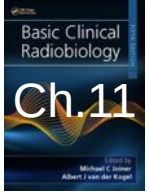
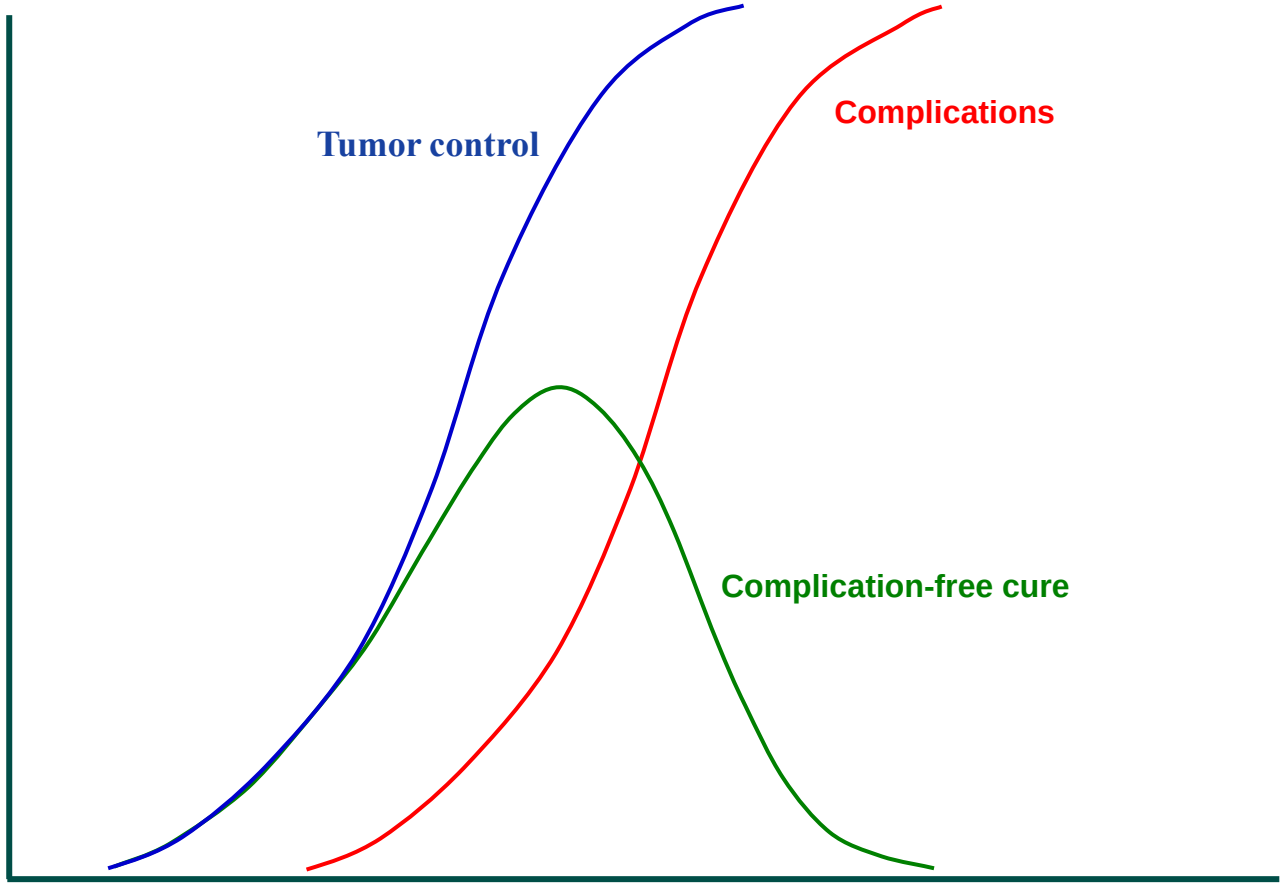


Hyper-, hypofractionation and accelerated radiotherapy

Prof. Vincent GREGOIRE, MD, PhD, FRCR
Centre Léon Bérard, Lyon, France

The paradigm of radiotherapy



Conventional fractionation

1.8 – 2.0 Gy per fraction, 5 fractions per week

IIIII IIIII IIIII IIIII IIIII IIIII IIIII

	Example	Dose (Gy)	Tumor control (%)
Sensitive	Seminoma, Lymphoma	≤ 45	≥ 90
Intermediate	SCC, Adeno-Ca	50	≥ 90 (subclinical)
		60	~ 85 (Ø 1 cm)
		70	~ 70 (Ø 3 cm)
			~ 30 (Ø 5 cm)
Resistant	Glioblastoma	≥ 60	none?
	Melanoma	≥ 60	none?

Prototypes of modified fractionation

- Hyperfractionation (HF)
- Accelerated fractionation (AF)
- (Hybrid schedules)
- Hypofractionation

Prototypes of modified fractionation

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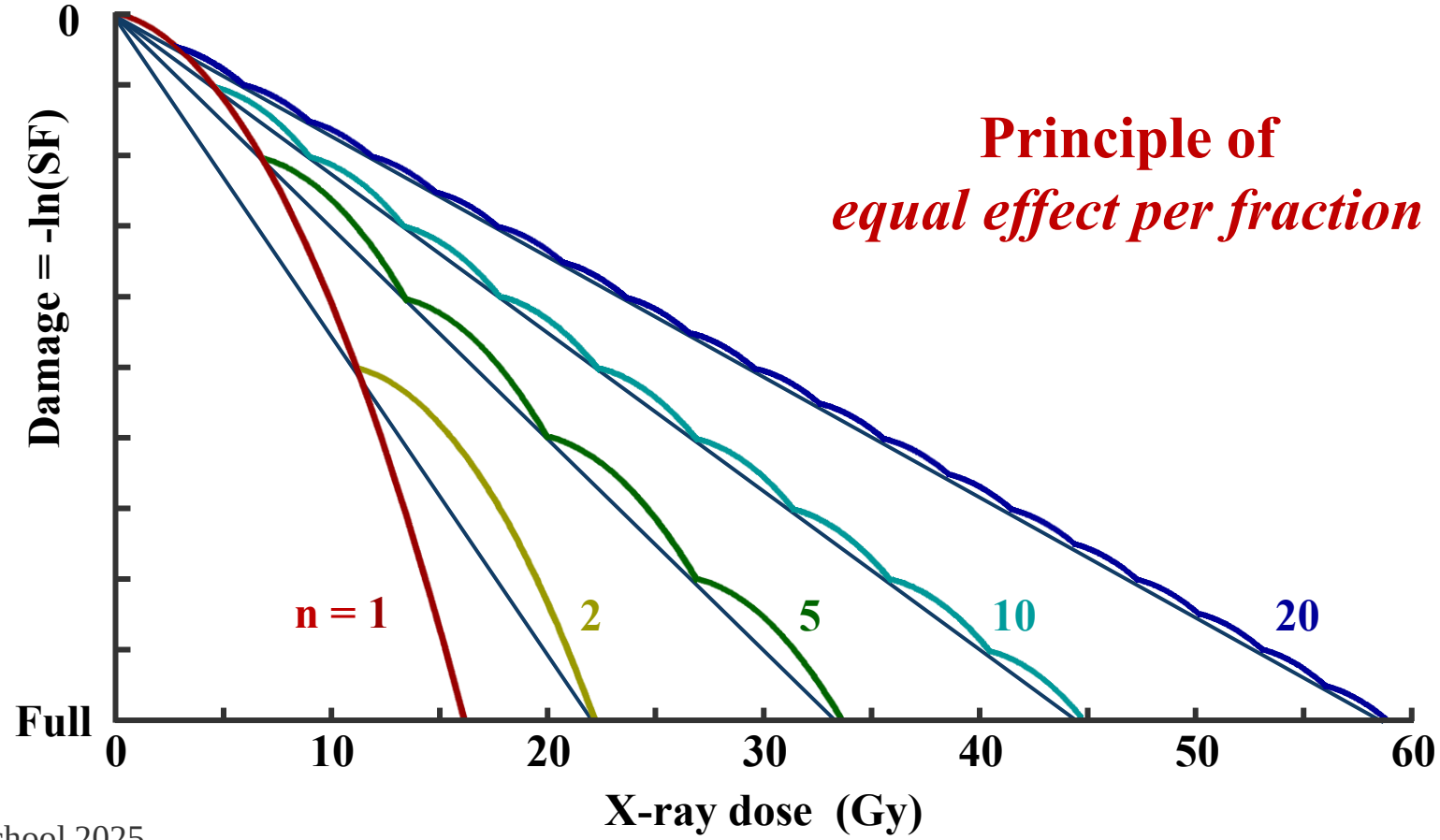
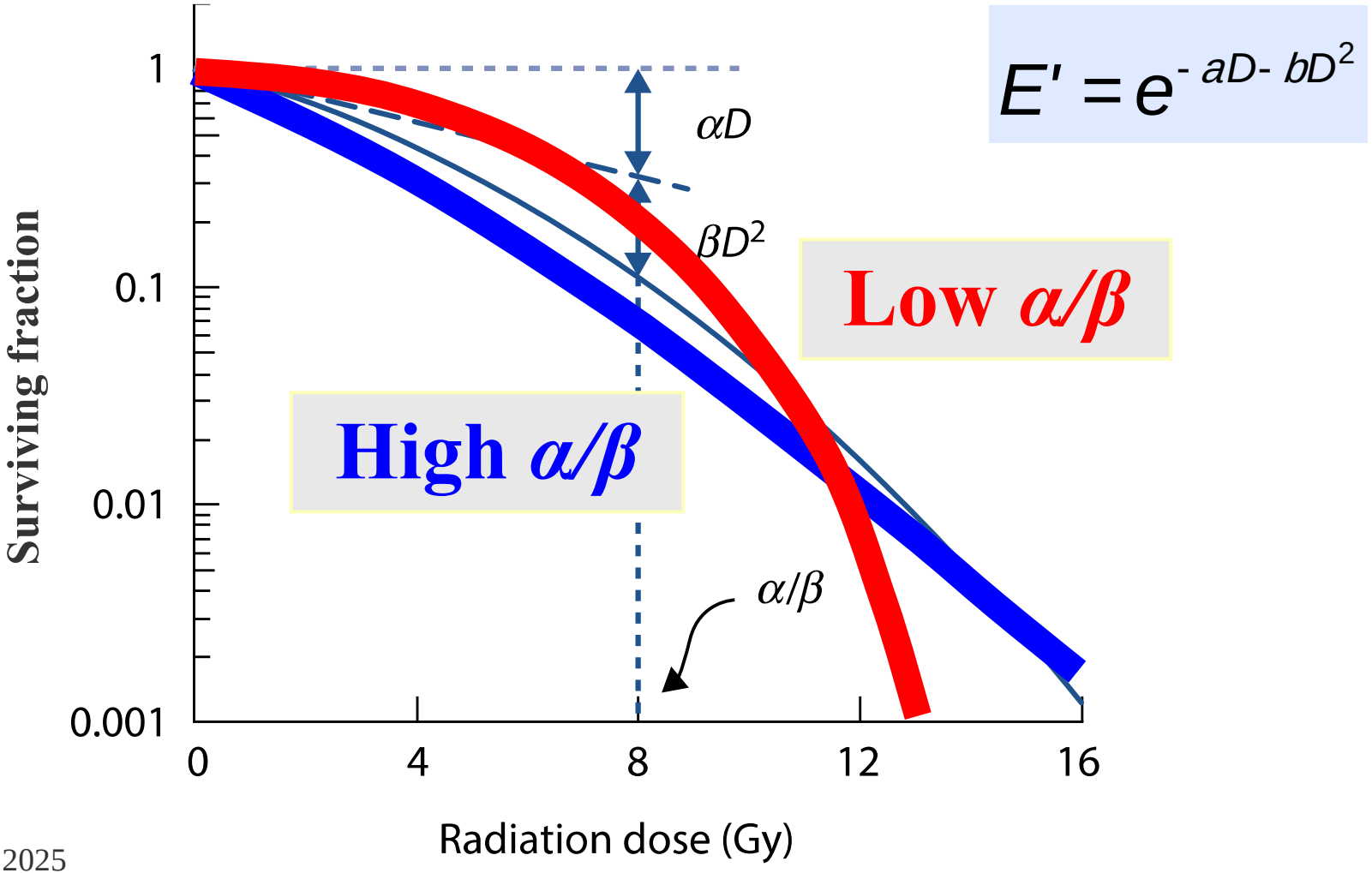
Less effect per gray at low doses per fraction

