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Ultrahypofractionation in breast cancer

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

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

Discussant: **Dr Ivica Ratosa**, Radiation Oncologist, Institute of Oncology Ljubljana, Ljubljana, Slovenia

Ultra-hypofractionation in breast cancer

Philip Poortmans, MD, PhD

Iridium Netwerk & Antwerp University, Antwerpen (B)

Former President

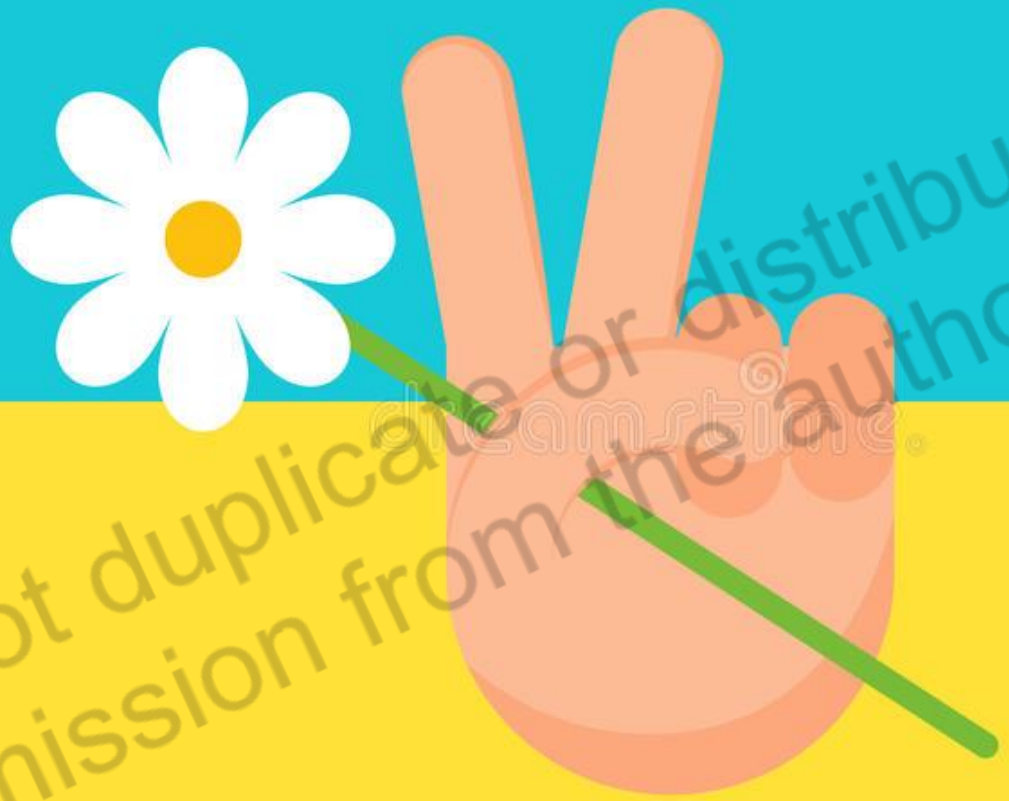
Conflict of interest

Philip Poortmans is medical advisor of Sordina IORT Technologies S.p.A.

Ultra-hypofractionation for breast cancer

1. Introduction
2. Basics of radiobiology
3. Evidence
4. Discussion
5. Conclusions

STOP



WAR!

Ultra-hypofractionation in BC: *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

ISSN 0942-
ISBN 978-3-64
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springer.com

Levitt · Purdy · Perez
Poortmans *Eds.*

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Diagnostic Imaging
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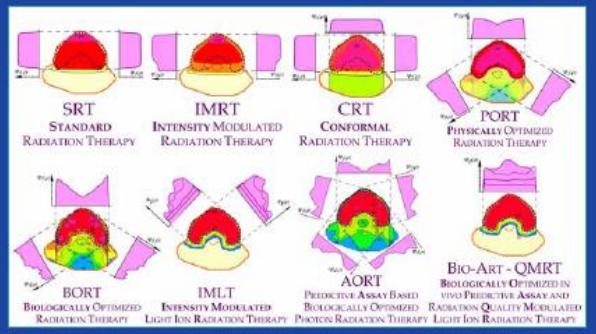

Technique serve the goal – not the other way around!

Ultra-hypofractionation in BC: *Introduction*

Radiotherapy and Oncology 114 (2015) 3–10

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

ESTRO consensus guidelines

ESTRO consensus guideline on target volume delineation for elective radiation therapy of early stage breast cancer

Birgitte V. Offersen [a,*], Liesbeth J. Boersma [b], Carine Kirkove [c], Sandra Hol [d], Marianne C. Aznar [e], Albert Biete Sola [f], Youlia M. Kirova [g], Jean-Philippe Pignol [h], Vincent Remouchamps [i], Karolien Verhoeven [j], Caroline Weltens [j], Meritxell Arenas [k], Dorota Gabrys [l], Neil Kopek [m], Mechthild Krause [n], Dan Lundstedt [o], Tanja Marinko [p], Angel Montero [q], John Yarnold [r], Philip Poortmans [s]

Radiotherapy and Oncology 118 (2016) 205–208

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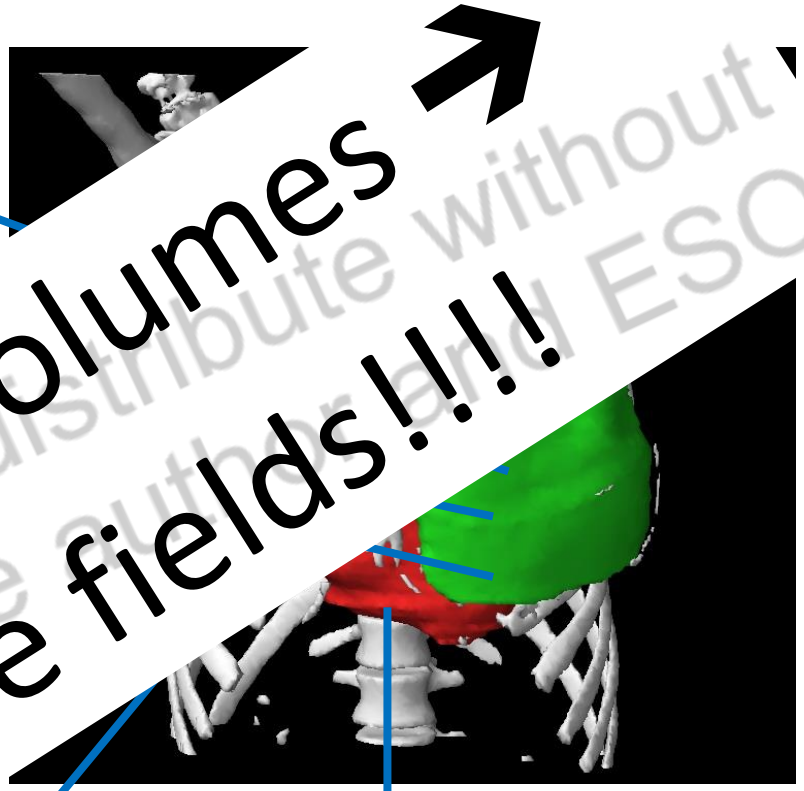
ESTRO breast cancer consensus guidelines

Ultra-hypofractionation in BC: *Introduction*

- Breast
- Boost
- PBI
- Thoracic wall
- LN supraclavicular
- LN axillary
- LN
- Mammary



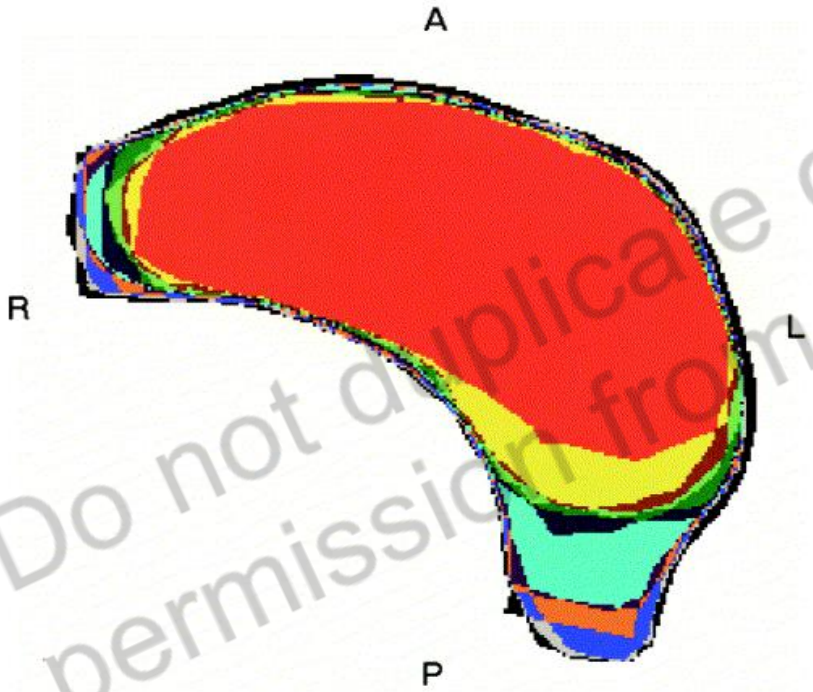
It's all about volumes
Forget the fields!!!!

Heart

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

Ultra-hypofractionation in BC: *Introduction*

Large inter-observer variation, especially at cranial, posterior and medial borders



NL: Hurkmans et al, IJROBP 2001

NL: Struikmans et al, R&O 2005

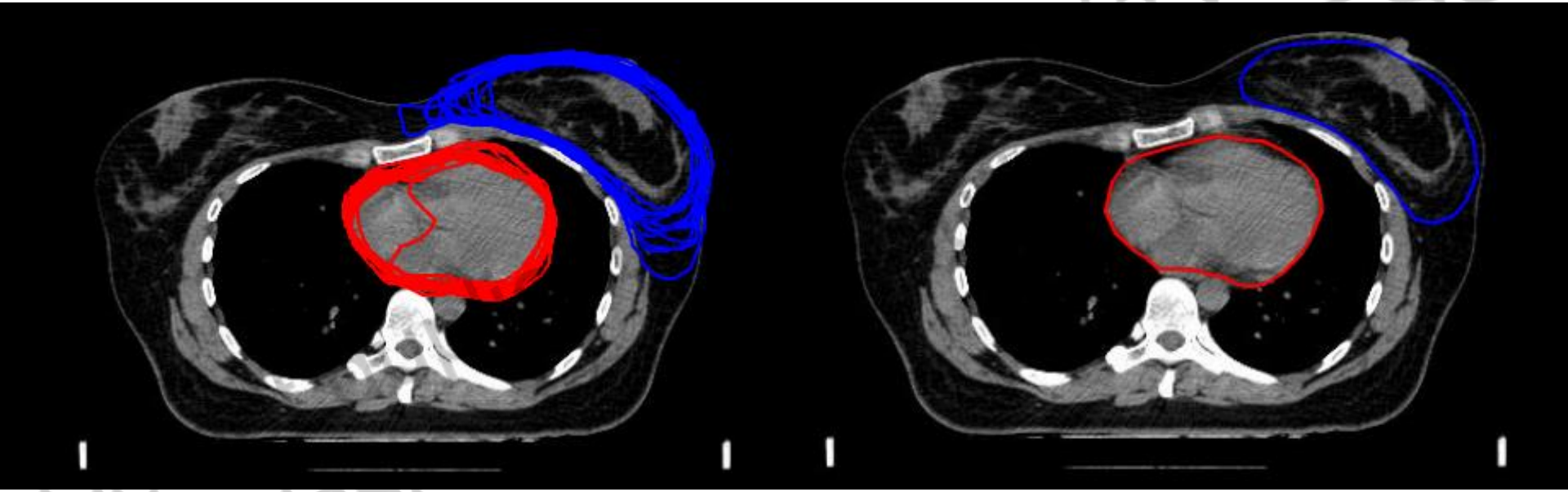
Ultra-hypofractionation in BC: *Introduction*

ESTRO

FALCON

Ultra-hypofractionation in BC: *Introduction*

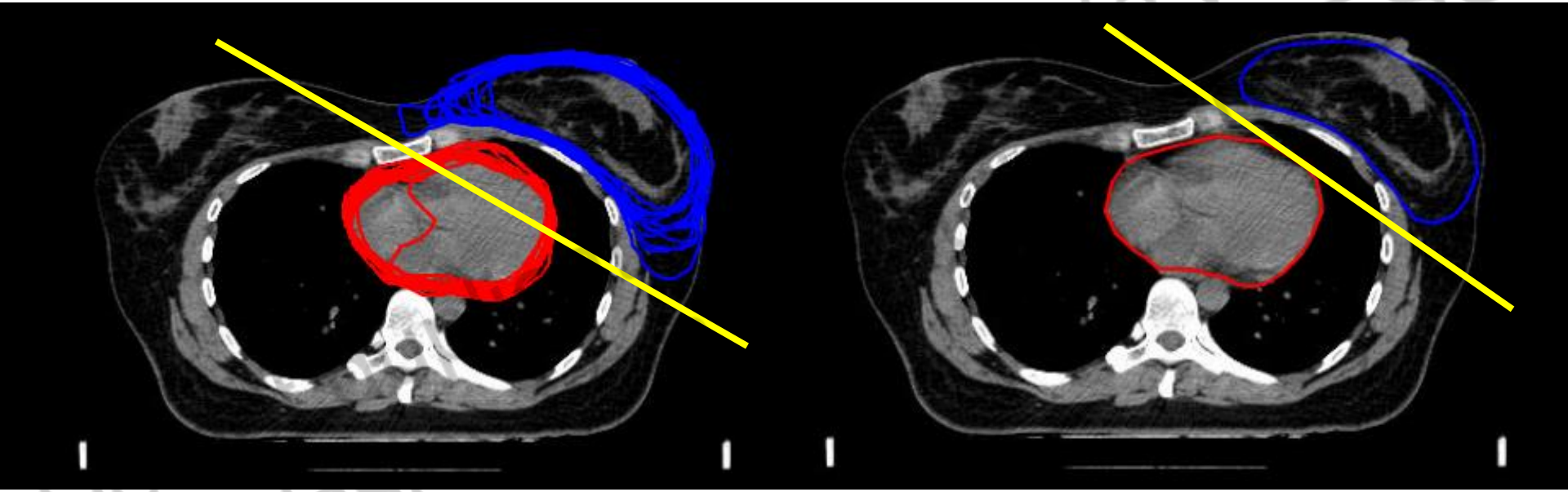
CTVp_breast



Delineations made by students attending ESTRO´s breast teaching course

Ultra-hypofractionation in BC: *Introduction*

CTVp_breast



Delineations made by students attending ESTRO´s breast teaching course

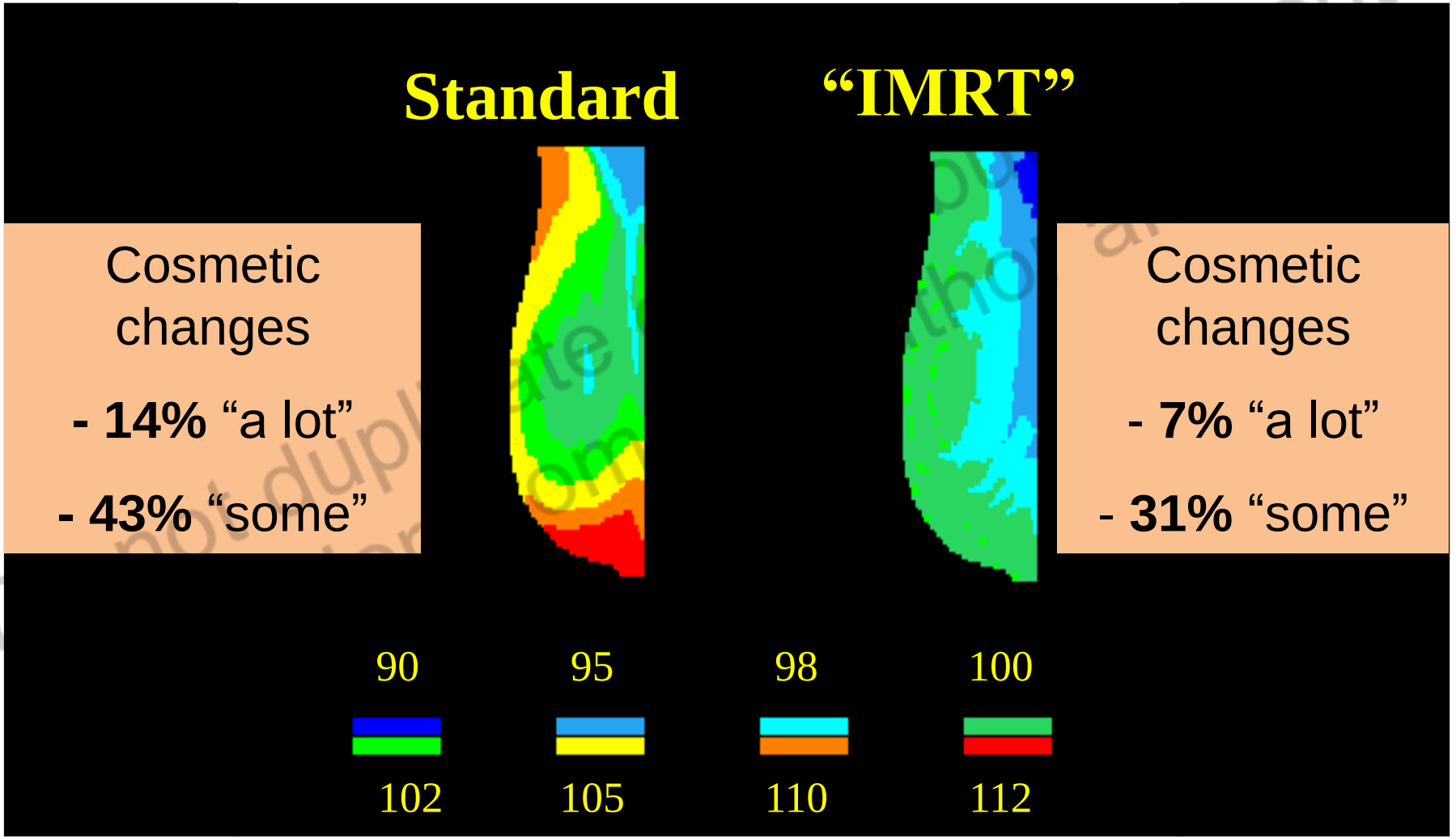
Ultra-hypofractionation in BC: *Introduction*

Modern techniques:

- CT-based treatment planning allows planning and evaluation in 3D➔ dose optimisation for TV and OAR.
- CTV contouring + margin = PTV allows inverse IMRT treatment planning.

Ultra-hypofractionation in BC: *Introduction*

Modern techniques: "*simple" IMRT*



Donovan et al. R&O 2007

Ultra-hypofractionation in BC: *Introduction*

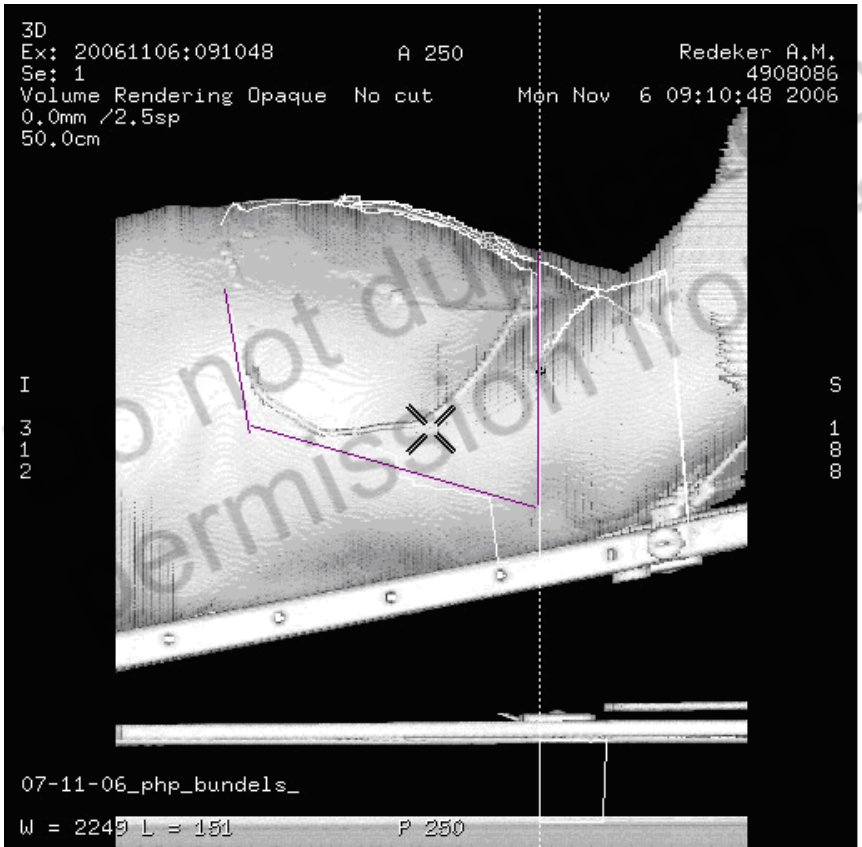
RT of the thoracic wall – with IM-MS.

