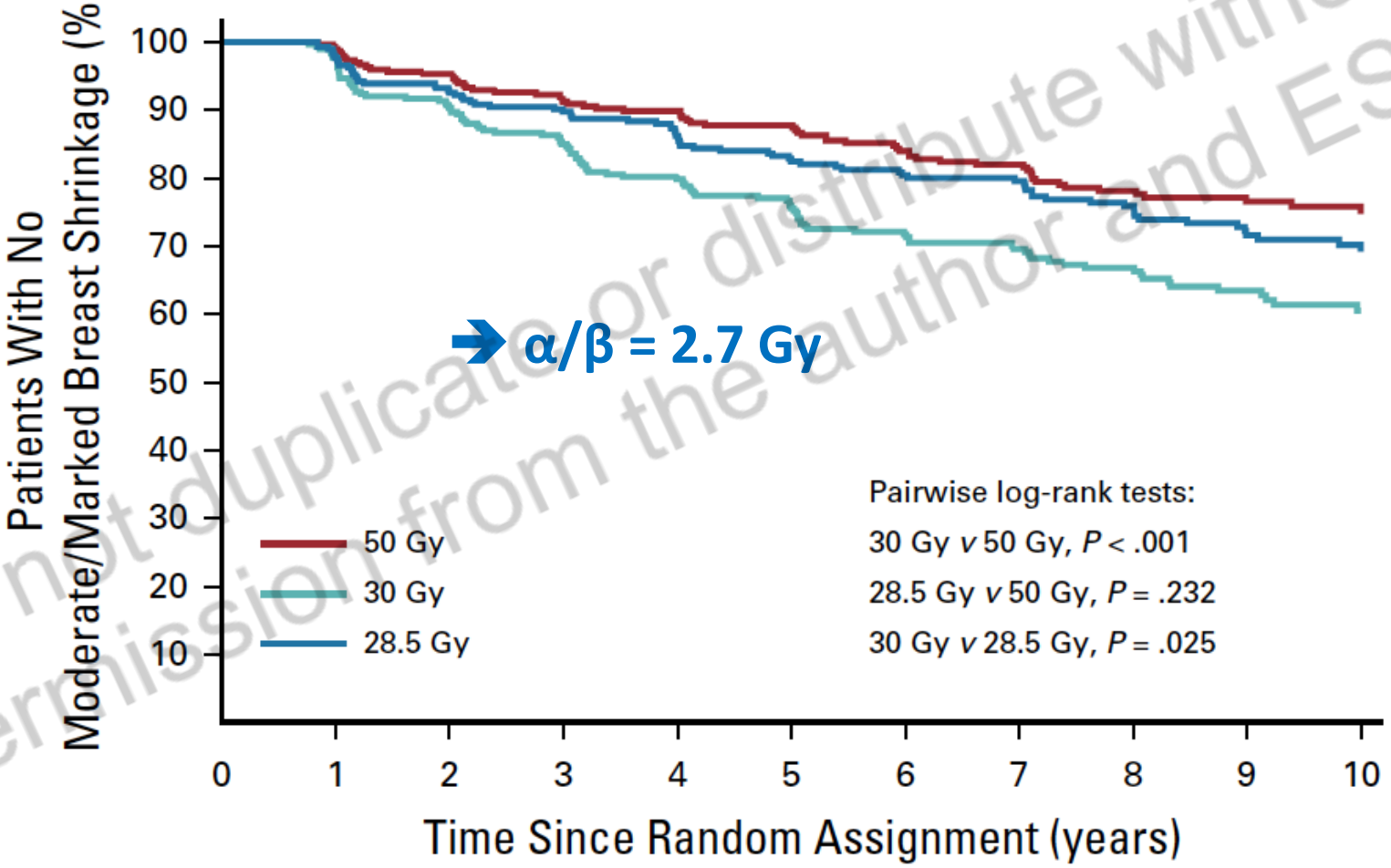
Where is the limit? ➔ FAST: side effects

	WBI 25 x 2 Gy	5 x 5.7 Gy (α/β-3 Gy)	5 x 6 Gy (α/β-4 Gy)
	all in 5 weeks		
Moist desquamation (5.2%)	12%	2%	3%
Moderate change in the appearance of the breast at 28m	19.3%	20.3%	26.2%
Marked change in the appearance of the breast at 28m	1.7%	3.7% (p=0.26)	9.3% (p<0.001)

Brunt AM, et al. J Clin Oncol. 2020 Oct 1;38(28):3261-3272.

Hypofractionation in breast RT: *Evidence*

Where is the limit? ➔ FAST: breast shrinkage



Brunt AM, et al. J Clin Oncol. 2020 Oct 1;38(28):3261-3272.

Hypofractionation in breast RT: *Evidence*

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

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

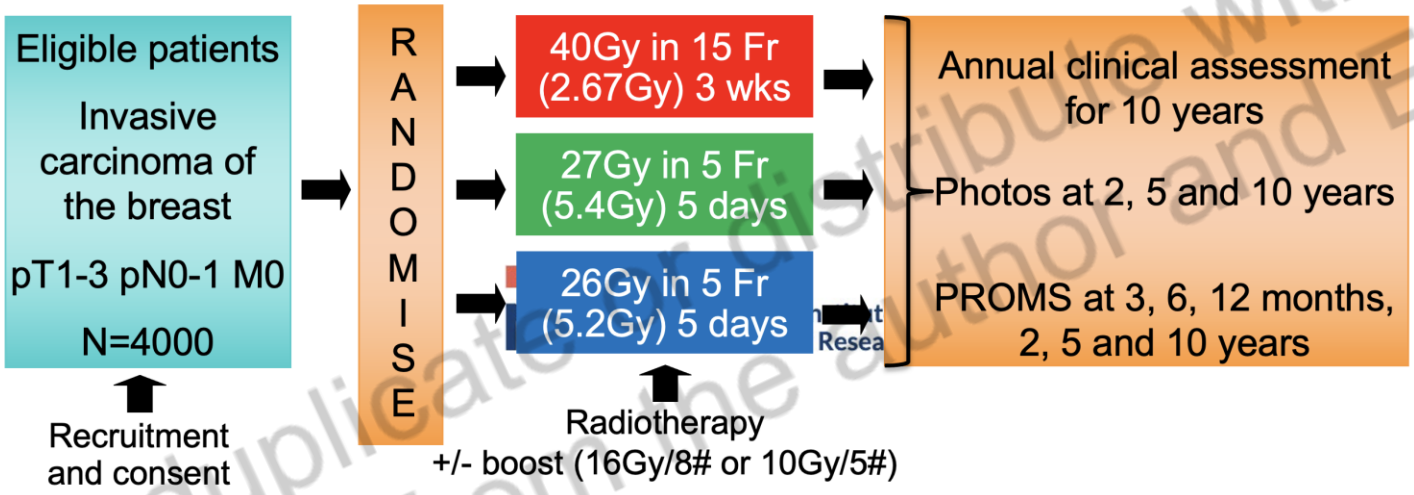
Brunt AM, et al. Lancet. 2020 May 23;395(10237):1613-1626.