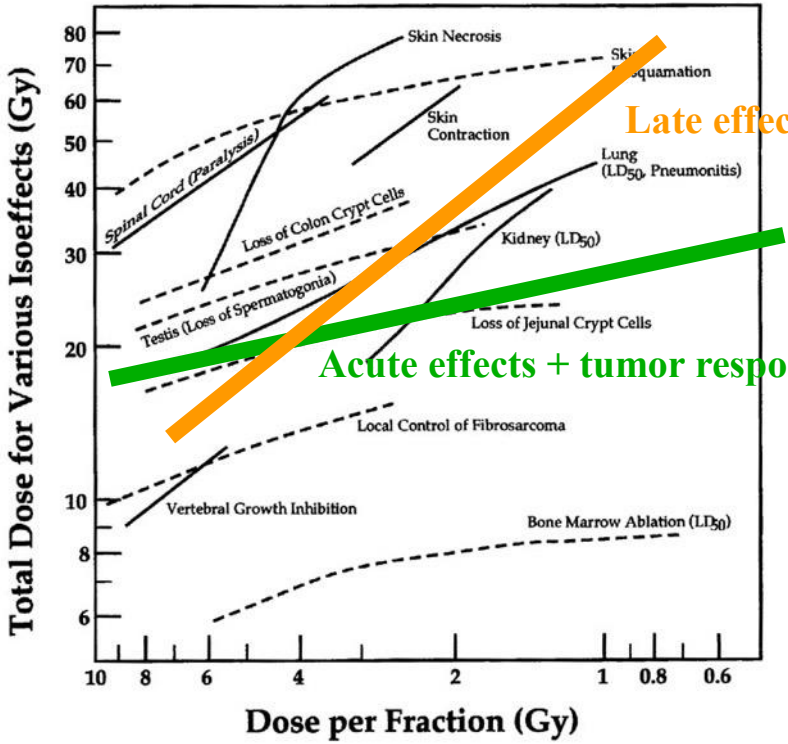



$E' = e^{-aD - bD^2}$
Surviving fraction
1
0.1
0.01
0.001
0
4
8
12
16
Radiation dose (Gy)
αD
βD²
α/β
Low α/β
High α/β

Fractionation sensitivity

"Typical" dose per fraction

- 1.8-2 Gy for standard fractionation
- 1.1-1.3 Gy for hyper-fractionation



Withers et al, 1983

Hyperfractionation (HF)

reduced dose per fraction (< 1.8 Gy)

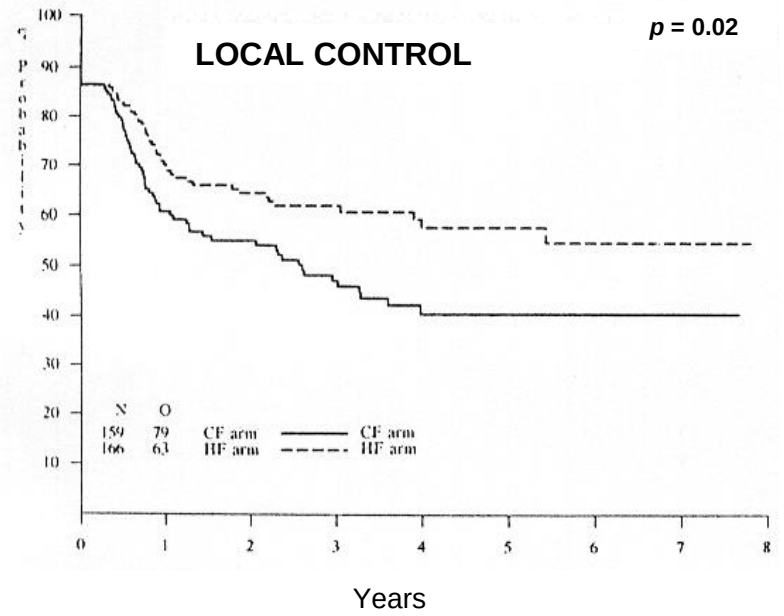
Expectations (dose-escalated HF):

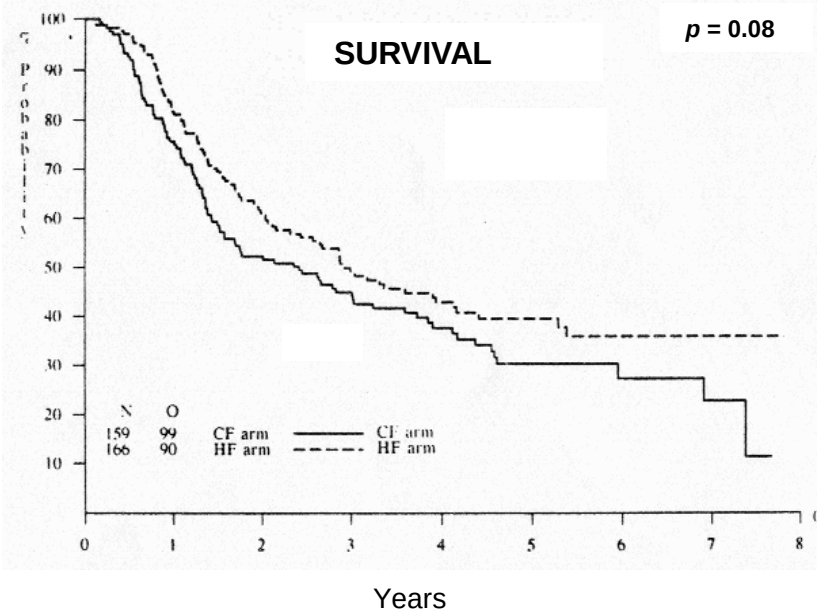
- Increased tumor control
- More severe early reactions
- Unchanged or less late reactions

EORTC Hyperfractionation trial in oropharynx cancer (N = 356)

Oropharyngeal Ca T2-3, N0-1

80.5 Gy - 70 fx - 7 wks vs 70 Gy - 35-40 fx - 7-8 wks





Horiot 1992

Toxicity of RT in HNSCC

Early effect in accelerated or hyperfrationation RxTh

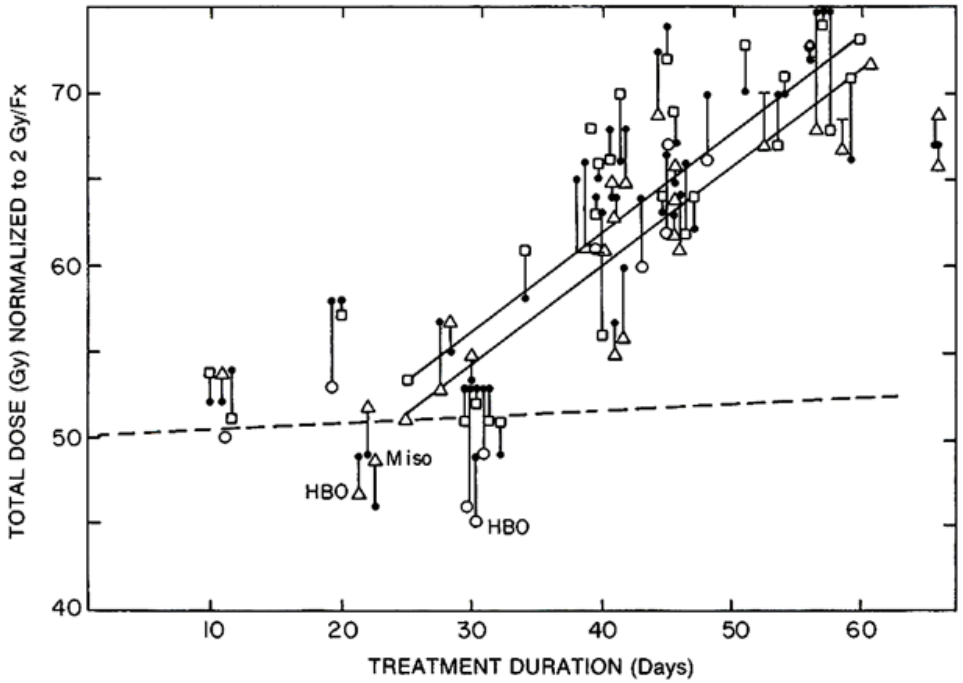
Author	Regimen	Grade 3-4 mucositis	
		Control	Experimental
Horiot (n=356)	HF	49%	67%
Horiot (n=512)	Acc. fract. + split	50%	67%
Dische (n=918)	CHART	43%	73%
Fu (n=536)	Acc. frac (CB)	25%	46%
Fu (n=542)	Acc. fract. + split	25%	41%
Fu (n=507)	HF	25%	42%
Skladowski (n=99)	Acc. Fract.	26%	56%

Dische, 1997
Horiot, 1992
Fu, 2000
Skladowski, 2000

Prototypes of modified fractionation

- Hyperfractionation (HF)
- Accelerated fractionation (AF)
- (Hybrid schedules)
- Hypofractionation

Influence of overall treatment time on HNSCC local control



Withers et al, 1988

Tissue proliferation and recovered dose D_{prolif}

Tissue	Endpoint	D_{prolif} (Gy day^{-1})	95% CL (Gy day^{-1})	T_k[b] (days)	Source
Early reactions					
Skin	Erythema	0.12	[−0.12; 0.22]	<12	Bentzen et al. (2001)
Mucosa	Mucositis	0.8	[0.7; 1.1]	<12	Bentzen et al. (2001)
Lung	Pneumonitis	0.54	[0.13; 0.95]		Bentzen et al. (2000)[a]
Tumours					
Head and neck					
Larynx		0.74	[0.30; 1.2]		Robertson et al. (1998)
Tonsils		0.73		30	Withers et al. (1995)
Various		0.8	[0.5; 1.1]	21	Robers et al. (1994)
Various		0.64	[0.42; 0.86]		Hendry et al. (1996)[a]
Breast		0.60	[0.10; 1.18]		Haviland et al. (2016)
Oesophagus		0.59	[0.18; 0.99]		Geh et al. (2005)
Non-small cell lung cancer		0.45	N/A		Koukourakis et al. (1996)
Medulloblastoma		0.52	[0.29; 0.75]	0 or 21	Hinata et al. (2001)
Prostate		0.24	[0.03; 0.44]	52	Thames et al. (2010)