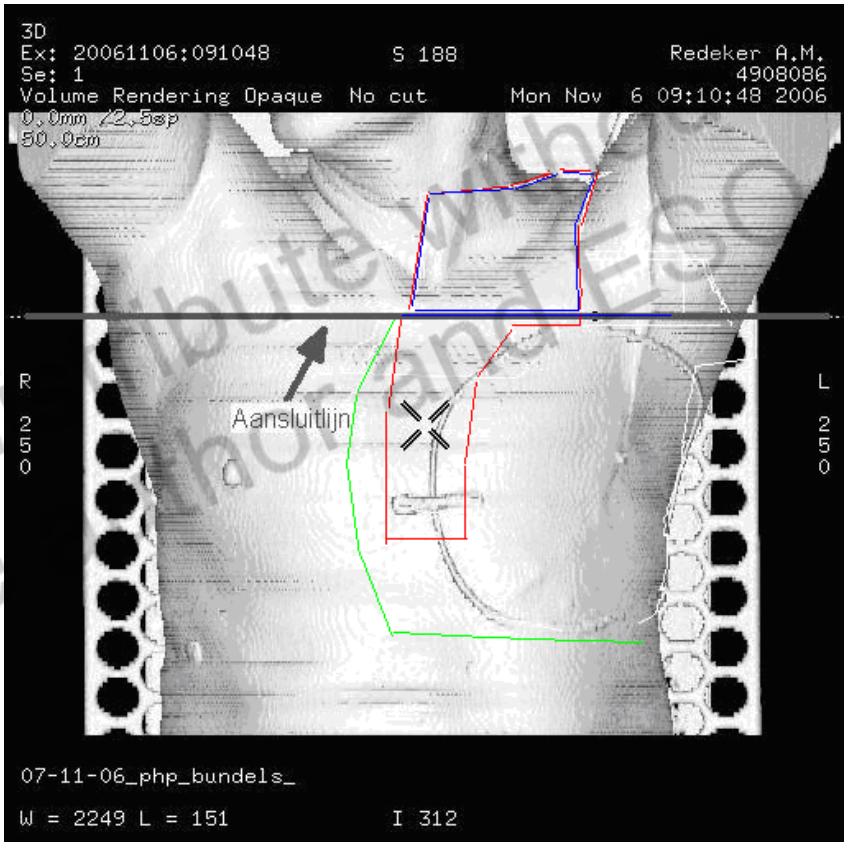
BVI photon technique

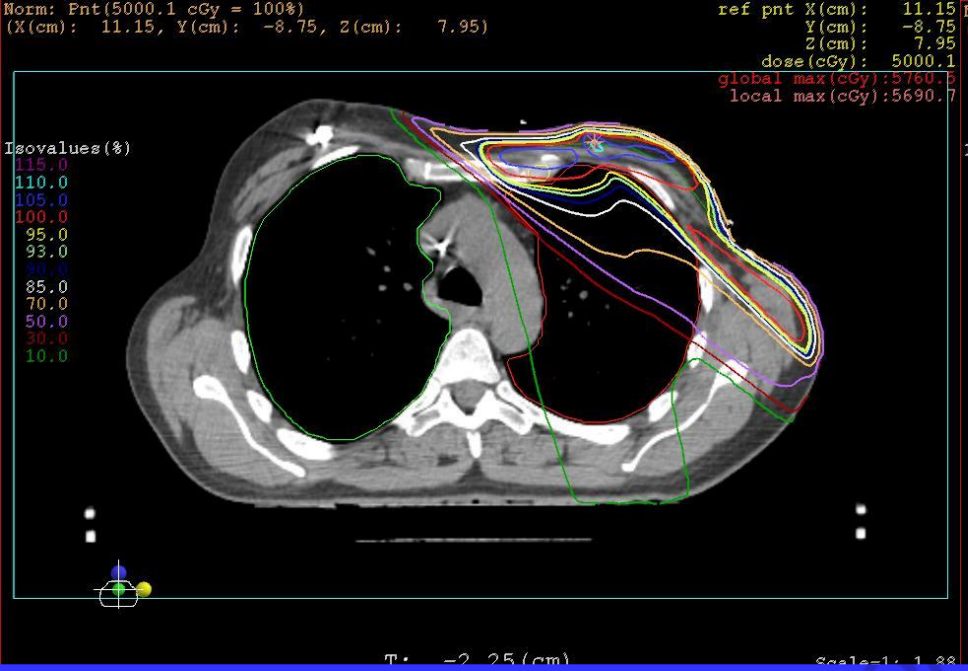
Ultra-hypofractionation in BC: *Introduction*

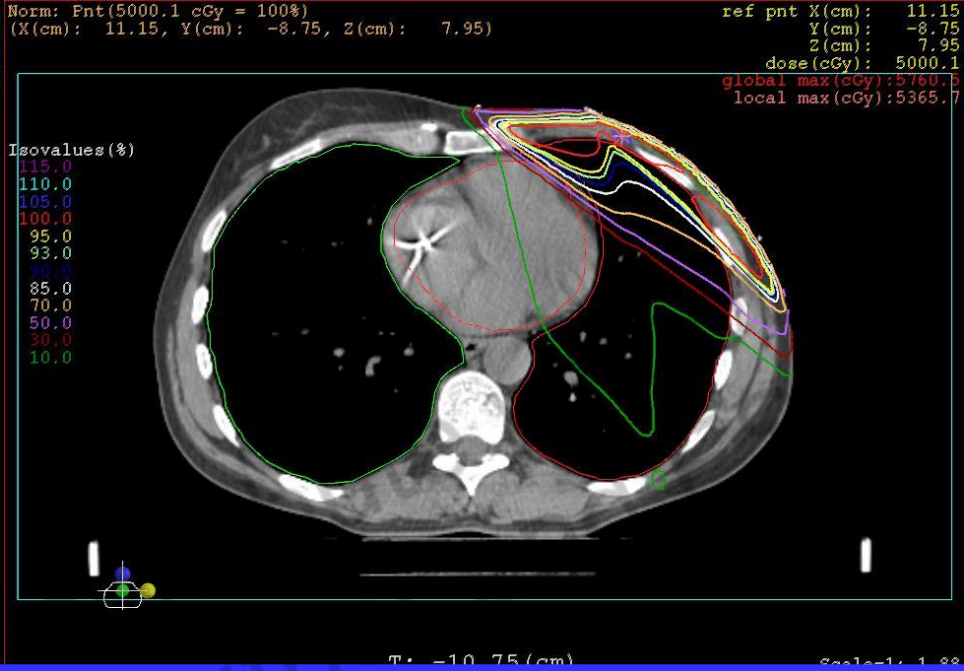
Photons

- 1 isocentre
- 4 main fields
- 3 gantry angles

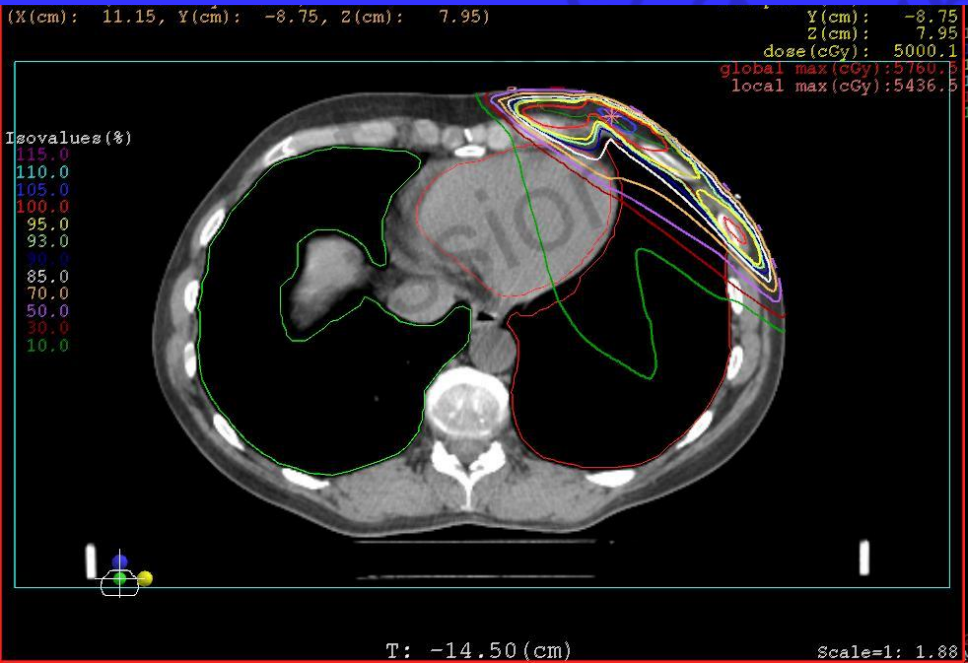


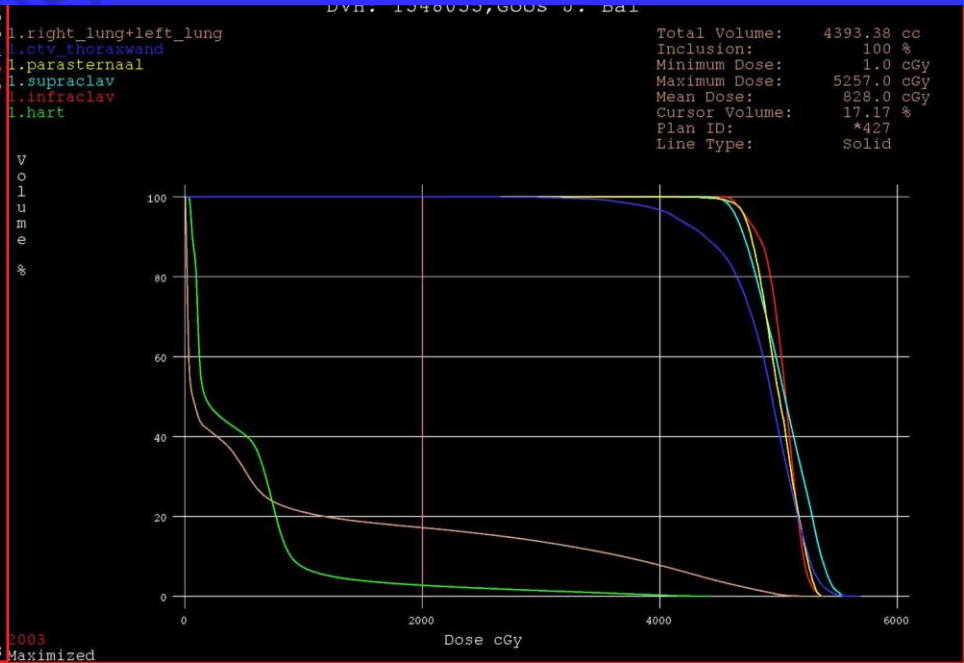






BVI photon technique including the IMC



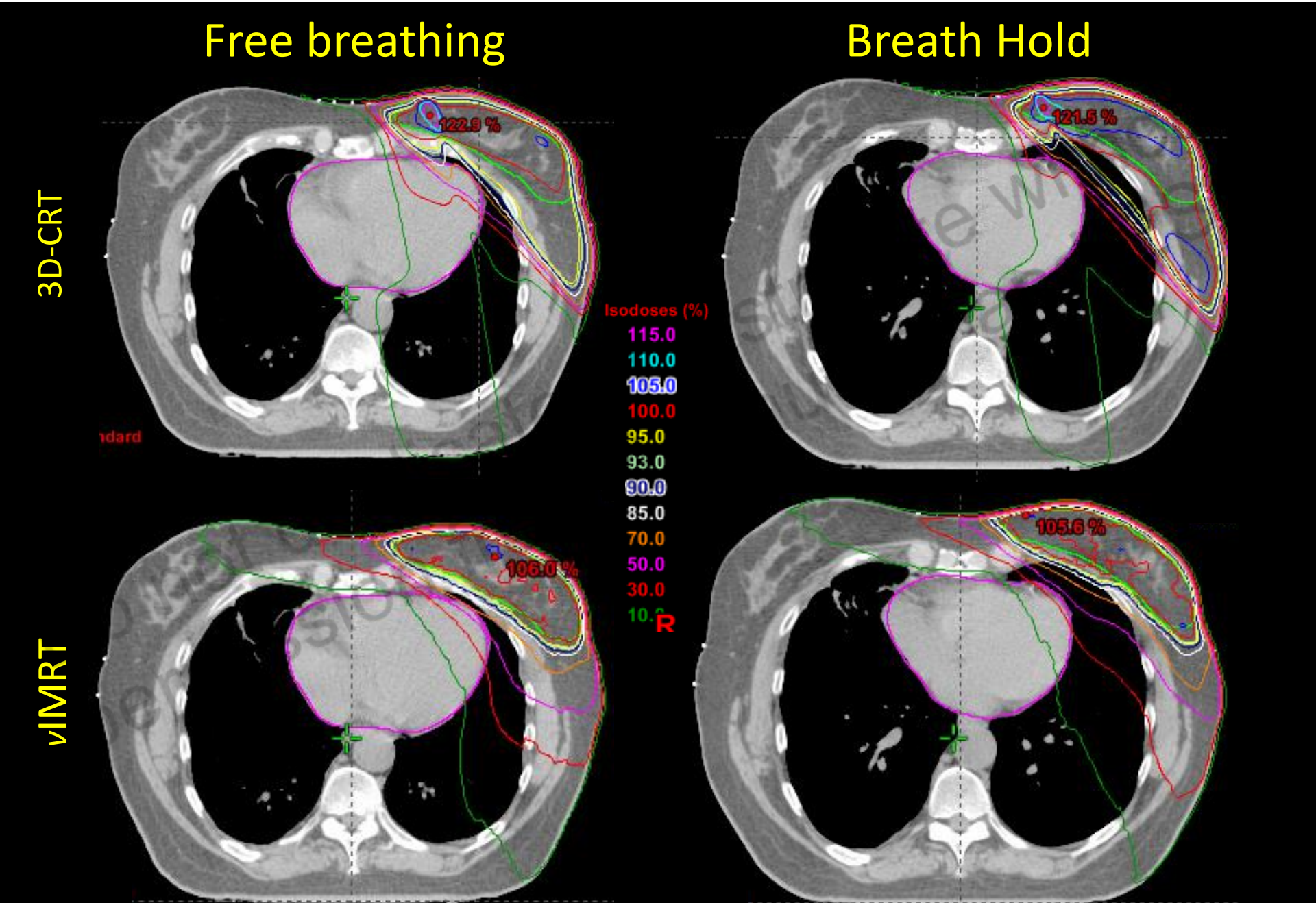


Ultra-hypofractionation in BC: *Introduction*

RT of the thoracic wall - with IM-MS:

the next steps.

Ultra-hypofractionation in BC: *Introduction*



Ultra-hypofractionation in BC: *Introduction*

	Free breathing		Breath hold	
	3D-CRT	*v*IMRT	3D-CRT	*v*IMRT
Heart V_{30Gy} (%)	2.7	0	0.5	0
Heart V_{20Gy} (%)	7.7	0.6	2.4	0.5
IL Lung V_{20Gy}(%)	16.4	5.8	16.5	5.3
IL Lung V_{10Gy}(%)	26.5	16.4	23.25	15.3
CL breast D_{mean}(Gy)	0.29	3.7	0.62	2.3

Osman SO, et al. Radiother Oncol. 2014;112:17-22.

Ultra-hypofractionation for breast cancer

1. Introduction
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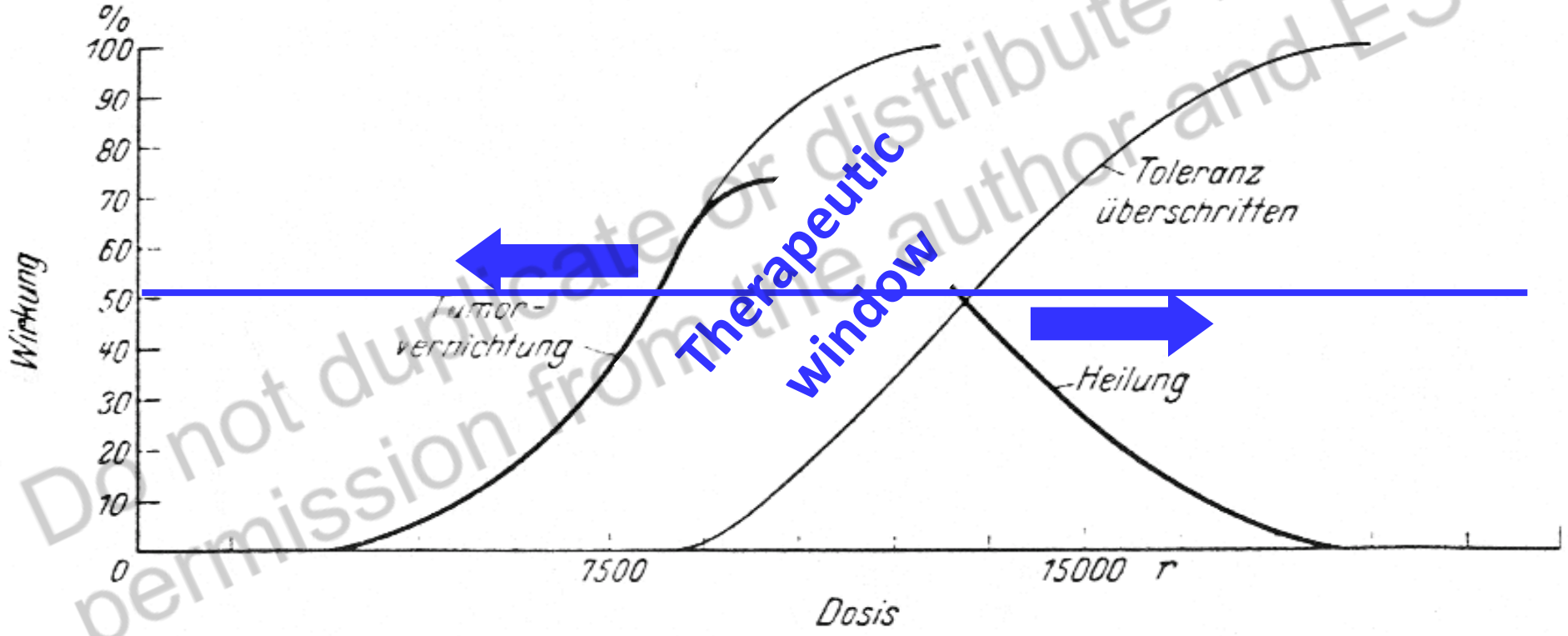
Ultra-hypofractionation in BC: *Basics of radiobiology*

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

Ultra-hypofractionation in BC: *Basics of radiobiology*

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

Ultra-hypofractionation in BC: *Basics of radiobiology*

1 x 10 Newton ≠ 10 x 1 Newton

1 x 20 Gy ≠ 10 x 2 Gy

Kellerer & Rossi, 1973; Hall, 2000

Ultra-hypofractionation in BC: *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.

Ultra-hypofractionation in BC: *Basics of radiobiology*

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

Ultra-hypofractionation in BC: *Basics of radiobiology*

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 □/□ ratio, thereby supporting the use of HipoF*

Qi et al. Radiother. Oncol 2011

Ultra-hypofractionation in BC: *Basics of radiobiology*

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

Ultra-hypofractionation for breast cancer

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Ultra-hypofractionation in BC: *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