Hypofractionation in breast RT: *Evidence*

FUNDED BY NIHR | National Institute for Health Research

FAST-Forward

CI: Murray Brunt
Chief Clinical Co-ordinator: Duncan Wheatley



Primary endpoint:
- Ipsilateral breast tumour relapse

Median follow-up: 6 years

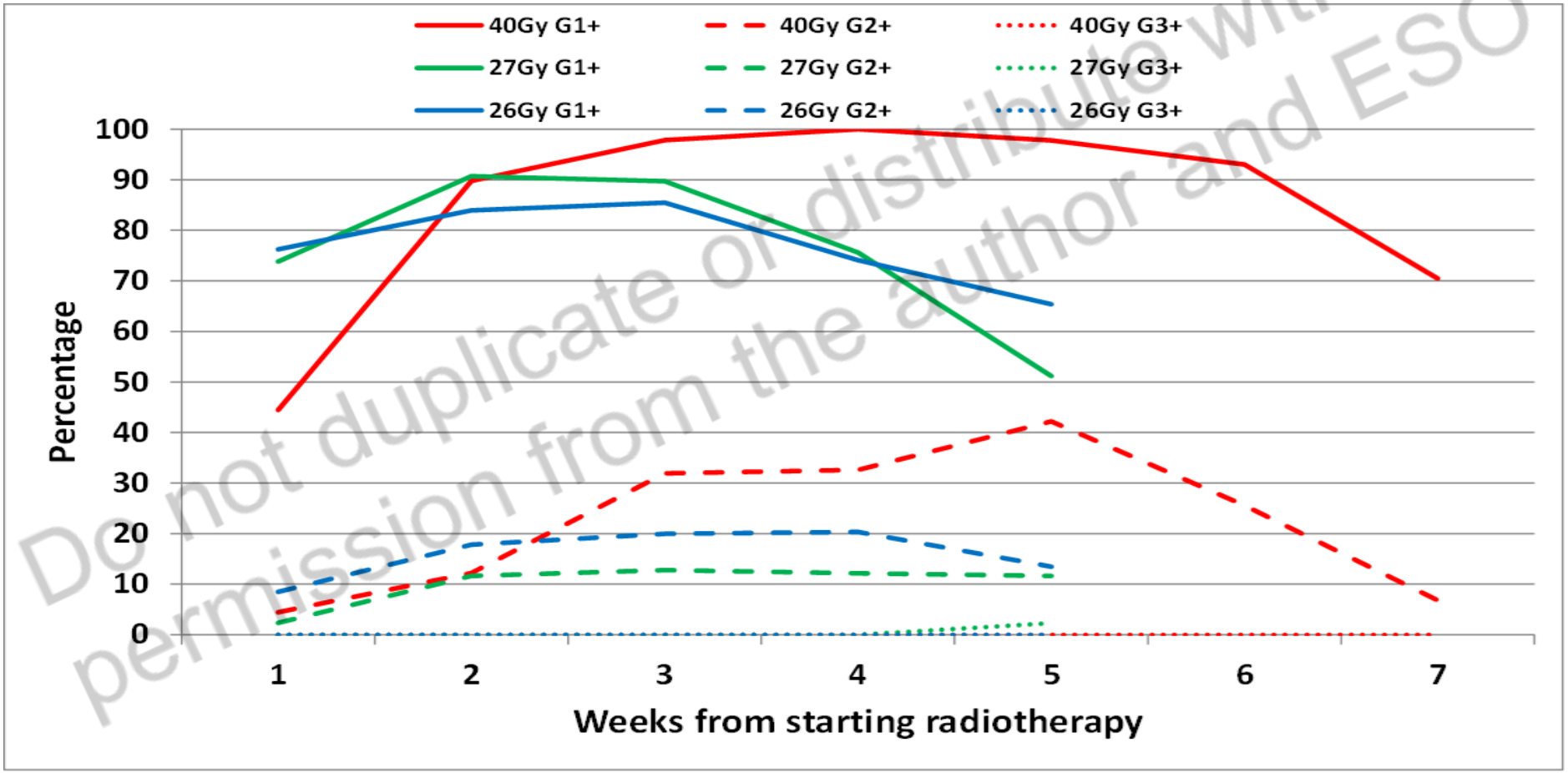
Secondary endpoints:
- early & late AE in normal tissues
- quality of life
- contralateral primary tumours
- regional & distant metastases
- survival

Courtesy of Murray Brunt & Jo Haviland

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

Hypofractionation in breast RT: *Evidence*

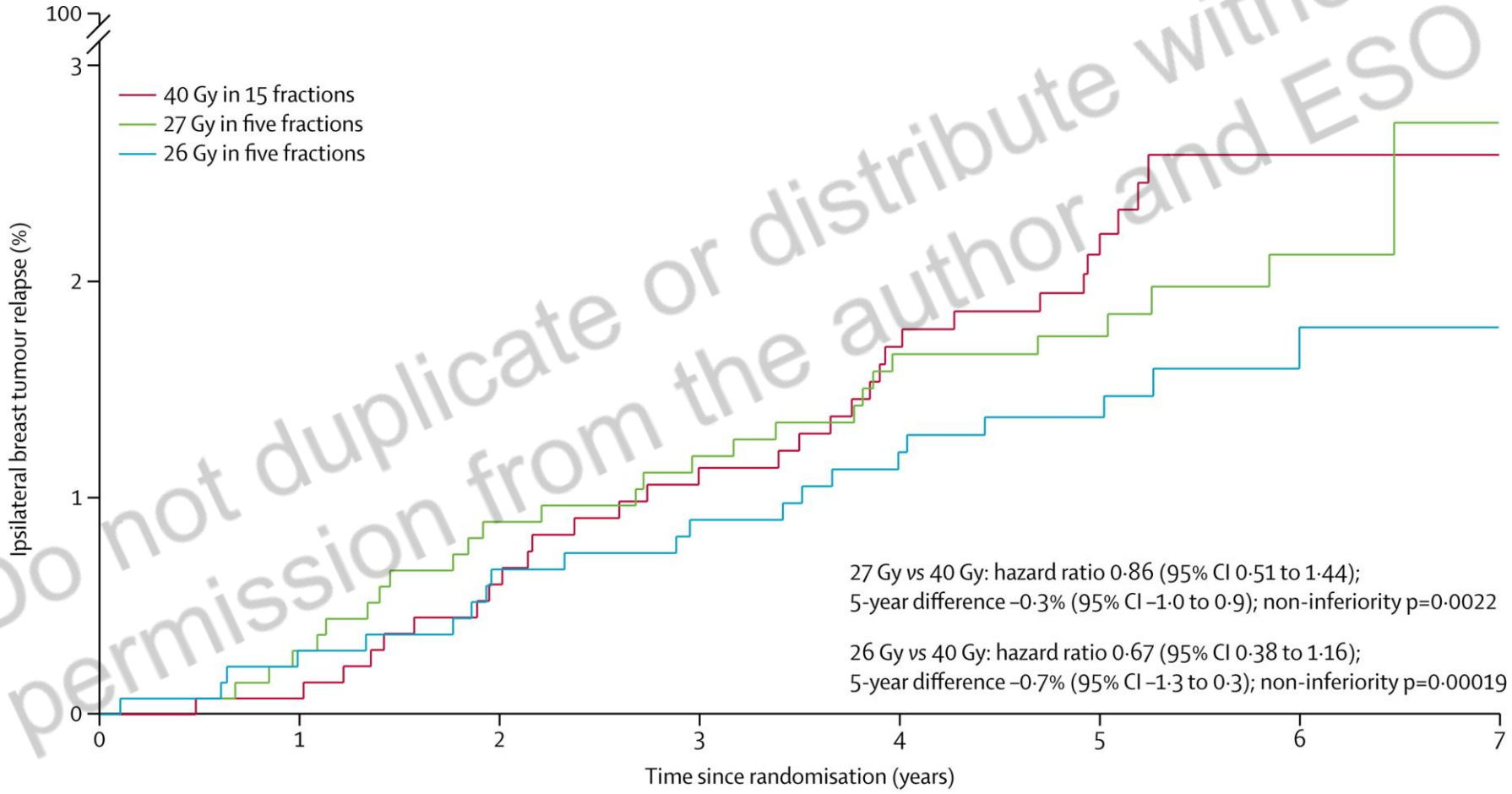
Acute skin toxicity



Brunt AM, et al. Radiother Oncol 2016.