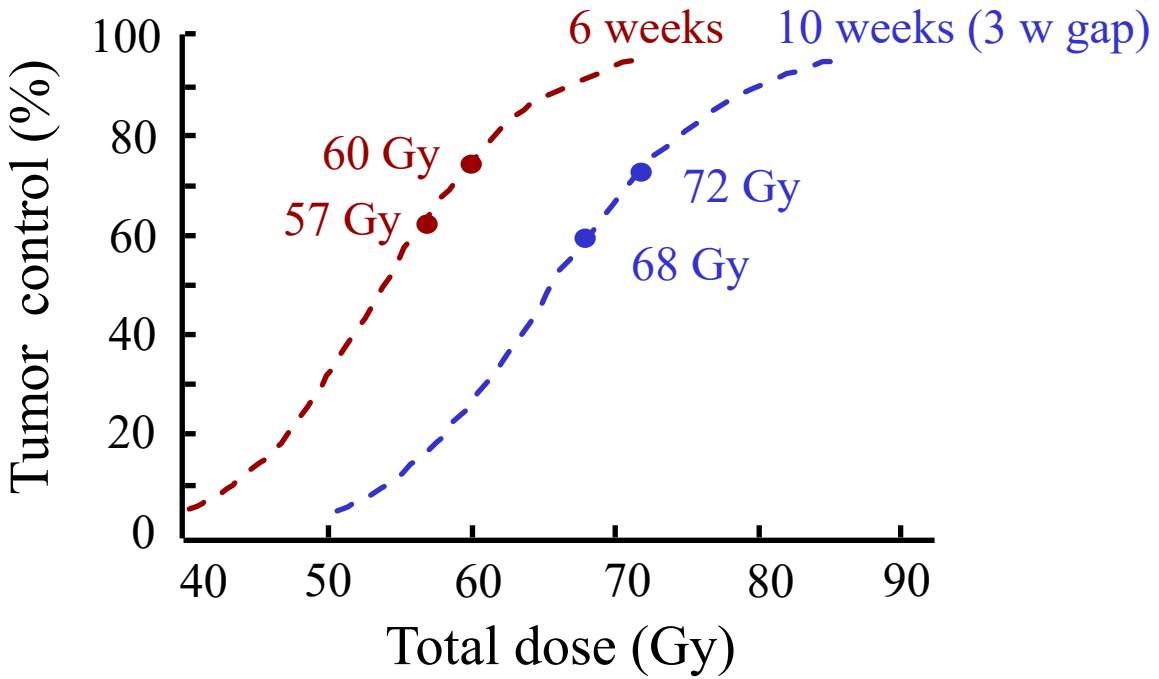
Note: Reference details are available from Søren Bentzen.

[a] Pooled estimate from a review of studies in the literature.

[b] T_k is the assumed time for the onset of accelerated proliferation.

Bentzen et al, 2002

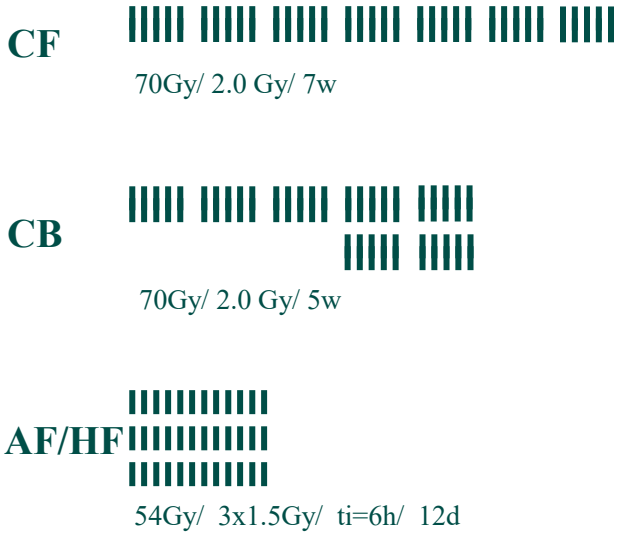
Influence of overall treatment time on HNSCC local control



Overgaard et al, 1988

Accelerated fractionation (AF)

Shortened overall treatment time, dose per week > 10 Gy



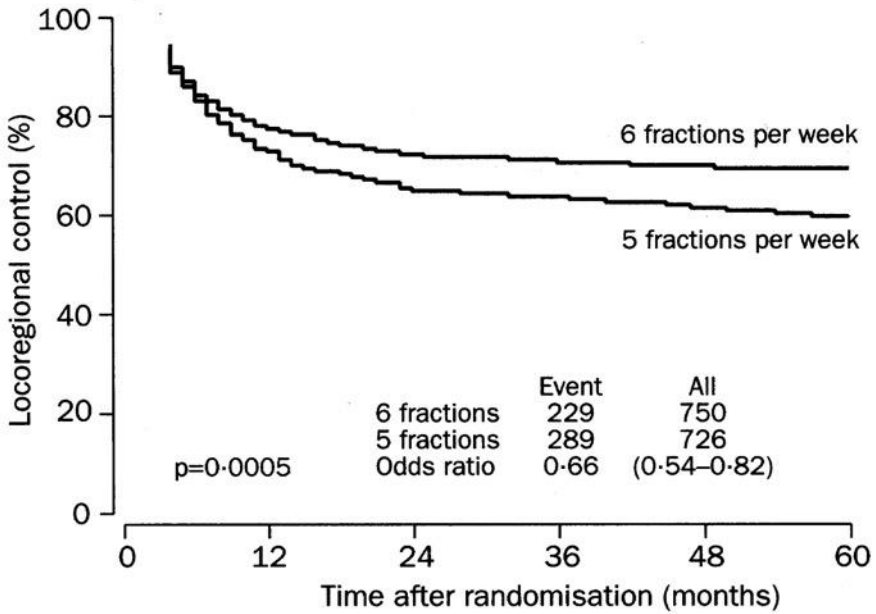
Expectations:

- Increased tumor control
- Increased early reactions
- Unchanged or decreased late damage (AF/HF and/or reduced total dose)

DAHANCA 6&7 - H&N

SCC - stage II-IV (n=1476)

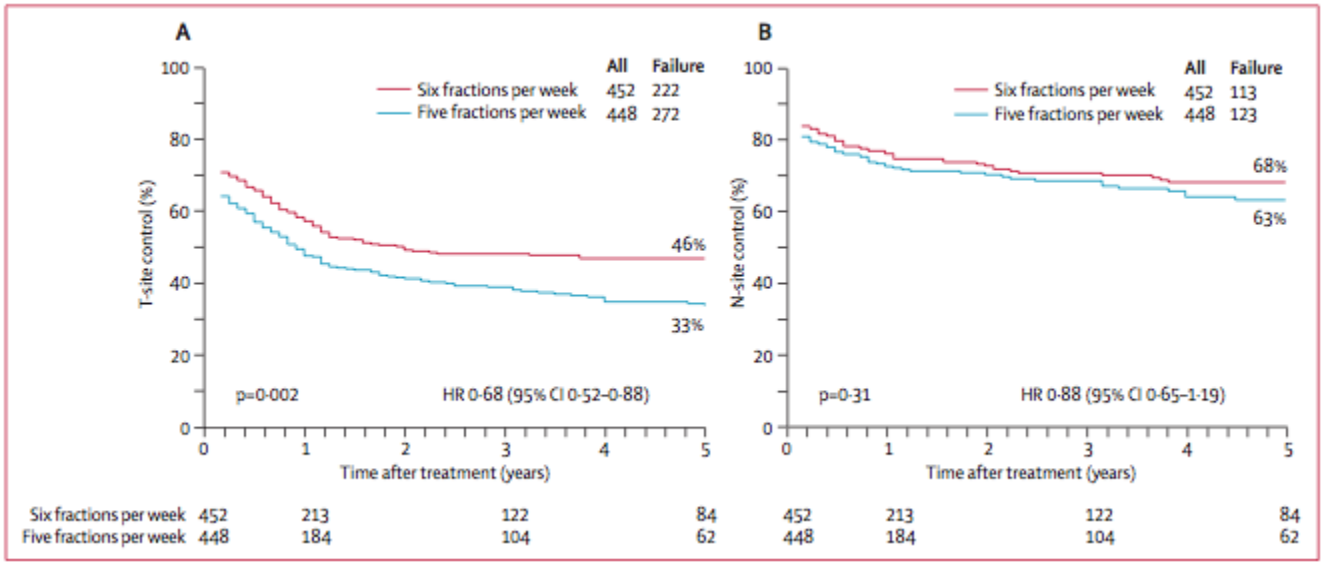
64-68 Gy/ 2.0 Gy/ 6.5w → 64-68 Gy/ 2.0 Gy/ 5.5w



Overgaard et al. Lancet, 2003

Five versus six fractions of radiotherapy per week for squamous-cell carcinoma of the head and neck (IAEA-ACC study): a randomized, multicentre trial

66-70 Gy/ 2.0 Gy/ 6.5-7.0 w → 66-70 Gy/ 2.0 Gy/ 5.5-6.0 w



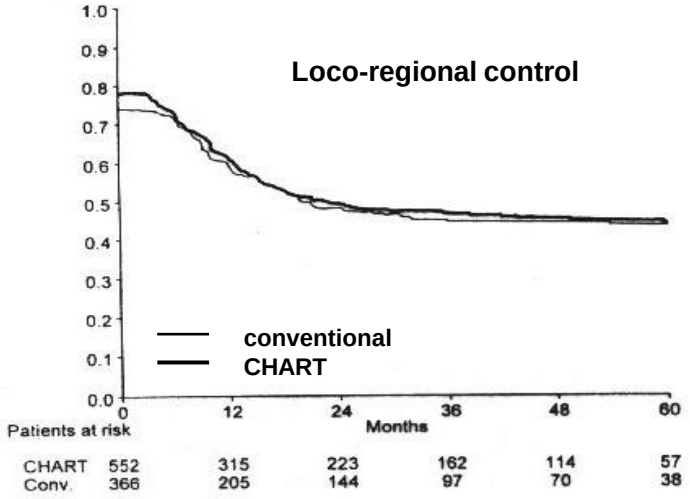
Overgaard et al. Lancet Oncol, 2010

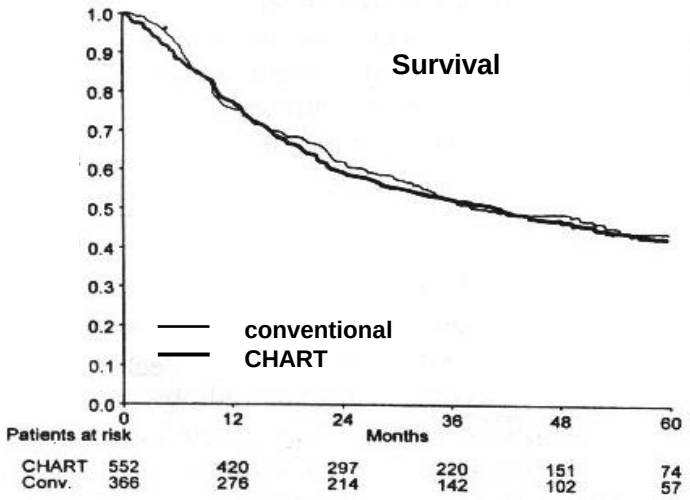
CHART - Head & Neck (MRC, UK)