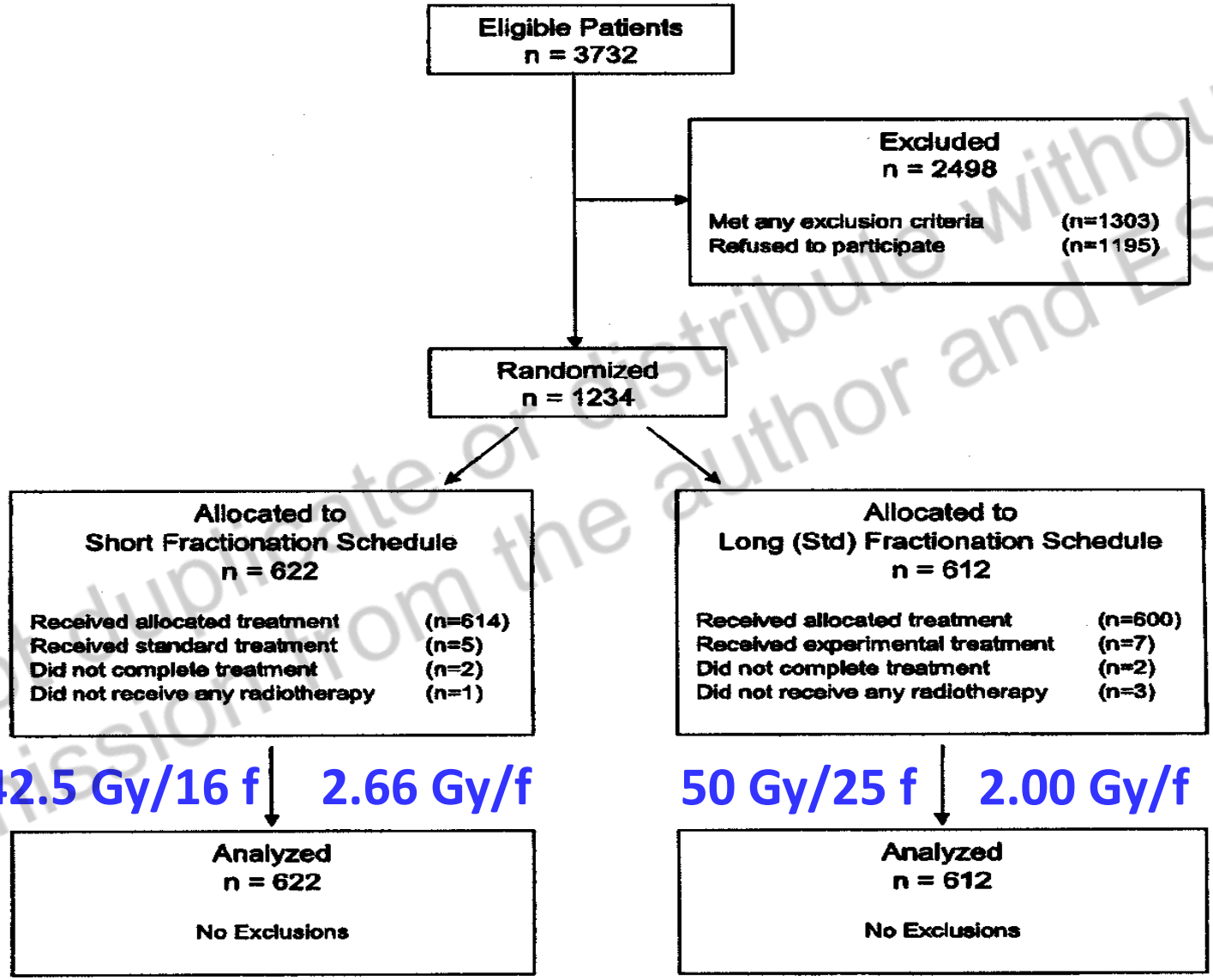
ORIGINAL ARTICLE

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*

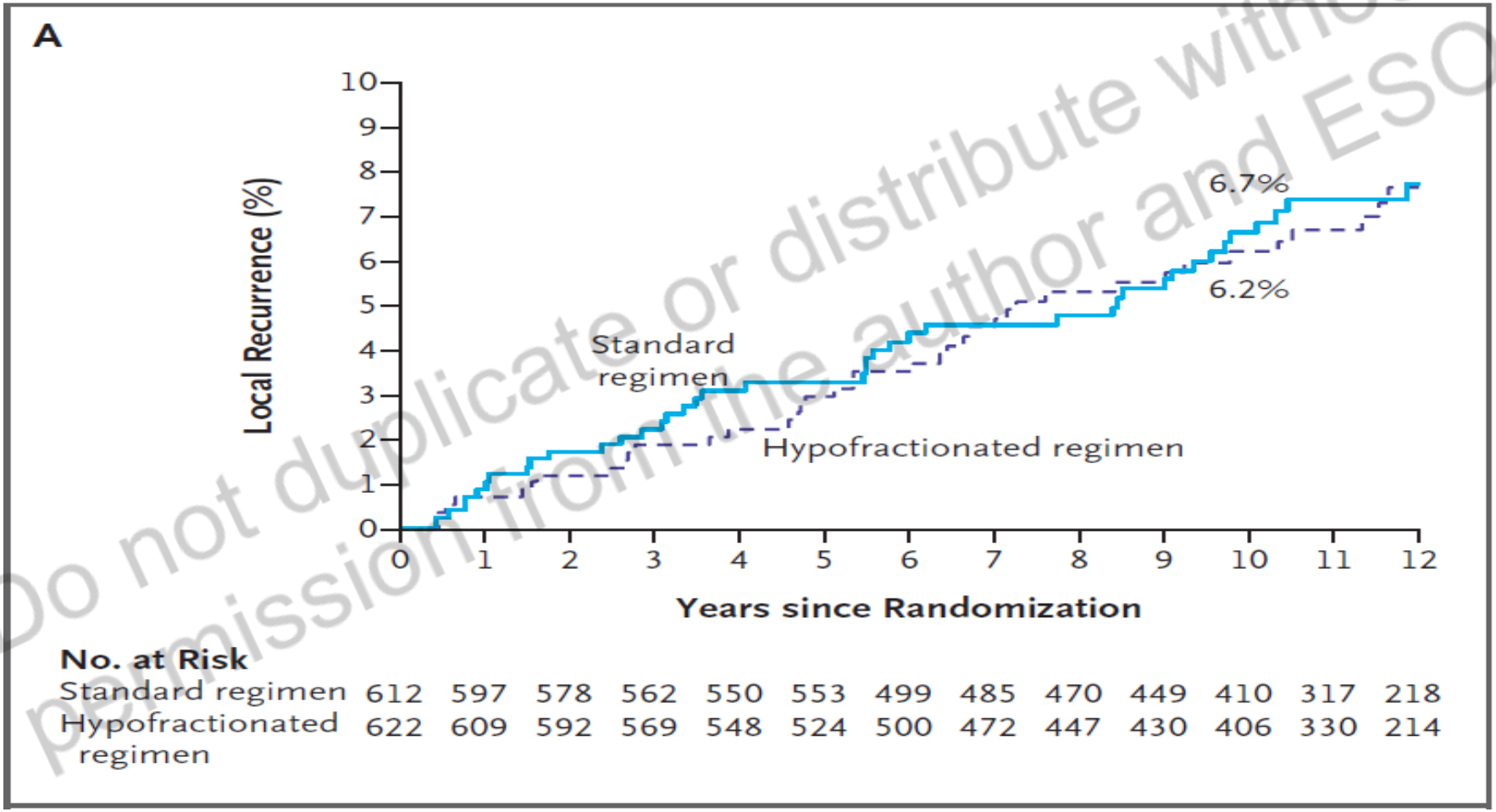
Ultra-hypofractionation in BC: *Evidence*



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

Ultra-hypofractionation in BC: *Evidence*

Local control



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

Ultra-hypofractionation in BC: *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*

Ultra-hypofractionation in BC: *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 & *Havilland et al. Lancet Oncol 2013;14:1086–94*

Ultra-hypofractionation in BC: *Evidence*

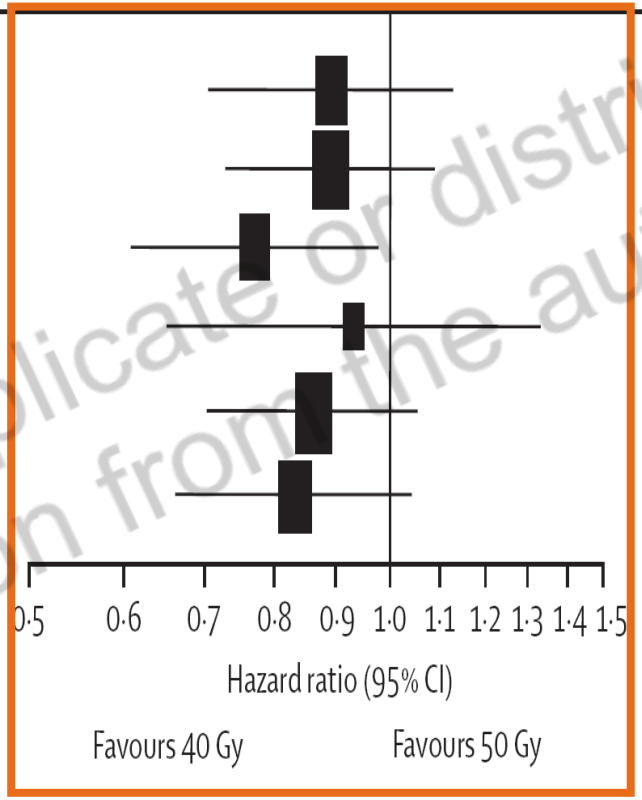
	Events/total (%)	Estimated % with event by 5 years (95% CI)	Crude hazard ratio (95% CI)	Log-rank test p value
Local relapse*				
50 Gy	34/1105 (3·1)	3·3 (2·2–4·4)	1	
40 Gy	25/1110 (2·2)	2·0 (1·1–2·8)	0·72 (0·43–1·21)	0·21
Local-regional relapse				
50 Gy	36/1105 (3·2)	3·3 (2·2–4·5)	1	
40 Gy	29/1110 (2·6)	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 & *Havilland et al. Lancet Oncol 2013;14:1086–94*

Ultra-hypofractionation in BC: *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 & *Havilland et al. Lancet Oncol 2013;14:1086–94*

Ultra-hypofractionation in BC: *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

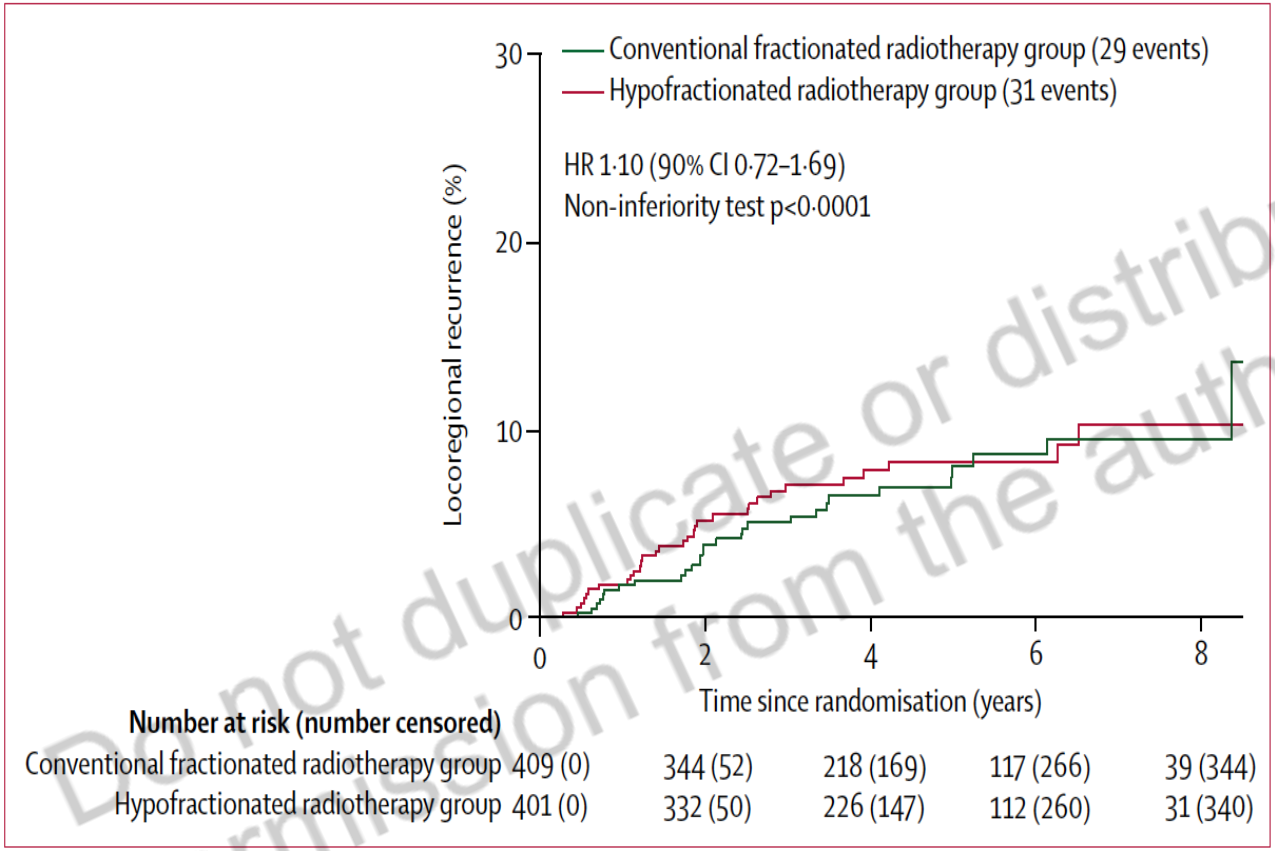
820 pts

- **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. 2019;20:352-60.

Ultra-hypofractionation in BC: *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. 2019;20:352-60.

Ultra-hypofractionation in BC: *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

Ultra-hypofractionation in BC: *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.

Ultra-hypofractionation in BC: *Evidence*

Where is the limit? ➔ FAST

Patient selection:

- ≥ 50 years
- < 3 cm
- N0
- 1^{ary} endpoint: photographic breast appearance chance @ 2 & 5 y
- 2^{ary} endpoints: physician assessments of NTE; local control

N = 915; median FU 9.9 years

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

Ultra-hypofractionation in BC: *Evidence*

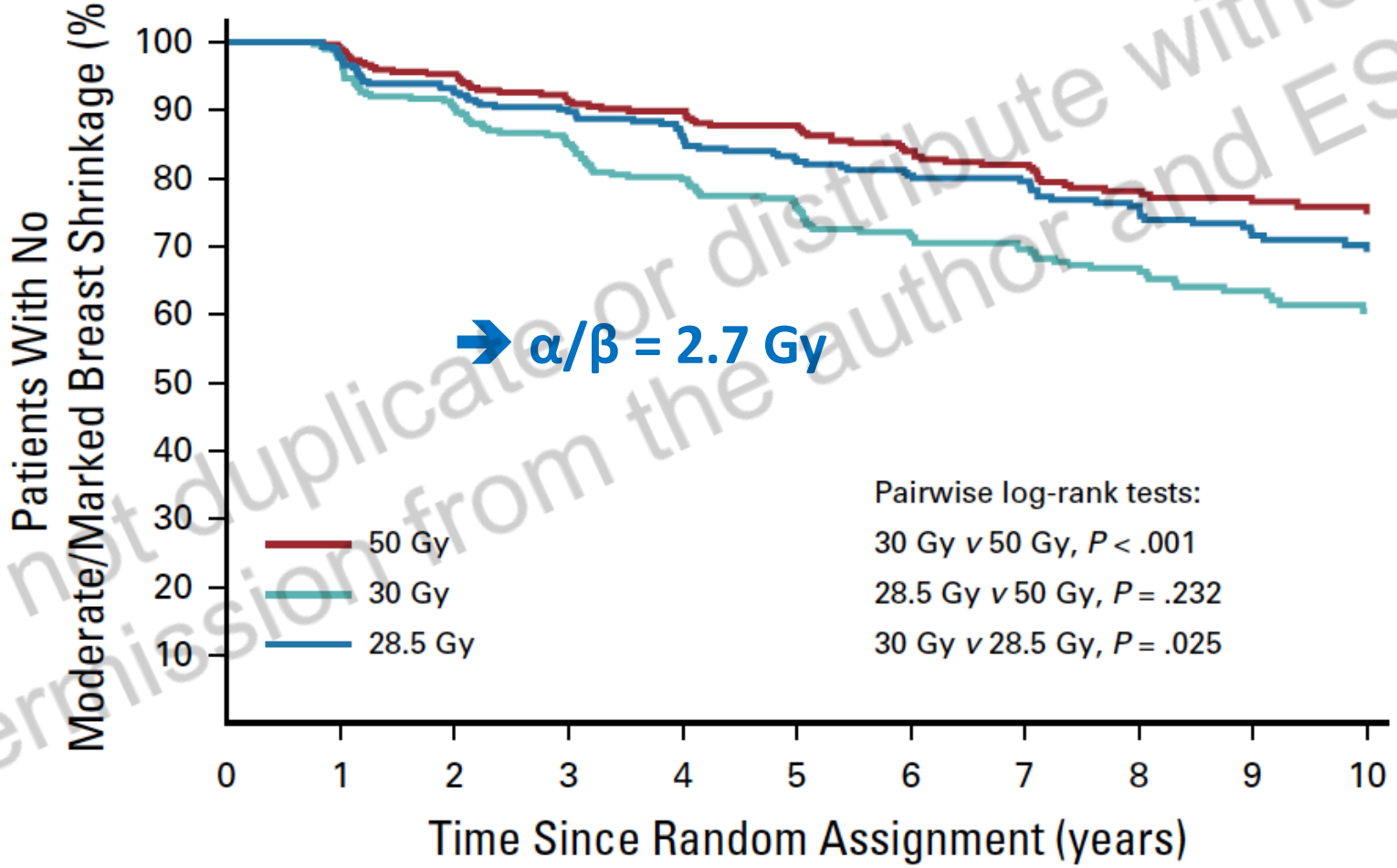
Where is the limit? ➔ FAST: side effects

	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.

Ultra-hypofractionation in BC: *Evidence*

Where is the limit? ➔ FAST: breast shrinkage



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

Ultra-hypofractionation in BC: *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*

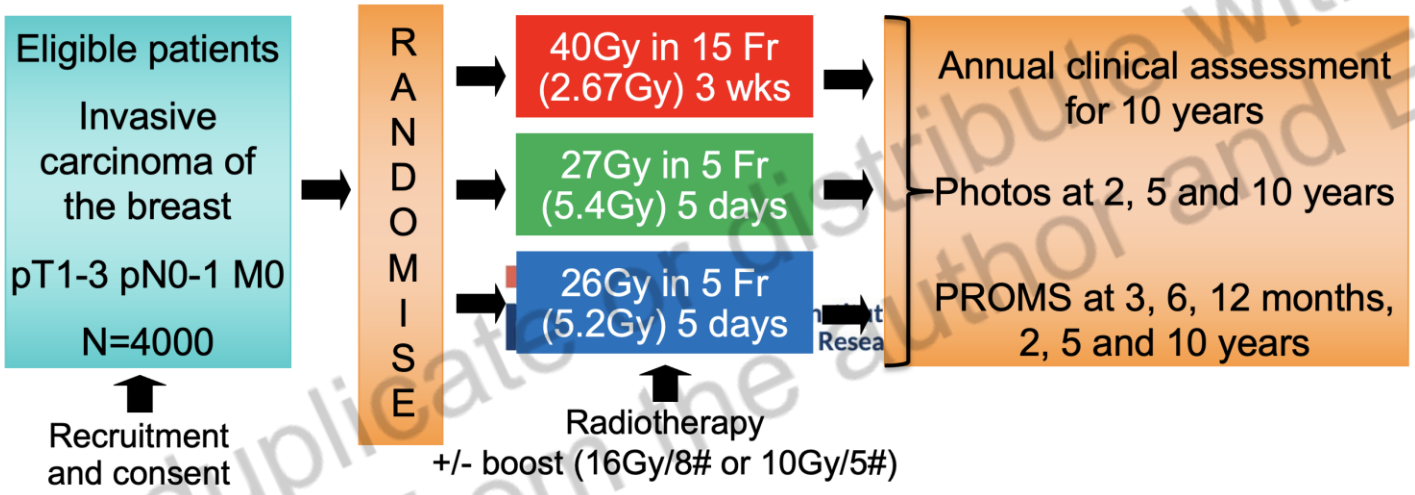
Brunt AM, et al. Lancet. 2020 May 23;395(10237):1613-1626.

Ultra-hypofractionation in BC: *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.

Ultra-hypofractionation in BC: *Evidence*

Where is the limit? ➔ FAST-FORWARD

<u>Patient selection:</u>

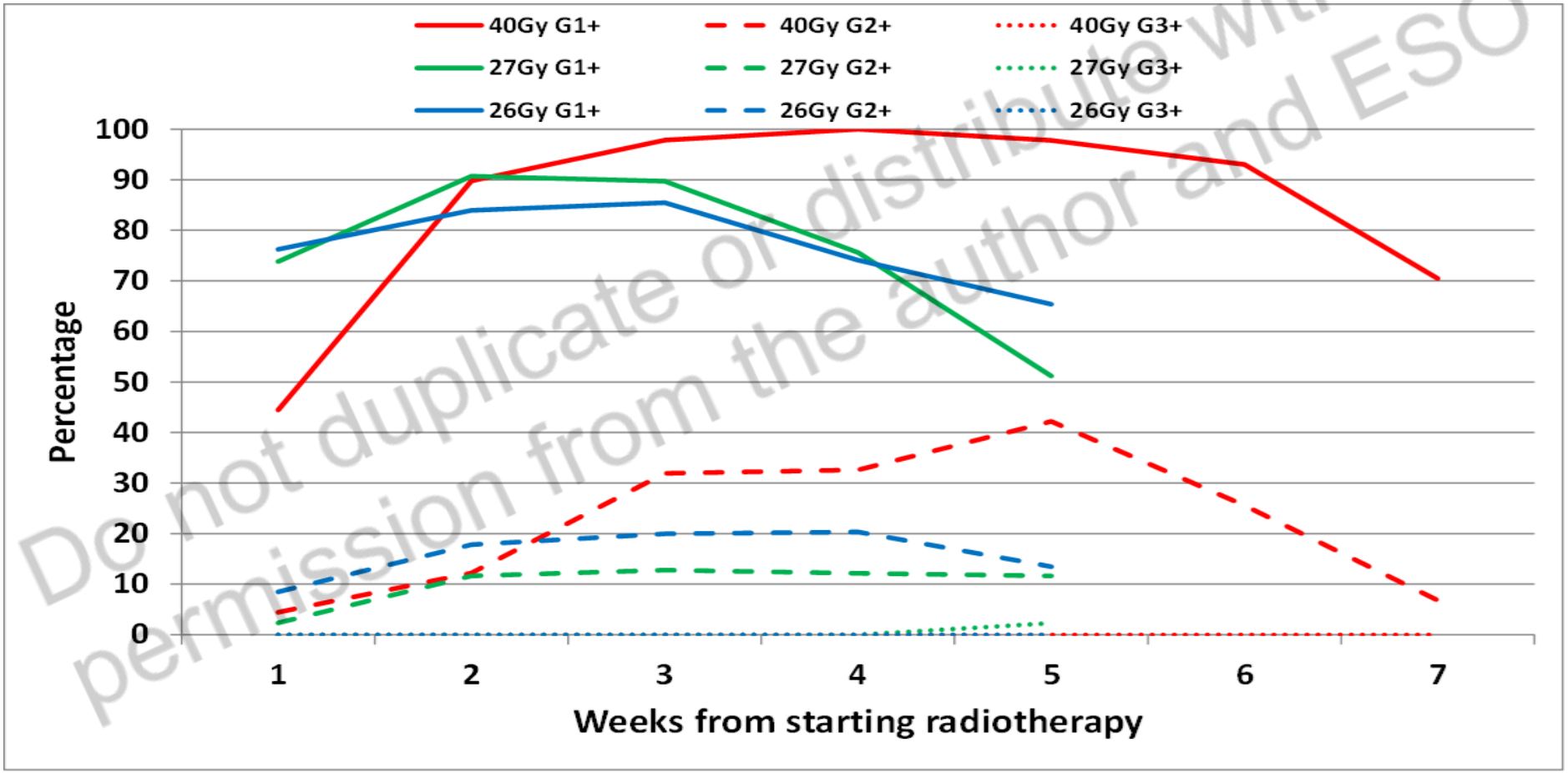
- ≥ 18 years
- pT1-3
- pN0-1
- 1^{ary} endpoint: IBTR @ 5 y (2% ➔ ≤1·6% excess, HR 1·81)
- 2^{ary} endpoints: physician + patient + photographic NTE assessment