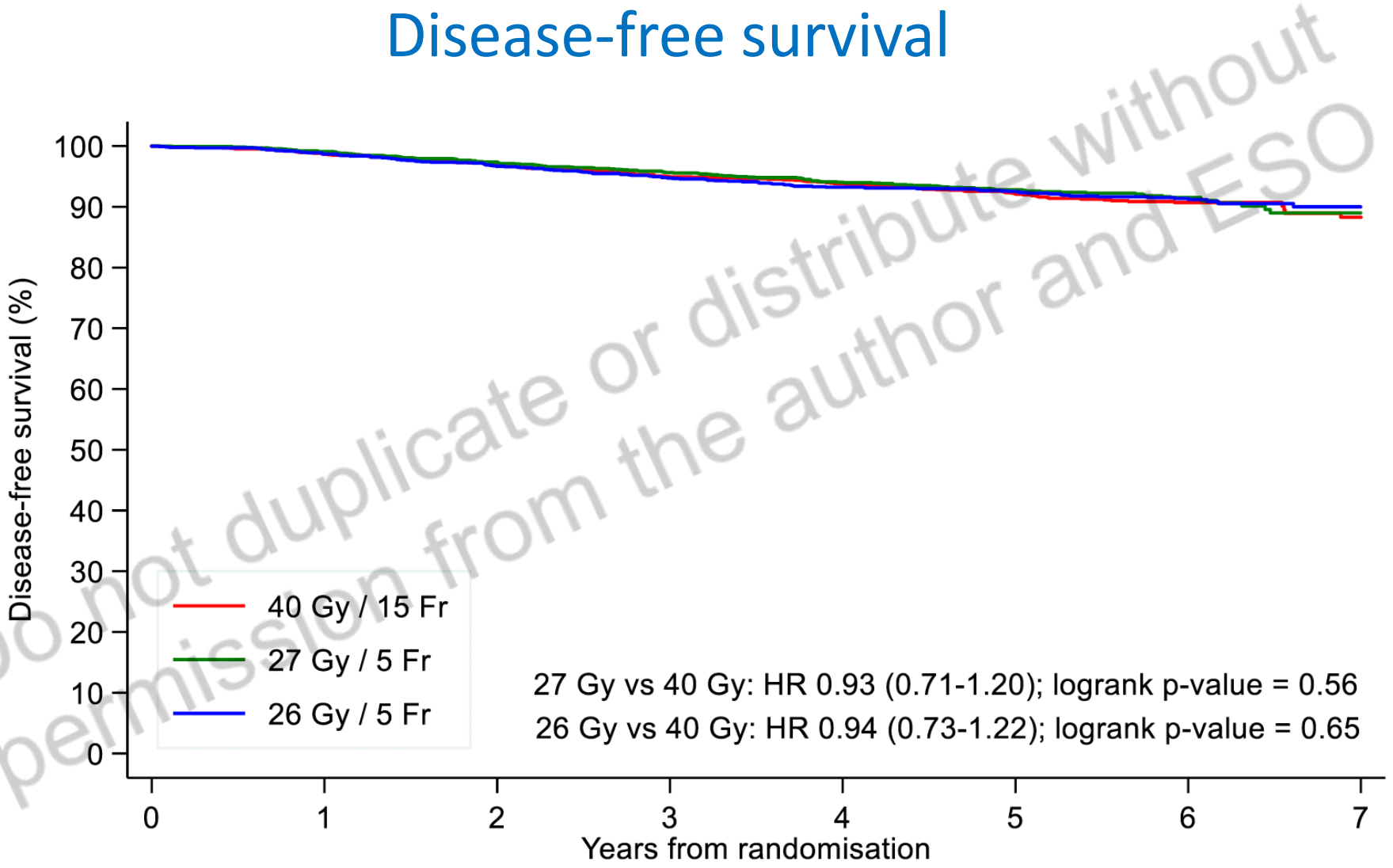
Hypofractionation in breast RT: *Evidence*

Primary Endpoint: Ipsilateral breast tumour relapse



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

Hypofractionation in breast RT: *Evidence*



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

Hypofractionation in breast RT: *Evidence*

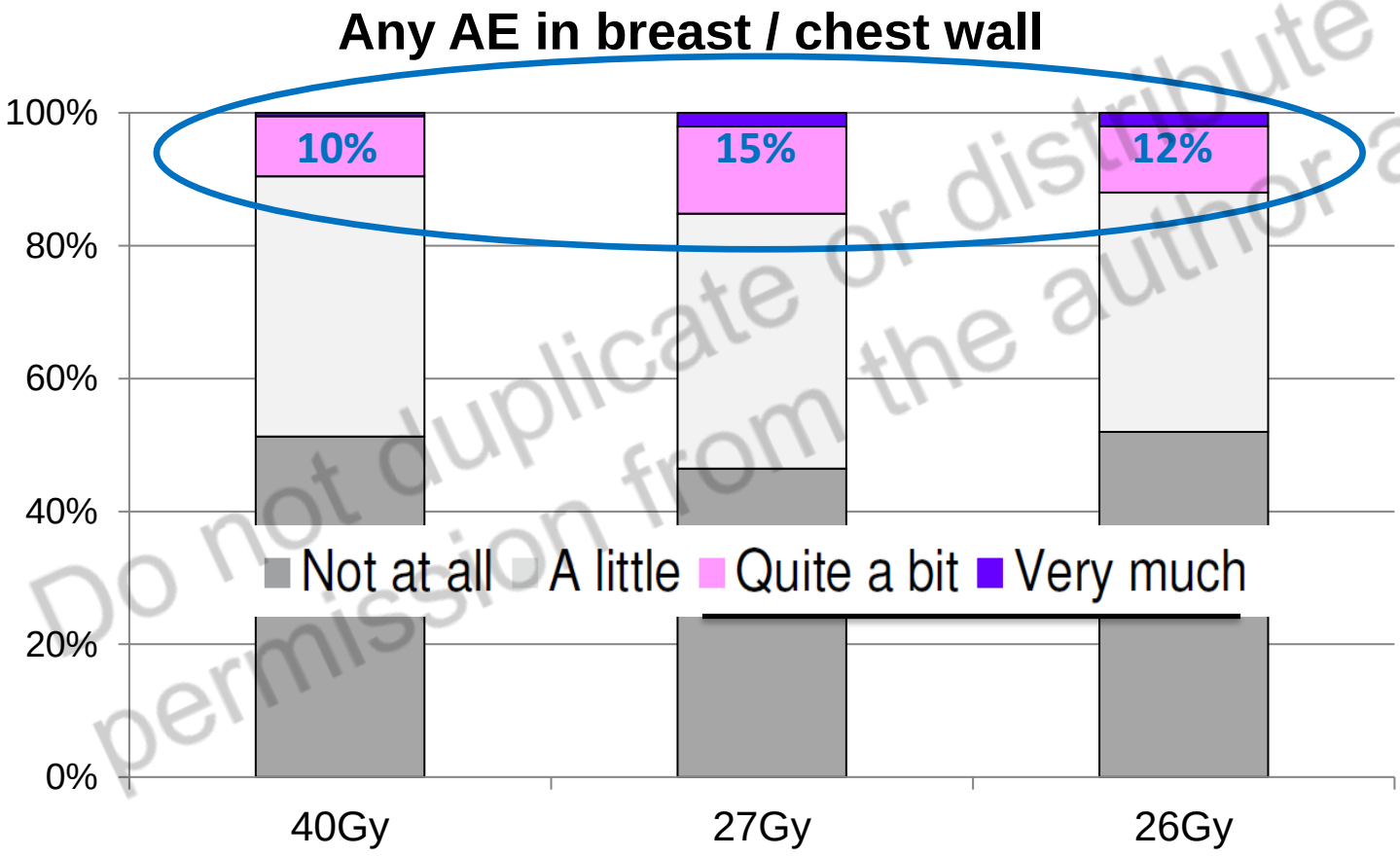
Clinician-assessed late adverse effects

	Number of moderate or marked events/total number of assessments over follow-up	Odds ratio for schedule (95% CI)	p value for comparison with 40 Gy	p value for comparison between 27 Gy and 26 Gy	Odds ratio for years of follow-up (95% CI); p value
Any adverse event in the breast or chest wall*	..	..	..	..	0·98 (0·96–1·00); 0·055
40 Gy	651/6121 (10·6%)	1 (ref)	..	..	..
27 Gy	1004/6303 (15·9%)	1·55 (1·32–1·83)	<0·0001	..	..
26 Gy	774/6327 (12·2%)	1·12 (0·94–1·34)	0·20	0·0001	..

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

Hypofractionation in breast RT: *Evidence*

Clinician assessments of adverse effects at 5 years



ORs for any moderate/marked AE vs. 40Gy:

- 1.55 (1.32-1.84, p<0.001) for 27Gy
- 1.12 (0.94-1.34, p=0.20) for 26Gy

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

Hypofractionation in breast RT: *Evidence*

Fractionation sensitivity (α/β) of late-responding normal tissues

Any clinician-reported moderate/marked AE in breast/chest wall

α/β estimate = 1.7 Gy (95% CI 1.2 – 2.3)

Photographic change in breast appearance

α/β estimate = 1.8 Gy (95% CI 1.1 – 2.4)

Patient-reported moderate/marked change in breast appearance

α/β estimate = 2.3 Gy (95% CI 1.8 – 2.9)

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

Hypofractionation in breast RT: *Evidence*

Conclusions & implications for clinical practice

- ✓Both 5-fraction schedules are non-inferior to 40 Gy/15 Fr for local tumour control
- ✓For late effects:
  - ✓ 26 Gy/5 Fr similar to 40 Gy/15 Fr &
  - ✓ 27 Gy/5 Fr consistent with 50 Gy/25 Fr
- ✓Benefits to patients
- ✓Benefits to healthcare systems
- ✓The UK has adopted 26 Gy/5 Fr at a consensus meeting 15/10/20

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

Hypofractionation in breast RT

1. Introduction
2. Evidence
3. Discussion
4. Conclusions

Hypofractionation in breast RT: *Discussion*

Critical Reviews in Oncology / Hematology 156 (2020) 103090

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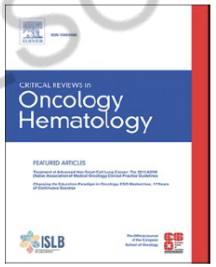


European School of Oncology – Review

The use of moderately hypofractionated post-operative radiation therapy for breast cancer in clinical practice: A critical review

Gustavo Nader Marta [a,b,*], Charlotte Coles [c], Orit Kaidar-Person [d], Icro Meattini [e,f], Tarek Hijal [g], Yvonne Zissiadis [h], Jean-Philippe Pignol [i], Duvern Ramiah [j], Alice Y. Ho [k], Skye Hung-Chun Cheng [l], Gemma Sancho [m], Birgitte Vrou Offersen [n,o], Philip Poortmans [p,q]

Marta GN, et al. CROH 2020;156:103090.