SCC , >T1 N0 M0, WHO 0-1 (n=918)

66 Gy/ 2.0 Gy/ 6.5 w (n=366)

54 Gy/ 3 x 1.5 Gy/ ti 6 h/ 12 d (n=552)





Dische et al., *Radiother. Oncol.* 44: 123-136, 1997

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Dishes, 1997
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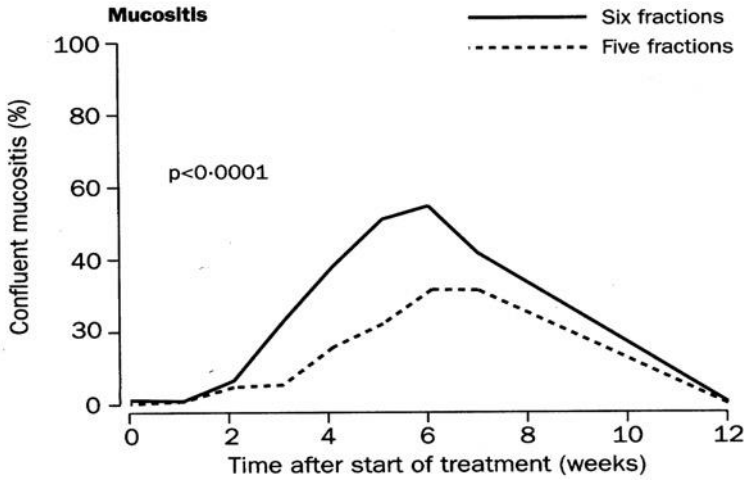

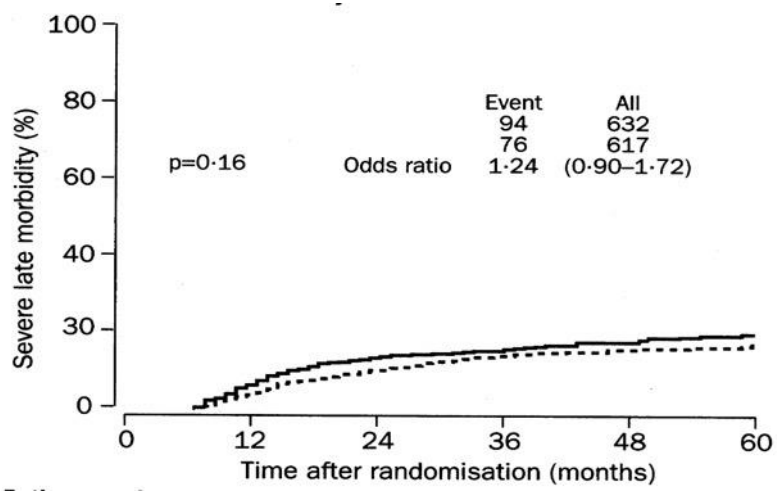

Overgaard et al. Lancet, 2003

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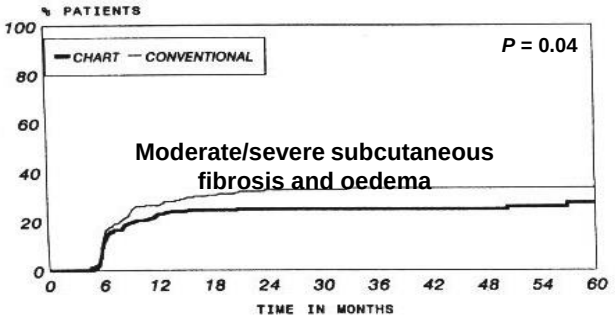
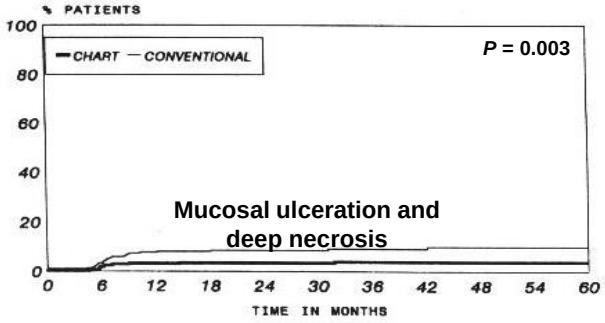
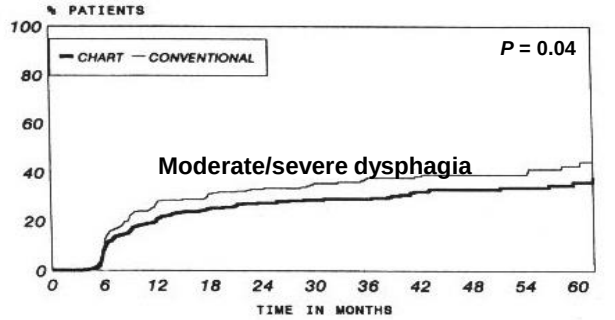
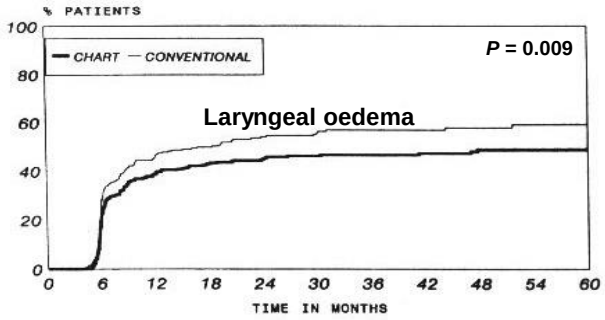




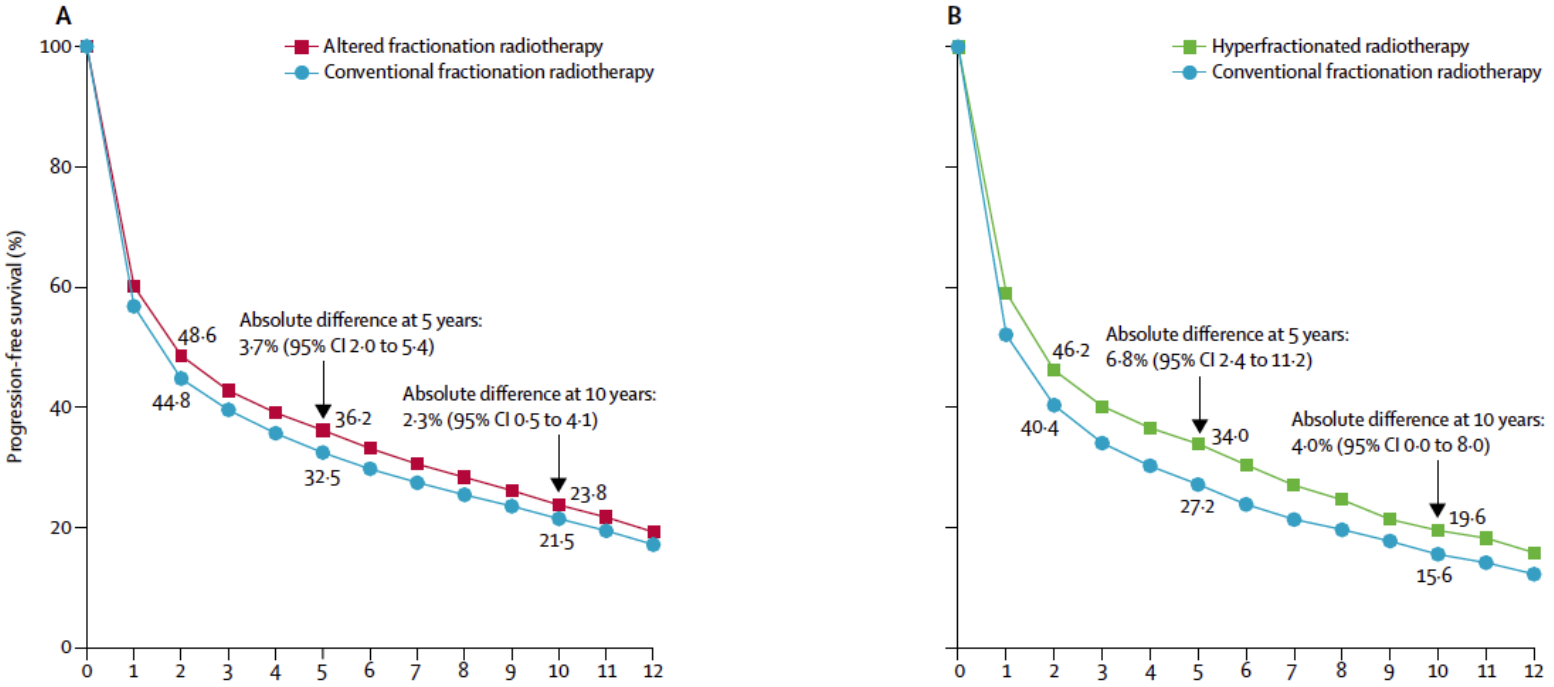




Dische et al., *Radiother. Oncol.* 44: 123-136, 1997

Meta-analysis on altered fractionation HNSCC

Randomized trials 1970-2010 (no postop RT)
33 trials included (11423 patients, individual data)