N = 4096; median FU 5.96 years

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

Ultra-hypofractionation in BC: *Evidence*

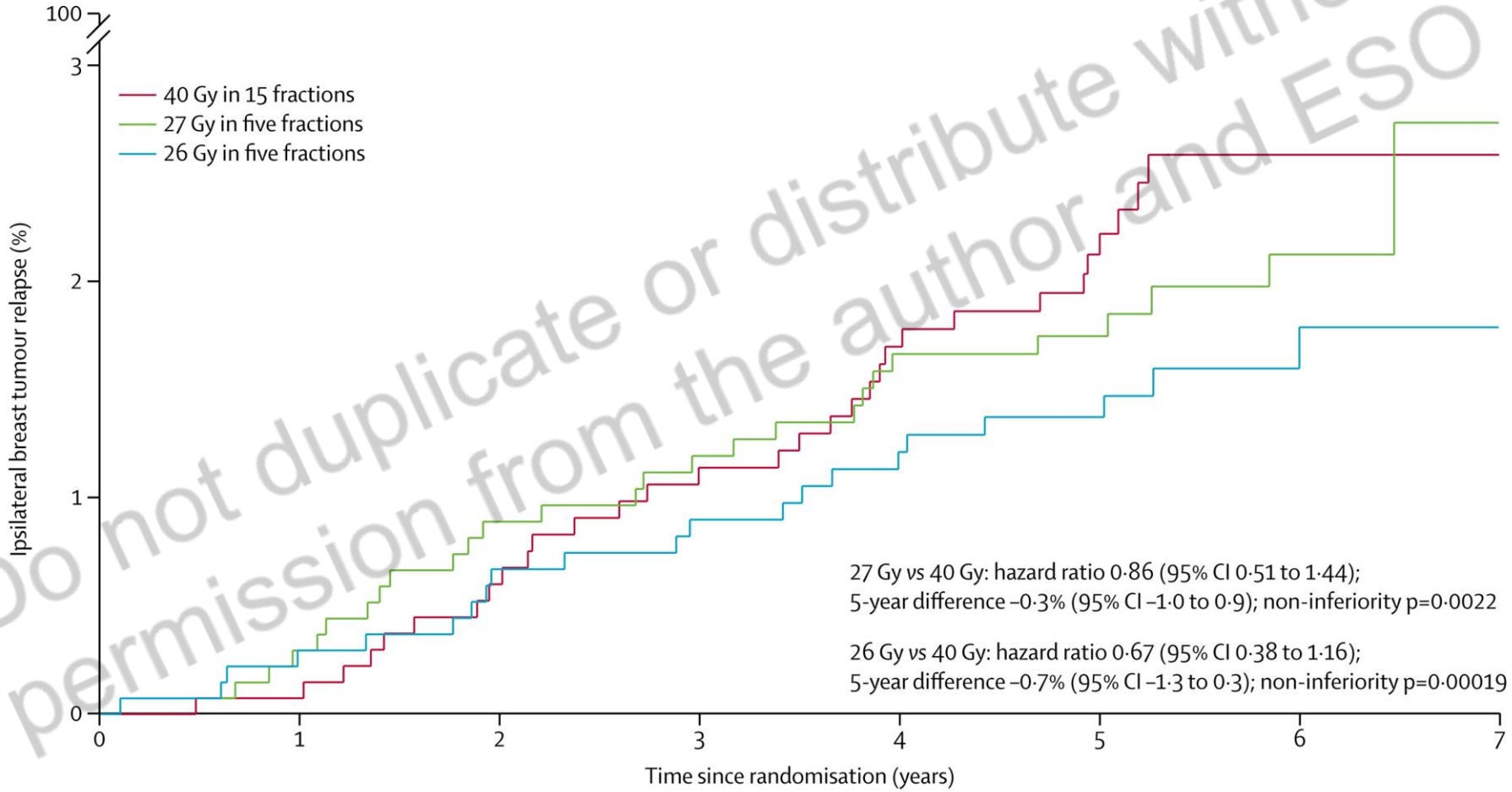
Acute skin toxicity



Brunt AM, et al. Radiother Oncol 2016.

Ultra-hypofractionation in BC: *Evidence*

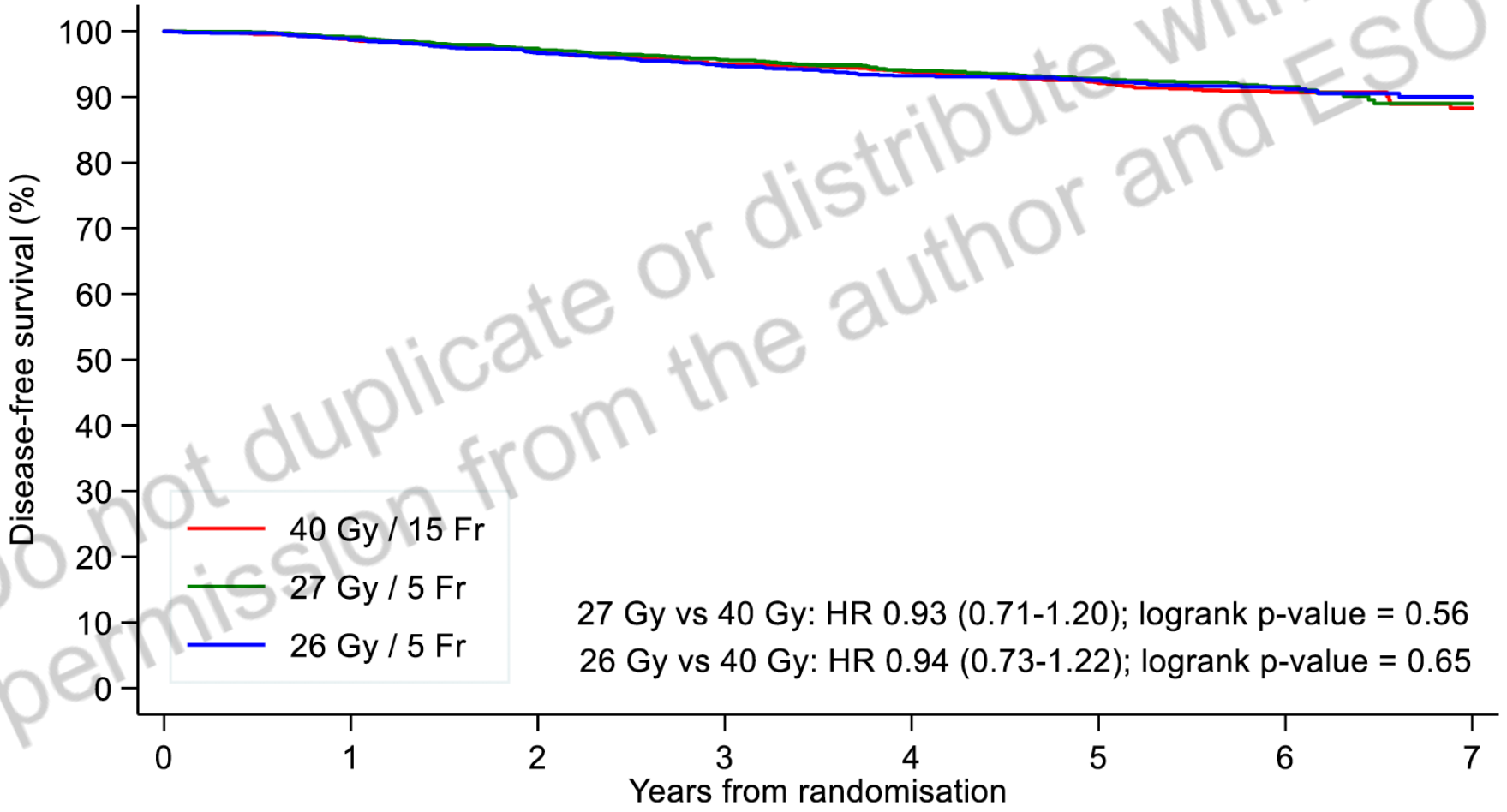
Primary Endpoint: Ipsilateral breast tumour relapse



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

Ultra-hypofractionation in BC: *Evidence*

Disease-free survival



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

Ultra-hypofractionation in BC: *Evidence*

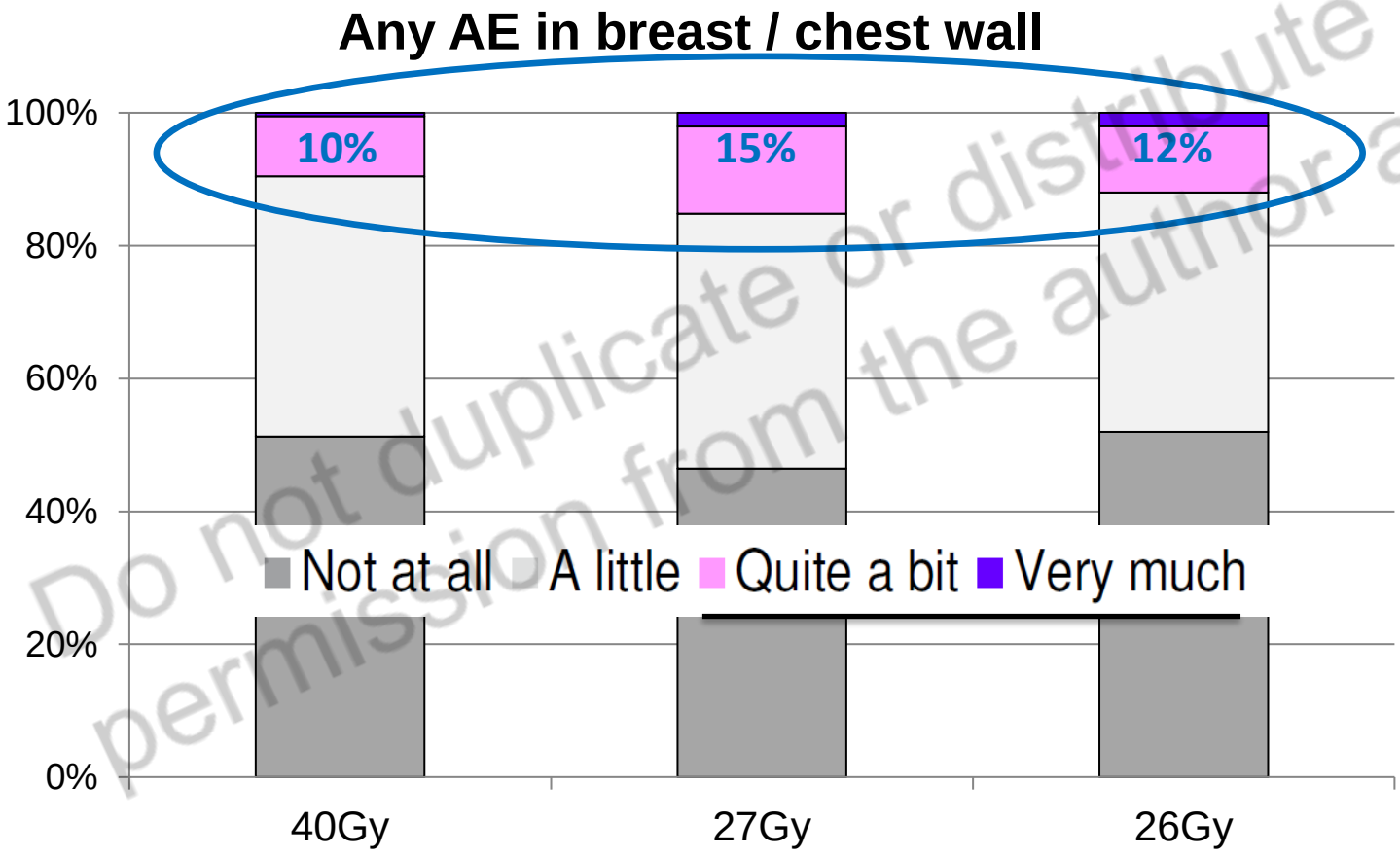
Clinician-assessed late adverse effects

	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.

Ultra-hypofractionation in BC: *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.

Ultra-hypofractionation in BC: *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.

Ultra-hypofractionation for breast cancer

1. Introduction
2. Basics of radiobiology
3. Evidence
4. Discussion
5. Conclusions

Ultra-hypofractionation in BC: *Discussion*

Critique:

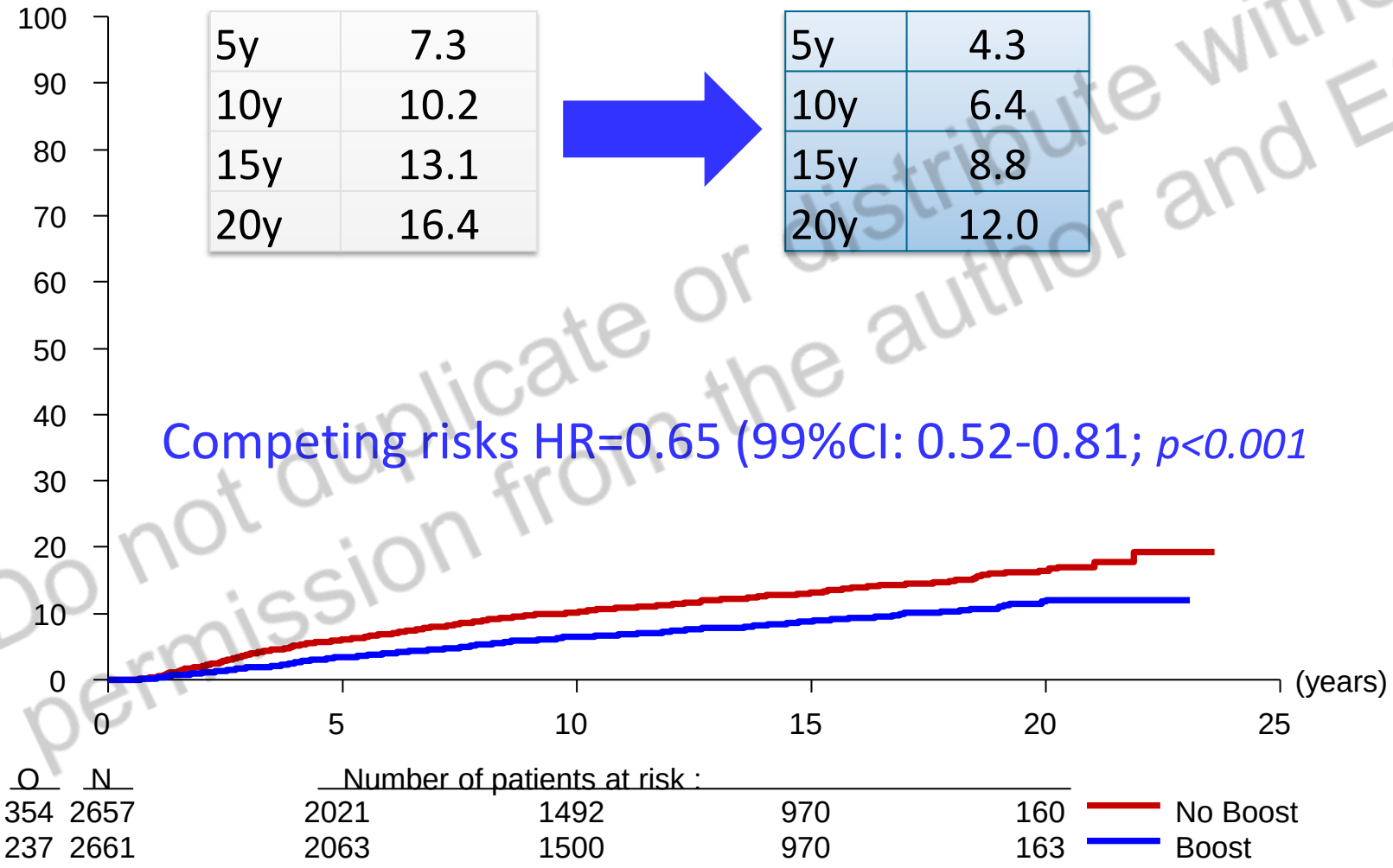
"Follow-up is too short!"

Ultra-hypofractionation in BC: *Discussion*

Local recurrence rates (%)

5y	7.3
10y	10.2
15y	13.1
20y	16.4

5y	4.3
10y	6.4
15y	8.8
20y	12.0

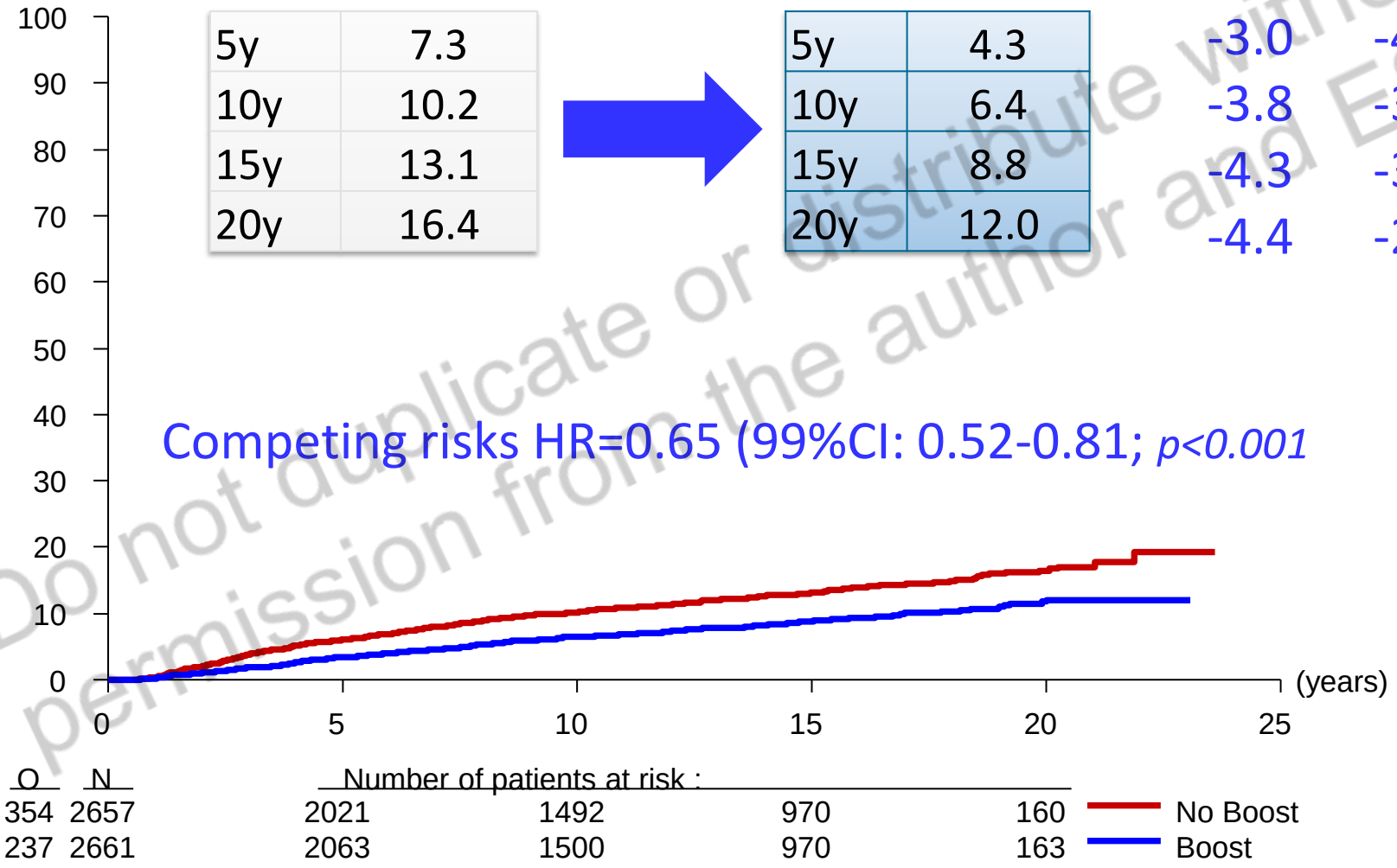


Bartelink, Horiot, Poortmans et al. NEJM 2001, JCO 2007, Lancet Oncol 2015.

Ultra-hypofractionation in BC: *Discussion*

Local recurrence rates (%)

			abs≠	rel≠
5y	7.3	5y	4.3	-3.0	-41%
10y	10.2	10y	6.4	-3.8	-37%
15y	13.1	15y	8.8	-4.3	-33%
20y	16.4	20y	12.0	-4.4	-27%



Bartelink, Horiot, Poortmans et al. NEJM 2001, JCO 2007, Lancet Oncol 2015.

