# Modified Fractionation Schedules (and Limits)

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# Disclosures

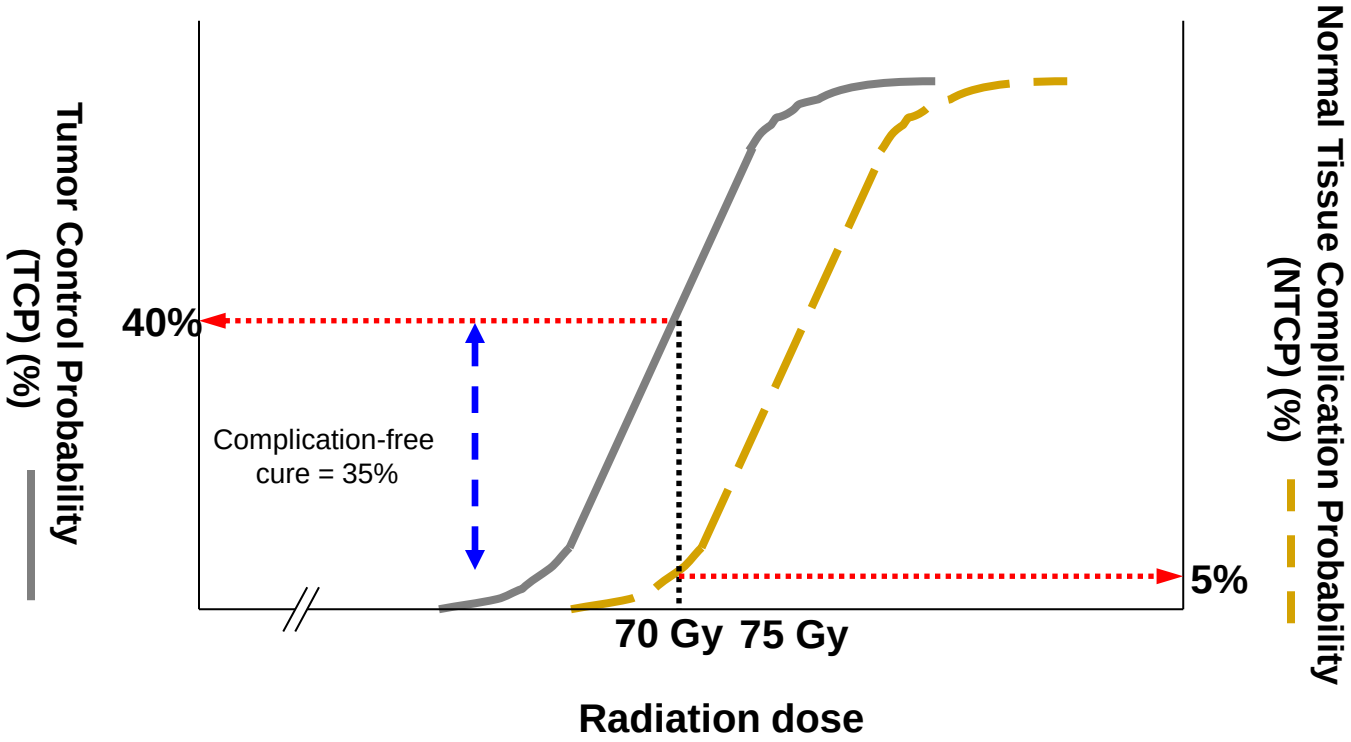
Patents/Licensing: Roche, Adela

Ownership: Adela

# Learning Objectives

- Define different types of fractionation schedules.
- Identify the balance between tumor control and early and late toxicity when changing dose-time-fractionation.
- Explain the interest in hypofractionation schedules in several tumor types.

# Therapeutic Index



# Standard/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 probability |
|---|---|---|---|
| *Sensitive* | Seminoma, Lymphoma | ≤ 45 | ≥ 90% |
| *Intermediate* | Most carcinomas (e.g., HNSCC, breast, prostate) | 50-70 | 30-90% |
| *Resistant* | Glioblastoma, Melanoma | ≥ 60 | <30% |

# **Overview:** Types of modified fractionation schedules

- Hyperfractionation
- Accelerated fractionation
- Hypofractionation

# **Overview:** Types of modified fractionation schedules

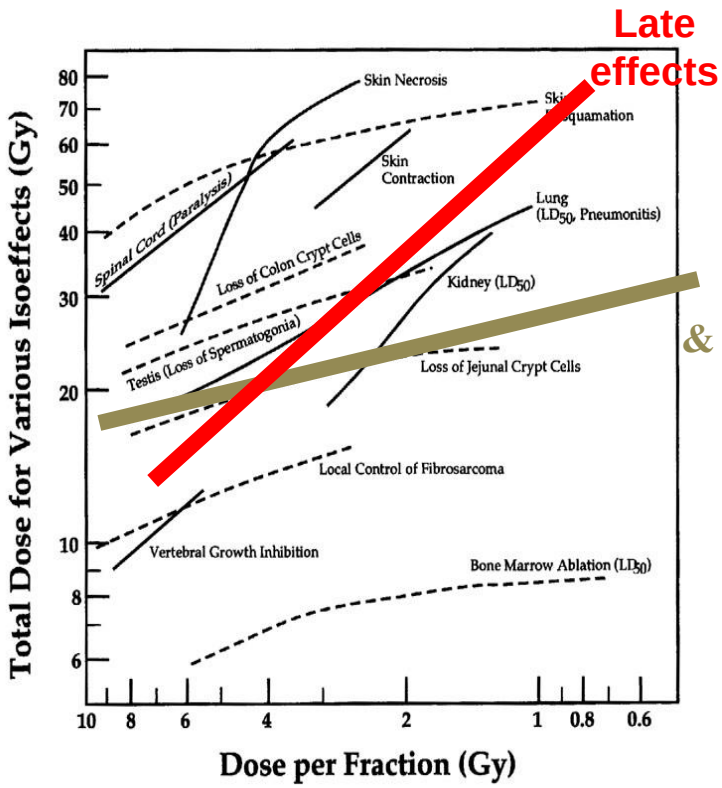
- **Hyperfractionation**
- Accelerated fractionation
- Hypofractionation