Lacas et al., 2017

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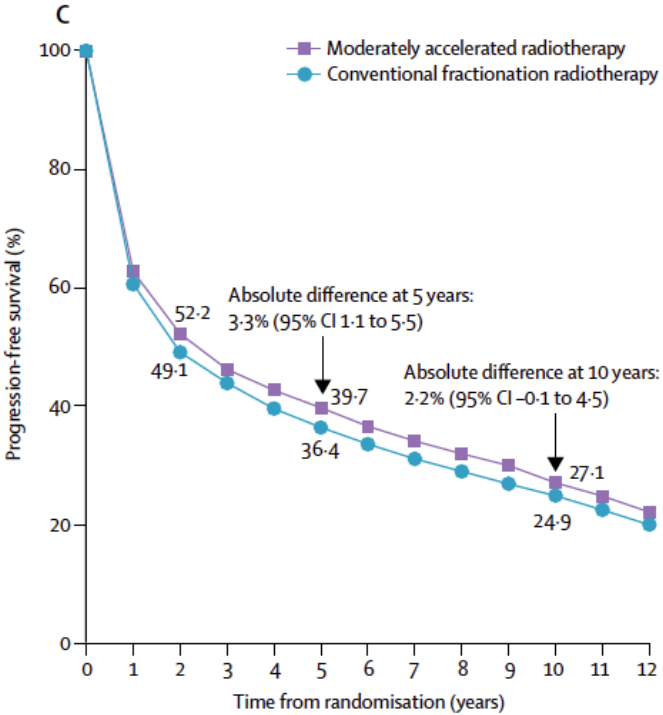
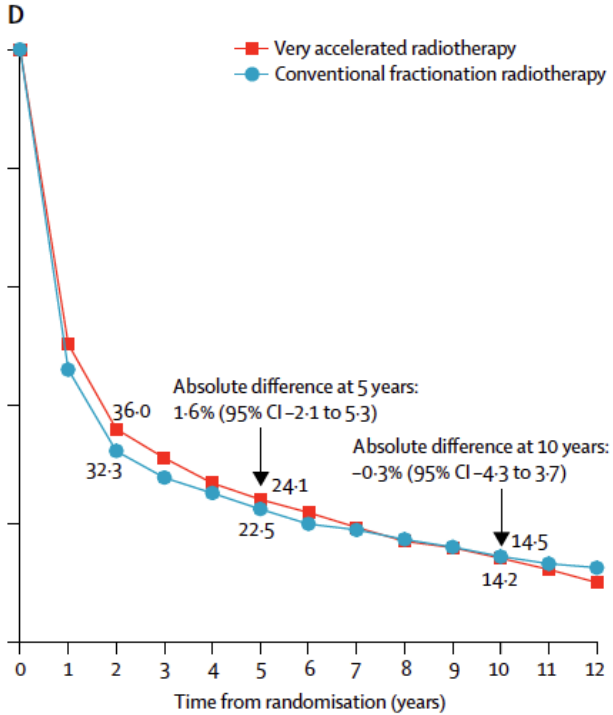


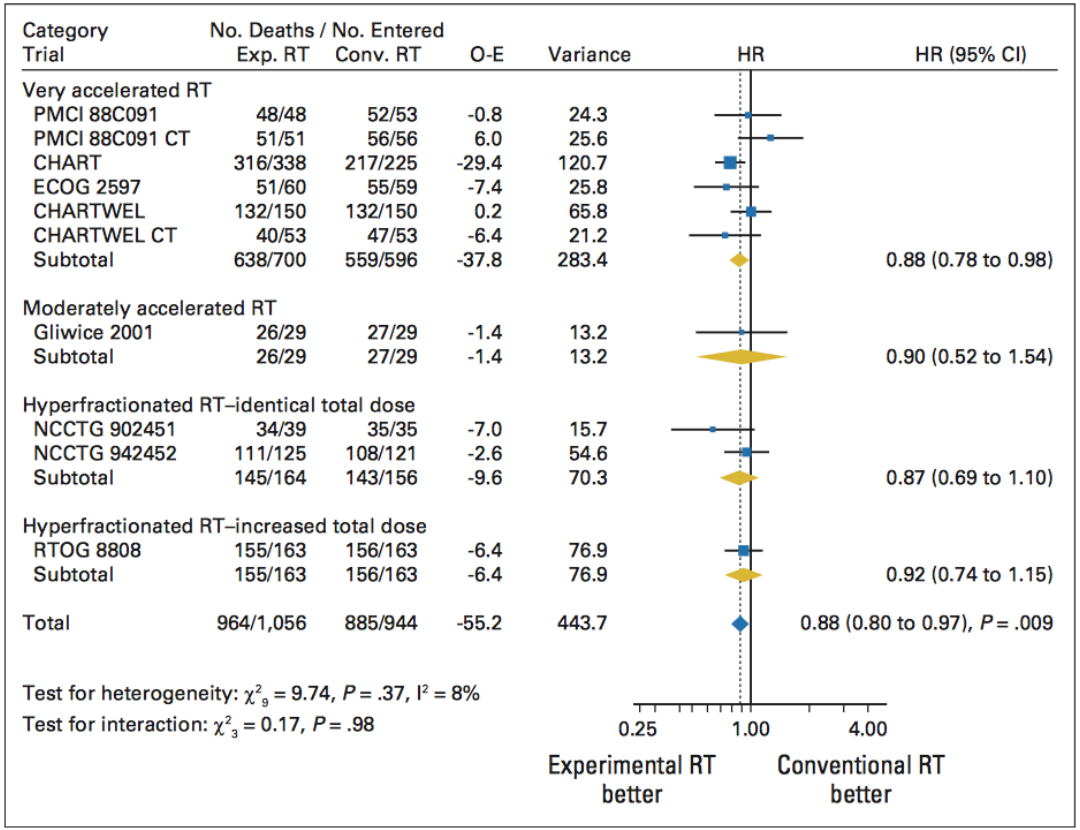


Lacas et al., 2017

Meta-analysis on altered fractionation in loc. adv. NSCLC

Randomized trials 1970-2005 (no postop RT)

10 trials included (2000 patients, individual data)



Mauguen et al., 2012

Summary…

- In case of increase in OTT,
  - for HNSCC, NSCLC, oesophageal carcinoma: compensation by accelerating the treatment
  - for cervix and anal canal carcinoma: data exist on the adverse effect of prolongation of OTT, thus compensation
  - for brain, prostate and breast carcinoma: no compensation
  - for palliative treatment : no compensation
- Keep in mind that radiotherapy is a very cost-effective treatment modality, providing it is properly delivered

Prototypes of modified fractionation

- Hyperfractionation (HF)
- Accelerated fractionation (AF)
- (Hybrid schedules)
- Hypofractionation

Hypofractionation (HypoF)

Increased dose per fraction (> 2.0 Gy)

CF

60Gy/ 2.0 Gy/ 6w

Conventional

m HypoF

75Gy/ 2.5 Gy/ 5w

Moderate Hypo F (curative)