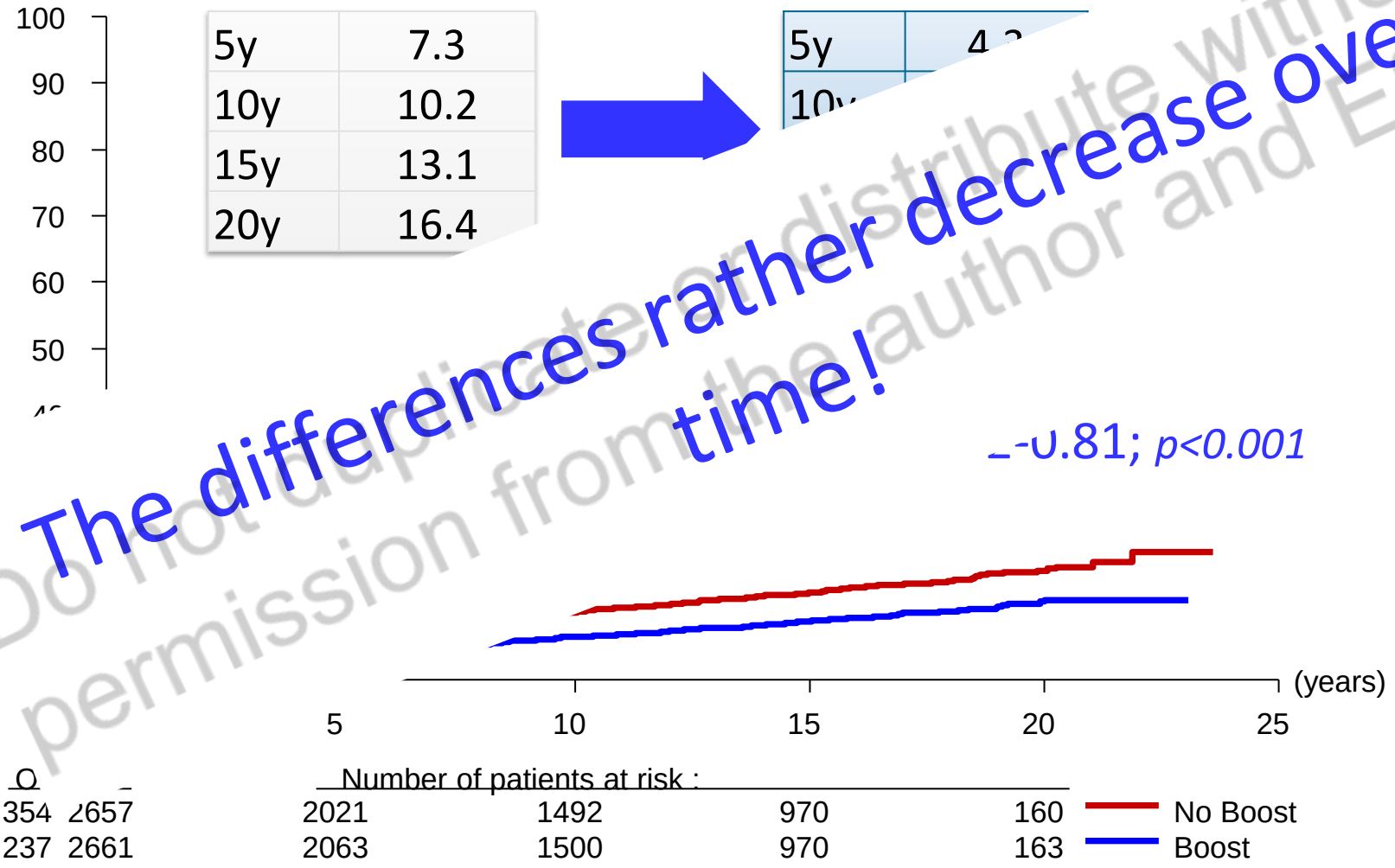
Ultra-hypofractionation in BC: *Discussion*

Local recurrence rates (%) abs≠

5y	7.3
10y	10.2
15y	13.1
20y	16.4

5y	4.2
10y	

The differences rather decrease over time!



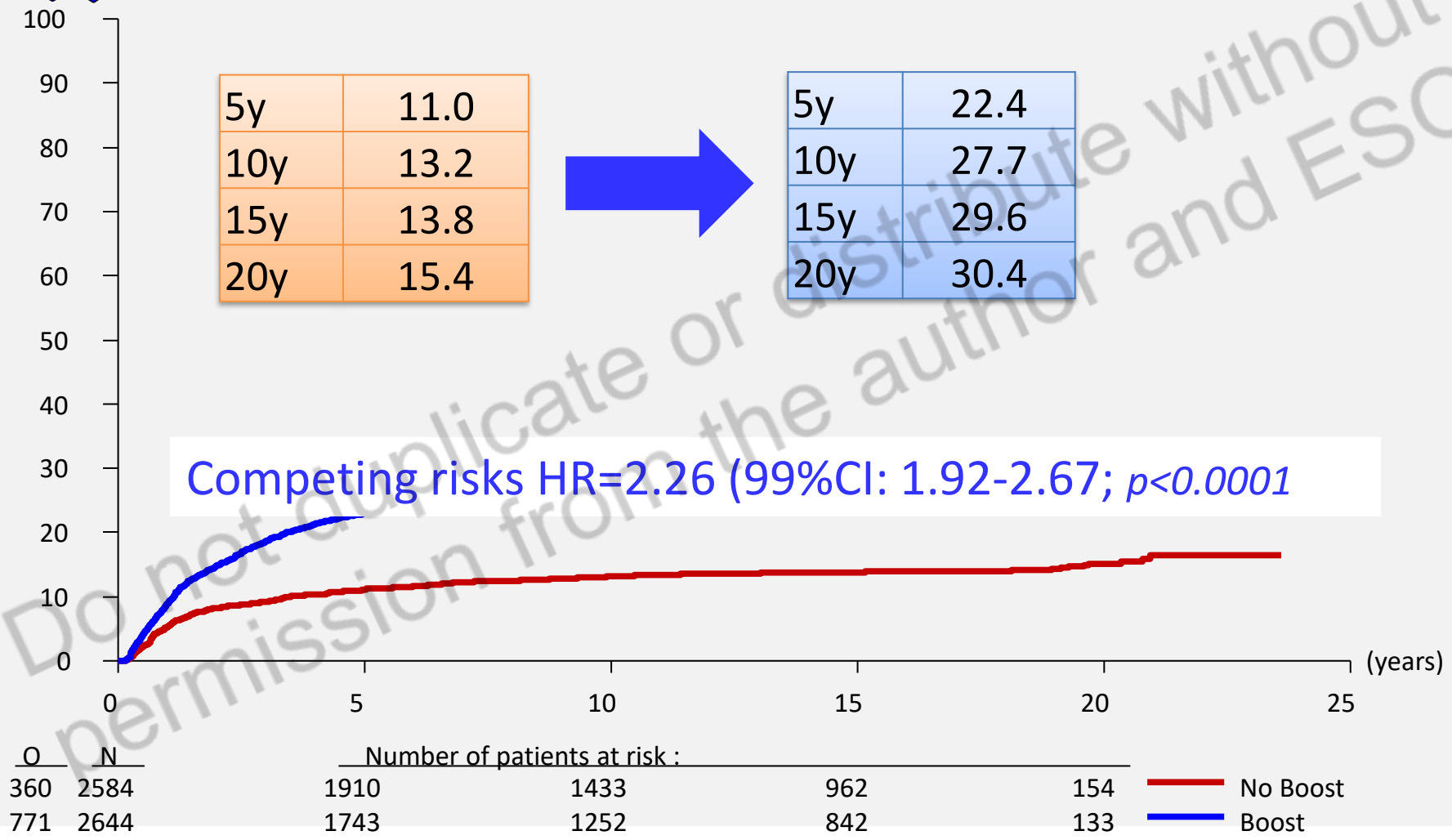
Bartelink, Horiot, Poortmans et al. NEJM 2001, JCO 2007, Lancet Oncol 2015.

Ultra-hypofractionation in BC: *Discussion*

Local recurrence rates (%)

5y	11.0
10y	13.2
15y	13.8
20y	15.4

5y	22.4
10y	27.7
15y	29.6
20y	30.4



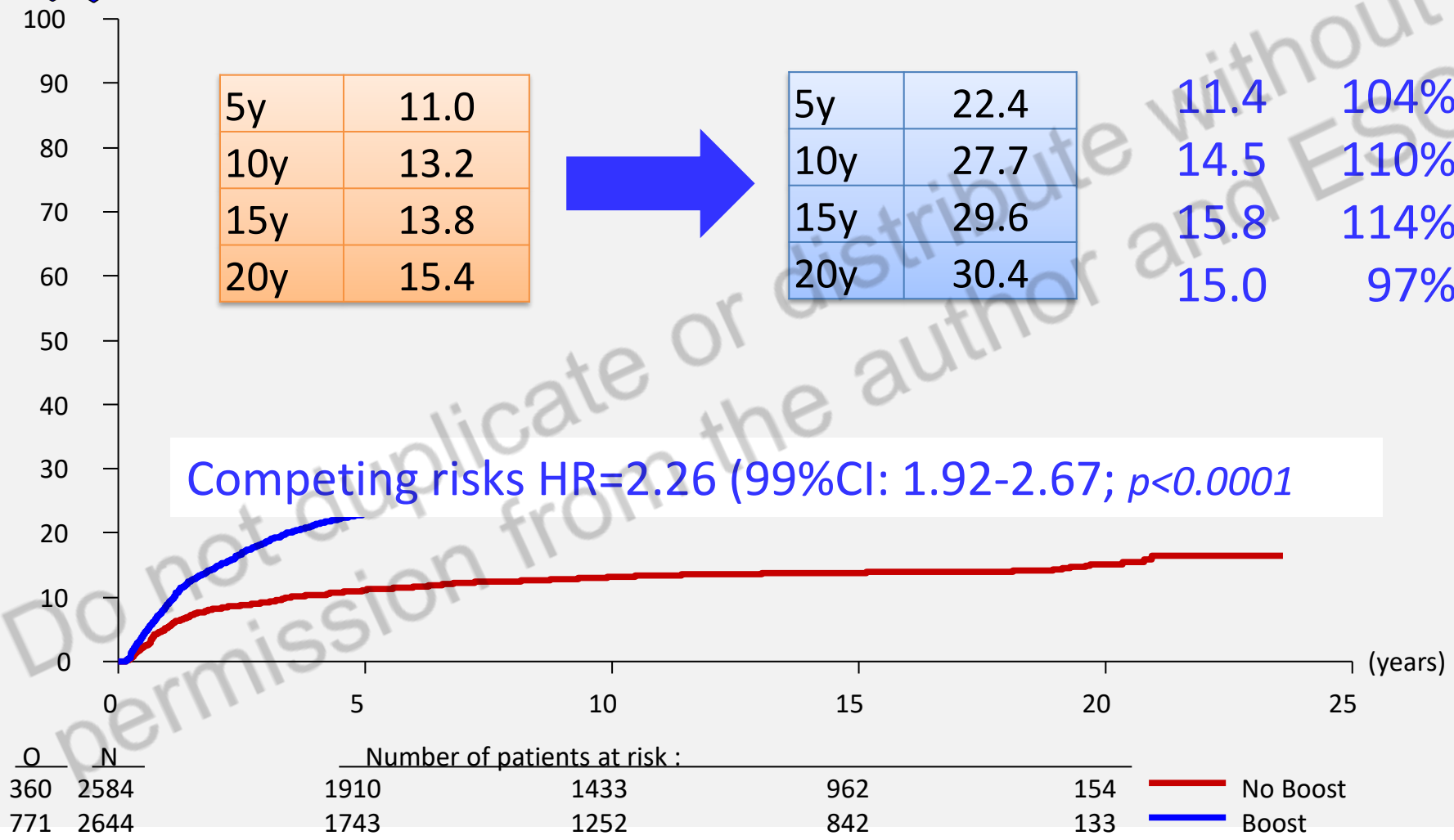
Bartelink, Horiot, Poortmans et al. NEJM 2001, JCO 2007, Lancet Oncol 2015.

Ultra-hypofractionation in BC: *Discussion*

Local recurrence rates (%)

5y	11.0
10y	13.2
15y	13.8
20y	15.4

		abs≠	rel≠
5y	22.4	11.4	104%
10y	27.7	14.5	110%
15y	29.6	15.8	114%
20y	30.4	15.0	97%



Bartelink, Horiot, Poortmans et al. NEJM 2001, JCO 2007, Lancet Oncol 2015.

Ultra-hypofractionation in BC: *Discussion*

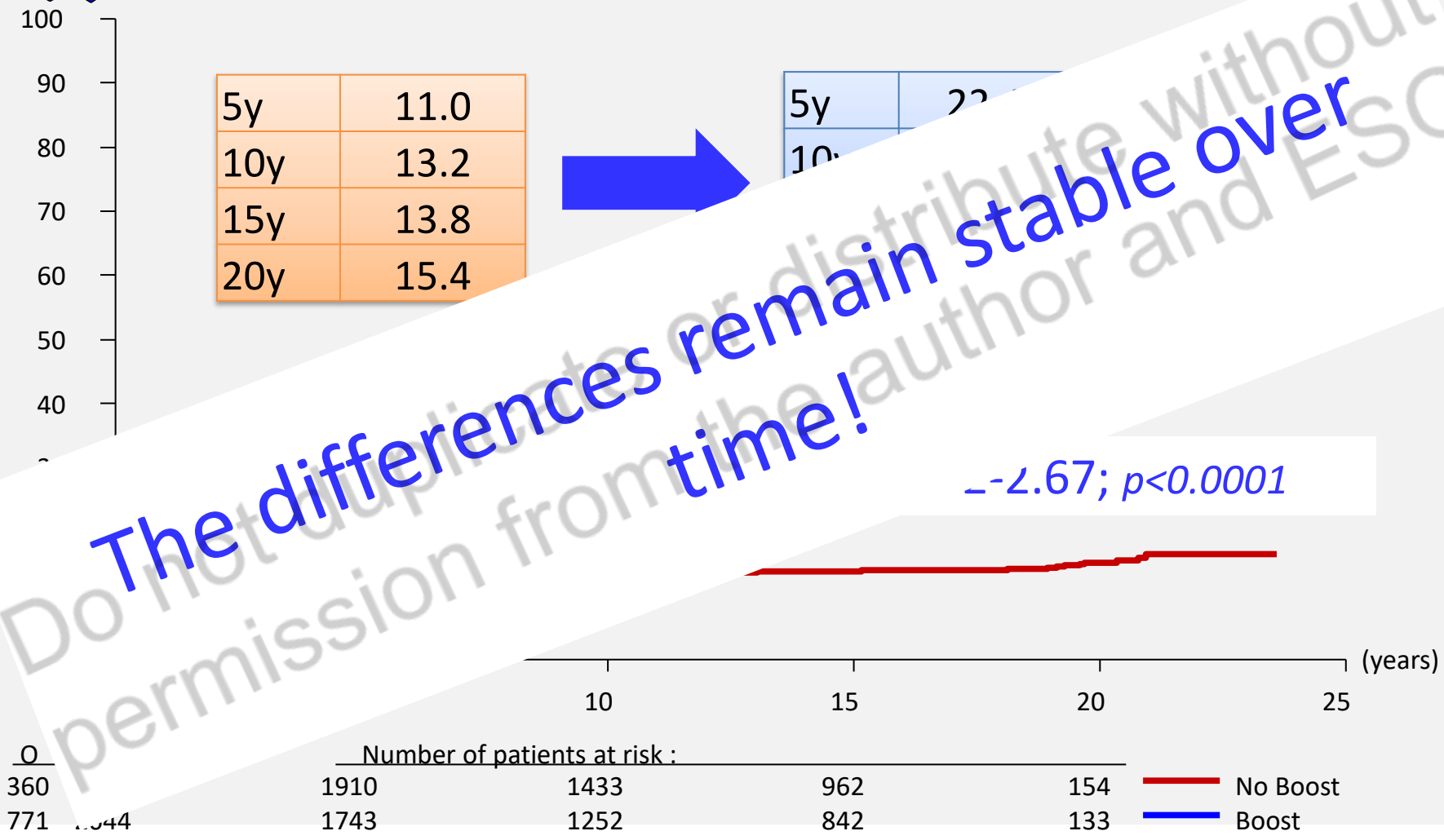
Local recurrence rates (%)

5y	11.0
10y	13.2
15y	13.8
20y	15.4

abs≠

5y	22
10y	

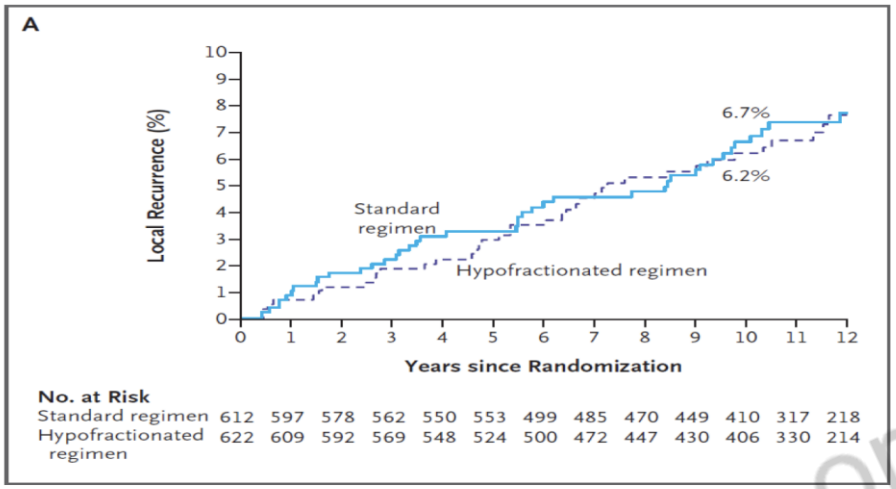
The differences remain stable over time!



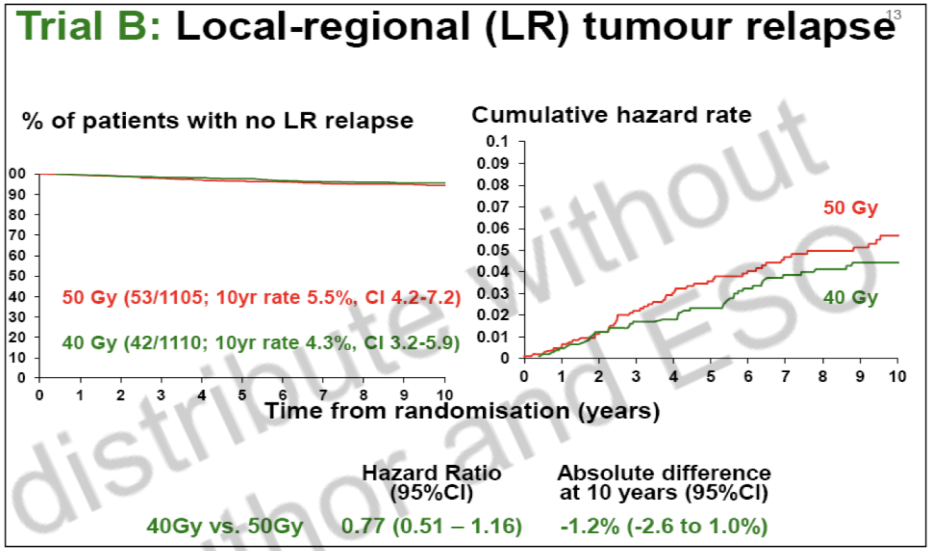
Bartelink, Horiot, Poortmans et al. NEJM 2001, JCO 2007, Lancet Oncol 2015.

Ultra-hypofractionation in BC: *Discussion*

Local control



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

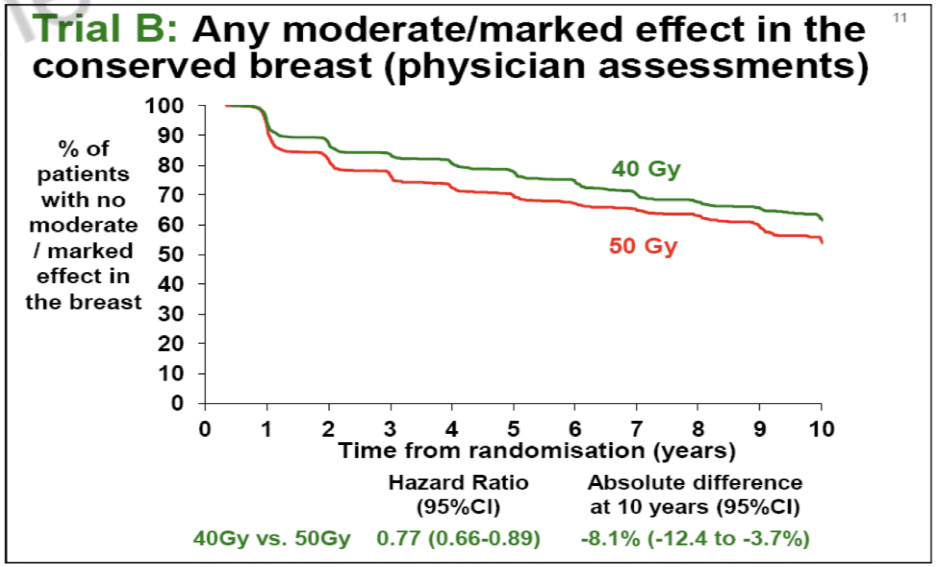


Yarnold et al. Lancet 2008;371:1098-107 & *Havilland et al. Lancet Oncol 2013;14:1086–94*

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

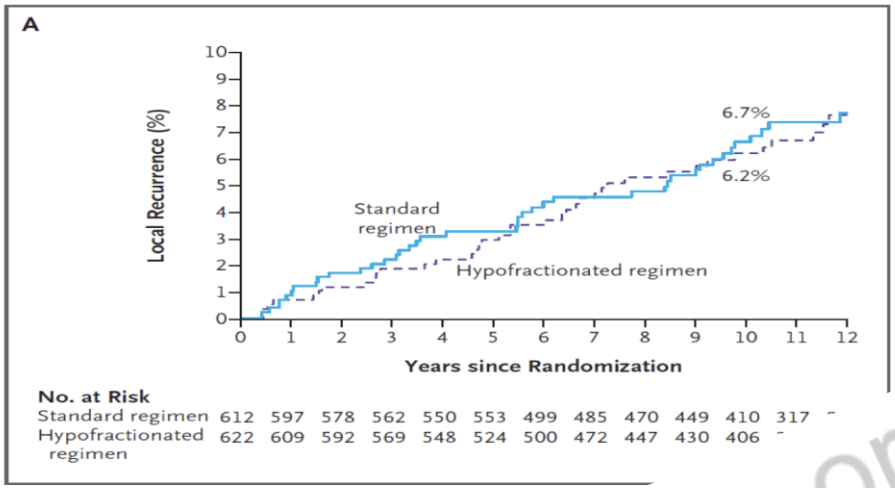
Multivariate analysis on cosmetic outcome: time since treatment, age, tumour size, NOT fractionation