Reduced dose per fraction, greater number of fractions

# Sensitivity of different tissues to fraction size

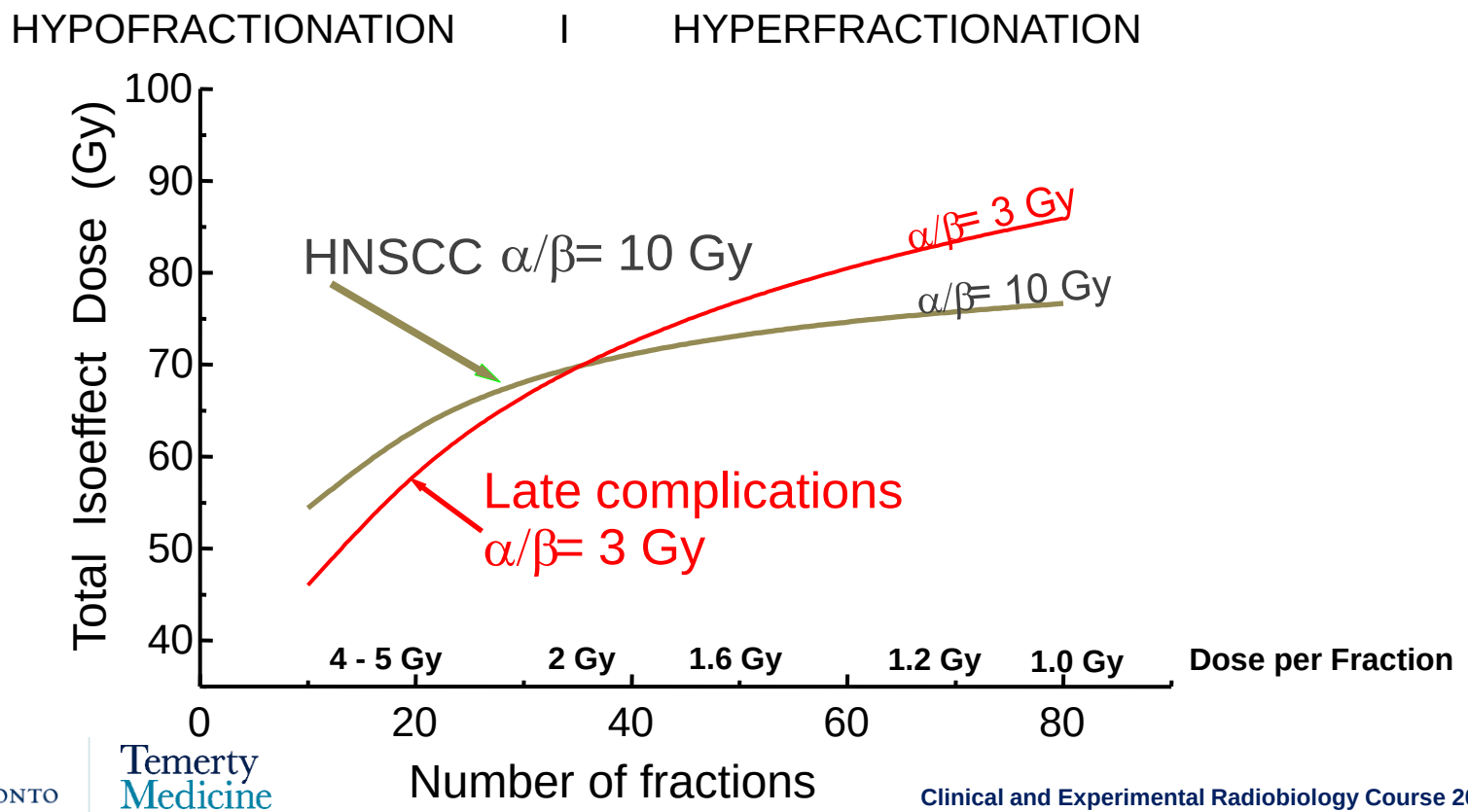
"Typical" dose per fraction

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




Withers et al, 1983

# Hyperfractionation in Head & Neck Squamous Cell Carcinoma (HNSCC)



# Hyperfractionation

## reduced dose per fraction (< 1.8 Gy, usually 1.1-1.3 Gy)

Conventional:

70Gy/ 2.0 Gy/ 7w

Hyperfractionated:

80.5Gy/ 2x1.15 Gy/ ti=6h/ 7w

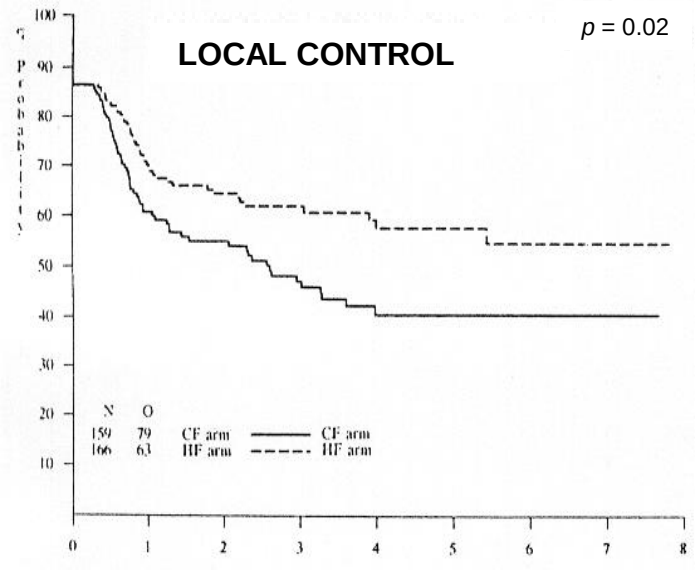
Goals & Expectations:

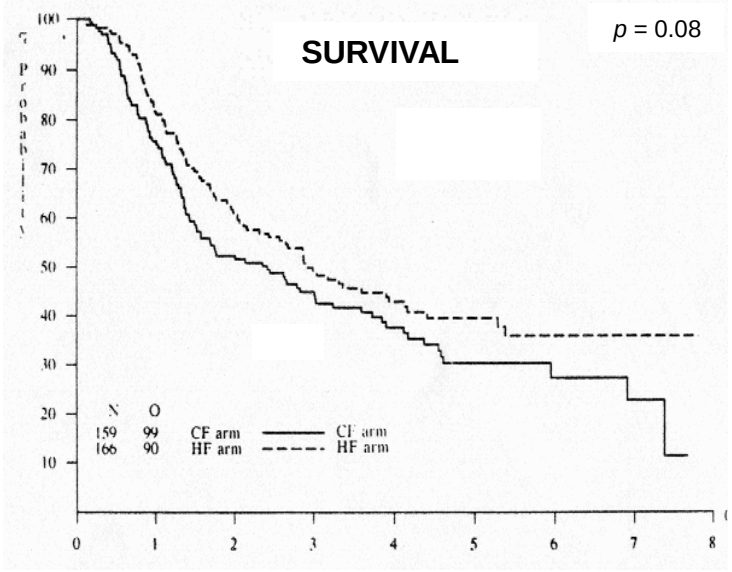
- Increased tumor control through dose-escalation
- More severe early reactions
- Unchanged or less late reactions