HypoF

67.5 Gy/13.5 Gy/ 2w

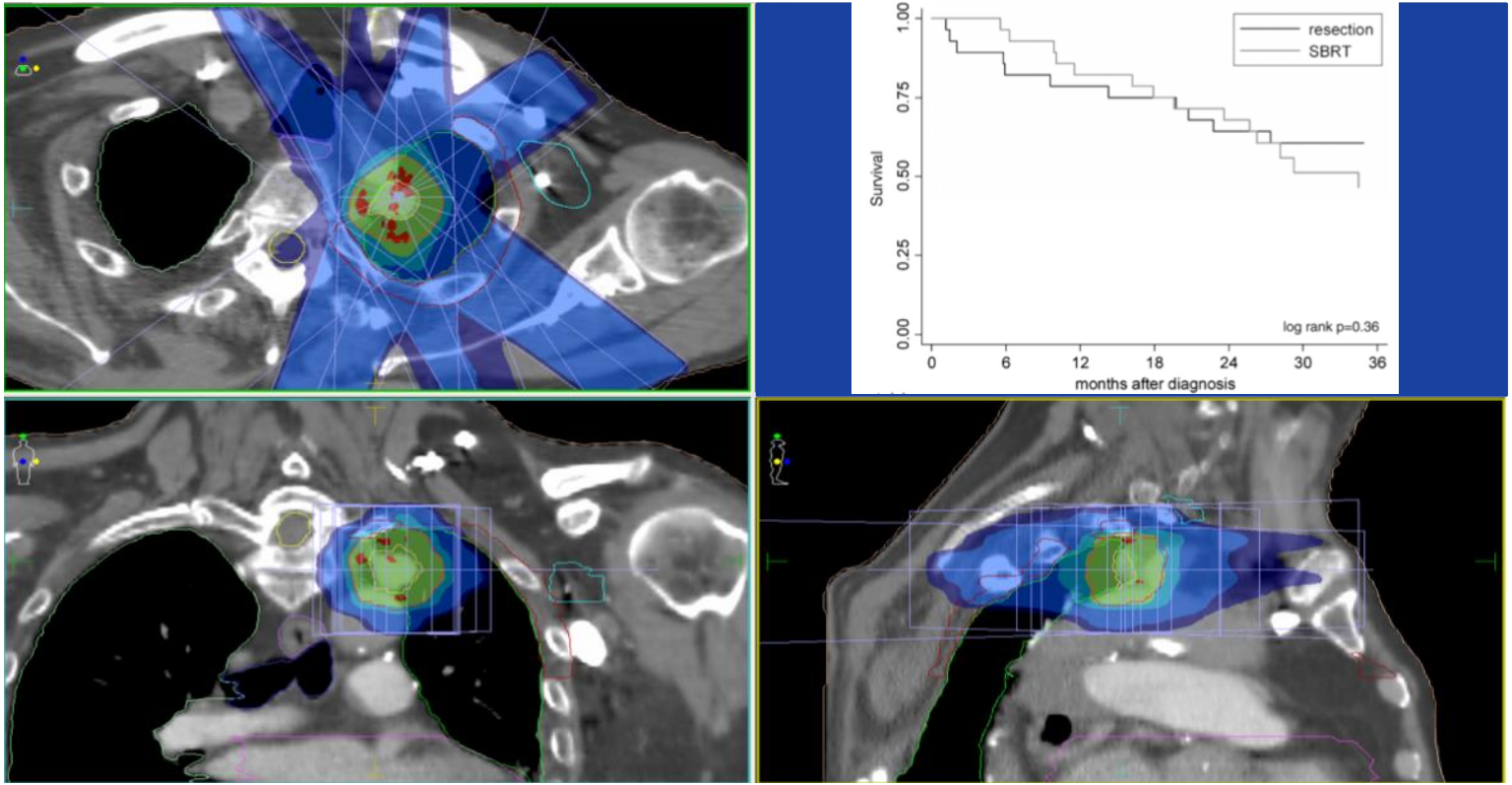
Curative RT

HypoF

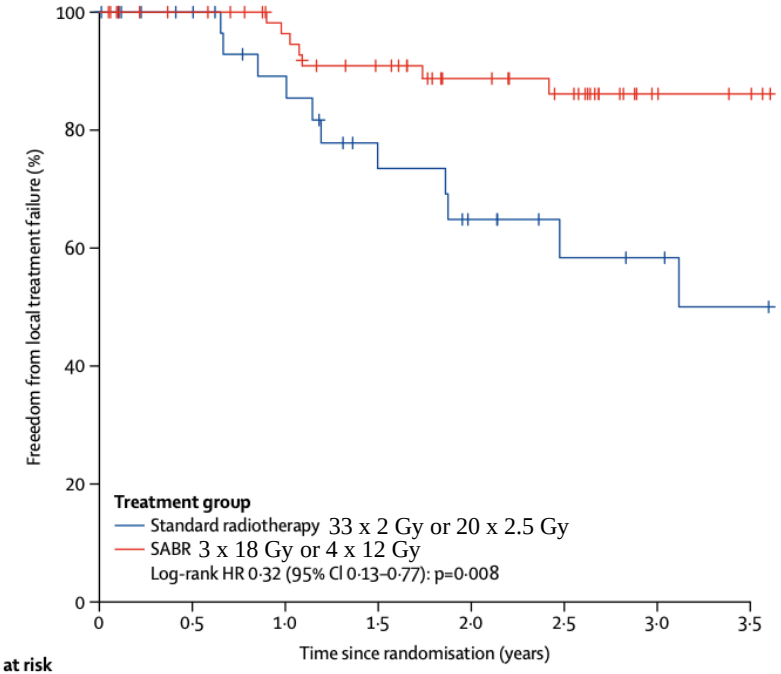
SD 8 Gy 30 Gy/ 3.0 Gy/ 2w

Palliative RT

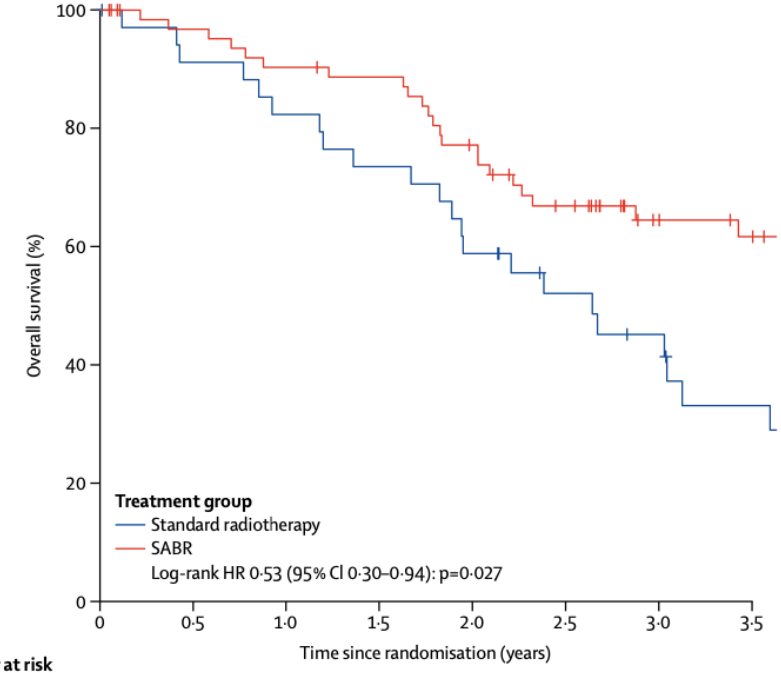
IMRT/SBRT for NSCLC



Stereotactic ablative radiotherapy versus standard radiotherapy in stage 1 non-small-cell lung cancer (TROG 09.02 CHISEL): a phase 3, open-label, randomised controlled trial



Number at risk (number censored)								
Standard radiotherapy	35 (0)	30 (5)	24 (8)	17 (11)	13 (13)	9 (16)	8 (17)	6 (18)
SABR	66 (0)	60 (6)	53 (11)	46 (15)	37 (23)	32 (27)	19 (40)	17 (42)



Number at risk (number censored)								
Standard radiotherapy	35 (0)	31 (1)	28 (1)	25 (1)	20 (1)	15 (4)	12 (5)	8 (6)
SABR	66 (0)	60 (4)	56 (4)	54 (5)	46 (6)	37 (9)	25 (20)	22 (22)

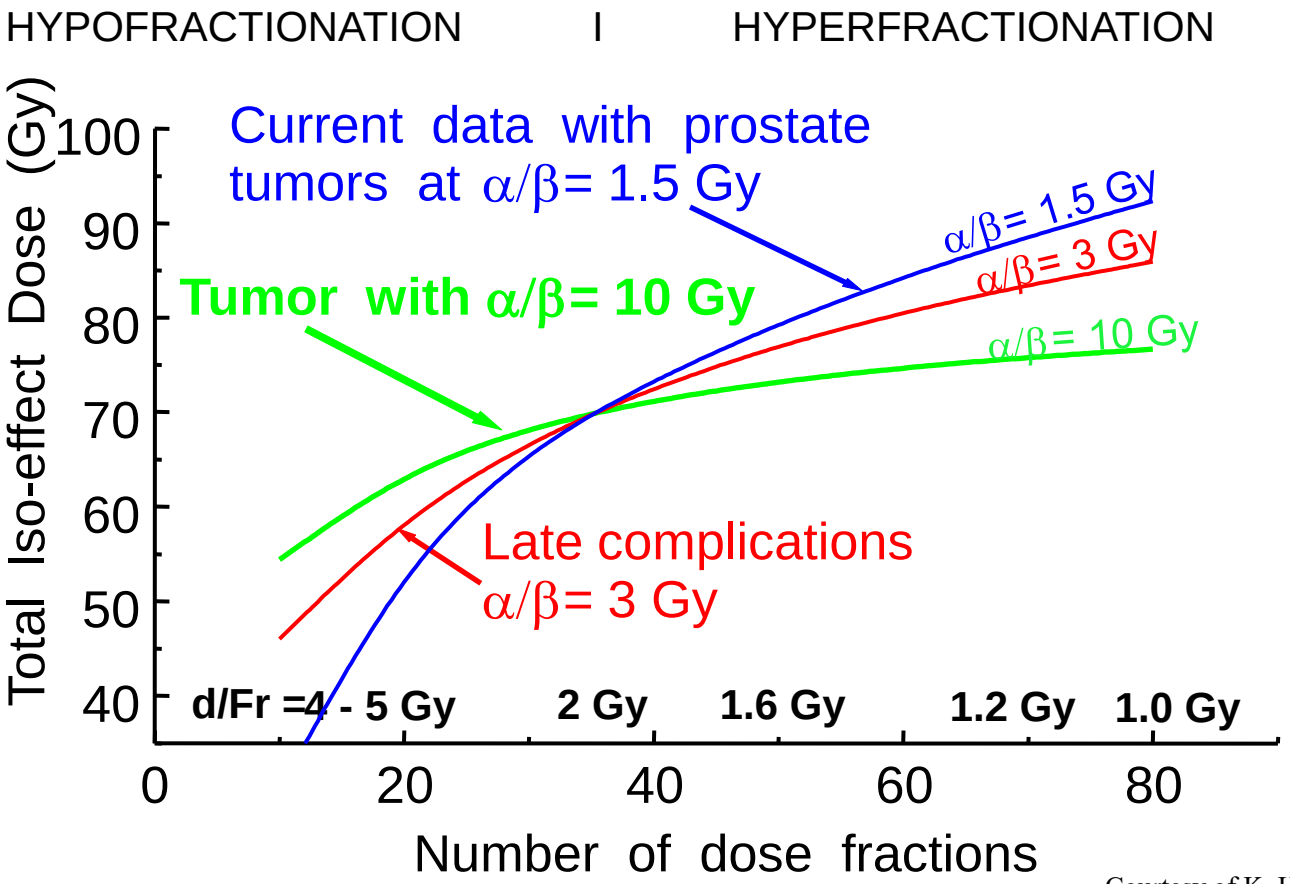
Ball et al., Lancet Oncol., 2019

SBRT – early/late toxicity

- Severe toxicity rate < 5%
- Pneumonia ≥ G3 in 0-5%
- Chest wall toxicity in peripherally located tumors: wall pain, fibrosis, rib fracture in 10%
- Plexopathy in upper tumors
- Severe toxicities (fatale hemoptysis, fistulae…) in centrally-located with 3 fraction schemes

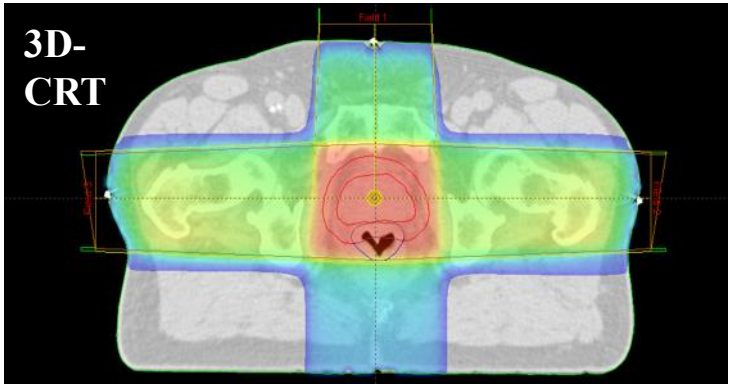
Hurkmans et al, Radiation Oncology 2009

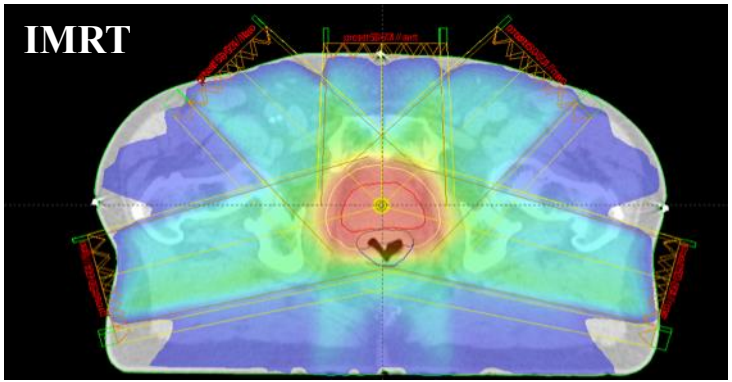
Radiobiological and clinical issues in IMRT for prostate C

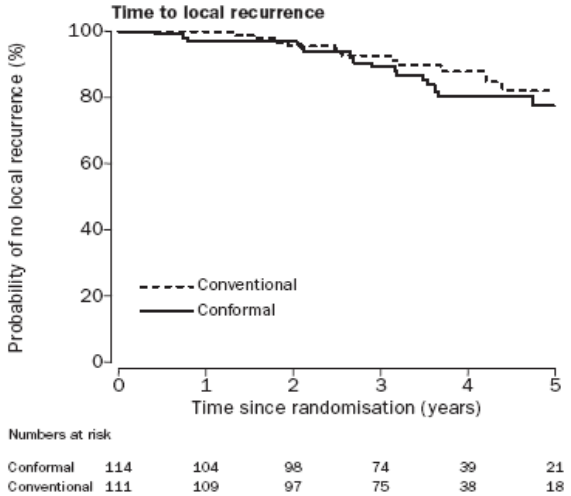


Courtesy of K. Haustermans

Conformal irradiation for prostate tumors







≥ grade 2 proctitis: 15% >< 5% (p= 0.01)