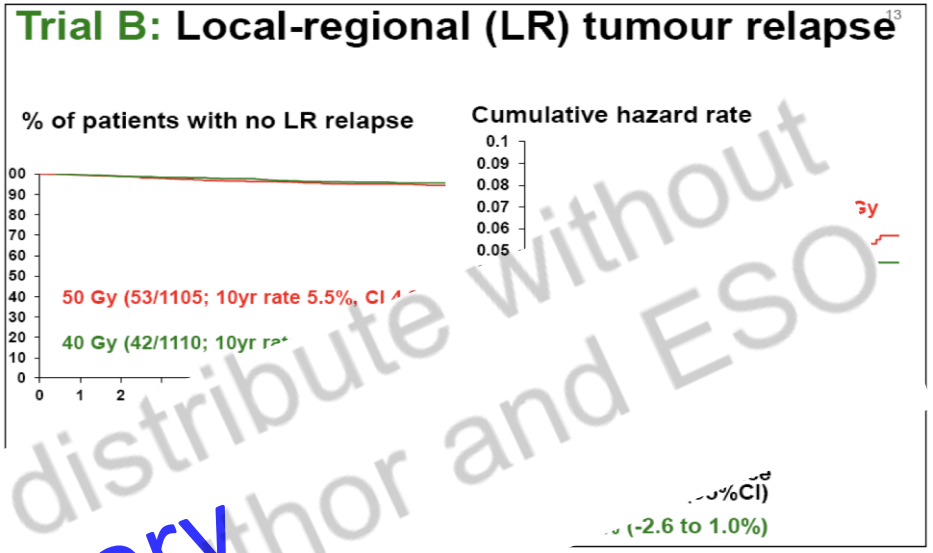
Whelan et al. JNCI 2002;94:1143-50 & *NEJM 2010;362:513-20* *Yarnold et al. Lancet 2008;371:1098-107* & *Havilland et al. Lancet Oncol 2013;14:1086–94*

Ultra-hypofractionation in BC: *Discussion*

Local control

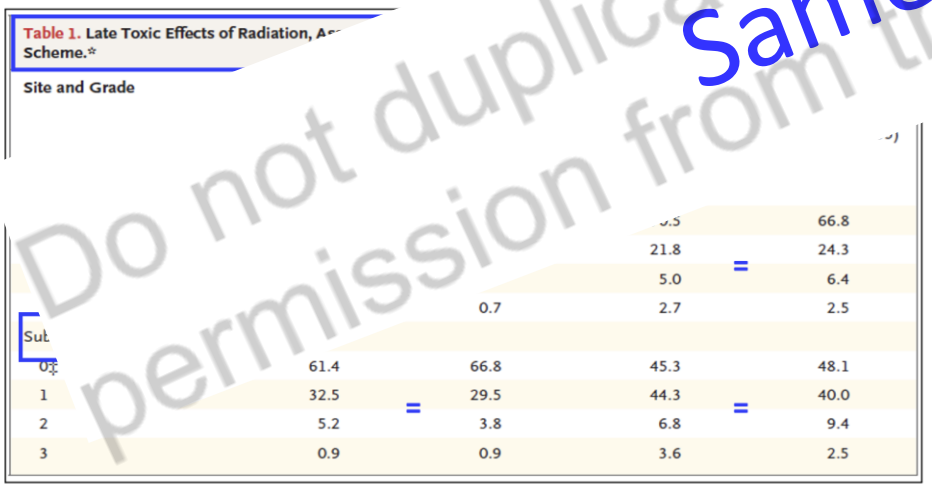


Whelan et al. JNCI 2002;94:1143-50 &

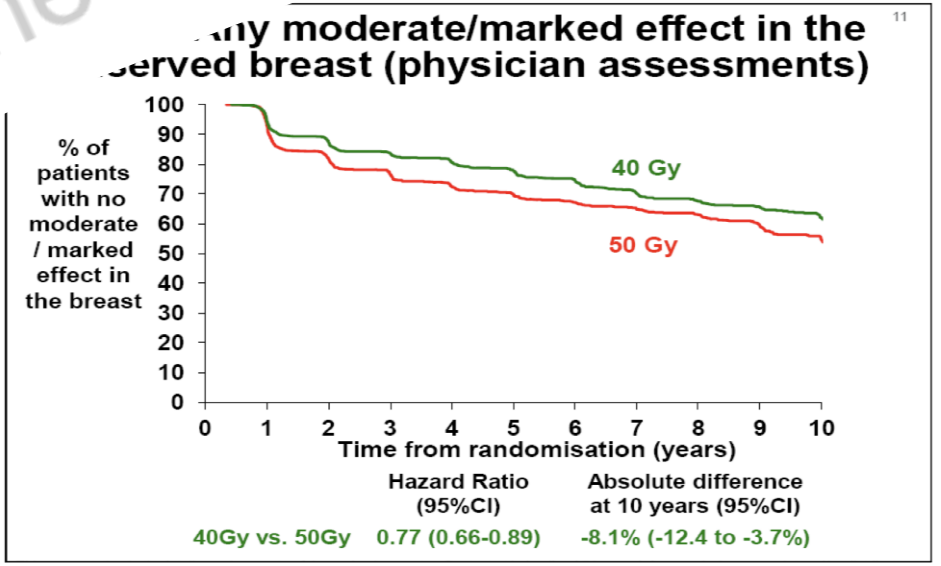


& *Havilland et al. Lancet Oncol 2013;14:1086–94*

Same story



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* *Yarnold et al. Lancet 2008;371:1098-107* & *Havilland et al. Lancet Oncol 2013;14:1086–94*

Ultra-hypofractionation in BC: *Discussion*

Conclusion:

For side effects no relative increase after 5 years!

Ultra-hypofractionation in BC: *Discussion*

Conclusion:

For local control no relative increase after 5 years!

Ultra-hypofractionation in BC: *Discussion*

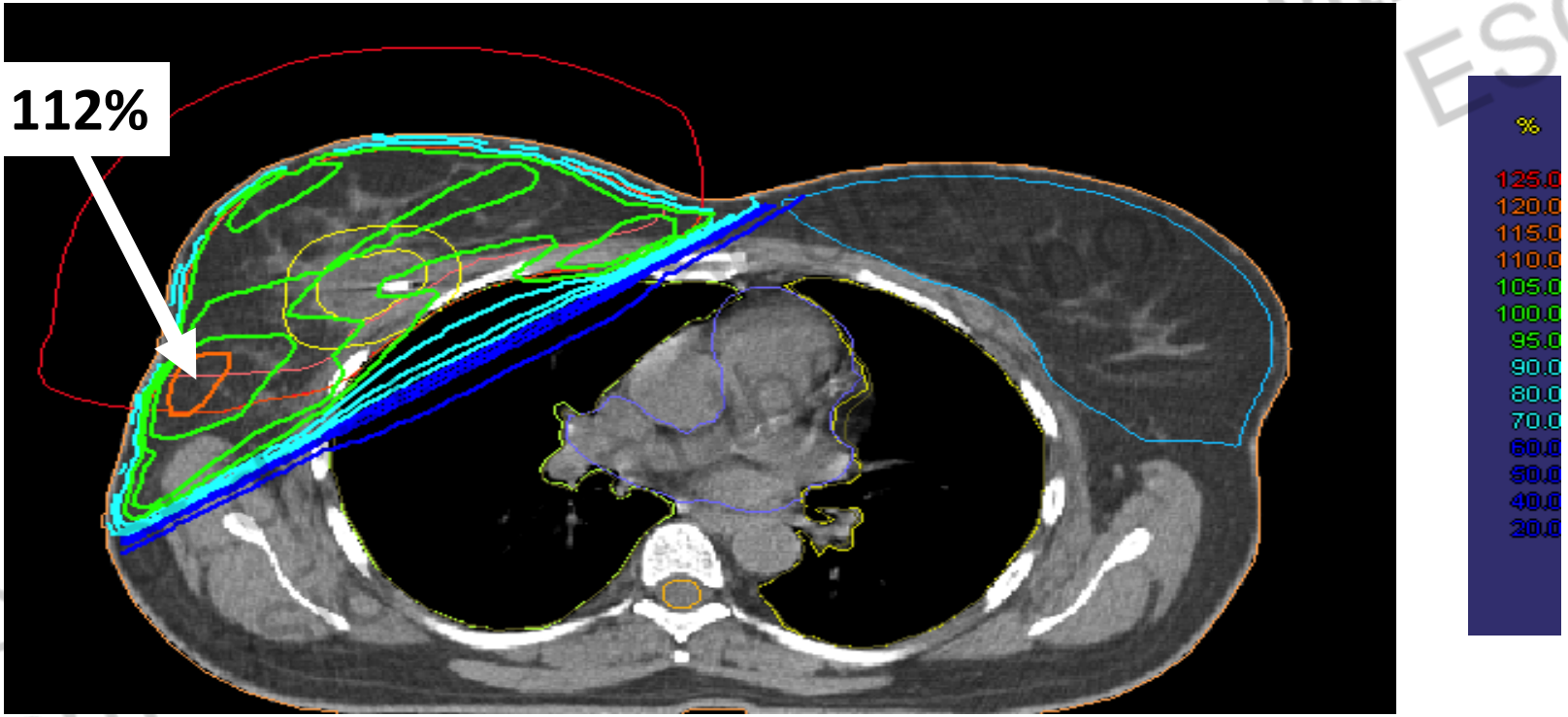
Critique:

"Dose inhomogeneity is a big issue!"

Ultra-hypofractionation in BC: *Discussion*

Physics aspects related to HF:

HypoF: be careful with treatment planning



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

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

Ultra-hypofractionation in BC: *Discussion*

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 HipoF RT:

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

➔ TRIPLE TROUBLE

Ultra-hypofractionation in BC: *Discussion*

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*

…ible“ (Withers 1992)

…points in HipoF RT:

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

➔ TRIPLE TROUBLE

But is this true????

Ultra-hypofractionation in BC: *Discussion*

Inhomogeneity of the dose in the breast	Equivalent total dose (Gy) if α/β=3 Gy, using fractions of....		
	2Gy	2.7Gy	5.2Gy
100 %	50.0	50.0	50.0
105 %	53.6 →	53.7 →	54.2

'double trouble'

'triple trouble'

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

Ultra-hypofractionation in BC: *Discussion*

Inhomogeneity of the dose in the breast

Equivalent to
$\alpha/\beta=3$

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

53.7 → 54.2

'triple trouble'

'double trouble'

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

Ultra-hypofractionation in BC: *Discussion*

Conclusion:

Yes … independent of the fractionation!

Ultra-hypofractionation in BC: *Discussion*

Critique:

"It's only validated for a limited patient population!"

Ultra-hypofractionation in BC: *Discussion*

The Breast 62 (2022) 84–92

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Moderately hypofractionated post-operative radiation therapy for breast cancer: Systematic review and meta-analysis of randomized clinical trials

Gustavo Nader Marta [a,b,*], Rachel Riera [c], Rafael Leite Pacheco [d], Ana Luiza Cabrera Martimbianco [e,f], Icro Meattini [g], Orit Kaidar-Person [h,i,j], Philip Poortmans [k]

Marta GN, et al. The Breast 2022;62:84-92.

Ultra-hypofractionation in BC: *Discussion*

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)

Study	Trial Register	Start/ End, year	Country	Sample size	Inclusion criteria	Histology, n (%)		Type of surgery, n (%)		Radiation therapy techniques	Interventions		Chemo therapy, n (%)	Boost, n (%)	Regional nodal irradiation, n (%)
						Invasive tumour	Ductal carcinoma in situ	Breast-conserving surgery	Mastectomy		Control arm	Experimental arm			
Chinese Trial (22)	NCT01413269	2010–2015	China	734	T1-2N0-3; M0	734 (100)	0 (0.0)	734 (100)	0 (0.0)	Conformal (3D) and Intensity modulated radiation therapy (IMRT)	50 Gy in 25 fractions (n = 366)	43.5 Gy in 15 fractions (n = 368)	477 (64.9)	732 (99.7)	28 (3.9)
DBCG HYPO Trial (21)	NCT00909818	2009–2014	Denmark	1882	pTis-T2, N0–N1 (mic); M0	1854 (86.7)	246 (13.2)	1854 (100)	0 (0.0)	Conformal (3D)	50 Gy in 25 fractions (n = 937)	40 Gy in 15 fractions (n = 917)	578 (30)	429 (23.1)	0 (0.0)
BIG 3–07/ TROG 07.01 (20)	NCT00470236	2007–2014	Multicentric trial	1608	pTis; N0M0	0 (0.0)	1208 (100)	1208 (100)	0 (0.0)	Conventional (2D) and conformal (3D)	50 Gy in 25 fractions plus boost 16Gy in 8 fractions (n = 415)	42.5 Gy in 16 fractions plus boost 16Gy in 8 fractions (n = 388)	0 (0.0)	803 (49.9)	0 (0.0)
Total n (%)	–	–	–	12139 (100)	–	10685 (88.9)	1454 (11.9)	10809 (89.1)	1333 (10.9)	–	–	–	3491 (28.7)	5035 (41.4)	1617 (13.3)

Marta GN, et al. CROH 2020;156:103090 + *The Breast 2022;62:84-92.*

Ultra-hypofractionation in BC: *Discussion*

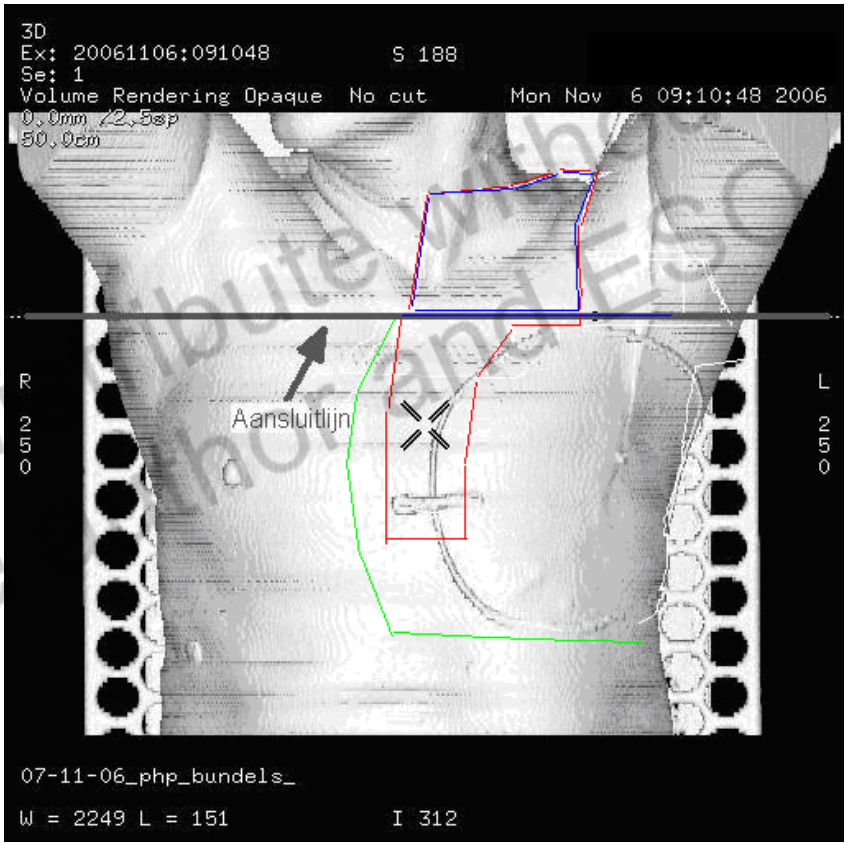
For tissues outside of the target volumes