Hypofractionation in breast RT: *Discussion*

Table 1
Characteristics of the prospective randomised studies comparing conventional with hypofractionation schedules in breast-cancer patients.

	RMH/GOC611	START A712	START B812	OCOG514	Beijing Trial[17]	Total N (%)
Number of patients	1410	2236	2215	1234	820	7915 (100)
Years of inclusion	1986 - 1998	1998 - 2002	1999 - 2001	1993 - 1996	2008–2016	–
Inclusion criteria	T1–3;N01;M0	T1–3;N0–1;M0	T1–3;N0–1;M0	T1–2;N0;M0	T3-T4;N2–3;M0	–
Median follow-up - years (range)	9.7 (7.8–11.8)	9.3 (8.0–10.0)	9.9 (7.5–10.1	12.0 ([a])	4.9 (3.7–6.8)	–
Type of surgery N (%)						
Breast-conserving surgery	1214 (86)	1900 (85)	2038 (92)	1098 (89)	0	6250 (79)
Mastectomy	0	336 (15)	177 (8)	0	820 (100)	1665 (21)
Chemotherapy N (%)	196 (14)	793 (35)	491 (22)	136 (11)	820 (100)	2436 (31)
Boost N (%)	1051 (75)	1152 (61)	875 (43)	0	0	3078 (39)
Regional nodal irradiation N (%)	290 (21)	318 (14)	161 (7)	0	840 (100)	1609 (20)

Marta GN, et al. CROH 2020;156:103090.

Hypofractionation in breast RT: *Discussion*

Please remember that the results are strictly valid only for the groups of patients who have participated.

Hypofractionation in breast RT: *Discussion*

RT after mastectomy:

	Canada	RMH/GOC	START A	START B
Mastectomy	0%	0%	15%	8%

➔ *?*

Hypofractionation in breast RT: *Discussion*

Lymph node RT:

	Canada	RMH/GOC	START A	START B
N+	0%	32.8%	28.8%	22.8%
LN RT	0%	20.6%	14.2%	7.3%

➔ *?*

Hypofractionation in breast RT: *Discussion*

RT for advanced stage:

	Canada	RMH/GOC	START A	START B
pT1-2	100%	94%	100%	100%

➔ *?*

Hypofractionation in breast RT: *Discussion*

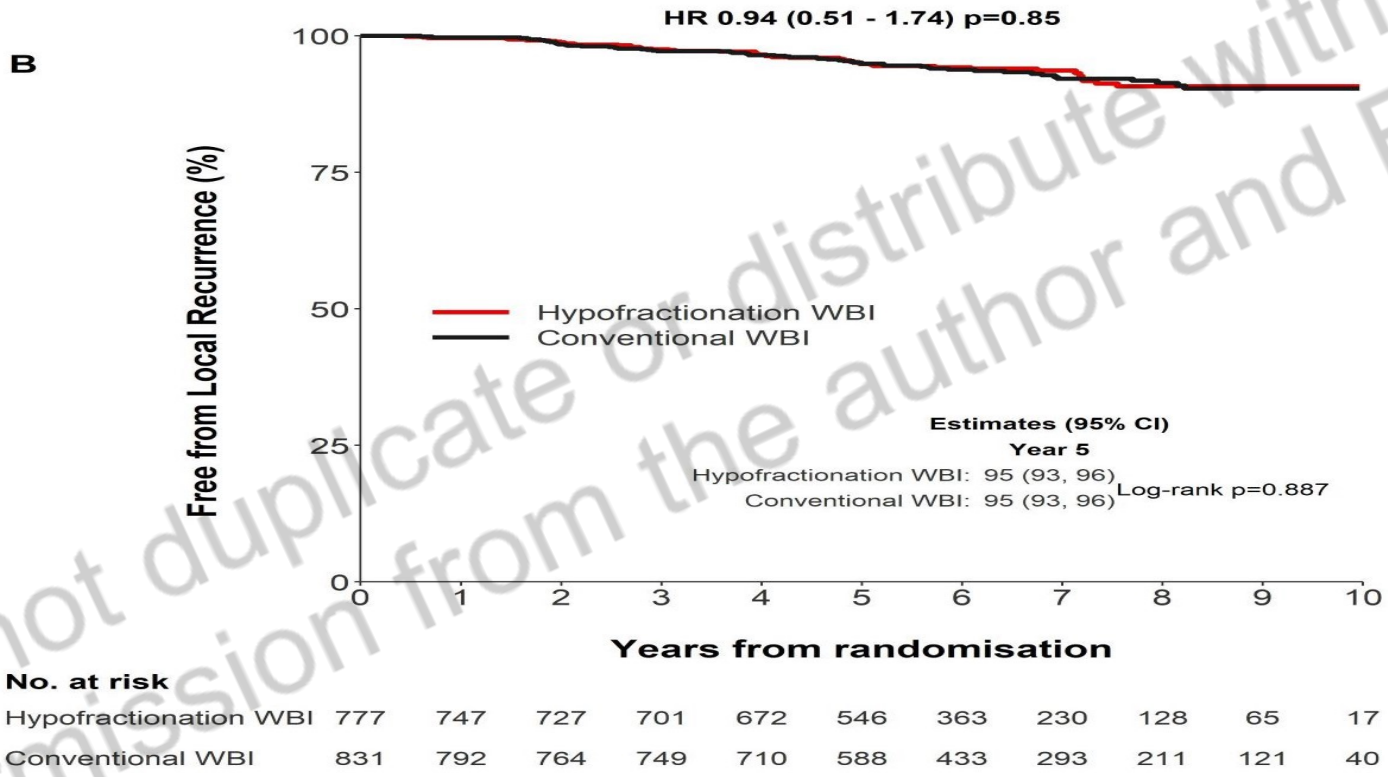
RT with a boost:

	Canada	RMH/GOC	START A	START B
Boost	0%	74.5%	60.6%	42.6%

Conventionally fractioned ➔ ?

Hypofractionation in breast RT: *Discussion*

RT for DCIS:

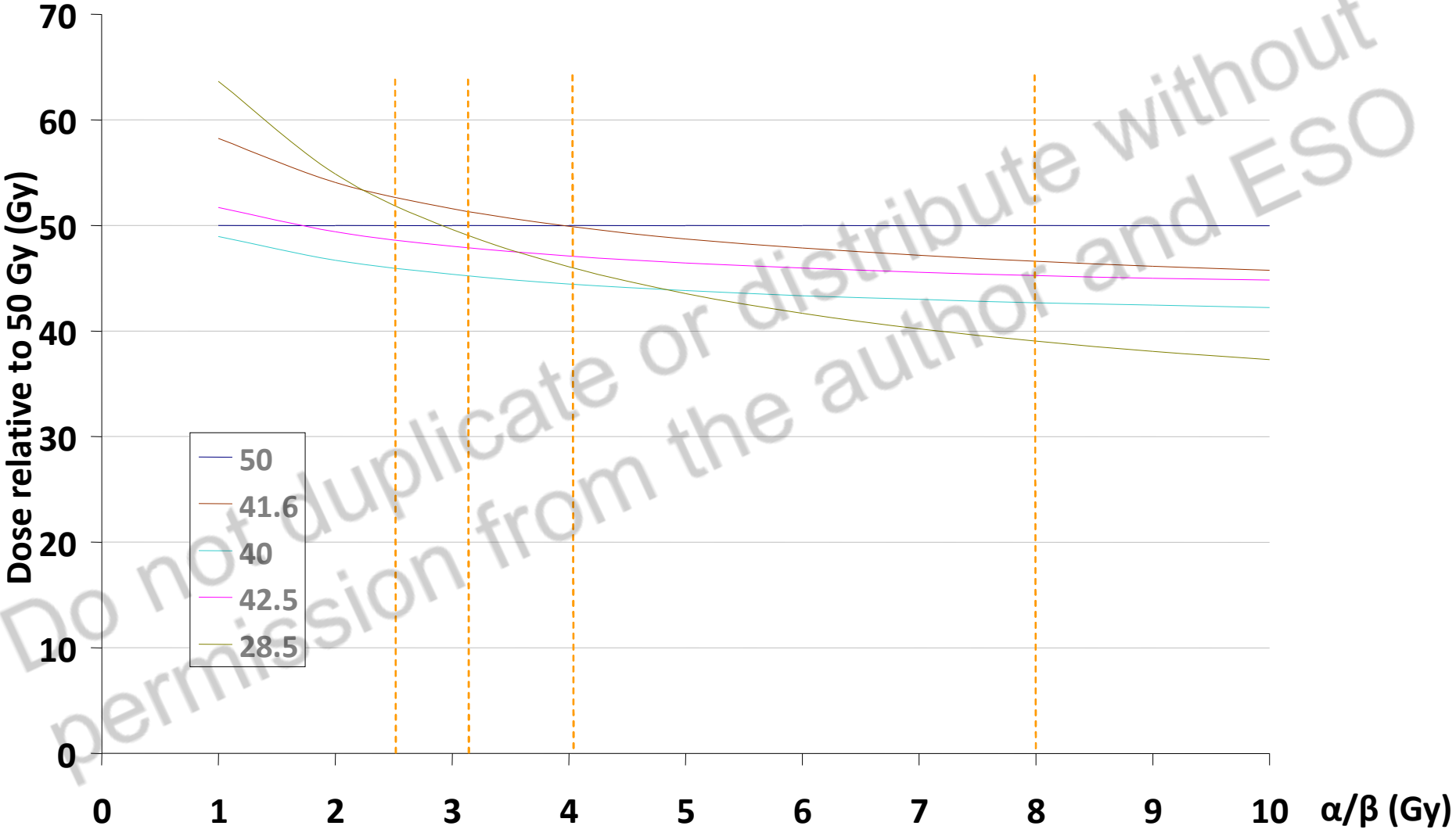


➔ *OK!*

Chua B, et al. SABCS 2020.

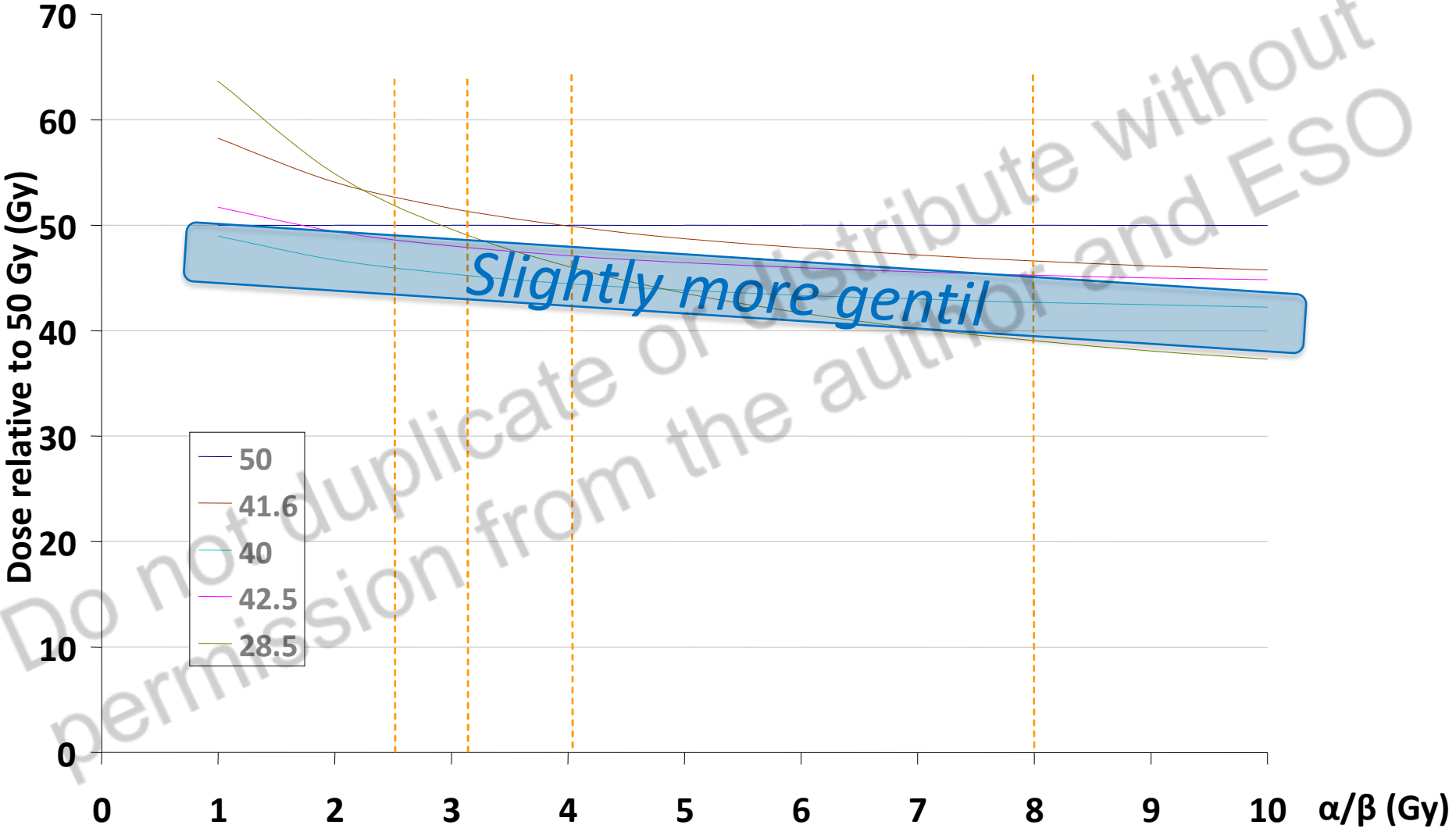
Hypofractionation in breast RT: *Discussion*

Radiobiology: LQ model vs. the trial results



Hypofractionation in breast RT: *Discussion*

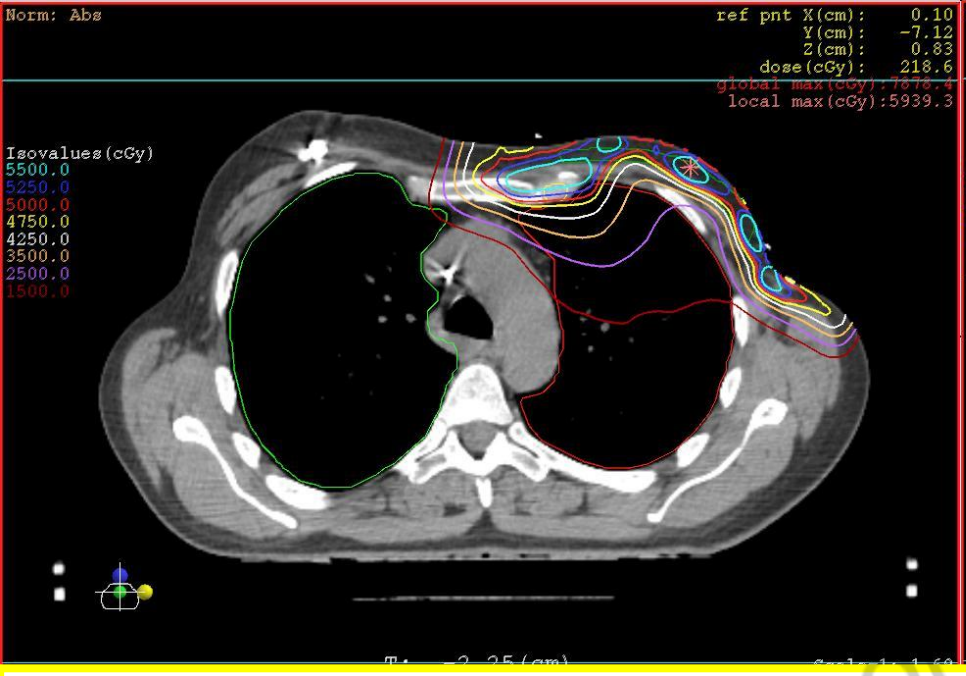
Radiobiology: LQ model vs. the trial results