# EORTC Hyperfractionation trial in oropharynx cancer

## Oropharyngeal Cancer T2-3, N0-1 (N = 356 patients)

70 Gy - 35-40 fx in 7 wks (Conventional) Vs. 80.5 Gy - 70 fx in 7 wks (Hyperfractionated)






EORTC 22791

Horiot et al., *Radiother. Oncol.* 25: 231-241, 1992

# EORTC Hyperfractionation trial in oropharynx cancer

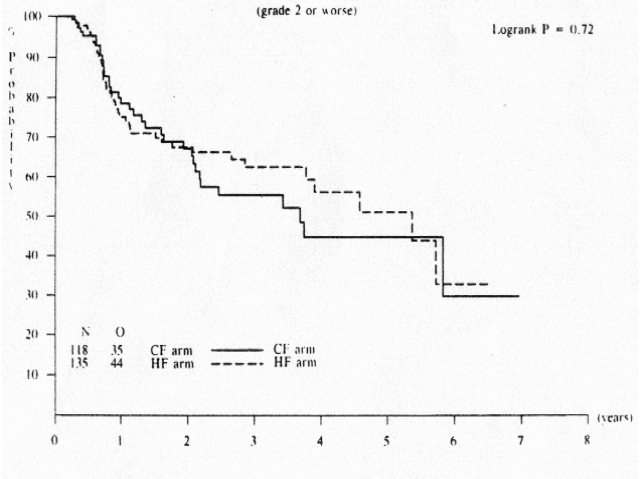
## Oropharyngeal Cancer T2-3, N0-1 (N = 356 patients)

70 Gy - 35-40 fx in 7 wks (Conventional) Vs. 80.5 Gy - 70 fx in 7 wks (Hyperfractionated)

### ACUTE TOXICITY

| | Treatment | | Total |
|---|---|---|---|
| | CF arm | HF arm | |
| Total | 159 | 166 | 325 |
| Inevaluable | 1 | 4 | 5 |
| Total | 158 | 162 | 320 |
| *Objective mucosal reactions:* | | | |
| None | 1 | – | 1 |
| $G_1$: mild mucositis | 13 (8%) | 7 (4.5%) | 20 |
| $G_2$: patchy mucositis | 66 (42%) | 47 (29%) | 113 |
| $G_3$: diffuse mucositis | 78 (49%) | 108 (66.5%) | 186 |
| *Functional mucosal reactions:* | | | |
| None | 1 | 2 | 3 |
| $G_1$: mild irritation | 21 (13%) | 13 (8%) | 34 |
| $G_2$: moderate irritation | 72 (45.5%) | 73 (45%) | 145 |
| $G_3$: liquid diet only | 47 (30%) | 48 (30%) | 95 |
| $G_4$: oral alim. impossible | 17 (11%) | 26 (16%) | 43 |
| Stopped <70 Gy | 7 (4.5%) | | |
| Stopped <80 Gy | | 12 (7.5%) | |

### LATE TOXICITY






EORTC 22791

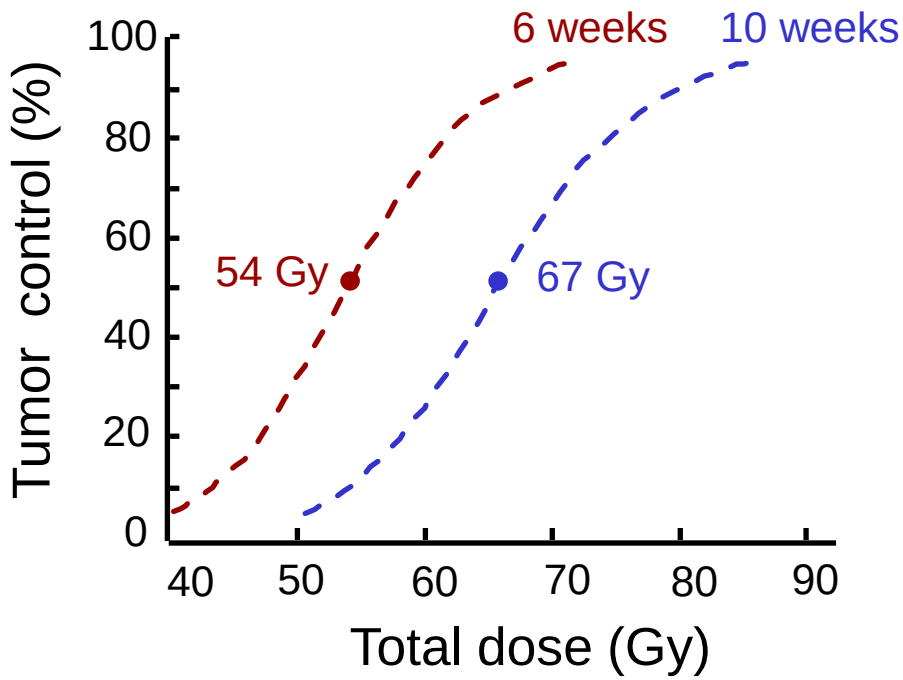
Horiot et al., *Radiother. Oncol.* 25: 231-241, 1992

# **Overview:** Types of modified fractionation schedules

- Hyperfractionation
- **Accelerated fractionation**
- Hypofractionation

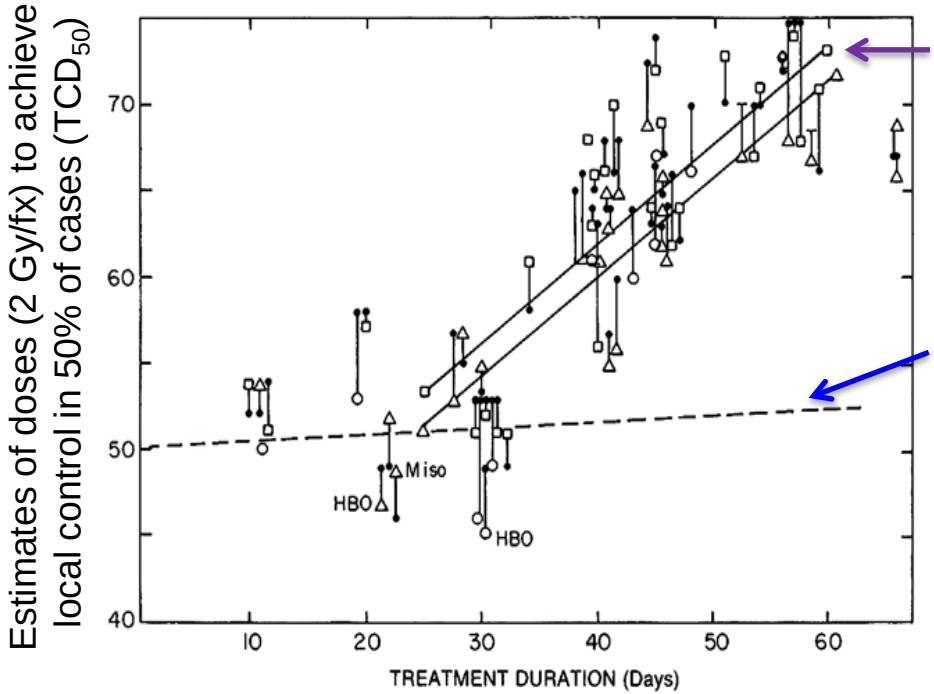
Shortened overall treatment time, dose per week > 10 Gy