Dearlaney, 1999

Hypofractionation in prostate Ca

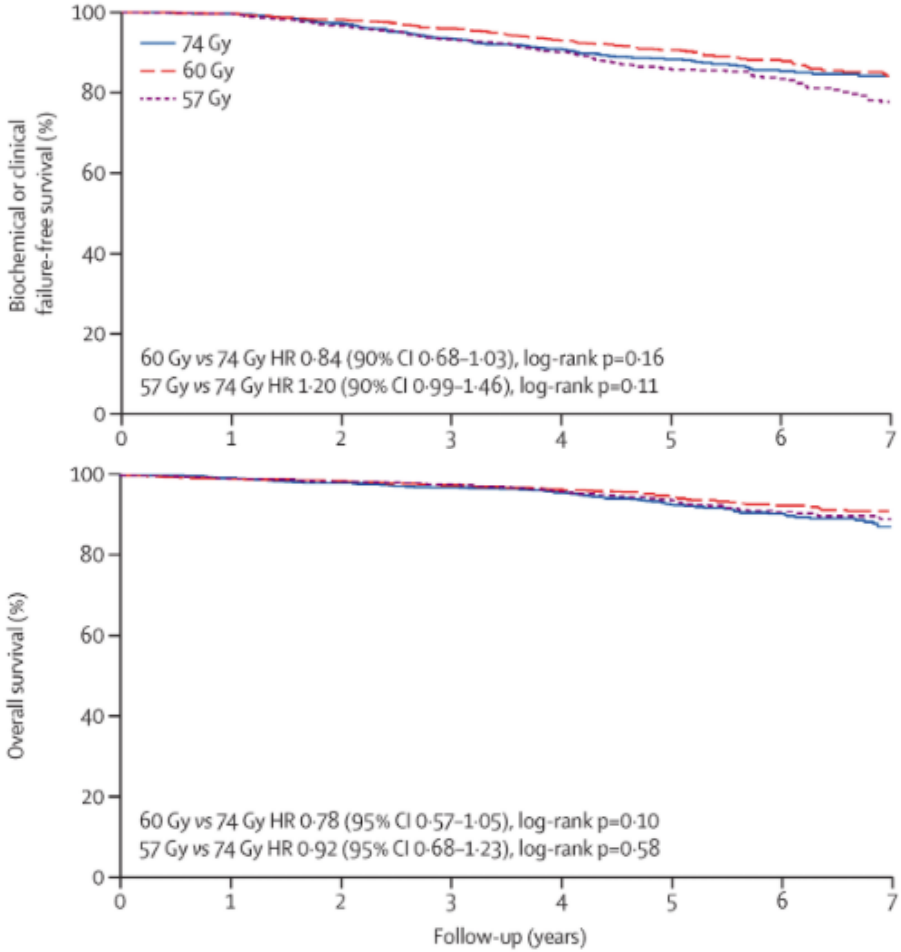
Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: 5-year outcomes of the randomised, non-inferiority, phase 3 CHHiP trial

David Dearnaley, Isabel Syndikus, Helen Mossop, Vincent Khoo, Alison Birtle, David Bloomfield, John Graham, Peter Kirkbride, John Logue, Zafar Malik, Julian Money-Kyrle, Joe M O'Sullivan, Miguel Panades, Chris Parker, Helen Patterson, Christopher Scrase, John Staffurth, Andrew Stockdale, Jean Tremlett, Margaret Bidmead, Helen Mayles, Olivia Naismith, Chris South, Annie Gao, Clare Cruickshank, Shama Hassan, Julia Pugh, Clare Griffin, Emma Hall, on behalf of the CHHiP Investigators*

74 Gy (37 x 2 Gy) in 7.4 w >< 60 Gy (20 x 3.0 Gy) in 4w >< 57 Gy (19 x 3 Gy) in 3.8w

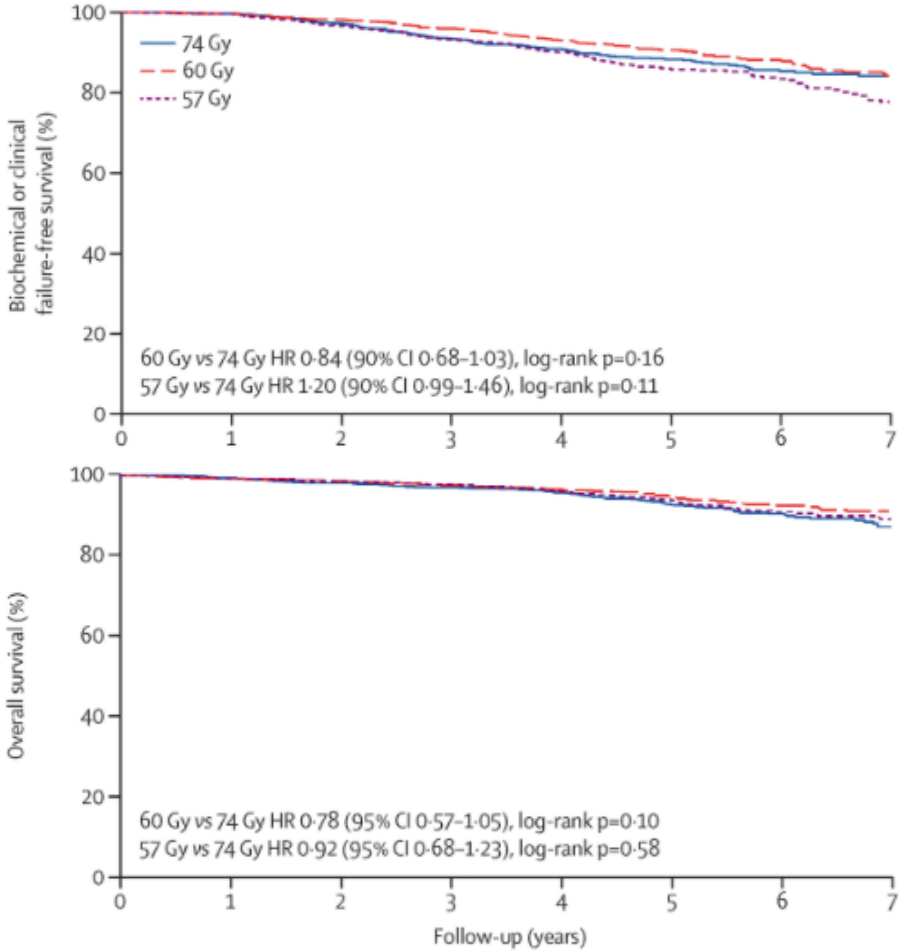
Dearnaley et al., Lancet Oncology, 2016

Hypofractionation in prostate Ca



Dearnaley et al., Lancet Oncology, 2016

Hypofractionation in prostate Ca

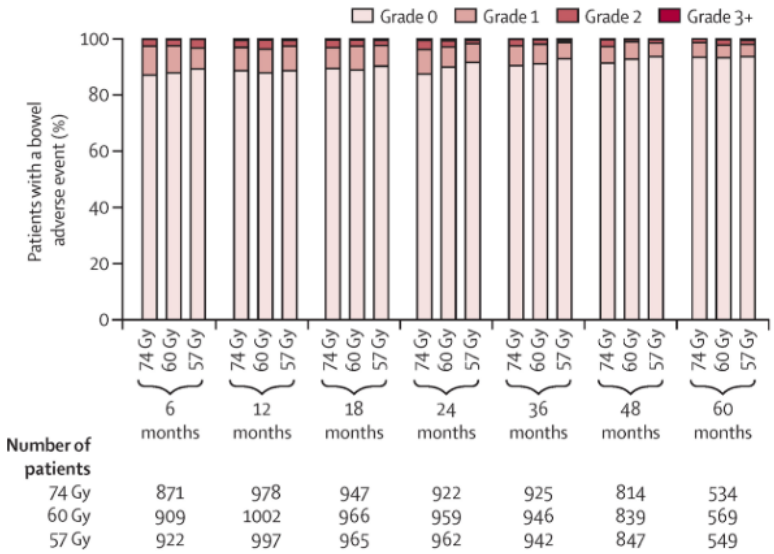


α/β: 1.8 Gy

Dearnaley et al., Lancet Oncology, 2016

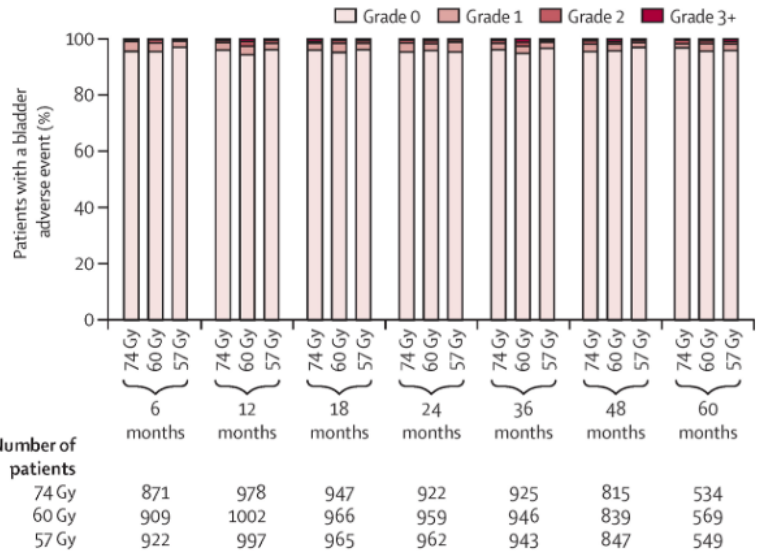
Hypofractionation in prostate Ca

Late bowel toxicity



Number of patients	6 months	12 months	18 months	24 months	36 months	48 months	60 months
74 Gy	871	978	947	922	925	814	534
60 Gy	909	1002	966	959	946	839	569
57 Gy	922	997	965	962	942	847	549

Late bladder toxicity



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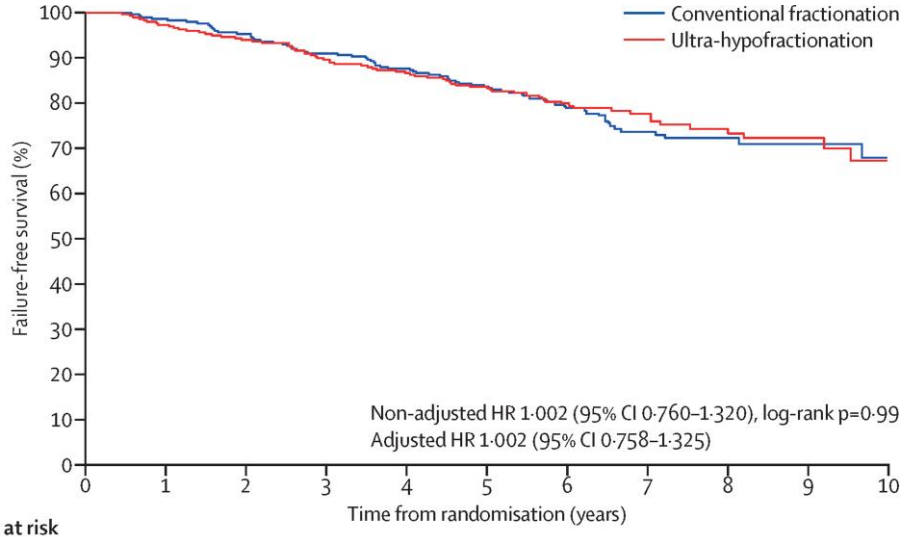