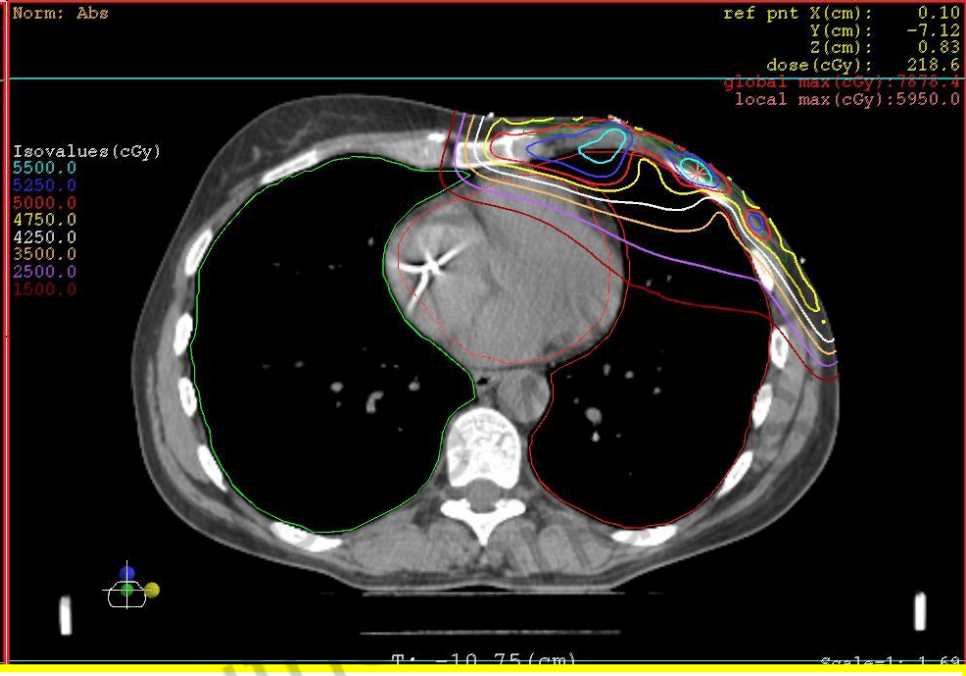


Hypofractionation in breast RT: *Discussion*

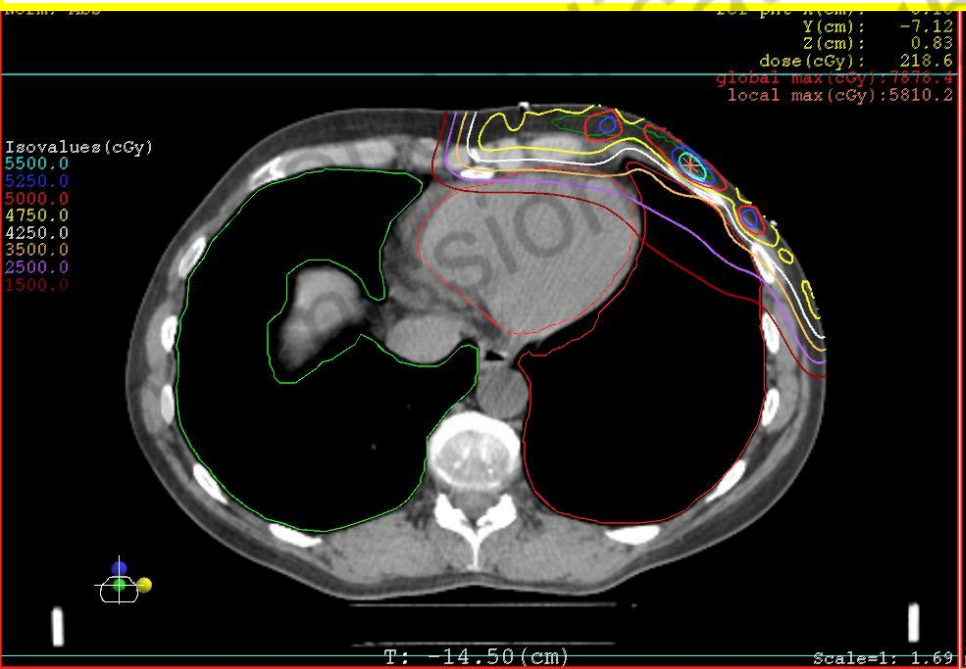
For tissues outside of the target volumes