# Influence of overall treatment time on HNSCC local control




Overgaard et al, 1988

# Influence of overall treatment time on HNSCC local control




Observed effect of accelerated repopulation

Effect of 2 month doubling time

Withers et al, 1988

# Tissue proliferation and recovered dose

| Tissue | $D_{prolif}$ ($Gy.d^{-1}$) | $T_k^*$ (days) |
|---|---|---|
| Early normal tissue reactions | | |
| Skin (erythema) | 0.12 (-0.12-0.22) | < 12 |
| Mucosa (mucositis) | 0.8 (0.7-1.1) | < 12 |
| Lung (pneumonitis) | 0.54 (0.13-0.95) | n.a. |
| Tumors | | |
| Head and neck | | |
| • larynx | 0.74 (0.3-1.2) | n.a. |
| • tonsils | 0.73 | 30 |
| • various | 0.8 (0.5-1.1) | 21 |
| • various | 0.64 (0.42-0.86) | n.a. |
| NSCLC | 0.45 | n.a. |
| Medulloblastoma | 0.52 (0.29-0.71 | 0 – 21 |

* onset of accelerated proliferation

# Accelerated fractionation

Shortened overall treatment time, dose per week > 10 Gy

Conventional

70Gy/ 2.0 Gy/ 7w

Pure accelerated fractionation

70Gy/ 2.0 Gy/ 6w

Concomitant boost

70Gy/ 2.0 Gy/ 5w

Goals & Expectations:

- Increased tumor control through reduced accelerated repopulation
- Increased early reactions
- Similar late toxicity

# DAHANCA 6&7 randomized trials

## HNSCC (n=1476 patients)

Conventional:

IIIII IIIII IIIII IIIII IIIII IIIII IIII

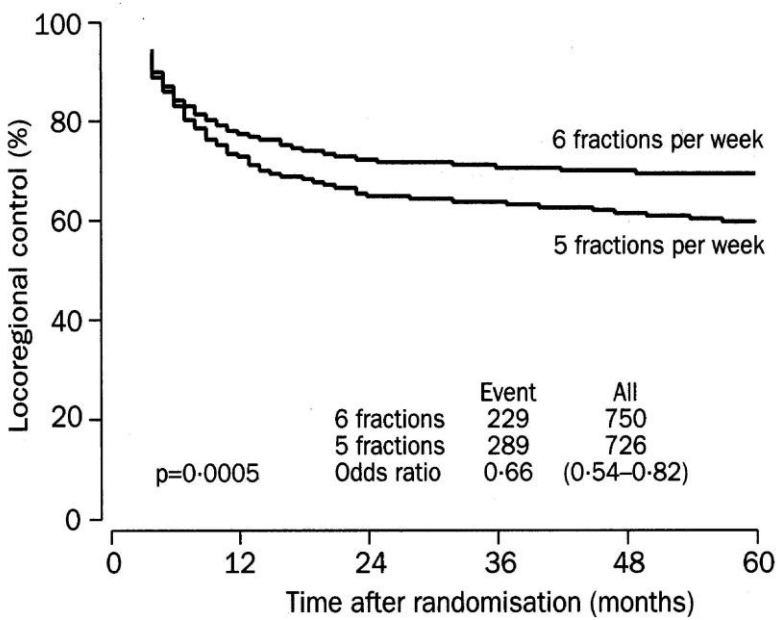
64-68 Gy/ 2.0 Gy/ 6.5w

Vs.

Accelerated:

IIIIII IIIIII IIIIII IIIIII IIIIII IIIIII

64-68 Gy/ 2.0 Gy/ 5.5w



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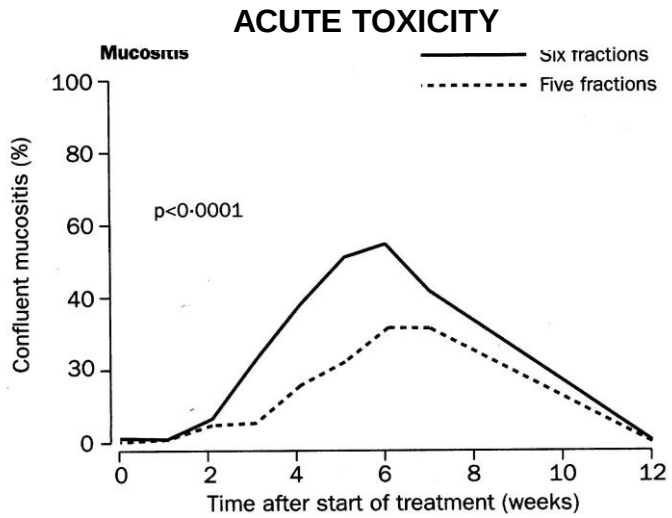
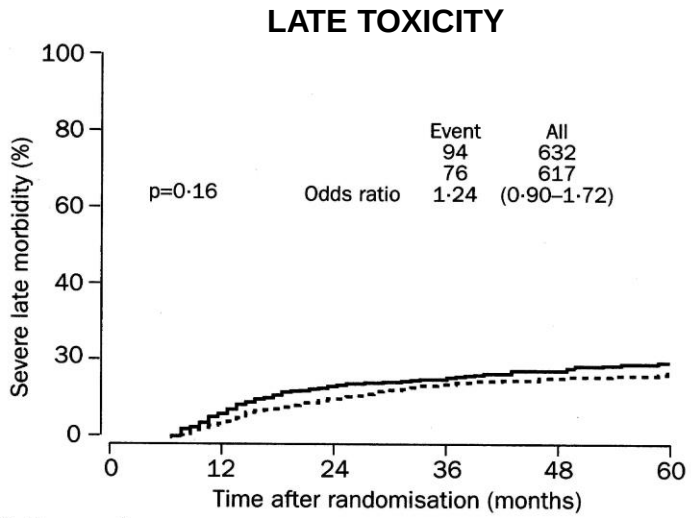





Overgaard et al. Lancet, 2003

# Accelerated Fractionation with Hyperfractionation

Shortened overall treatment time

Dose per week > 10 Gy

Reduced dose per fraction

Conventional:

66Gy/ 2.0 Gy/ 6.5w

Accelerated/hyperfractionated:

54Gy/ 3x1.5Gy/ ti=6h/ 12d

## Goals & Expectations:

- Increased tumor control
- Increased (and faster) early reactions
- Reduced late toxicity

# CHART randomized trial (MRC UK)

## HNSCC (n=918 patients)

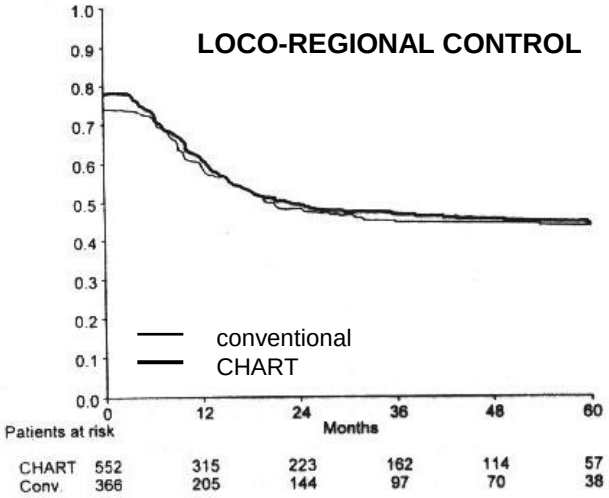
Conventional:

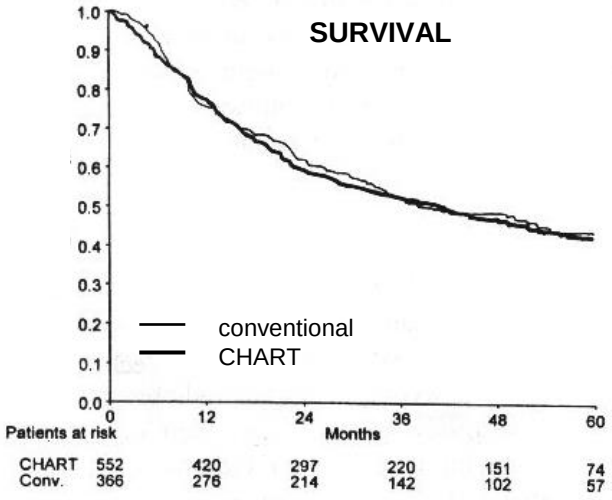
66Gy/ 2.0 Gy/ 6.5w

Vs.

Accelerated/hyperfractionated (CHART):

54Gy/ 3x1.5Gy/ ti=6h/ 12d






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

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## HNSCC (n=918 patients)

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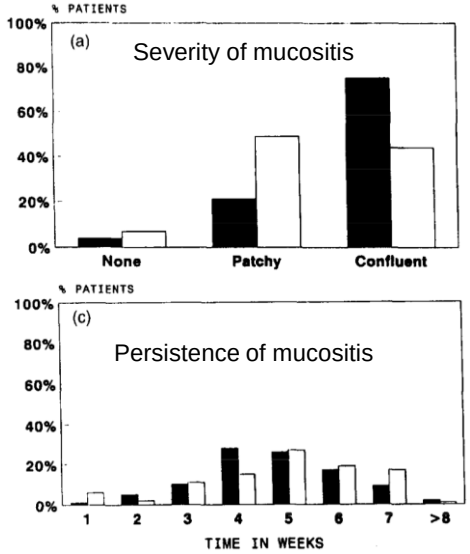
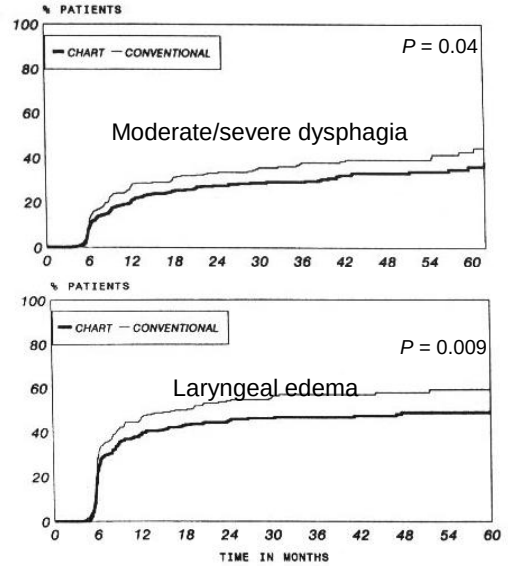
**ACUTE TOXICITY**



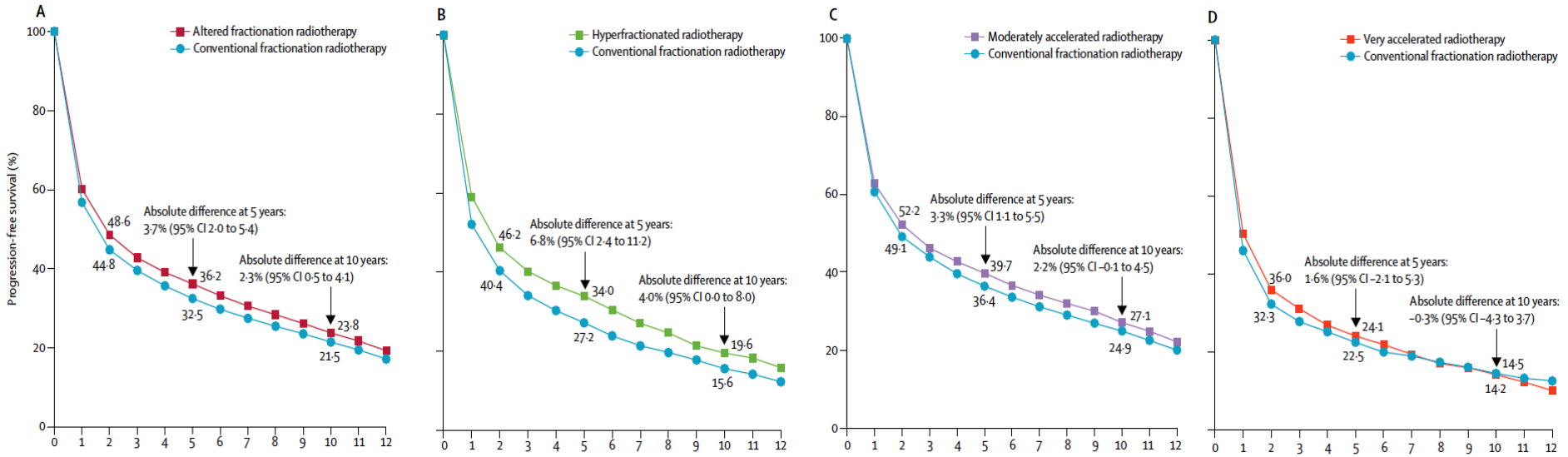

**LATE TOXICITY**




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 (11,423 patients, individual data)