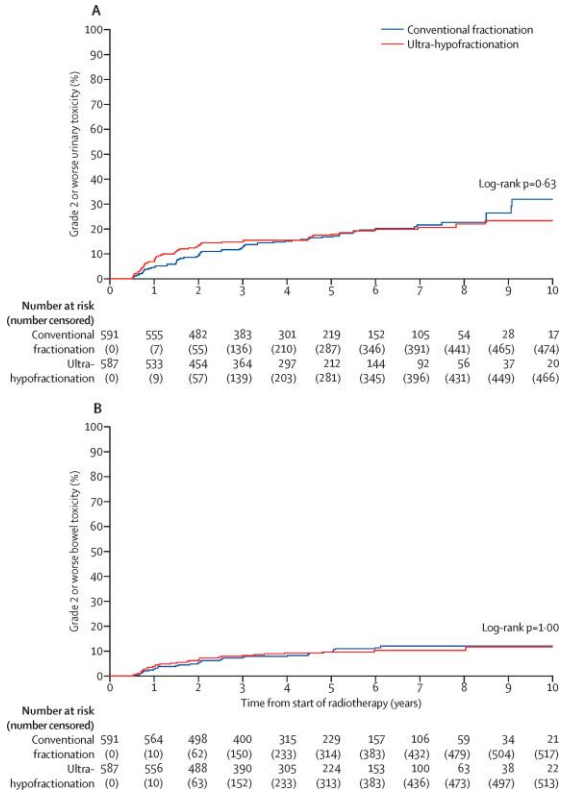
Number at risk (number censored)											
Conventional fractionation	591 (0)	580 (4)	540 (24)	433 (108)	332 (196)	242 (273)	171 (332)	108 (386)	67 (425)	37 (454)	23 (467)
Ultra-hypofractionation	589 (0)	569 (4)	527 (27)	408 (125)	325 (196)	242 (269)	160 (342)	113 (385)	71 (423)	38 (454)	20 (470)

Intermediate-to-high-risk prostate cancer

78 Gy (39 x 2 Gy) in 8 w >< 42.7 Gy (7 x 6.1 Gy) in 2.5w

Widmark et al., Lancet, 2019

Hypofractionation in prostate Ca



Intermediate-to-high-risk prostate cancer

78 Gy (39 x 2 Gy) in 8 w >< 42.7 Gy (7 x 6.1 Gy) in 2.5w

Widmark et al., Lancet, 2019

Hypofractionation in breast cancer

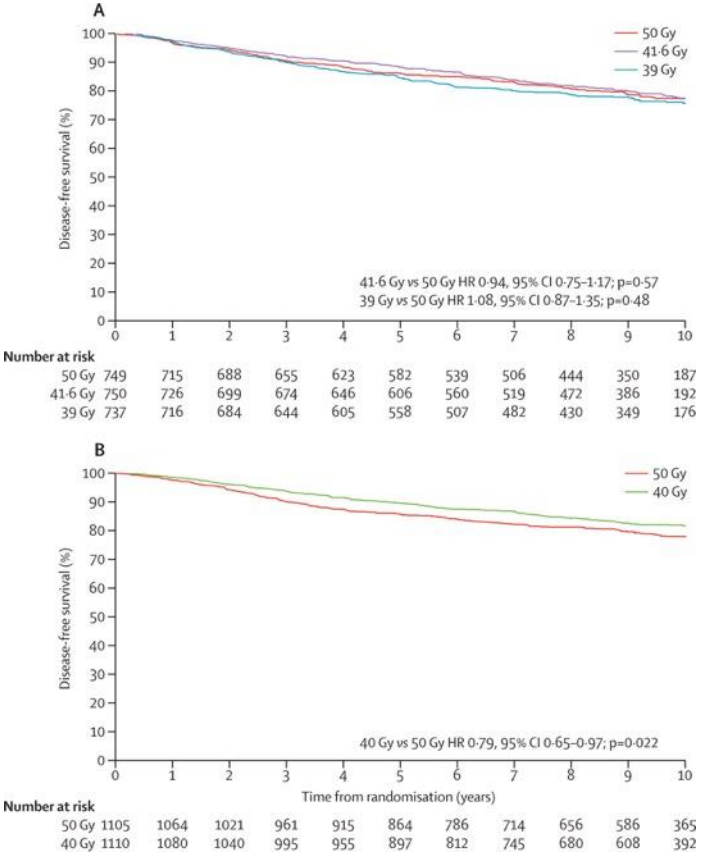
The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials

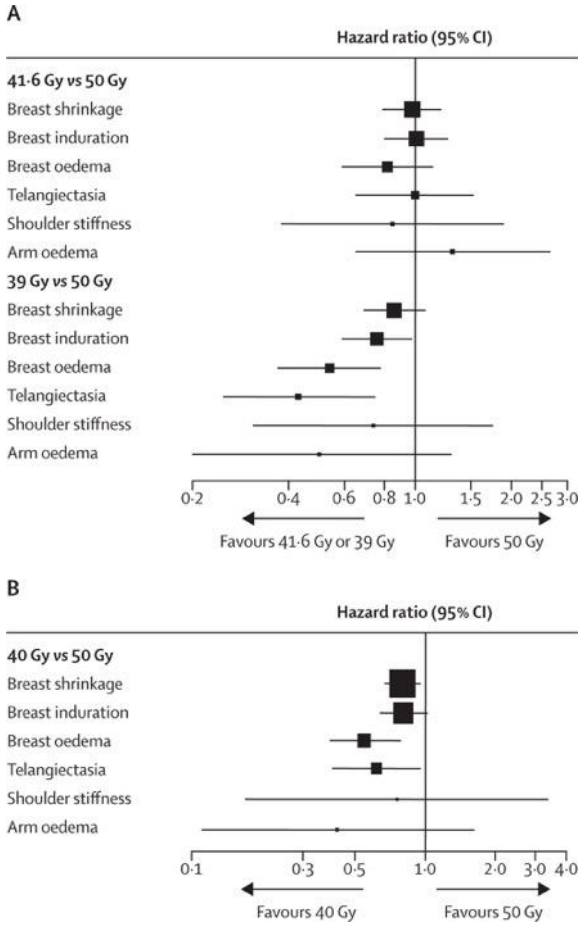
Joanne S Haviland, J Roger Owen, John A Dewar, Rajiv K Agrawal, Jane Barrett, Peter J Barrett-Lee, H Jane Dobbs, Penelope Hopwood, Pat A Lawton, Brian J Magee, Judith Mills, Sandra Simmons, Mark A Sydenham, Karen Venables, Judith M Bliss, John R Yarnold*, on behalf of the START Trialists' Group†*

50 Gy (25 x 2 Gy) in 5 w ≈ 40 Gy (15 x 3.3 Gy) in 3w

Haviland, Lancet Oncology, 2013

Hypofractionation in breast cancer (START)



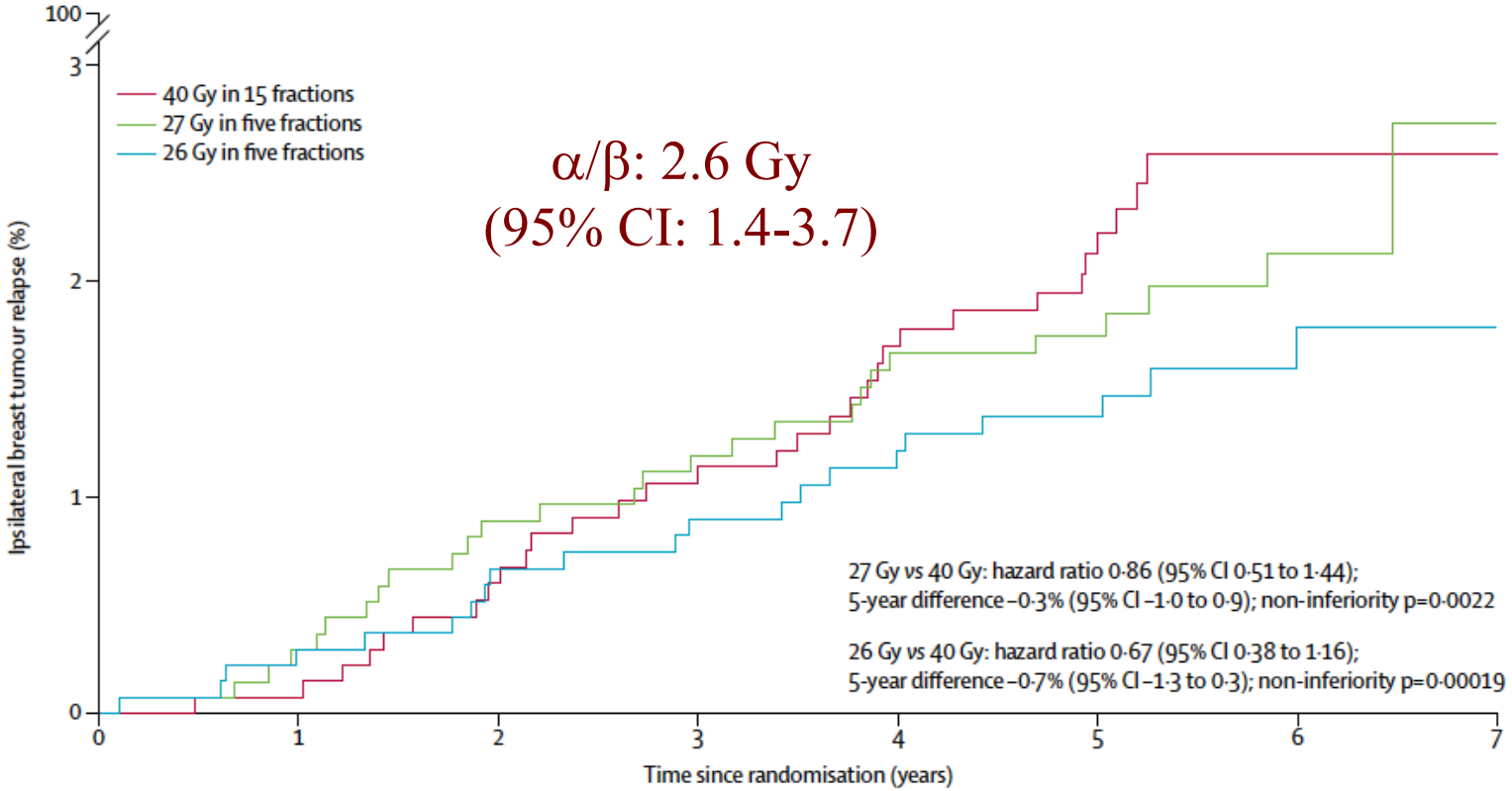


UPLIFT school 2025

α/β: 3.5 Gy (95% CI: 1.2-5.7)

Haviland, Lancet Oncology, 2013

Hypofractionation in breast cancer (FAST-forward)



40 Gy (15 x 2.67 Gy) in 3w >< 27 Gy (5 x 5.4 Gy) in 1w >< 26 Gy (5 x 5.2 Gy) in 1w

Brunt et al, Lancet Oncology, 2020

Conclusions

- Benefit of hyper- and accelerated fractionation for loco-regional control probability
- Slight increase in acute toxicity but no change in late toxicity
- Moderately hypofractionation for tumors with low α/β
- Extreme hypofractionation for well selected indications, e.g. small peripheral lung tumors (dose distribution effect only!)