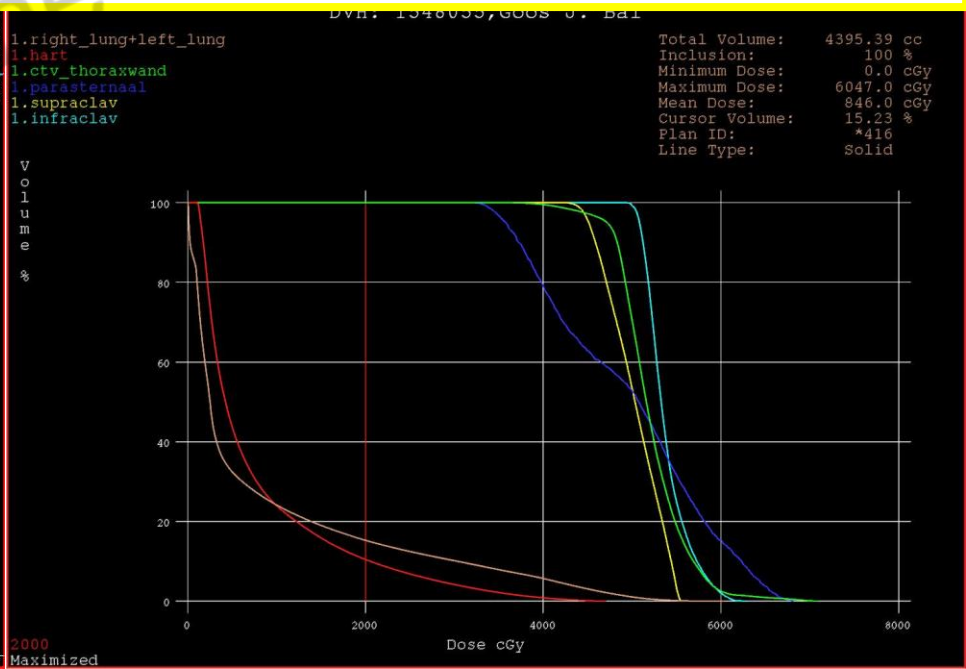
Mathematics by Philip

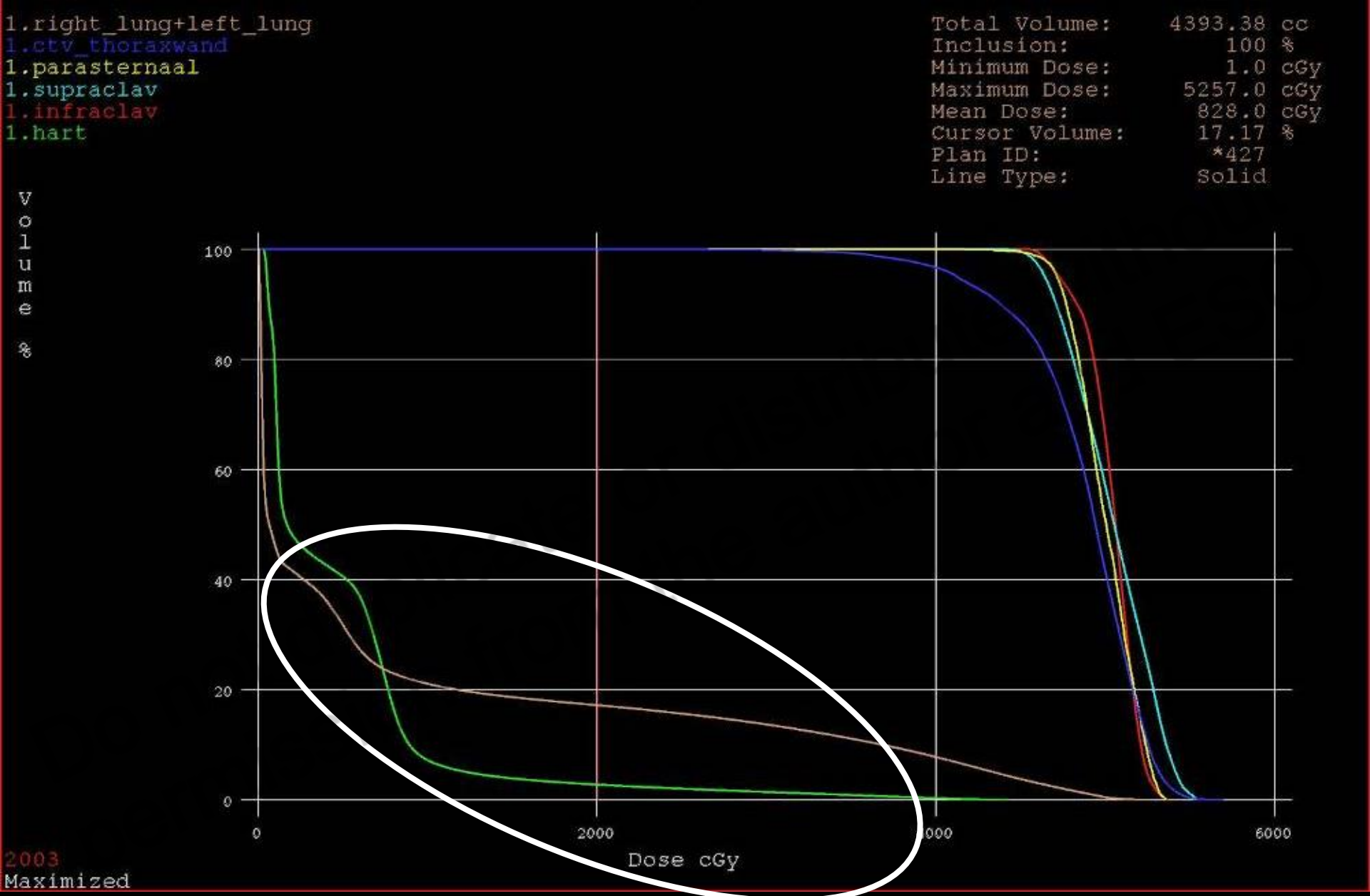




5-field electron technique including the IMC







0	0.5	1.0	1.5	2.0
0	0.67	1.33	2.0	2.66

Hypofractionation in breast RT: *Discussion*

Realistic scenario: α/β = 2 Gy LNT & 3.5 Gy BC

Protocol	schedule	α/β NT 2 Gy	α/β T 3.5 Gy
START	15 x 2.67	46.76	44.93
Canadian	16 x 2.66	49.58	47.67
Standard	25 x 2	50	50

100	**2,66**	**49,58**	**2,00**	**50,00**
95	**2,53**	**46,93**	**1,90**	**47,50**
90	**2,39**	**44,29**	**1,80**	**45,00**
85	**2,26**	**41,66**	**1,70**	**42,50**
70	**1,86**	**33,84**	**1,40**	**35,00**
50	**1,33**	**23,62**	**1,00**	**25,00**
25	**0,67**	**11,34**	**0,50**	**12,50**

Mathematics by Philip

Hypofractionation in breast RT: *Discussion*

Optimistic scenario: α/β = 3 Gy LNT & 3 Gy BC

Protocol	schedule	α/β NT 3 Gy	α/β T 3 Gy
START	15 x 2.67	45.42	45.42
Canadian	16 x 2.66	48.18	48.18
Standard	25 x 2	50	50

100	**2,66**	**48,18**	**2,00**	**50,00**
95	**2,53**	**45,61**	**1,90**	**47,50**
90	**2,39**	**43,04**	**1,80**	**45,00**
85	**2,26**	**40,49**	**1,70**	**42,50**
70	**1,86**	**32,92**	**1,40**	**35,00**
50	**1,33**	**23,04**	**1,00**	**25,00**
25	**0,67**	**11,14**	**0,50**	**12,50**

Mathematics by Philip

Hypofractionation in breast RT: *Discussion*

Worst scenario: α/β = *1 Gy LNT & 5 Gy BC*

Protocol	schedule	α/β NT 1 Gy	α/β T 5 Gy
START	15 x 2.67	48,99	43.88
Canadian	16 x 2.66	51.92	46.57
Standard	25 x 2	50	50

100	**2,66**	**51,92**	**2,00**	**50,00**
95	**2,53**	**49,17**	**1,90**	**47,50**
90	**2,39**	**46,43**	**1,80**	**45,00**
85	**2,26**	**43,69**	**1,70**	**42,50**
70	**1,86**	**35,53**	**1,40**	**35,00**
50	**1,33**	**24,79**	**1,00**	**25,00**
25	**0,67**	**11,81**	**0,50**	**12,50**

Mathematics by Philip

Hypofractionation in breast RT: *Discussion*

The mathematics matches the results

➔ *by reducing the total dose we even lower the expected effect in the regions outside of the non-therapeutic doses!*

Hypofractionation in breast RT: *Discussion*

Dutch protocol 2009 (!!!!):

- 2,66 Gy as highest dose to part of the target volume
- No discussion for: breast/thoracic wall; SIB
- ≤ 50 years: limitation taken away after closure YBT (2011)
- Some doubts about regional RT
- More doubts about combination with reconstructive surgery

Hypofractionation in breast RT: *Discussion*

• Breast:	2 Gy	50 Gy in 25 fractions
• Boost:	2 Gy	16 Gy in 08 fractions
• TOTAL:	2 Gy	66 Gy in 33 fractions

Hypofractionation in breast RT: *Discussion*

• Breast:	2 Gy	50 Gy in 25 fractions
• Boost:	2 Gy	16 Gy in 08 fractions
• TOTAL:	2 Gy	66 Gy in 33 fractions
• Breast:	1,81 Gy	50,68 Gy in 28 fractions
• Boost:	0,49 Gy	13,72 Gy in 28 fractions
• TOTAL:	2,3 Gy	64,40 Gy in 28 fractions

Hypofractionation in breast RT: *Discussion*

• Breast:	2 Gy	50 Gy in 25 fractions
• Boost:	2 Gy	16 Gy in 08 fractions
• TOTAL:	2 Gy	66 Gy in 33 fractions

• Breast:	1,81 Gy	50,68 Gy in 28 fractions
• Boost:	0,49 Gy	13,72 Gy in 28 fractions
• TOTAL:	2,3 Gy	64,40 Gy in 28 fractions

• Breast:	2,17 Gy	45,57 Gy in 21 fractions
• Boost:	0,49 Gy	10,29 Gy in 21 fractions
• TOTAL:	2,66 Gy	55,86 Gy in 21 fractions

Hypofractionation in breast RT: *Discussion*

Current Dutch protocol:

- Transition to UK schedule (40/15) in 2020

Hypofractionation in breast RT: *Discussion*

Current protocol in many countries:

- Repopulation
- Redistribution
- Reoxygenation
- Repair

Hypofractionation in breast RT: *Discussion*

Current protocol in many countries:

- Repopulation
- Redistribution
- Reoxygenation
- Repair
- Resistance

Hypofractionation in breast RT: *Discussion*

Current protocol in many countries:

- Repopulation
- Redistribution
- Reoxygenation
- Repair
- Resistance
- Reimbursement

Hypofractionation in breast RT: *Discussion*

The Breast 55 (2021) 128–135

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Viewpoints and debate

Why is appropriate healthcare inaccessible for many European breast cancer patients? – The EBCC 12 manifesto

Fatima Cardoso [a, *], Fiona MacNeill [b], Frederique Penault-Llorca [c], Alexandru Eniu [d, e], Francesco Sardanelli [f, g], Elizabeth Bergsten Nordström [h], Philip Poortmans [i], on behalf of the EBCC12-Faculty

Hypofractionation in breast RT: *Discussion*

Radiation Oncology

Moderate hypofractionated post-operative radiation therapy	Moderate hypofractionation schedules (15–16 fractions of <3 Gy/fraction) are recommended for routine postoperative RT of breast cancer ([17]). However, reimbursement rules are per fraction based and therefore favour conventional fractionation leading hospital management to force limited use of hypofractionation.

Cardoso F, et al. Breast. 2021;55:128-135.