Radiation Oncology
UNIVERSITY OF TORONTO

Temerty Medicine

Lacas et al., Lancet Oncol. 2017; 18(9):1221-1237

# Meta-analysis on altered fractionation HNSCC

| | Comparisons (n) | Patients (n) | Proportion of patients with toxicity receiving altered fractionation radiotherapy* | Proportion of patients with toxicity receiving conventional radiotherapy, n/N (%) | Odds ratio (95% CI) | p value for safety | $I^2$ | p value for heterogeneity |
|---|---|---|---|---|---|---|---|---|
| **Acute toxicities** | | | | | | | | |
| Mucositis (all trials) | 20 | 8541 | 38·9% | 1155/4233 (27·3%) | 2·02 (1·81–2·26) | <0·0001 | 78% | <0·0001 |
| Mucositis (no heterogeneity) | 16 | 7051 | 35·2% | 845/3499 (24·1%) | 2·10 (1·84–2·41) | <0·0001 | 0% | 0·66 |
| Dermatitis (all trials) | 15 | 4997 | 17·7% | 410/2483 (16·5%) | 1·09 (0·93–1·29) | 0·29 | 36% | 0·083 |
| Dermatitis (no heterogeneity) | 13 | 4314 | 20·1% | 376/2143 (17·5%) | 1·20 (1·01–1·42) | 0·041 | 0% | 0·83 |
| Weight loss (all trials) | 5 | 2053 | 3·6% | 43/1023 (4·2%) | 0·87 (0·56–1·36) | 0·54 | 7% | 0·37 |
| Need for feeding tube (all trials) | 6 | 2859 | 52·1% | 563/1420 (39·6%) | 1·75 (1·49–2·05) | <0·0001 | 89% | <0·0001 |
| Need for feeding tube (no heterogeneity) | 4 | 1871 | 35·6% | 252/929 (27·1%) | 1·63 (1·34–1·99) | <0·0001 | 3% | 0·38 |
| **Late toxicities** | | | | | | | | |
| Xerostomia (all trials) | 12 | 4726 | 51·3% | 1193/2337 (51·0%) | 1·01 (0·88–1·14) | 0·94 | 20% | 0·25 |
| Xerostomia (no heterogeneity) | 11 | 4414 | 54·6% | 1181/2182 (54·1%) | 1·02 (0·90–1·17) | 0·73 | 0% | 0·50 |
| Bone toxicity (all trials) | 11 | 3219 | 4·4% | 64/1585 (4·0%) | 1·12 (0·80–1·57) | 0·52 | 0% | 0·77 |
| Mucosal toxicity (all trials) | 8 | 2298 | 14·5% | 149/1114 (13·4%) | 1·10 (0·87–1·40) | 0·41 | 49% | 0·058 |
| Mucosal toxicity (no heterogeneity) | 7 | 1921 | 14·4% | 140/937 (14·9%) | 0·96 (0·74–1·24) | 0·74 | 0% | 0·64 |
| Neck fibrosis (all trials) | 15 | 5557 | 7·6% | 188/2744 (6·9%) | 1·13 (0·92–1·39) | 0·23 | 70% | <0·0001 |
| Neck fibrosis (no heterogeneity) | 12 | 4250 | 7·0% | 138/2109 (6·5%) | 1·09 (0·85–1·38) | 0·50 | 0% | 0·45 |