Mathematics by Philip

Ultra-hypofractionation in BC: *Discussion*

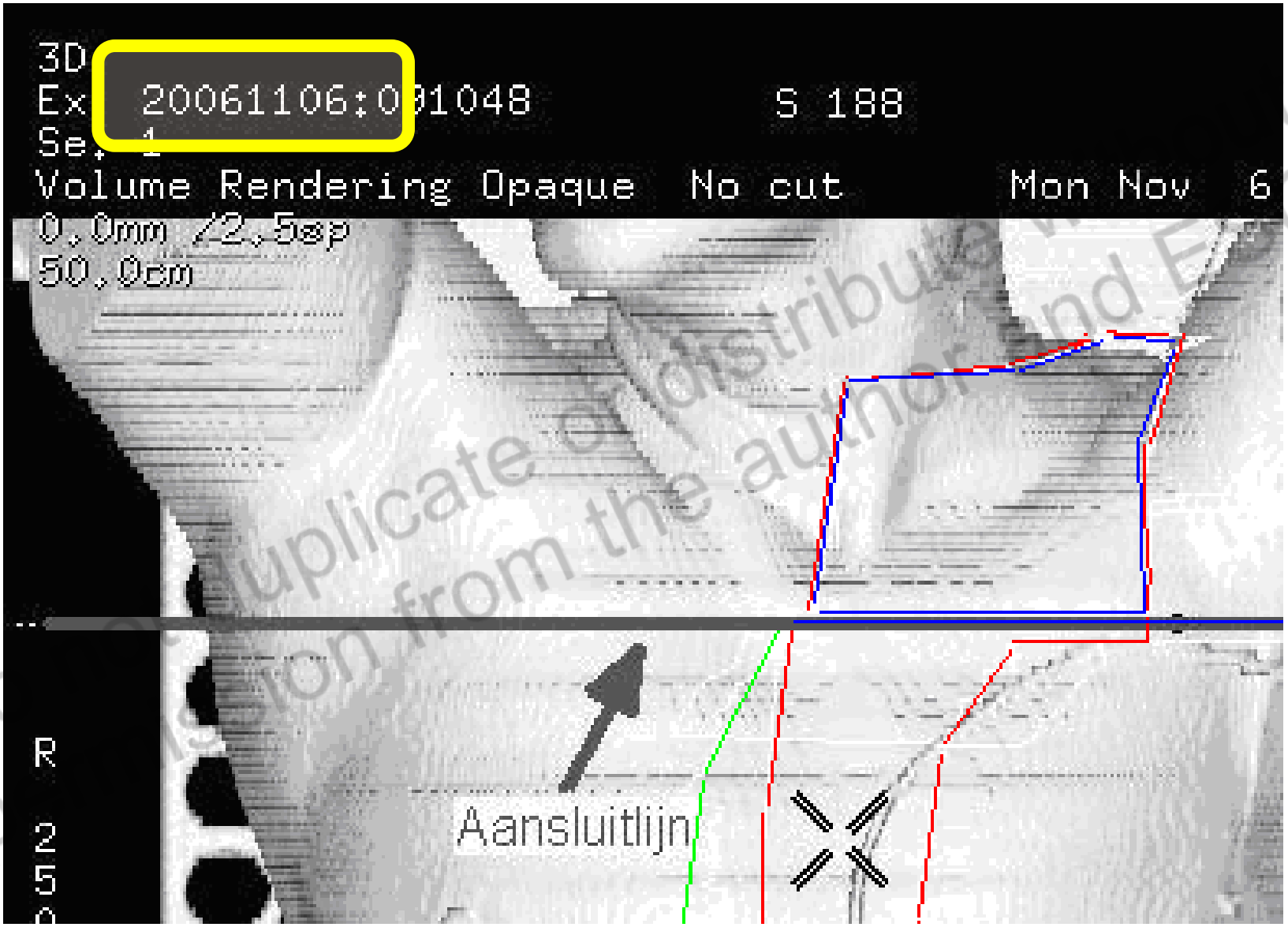
Photons

- 1 isocentre
- 4 main fields
- 3 gantry angles

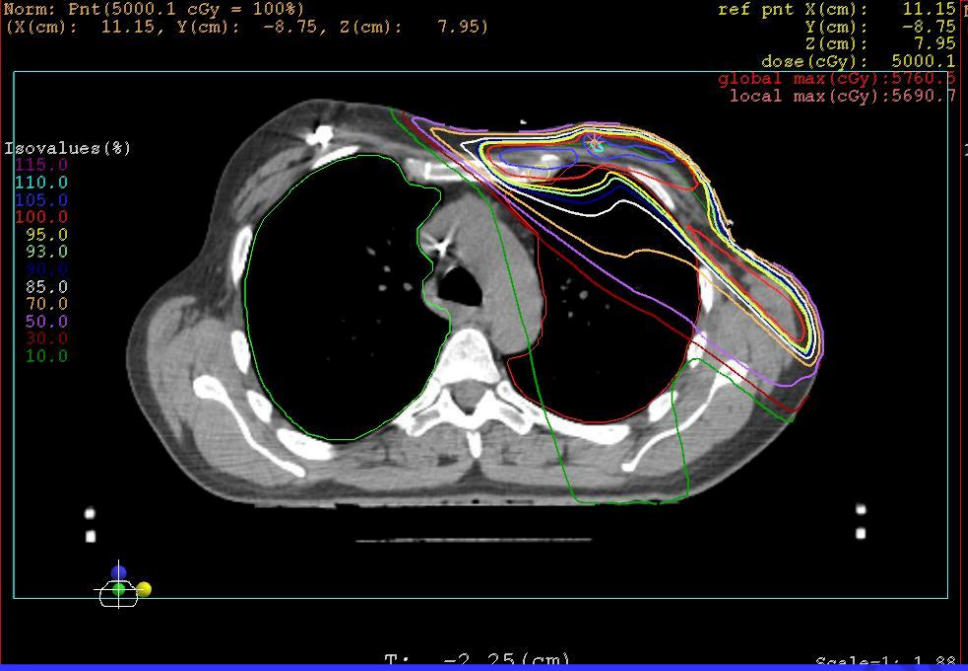


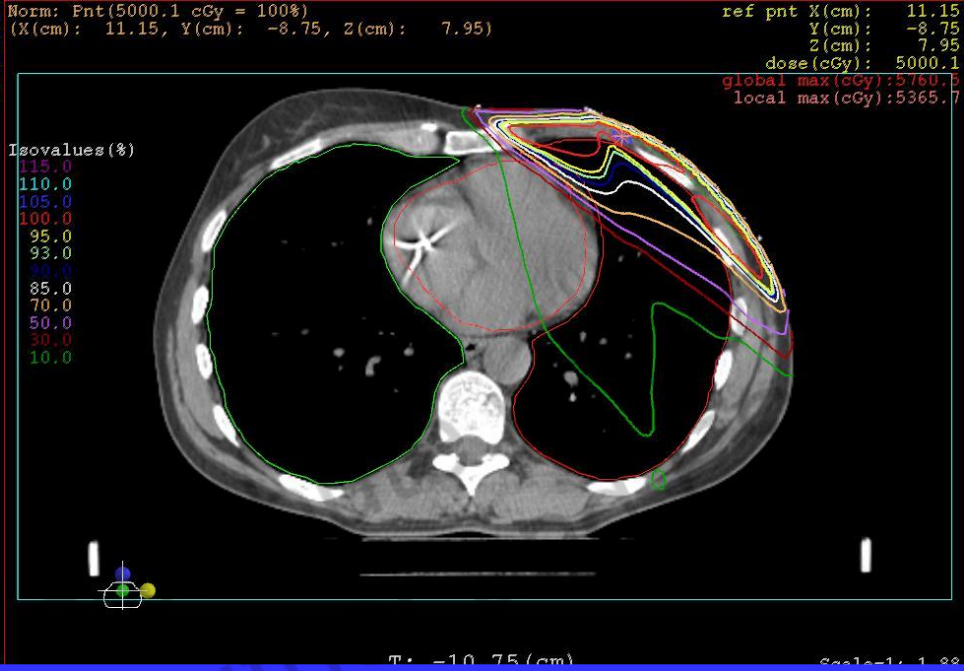
Mathematics by Philip

Ultra-hypofractionation in BC: *Discussion*

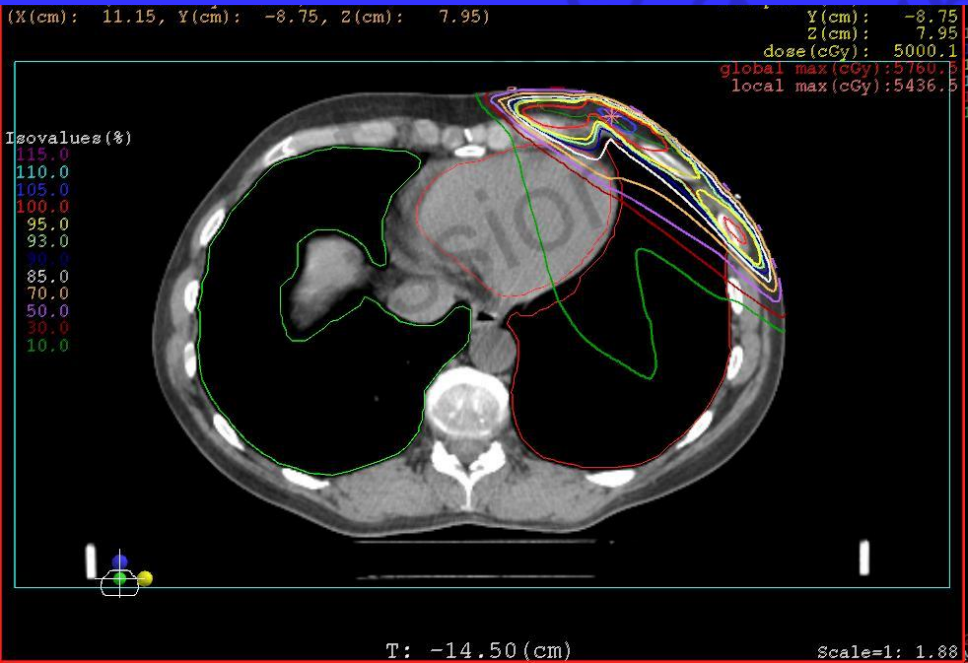


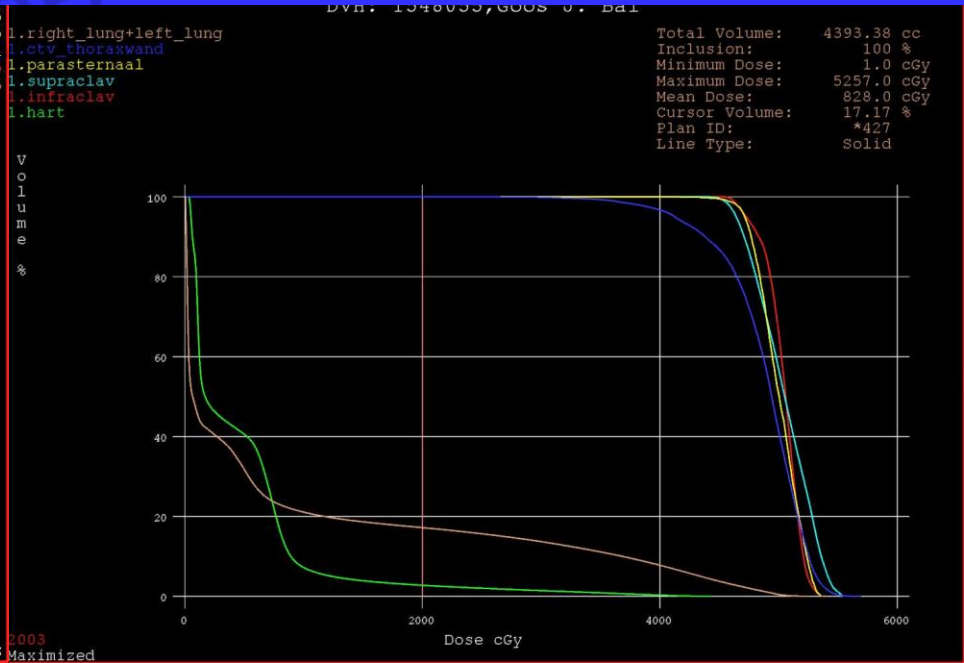
Mathematics by Philip

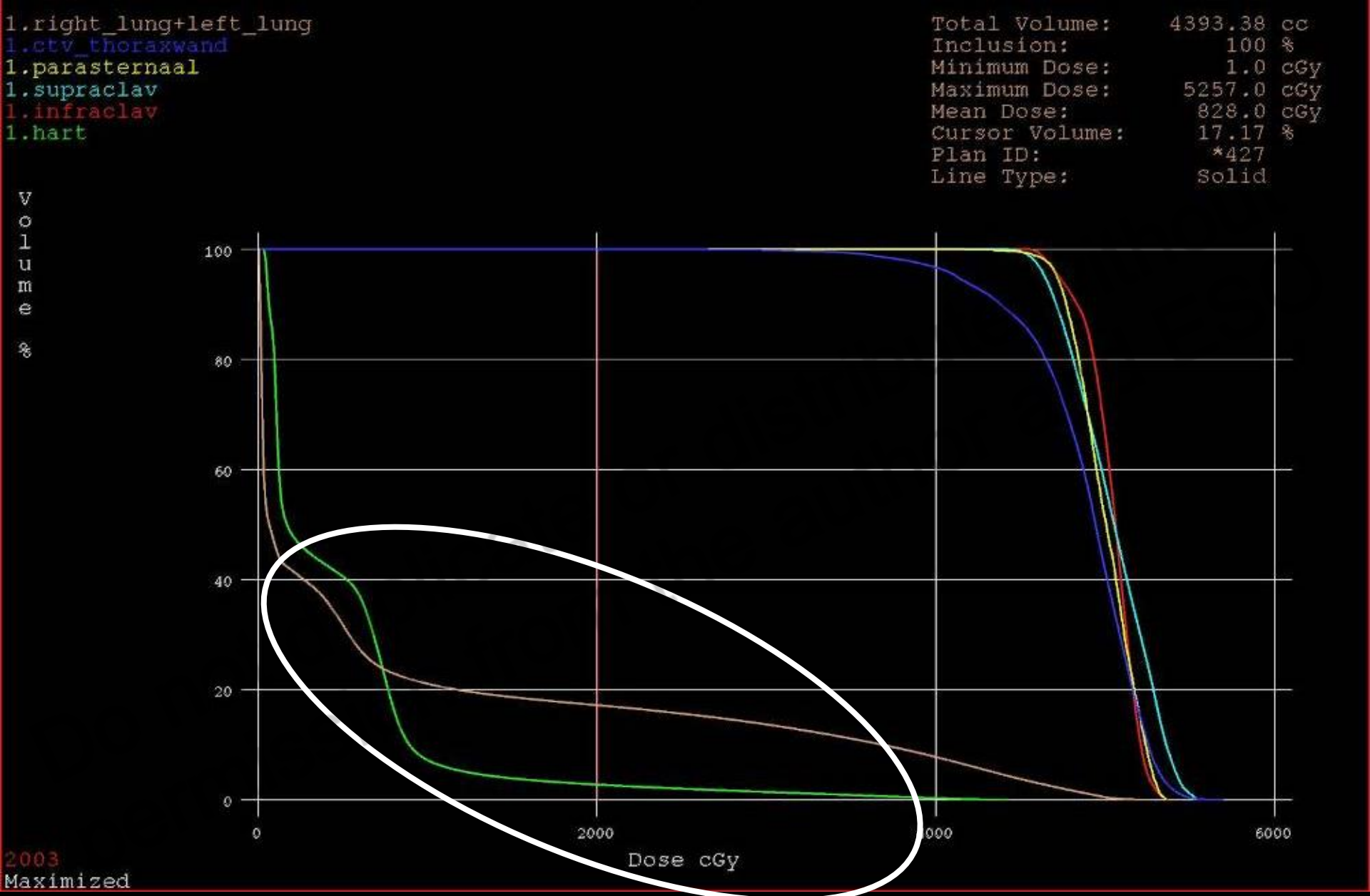




BVI photon technique including the IMC







0	0.5	1.0	1.5	2.0
0	0.67	1.33	2.0	2.66

Ultra-hypofractionation in BC: *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

Ultra-hypofractionation in BC: *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

Ultra-hypofractionation in BC: *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

Ultra-hypofractionation in BC: *Discussion*

	20th century 25*2	
a/b = 2		
100	2,00	50,00
95	1,90	47,50
90	1,80	45,00
85	1,70	42,50
70	1,40	35,00
50	1,00	25,00
25	0,50	12,50
10	0,20	5,00
a/b = 10		
100	2,00	50,00
95	1,90	47,50
90	1,80	45,00
85	1,70	42,50
70	1,40	35,00
50	1,00	25,00
25	0,50	12,50
10	0,20	5,00

Mathematics by Philip

Ultra-hypofractionation in BC: *Discussion*

	Canadian 16*2,66		20th century 25*2		UK START 15*2,67	
a/b = 2						
100	2,66	49,58	2,00	50,00	2,67	46,76
95	2,53	46,93	1,90	47,50	2,54	44,26
90	2,39	44,29	1,80	45,00	2,40	41,76
85	2,26	41,66	1,70	42,50	2,27	39,28
70	1,86	33,84	1,40	35,00	1,87	31,90
50	1,33	23,62	1,00	25,00	1,34	22,26
25	0,67	11,34	0,50	12,50	0,67	10,68
10	0,27	4,38	0,20	5,00	0,27	4,13
a/b = 10						
100	2,66	44,90	2,00	50,00	2,67	42,29
95	2,53	42,56	1,90	47,50	2,54	40,08
90	2,39	40,23	1,80	45,00	2,40	37,89
85	2,26	37,91	1,70	42,50	2,27	35,70
70	1,86	31,00	1,40	35,00	1,87	29,19
50	1,33	21,92	1,00	25,00	1,34	20,63
25	0,67	10,81	0,50	12,50	0,67	10,17
10	0,27	4,28	0,20	5,00	0,27	4,03

Mathematics by Philip

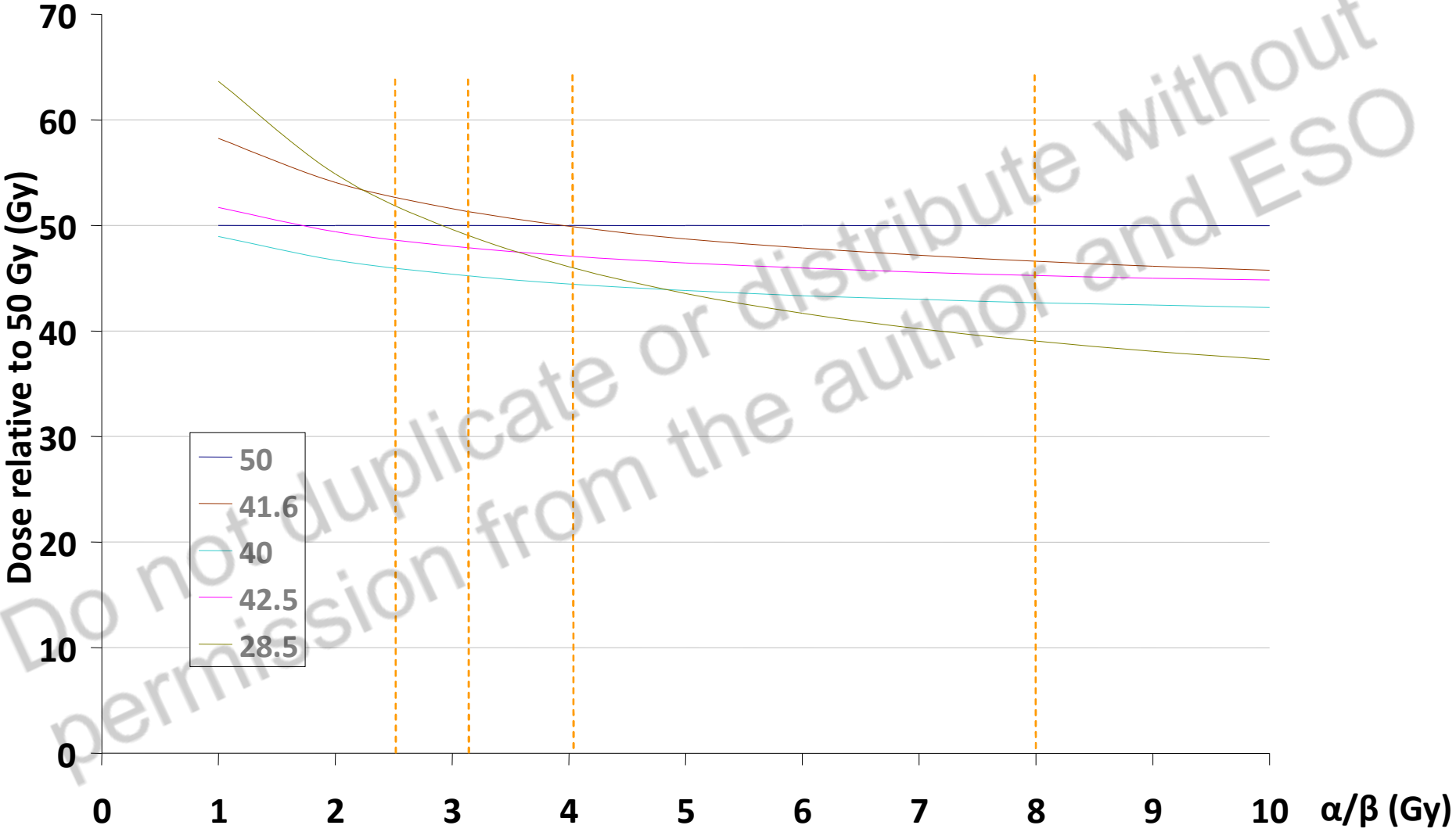
Ultra-hypofractionation in BC: *Discussion*

	Canadian 16*2,66		20th century 25*2		UK START 15*2,67		UK FF 5*5,2	
a/b = 2								
100	2,66	49,58	2,00	50,00	2,67	46,76	5,20	46,80
95	2,53	46,93	1,90	47,50	2,54	44,26	4,94	43,95
90	2,39	44,29	1,80	45,00	2,40	41,76	4,68	41,13
85	2,26	41,66	1,70	42,50	2,27	39,28	4,42	38,35
70	1,86	33,84	1,40	35,00	1,87	31,90	3,64	30,19
50	1,33	23,62	1,00	25,00	1,34	22,26	2,60	19,93
25	0,67	11,34	0,50	12,50	0,67	10,68	1,30	8,58
10	0,27	4,38	0,20	5,00	0,27	4,13	0,52	2,98
a/b = 10								
100	2,66	44,90	2,00	50,00	2,67	42,29	5,20	32,93
95	2,53	42,56	1,90	47,50	2,54	40,08	4,94	31,01
90	2,39	40,23	1,80	45,00	2,40	37,89	4,68	29,11
85	2,26	37,91	1,70	42,50	2,27	35,70	4,42	27,24
70	1,86	31,00	1,40	35,00	1,87	29,19	3,64	21,78
50	1,33	21,92	1,00	25,00	1,34	20,63	2,60	14,89
25	0,67	10,81	0,50	12,50	0,67	10,17	1,30	7,00
10	0,27	4,28	0,20	5,00	0,27	4,03	0,52	2,68

Mathematics by Philip

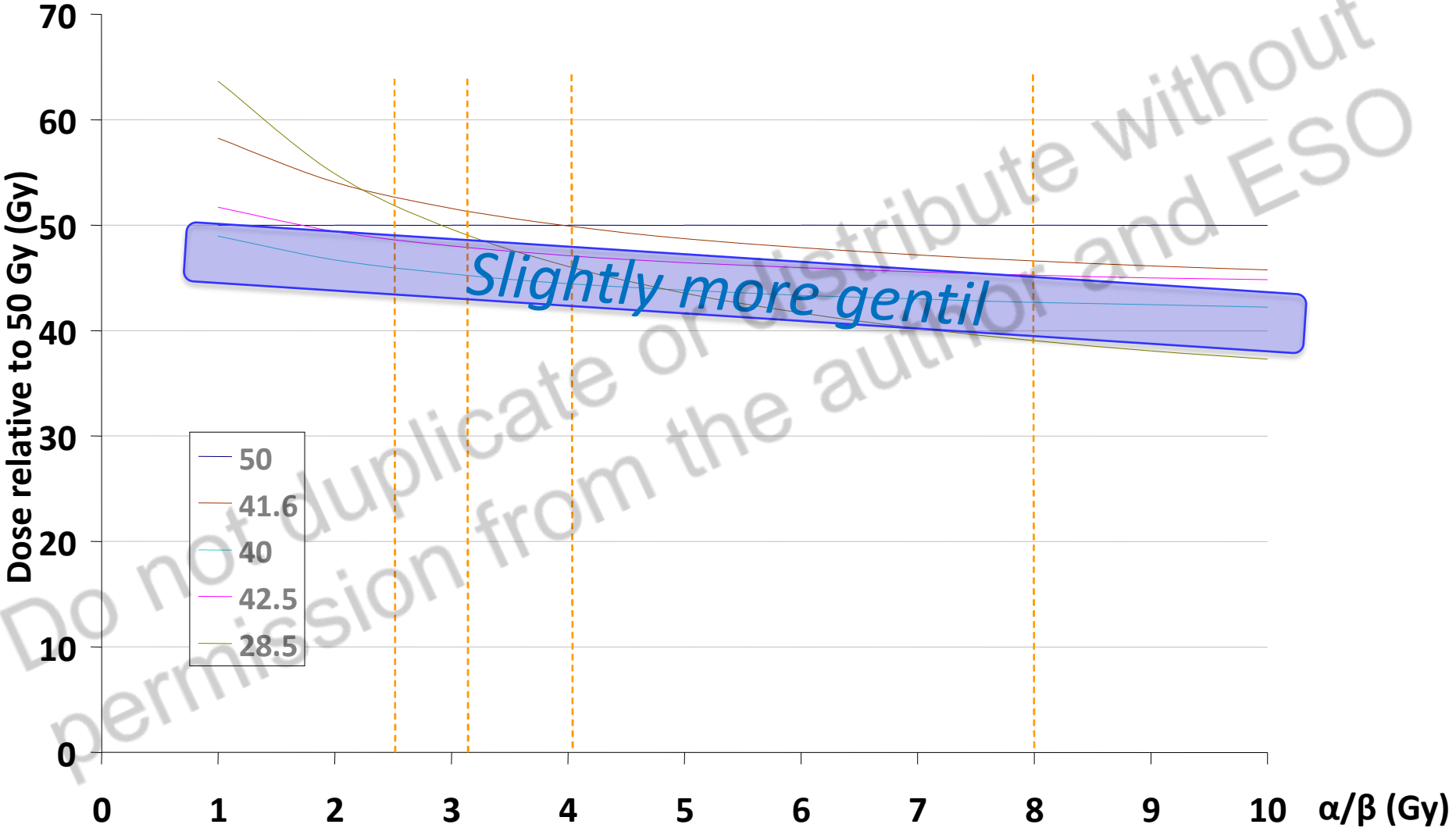
Ultra-hypofractionation in BC: *Discussion*