Hypofractionation in breast RT: *Discussion*

Contents lists available at ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

Original Article

The Financial Impact on Reimbursement of Moderately Hypofractionated Postoperative Radiation Therapy for Breast Cancer: An International Consortium Report

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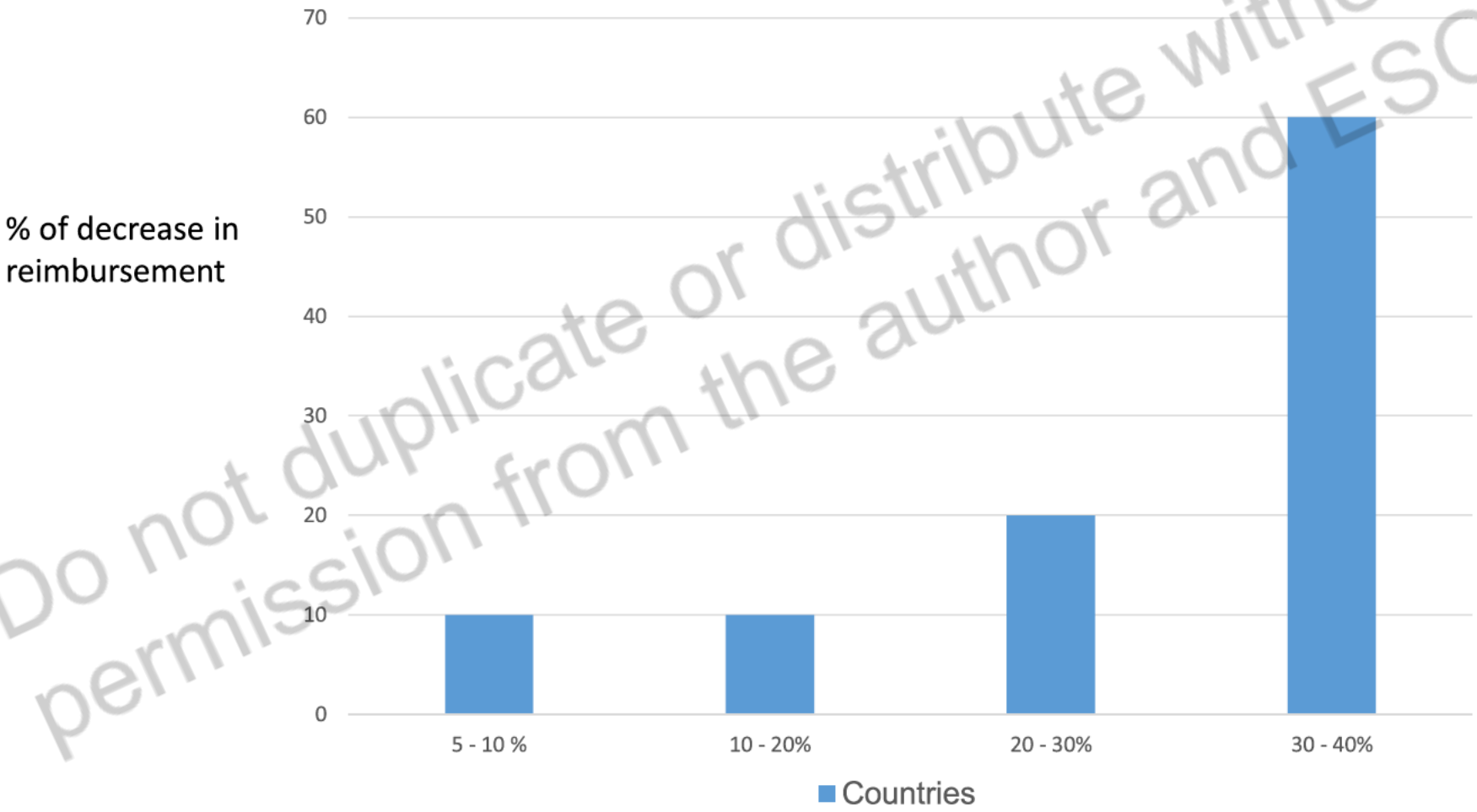
Marta GN, et al. Clin Oncol 2021; in press.

Hypofractionation in breast RT: *Discussion*

Decrease in reimbursement from hypofractionation



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Hypofractionation in breast RT

1. Introduction
2. Evidence
3. Discussion

4. Conclusions

Hypofractionation in breast RT: *Conclusions*

Moderately hypofractionated breast radiation therapy: is more evidence needed?

Gustavo Nader Marta; Philip Poortmans

The question is, however, to which extent any further evidence is still required. In countries as The Netherlands, hypofractionation is the standard for nearly every indication for several years now, using the argument that with modern homogeneously delivered volume-based RT techniques the biological effects should be identical independent from the target volumes. Similarly, we don't question whether fractionation schedules for head- and neck cancer should be dependent from the anatomical sub-site? Or aren't it rather reimbursement issues that refrain hospital managers and doctors from allowing brother introduction of schedules with a lower number of fractions and a lower total dose? *Even more in countries with limited resources we should not wait until further evidence becomes available before generalizing hypofractionated breast irradiation!*

Marta GN, Poortmans P. Lancet Oncol. 2019 May;20(5):e226.

Hypofractionation in breast RT: *Conclusions*

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And now a trial from a country with limited resources, using radiation therapy techniques from 25 years ago should help to convince centres in countries with modern infrastructures and excellent contemporary radiation delivery help to convince? Please! Let's cut the crap and make a point on this, like we did (maybe too gently but happy to make it clearer) in our last paragraph.

Anyway, we aim to stimulate the readers the readers of The Lancet Oncology in their reflections and decision-making of whether or not to accept hypofractionated breast radiation therapy in their daily clinical practice.

We confirm that we have no financial incentives associated with publishing this letter (working in France I could rather say the inverse is true).

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Hypofractionation in breast RT: *Conclusions*

Trust in hypofractionation:

- Aim at homogenous dose distributions
- The 26/5/1 “FAST-Forward” fractionation is my 1st choice for: breast only; chest wall only; PBI
- The 30/5/5 “FAST” fractionation can be used for frail patients
- Limit the fraction size to ≤ 2,67 Gy for locoregional RT (for now…)

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And what with 50/25/5?

- When combined with radiosensitisers (systemic therapy; hyperthermia)
- To be considered for re-irradiation (but 40/15/3 preferable)
- And else?

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Hypofractionation in breast RT: *Conclusions*

ESTRO ACROP Consensus recommendations on patient selection and dose/fractionation for external beam radiation therapy in early breast cancer

ESTRO

Core Group: Icro Meattini (IT), Charlotte Coles (UK), Philip Poortmans (B), Liesbeth Boersma (NL), Orit Kaidar-Person (IL), Gustavo Nader Marta (Brasil), Angel Montero-Luis (E), Birgitte Offersen (DK), and Carlotta Becherini (IT, Secretariat)

Extended Consensus Panel: representatives of radiation/clinical oncologists, radiobiologists, medical physicists, RTTs, and patient advocates.

November, 2020	**Identification of the writing-committee* including the experts ECP (CG)** **Define clinical questions, key-topics, and existing LoE (CG)**
January, 2021	Literature review and consensus recommendations (CG) Definition of consensus draft-statements (CG)
February-March, 2021	Consensus round one: first Delphi round on draft-statements (CG, ECP) Compile ratings and comments (CG) Review results (CG, ECP)
April, 2021	Consensus round two-three: second-third Delphi round on key-statements (CG, ECP) New and previous iterations of recommendations are presented (CG, ECP)
May, 2021	Discussion of the key-statements and assessment of the agreement (CG, ECP) Ratings are accepted if consensus is achieved (CG, ECP)
May, 2021	Two rounds of e-mail sharing of the discussed key-statements for minor amendments (CG, ECP)
June, 2021	Finalizing of manuscript (CG, ECP)
August, 2021	Public discussion or writing-committee meeting at the ESTRO Congress 2021 (27-31 Aug, Madrid)

Abbreviations: CG, core group; ECP, extended consensus panel; LoE, level-of-evidence; ESTRO, European SocieTy for Radiotherapy and Oncology.
**Writing-committee included CG and ECP members.*

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To be released soon ➔ please use them!

Hypofractionation in BC: *Acknowledgements*

- All the patients participating to the trials.
- All the investigators participating to the trials.
- The research teams of the trials.
- The research fellows involved in the trials.
- Special words of thanks to (alphabetically): Marianne Aznar; Harry Bartelink; Liesbeth Boersma; Murray Brunt; Charlotte Coles; Laurence & Sandra Collette; Marion Essers; Sandra Hol; Orit Kaidar-Person; Icro Meattini; Gustavo Marta Nader; Birgitte Offersen; John Yarnold; Timothy Whelan
- In fact: to many to list here!!!!