Lacas et al., Lancet Oncol. 2017; 18(9):1221-1237

# **Overview:** Types of modified fractionation schedules

- Hyperfractionation
- Accelerated fractionation
- **Hypofractionation**

Increased dose per fraction, smaller number of fractions

# Hypofractionation

## Increased dose per fraction (> 2.2 Gy)

78Gy/ 2.0 Gy/ 8w

Conventional Fractionation

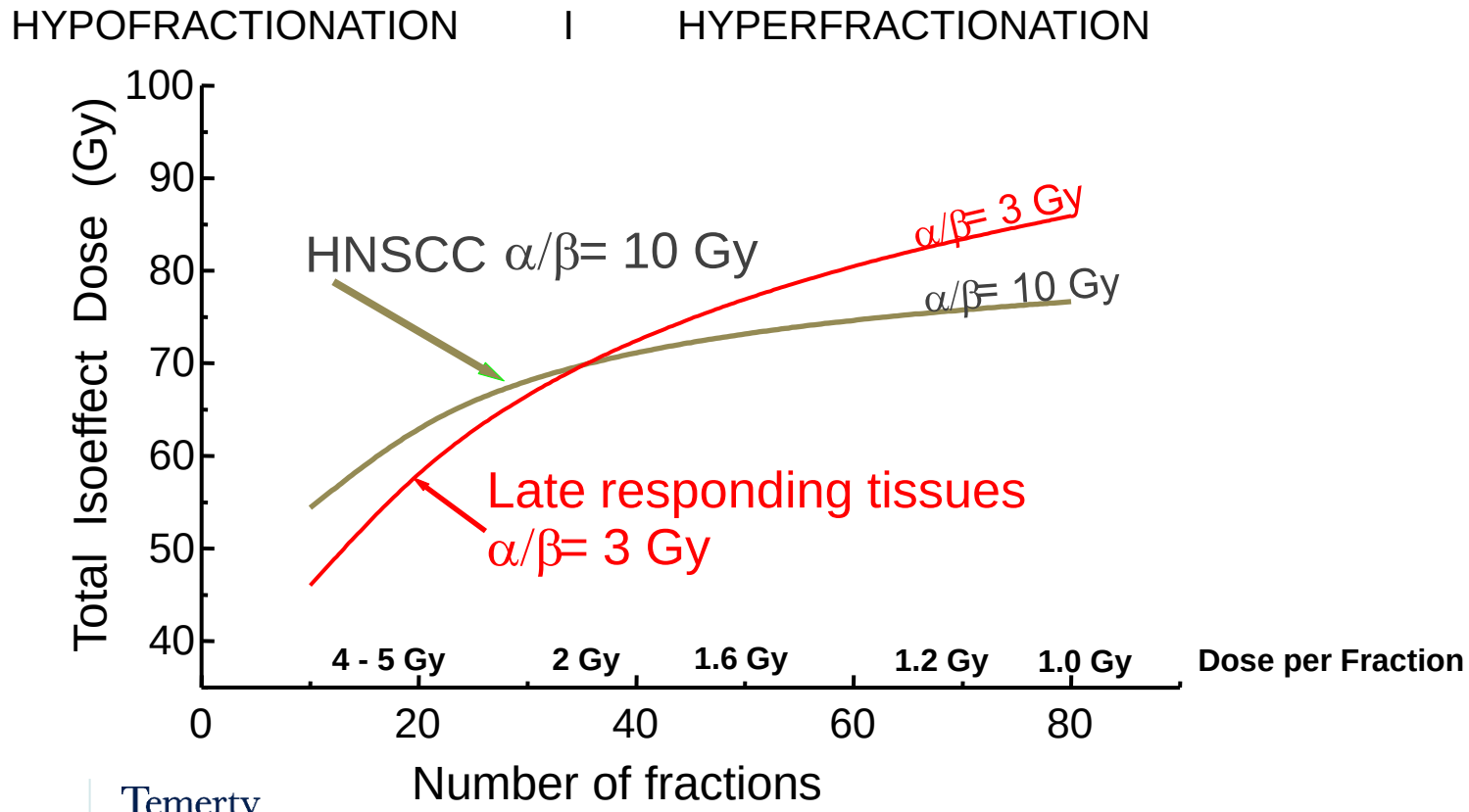
60Gy/ 3 Gy/ 4w

Moderate Hypofractation with Acceleration

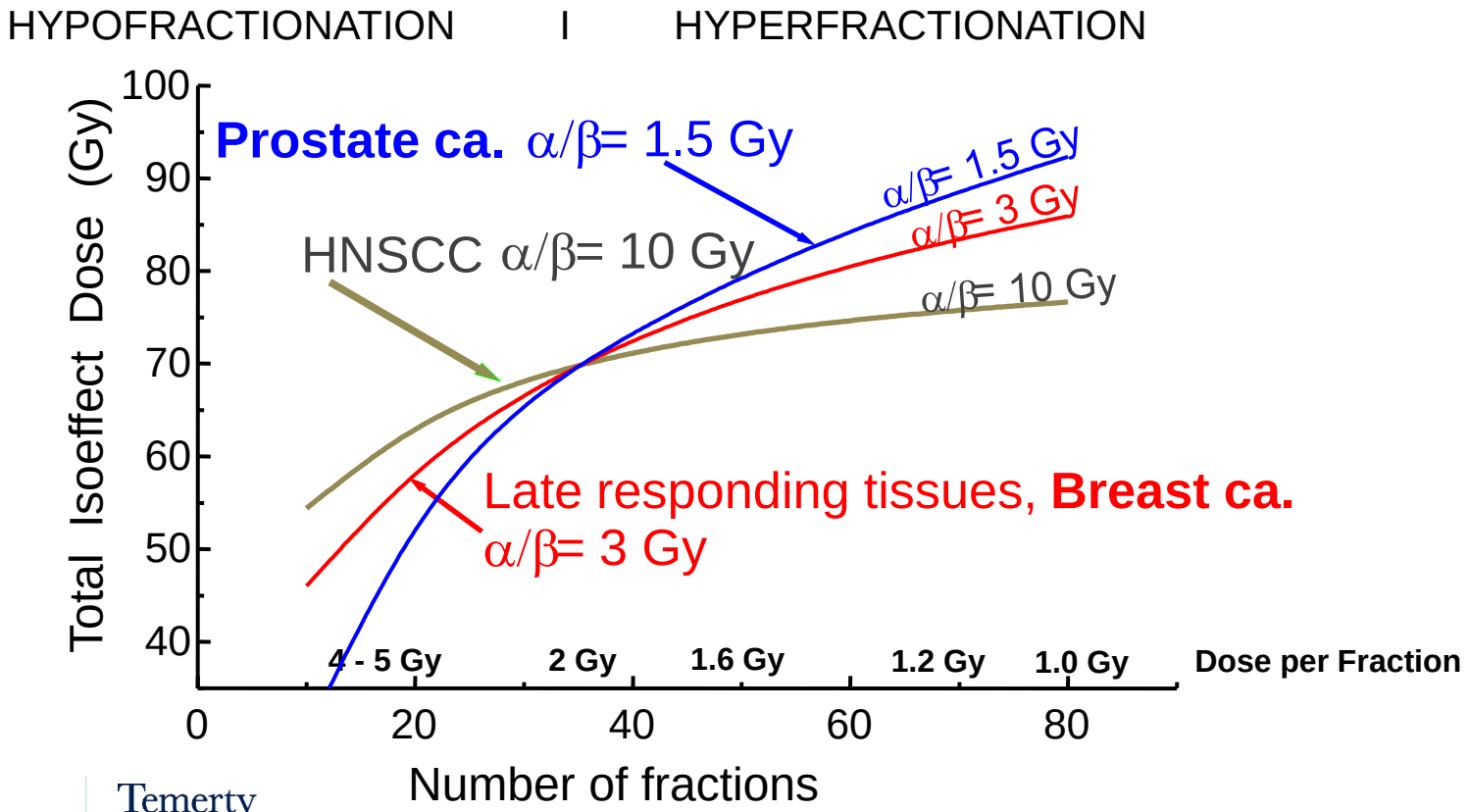
42.7 Gy/ 6.1 Gy/ 2.5w

Ultra Hypofractionation with Acceleration

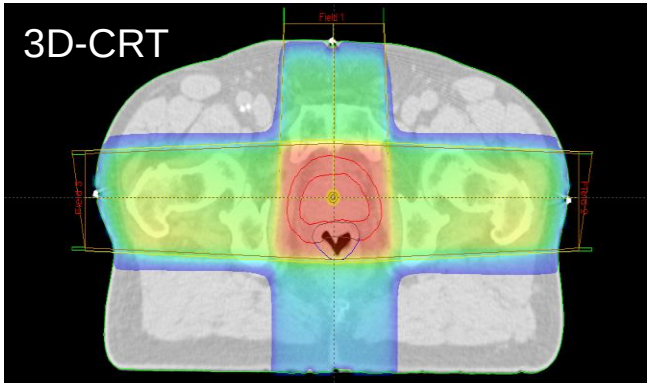
# Hypofractionation in Prostate and Breast Cancers

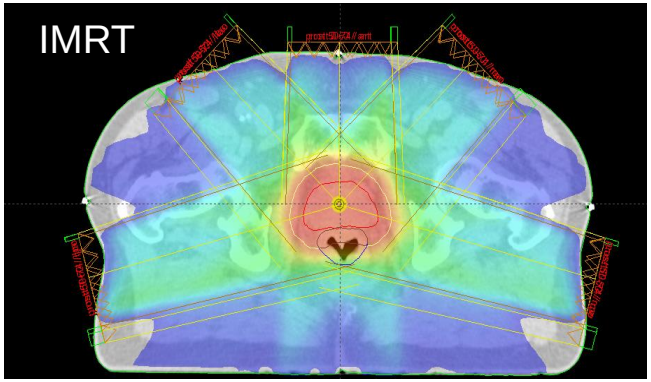


# Hypofractionation in Prostate and Breast Cancers



# Improvements in conformal irradiation of prostate cancer




Dearlaney, 1999

# Moderate Hypofractionation in Prostate Cancer

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

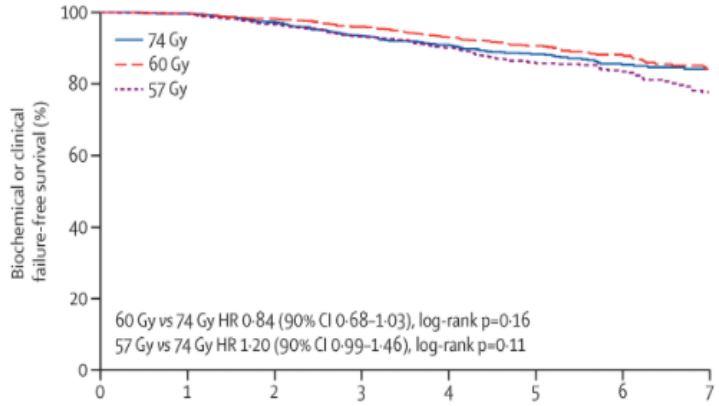
*David Dearnaley, Isabel Syndikus, Helen Mossop, Vincent Khoo, Alison Birtle, David Bloomfield, John Graham, Peter Kirkbride, John Logue, Zafar Malik, Julian Money-Kyrle, Joe M O'Sullivan, Miguel Panades, Chris Parker, Helen Patterson*, Christopher Scrase, John Staffurth, Andrew Stockdale, Jean Tremlett, 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 vs. 60 Gy (20 x 3.0 Gy) in 4w vs. 57 Gy (19 x 3 Gy) in 3.8w