Radiobiology: LQ model vs. the trial results



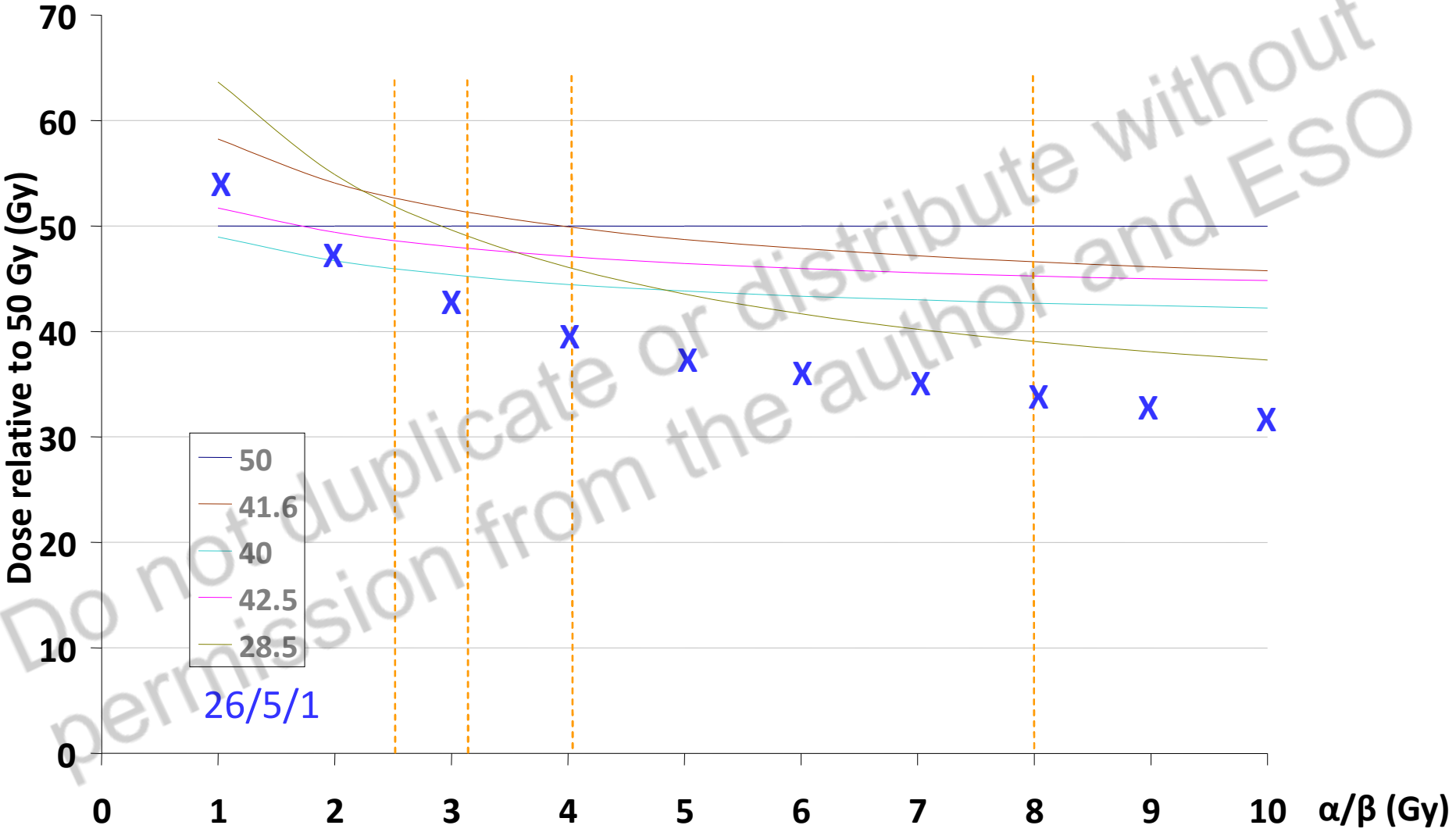
Ultra-hypofractionation in BC: *Discussion*

Radiobiology: LQ model vs. the trial results



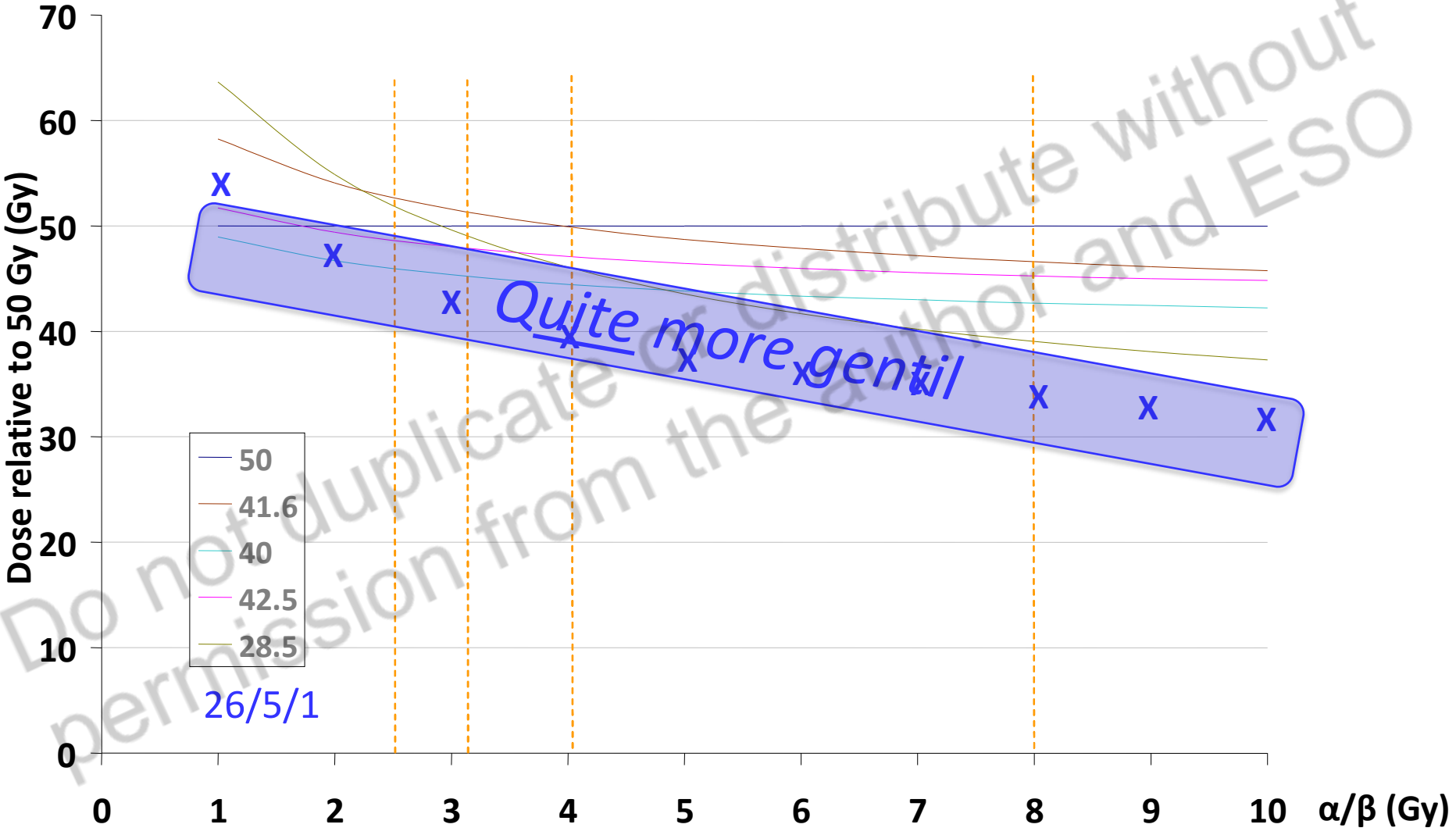
Ultra-hypofractionation in BC: *Discussion*

Radiobiology: LQ model vs. the trial results



Ultra-hypofractionation in BC: *Discussion*

Radiobiology: LQ model vs. the trial results



Ultra-hypofractionation in BC: *Discussion*

For ultra-HF: only data about breast/chest wall

Conclusion:

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!*

Mathematics by Philip

Ultra-hypofractionation in BC: *Discussion*

Critique:

"Our hospital direction doesn't like it!"

Ultra-hypofractionation in BC: *Discussion*

Several other current protocols:

- Repopulation
- Redistribution
- Reoxygenation
- Repair
- Resistance

Ultra-hypofractionation in BC: *Discussion*

Several other current protocols:

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

Ultra-hypofractionation in BC: *Discussion*

Contents lists available at ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

Original Article

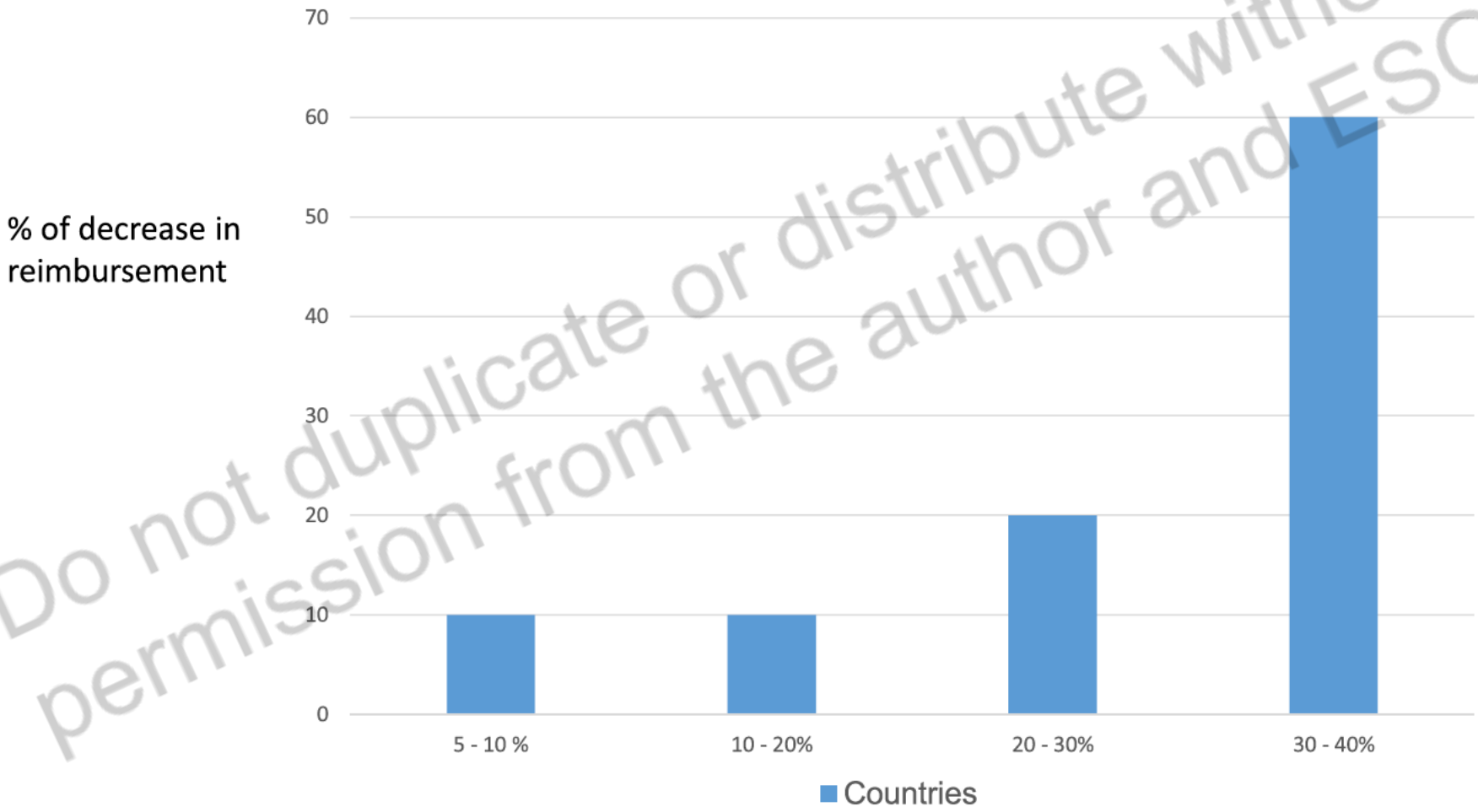
The Financial Impact on Reimbursement of Moderately Hypofractionated Postoperative Radiation Therapy for Breast Cancer: An International Consortium Report

G.N. Marta *, D. Ramiah †, O. Kaidar-Person ‡, A. Kirby §¶, C. Coles ||, R. Jagsi **, T. Hijal ††, G. Sancho ‡‡, Y. Zissiadis §§, J.-P. Pignol ¶¶, A.Y. Ho ||||, S.H.-C. Cheng ***, B.V. Offersen †††‡‡‡, I. Meattini §§§¶¶¶, P. Poortmans ||||||****

Marta GN, et al. Clin Oncol 2021;33:322-30.

Ultra-hypofractionation in BC: *Discussion*

Decrease in reimbursement from hypofractionation



Marta GN, et al. Clin Oncol 2021;33:322-30.

Ultra-hypofractionation in BC: *Discussion*

The Breast 55 (2021) 128–135

Contents lists available at ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

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

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

Ultra-hypofractionation in BC: *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.

Ultra-hypofractionation in BC: *Discussion*

Modelling based on tariffs F centre, public, data 2019:

- ✓Exclusively 50/26/5 ➔ fully 40/15/3
- ✓n = 1000; 2/3 BCT; 1/3 PMRT
- ✓Indication for a boost with BCS 100% (16/8/1.5) ➔ 40% (10/5/1)

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

Ultra-hypofractionation in BC: *Discussion*

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- ✓n = 1000; 2/3 BCT; 1/3 PMRT
- ✓Indication for a boost with BCS 100% (16/8/1.5) ➔ 40% (10/5/1)

	Historical	# fractions/treatment	# fractions total	euro	Conventional HF & less boost	# fractions/treatment	# fractions total	euro
Preparation	1000			1028000	1000			1028000
Patients BCT boost (8 for CF; 5 for HF)	667	33	22011	4094046	267	20	5340	993240
Patients BCT no boost	0	25	0	0	400	15	6000	1116000
Patients PMRT	333	25	8325	1548450	333	15	4995	929070
TOTAL fractions	1000		30336	5642496	1000		16335	3038310
TOTAL fractions + preparation				6670496				4066310

Estimated loss for the hospital:

-2.6M€ (-39%)

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

Ultra-hypofractionation in BC: *Discussion*

Modelling based on tariffs F centre, public, data 2019:

- ✓Exclusively 50/26/5 ➔ fully 40/15/3 ➔ 26/5/1 ± boost 10/5/1
- ✓n = 1000; 2/3 BCT; 1/3 PMRT; 1/2 breast/CW only & 1/2 with LN
- ✓Indication for a boost with BCS 100% (16/8/1.5) ➔ 40% (10/5/1)

	HypoF & less boost	# fractions/treatment	# fractions total	euro	Difference vs historical	Difference vs historical (%)	Difference vs conventional HF	Difference vs conventional HF (%)
Preparation	1000			1028000	0	0%	0	0%
Patients BCT boost (8 for CF; 5 for HF)	142	10	1420	264120	-2806926	-69%	-822120	-133%
Patients BCT no boost	125	20	2500	465000				
Patients PMRT	300	5	1500	279000				
TOTAL fractions	100	15	1500	279000				
TOTAL fractions + preparation	58	5	290	53940	-727260	-47%	-107880	-12%
	275	15	4125	767250				
	1000		11335	2108310	-3534186	-63%	-930000	-31%
				3136310	-3534186	-53%	-930000	-23%

Estimated loss for the hospital:

-3.5M€ (-53%) -0.9M€ (-23%)

Modified/extended from Cardoso F, et al. Breast. 2021;55:128-135.

Ultra-hypofractionation in BC: *Discussion*

<u>Influence of reimbursement:</u>

✓Varies from country to country

✓Many countries high-impact

✓This is not only the case for radiation oncology!

➔ unaffordable to apply EBM

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

Ultra-hypofractionation in BC: *Discussion*

Conclusion:

That might be a serious issue!

Ultra-hypofractionation for breast cancer

1. Introduction
2. Basics of radiobiology
3. Evidence
4. Discussion

5. Conclusions

Ultra-hypofractionation in BC: *Conclusions*

Trust in hypofractionation:

- Aim at homogenous dose distributions, independent of the fractionation schedule
- 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…)

Ultra-hypofractionation in BC: *Conclusions*

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Clinical Oncology 33 (2021) e166–e171

Contents lists available at ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

Editorial

Accelerated Adaptation of Ultrahypofractionated Radiation Therapy for Breast Cancer at the Time of the COVID-19 Pandemic

M. Machiels *†, R. Weytjens *†, W. Bauwens *, W. Vingerhoed *, C. Billiet *†, P. Huget *, D. Verellen *†, P. Dirix *†, P. Meijnders *†, P. Poortmans *†, O. Kaidar-Person ‡§¶

Ultra-hypofractionation in BC: *Conclusions*

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Ultra-hypofractionation in BC: *Conclusions*

Trust in hypofractionation:

- Aim at homogenous dose distributions, independent of the fractionation schedule
- 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…)
- Re-irradiation: favour 40/15/3 in view of lacking experience with 26/5/1

Ultra-hypofractionation in BC: *Conclusions*

Trust in hypofractionation for breast/chest wall:

- Aim at homogenous dose distributions, independent of the fractionation schedule
- 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…)
- Re-irradiation: favour 40/15/3 in view of lacking experience with 26/5/1

Importance of target volume definition and contouring, independent of the fractionation!

Ultra-hypofractionation in BC: *Conclusions*

And what with 50/25/5?

- When combined concurrently with radiosensitisers:
  - Superficial recurrences ➔ + hyperthermia
  - SCC ➔ + weekly cDDP (IV, A)
  - TN-LABC in PD on PST ➔ + capecitabine (III, B)
  - BRCA-LABC in PD on PST ➔ + PARPi (III, B)
- And else?

Ultra-hypofractionation in BC: *Conclusions*

And what with 50/25/5?

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Ultra-hypofractionation in BC: *Conclusions*

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  - SCC ➔ + weekly cDDP (IV, A)
  - TN-LABC in PD on PST ➔ + capecitabine (III, B)
  - BRCA-LABC in PD on PST ➔ + PARPi (III, B)

- And else **“historical”**

Ultra-hypofractionation in BC: *Conclusions*

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

Icro Meattini, Carlotta Becherini, Liesbeth Boersma, Orit Kaidar-Person, Gustavo Nader Marta, Angel Montero, Birgitte Vrou Offersen, Marianne C Aznar, Claus Belka, Adrian Murray Brunt, Samantha Dicuonzo, Pierfrancesco Franco, Mechthild Krause, Mairead MacKenzie, Tanja Marinko, Livia Marrazzo, Ivica Ratosa, Astrid Scholten, Elżbieta Senkus, Hilary Stobart, Philip Poortmans, Charlotte E Coles**

Meattini I, et al. Lancet Oncol 2022;23:e21–31.

Ultra-hypofractionation in BC: *Conclusions*

Panel: **Final consensus statements**

1. Whole breast irradiation

a Moderate hypofractionated whole breast irradiation should be offered regardless of age at breast cancer diagnosis, pathological tumour stage, breast cancer biology, surgical margins status, tumour bed boost, breast size, invasive or pre-invasive ductal carcinoma in situ (DCIS) disease, oncoplastic breast conserving surgery, and use of systemic therapy

b Ultrahypofractionated (26 Gy in five fractions) whole breast irradiation can be offered as (1) standard of care or (2) within a randomised controlled trial or prospective registration cohort

2. Chest wall irradiation

a Moderate hypofractionation can be offered for chest wall irradiation without breast reconstruction

b Moderate hypofractionation can be offered for chest wall irradiation regardless of time and type of breast reconstruction

c Ultrahypofractionation (26 Gy in five fractions) for chest wall irradiation without breast reconstruction can be offered as (1) standard of care or (2) within a randomised controlled trial or prospective registration cohort

d Ultrahypofractionation (26 Gy in five fractions) for chest wall irradiation after breast reconstruction can be offered within a randomised controlled trial or prospective registration cohort

3. Nodal irradiation

a Moderate hypofractionation should be offered for nodal irradiation

b Ultrahypofractionation (26 Gy in five fractions) should not be offered for nodal irradiation until ongoing trials results are reported

4. Partial breast irradiation–patient selection for external beam radiotherapy

Low risk-features suitable for partial breast irradiation are: luminal-like subtypes small tumour (≤3 cm), absence of lymph vascular space invasion, non-lobular invasive carcinoma, tumour grade 1–2, low-to-intermediate grade DCIS (sized ≤2·5 cm with clear surgical margins ≥3 mm), age at diagnosis 50 years or more, unicentric or unifocal lesion, clear surgical margins (>2 mm), node negative (including isolated tumour cells), and no use of primary systemic therapy and neoadjuvant chemotherapy

5. Partial breast irradiation–dose and fractionation

a Moderate hypofractionation (40 Gy in 15 fractions) and ultrahypofractionation (26–30 Gy in five fractions) represent acceptable schedules for external beam partial breast irradiation

b Twice a day external beam partial breast irradiation dose and fractionations similar to those used in the RAPID trial should not be offered

DCIS=ductal carcinoma in situ.

Meattini I, et al. Lancet Oncol 2022;23:e21–31.

Ultra-hypofractionation in BC: *Conclusions*

Bullet points:

- The level of evidence in favour of ultra-HF is sufficient for practice changing
- No clear contra-indications exist for ultra-HF for breast; chest wall and partial breast RT
- Reasons for not applying ultra-HF are not directly related to fractionation/radiobiology
- Research in ultra-HF now has to focus on items such as immediate breast reconstruction, SIB, preoperative RT, combination with other treatments; nodal RT

Orit Kaidar-Person · Icro Meattini · Philip Poortmans *Editors*

Breast Cancer Radiation Therapy

A Practical Guide for Technical Applications

The book provides, in a comprehensive yet concise way, essential information to improve the knowledge and skills of all healthcare providers involved in the treatment of patients with breast cancer. The content does not focus on general information that is widely available via different sources, but on technical aspects – "hands-on" daily practices and principles of radiation oncology that are not included in other books. Drawing on information taught in courses at e.g. the ESTRO School, as well as the authors' broad clinical experience, the respective contributions reflect and share the expertise of leading experts in breast cancer radiation therapy, supported by sound data and evidence. Each chapter includes a short introduction summarizing the evidence in the literature and "pearls" (a short bullet-point summary), and is enriched by tables, figures and illustrations to provide a concise, easy-to-follow and appealing overview.

The book, containing also useful electronic supplementary material, will be of interest to a wide range of readers, including radiation oncologists, radiation technicians, medical physicists, and others involved in breast cancer care.

ISBN 978-3-030-91169-0

▸ springer.com

Kaidar-Person · Meattini · Poortmans *Eds.*

Breast Cancer Radiation Therapy

Breast Cancer Radiation Therapy

A Practical Guide for Technical Applications

Orit Kaidar-Person
Icro Meattini
Philip Poortmans
Editors

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