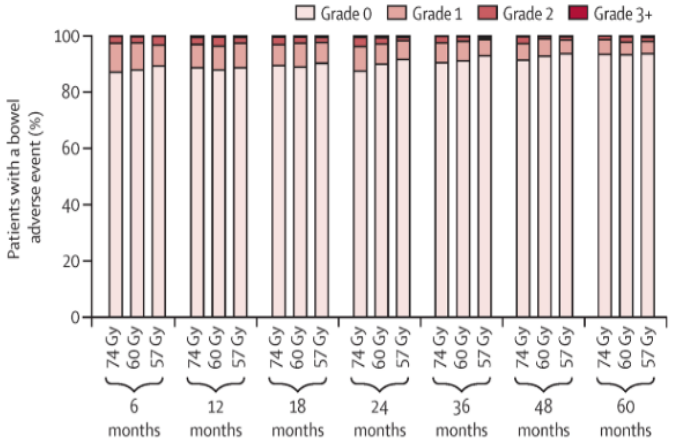
Conventional | Hypofractionated/Accelerated | Hypofractionated/Accelerated

# Moderate Hypofractionation in Prostate Cancer

## DISEASE CONTROL




## BOWEL TOXICITY






Dearnaley et al., Lancet Oncology, 2016

# Ultra-Hypofractionation in Prostate Cancer

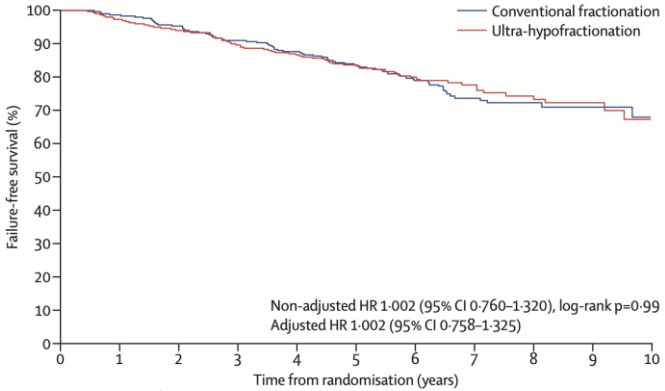
*Lancet* 2019; 394: 385–95

## Ultra-hypofractionated versus conventionally fractionated radiotherapy for prostate cancer: 5-year outcomes of the HYPO-RT-PC randomised, non-inferiority, phase 3 trial

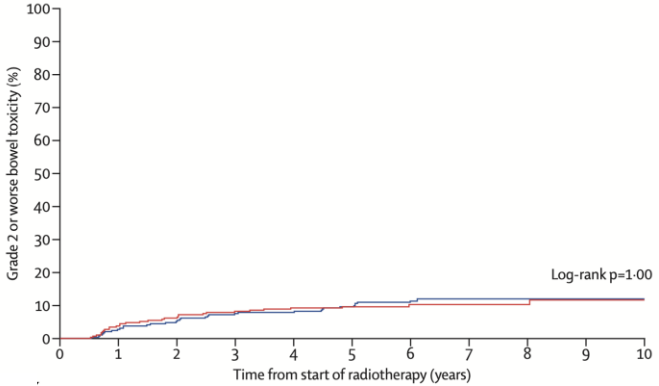
*Anders Widmark, Adalsteinn Gunnlaugsson, Lars Beckman, Camilla Thellenberg-Karlsson, Morten Hoyer, Magnus Lagerlund, Jon Kindblom, Claes Ginman, Bengt Johansson, Kirsten Björnlinger, Mihajl Seke, Måns Agrup, Per Fransson, Björn Tavelin, David Norman, Björn Zackrisson, Harald Anderson, Elisabeth Kjellén, Lars Franzén, Per Nilsson*

Conventional
78 Gy (39 x 2 Gy) in 8 w vs. Ultra-Hypofractionated
42.7 Gy (7 x 6.1 Gy) in 2.5w

### DISEASE CONTROL




### BOWEL TOXICITY



# 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†*

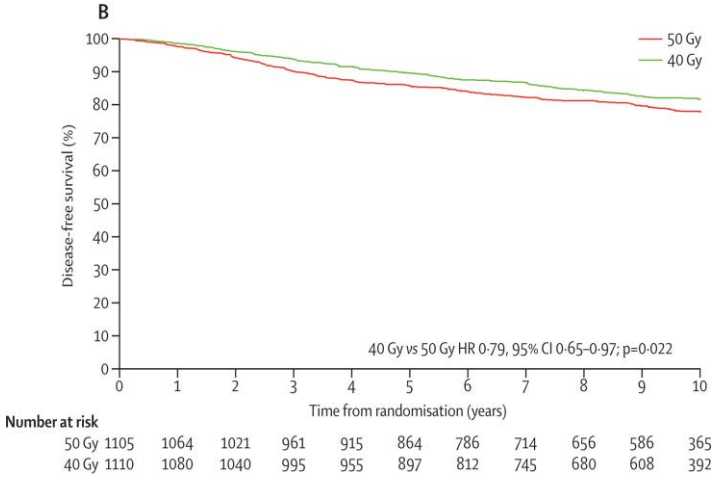
Conventional
50 Gy (25 x 2 Gy) in 5 w

Vs.

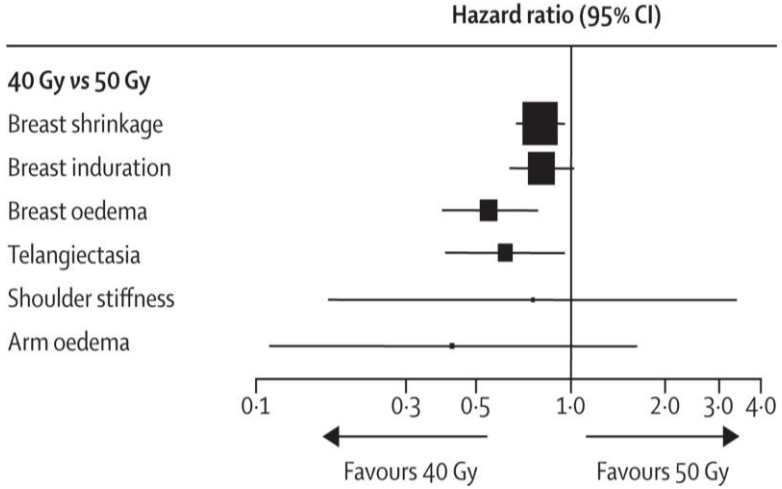
Hypofractionated/Accelerated
40 Gy (15 x 3.3 Gy) in 3w

# Hypofractionation in Breast Cancer

## EFFICACY




## LATE TOXICITY




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

Hypofractionated/Accelerated



Haviland et al., Lancet Oncology, 2013

# Conclusions

- For tumors with higher $\alpha/\beta$ than surrounding critical normal tissues (e.g., HNSCC), randomized trials have demonstrated benefit of hyper- and accelerated fractionation for disease control with some increase in acute toxicity but no significant change in late toxicity

- For tumors with lower/similar $\alpha/\beta$ than surrounding critical normal tissues (e.g., prostate cancer, breast cancer), randomized trials have demonstrated similar disease control and toxicity with hypofractionation

# Questions?

# Thank you!

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