The mathematics of dose-fractionation
Linear-Quadratic Modeling – Current Status and Where to Next?

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Professor John Francis 'Jack' Fowler DSc FInstP
1925-2016

January 1994

Towards understanding RT dose-response

Advances in dosimetry

Chemical dosimetry
Guido Holzknecht 1902

Ionization chambers
Paul Villard 1906

~1910-1920
Increasing awareness of late effect of radiation

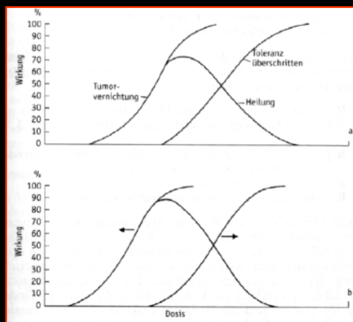
Hermann Holthusen 1886–1971

Systematic studies linking dose to probability of biological effect

Mathematical and statistical models of dose-response

"The 1936 paper"

Therapeutic window concept



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Holthusen, *Strahlentherapie* 57: 254, 1936

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Power law models and bioeffect

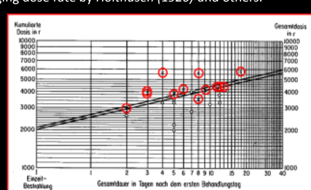
The Schwarzschild law of photochemistry

$$E = I \cdot T^p = \frac{D}{T} \cdot T^p = D \cdot T^{(p-1)}$$

where *I* is intensity, *T* is time and *p* is a parameter, *p*<1.
Applied to erythema with changing dose rate by *Holthusen (1926)* and others.

This led to double logarithmic plots of isoeffect dose-time relationships.
Witte 1941

This representation was chosen by *Strandqvist 1944* ⇨ ⇨ ⇨



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Evolution of the NSD concept

Strandqvist (1944):

$$D = k \cdot T^{0.22}$$

SQCA, wound healing/necrosis

Cohen (1949):

$$D = k \cdot T^n$$

SQCA: n=0.22
Skin: n=0.33

Ellis (1969):

$$D = NSD \cdot N^{0.22} \cdot T^{0.11}$$

Frank Ellis, MD, OBE (1905–2006)

- Difference in recovery exponent
- *N* is more important than *T* (at least for *T*<28days) in pig skin (**Fowler 1963**)

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Ellis *Clin Radiol* 20: 1 (1969)

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Liversage's criticisms (1971)

$$D = NSD \cdot N^{\nu} \cdot T^{\tau}$$

Ellis: ν is the same for tumours and normal tissues
τ is zero for tumours

- The difference in recovery exponents is an artefact !!
- ν varies from one tumour to another
- The value of τ depends on the data set being used
- In particular, two animal studies gave different values of τ
- Isoeffect curves in the Strandqvist plot are not linear !!

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Liversage *BJR* 44: 91 (1971)

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…the Ellis formulae are derived by applying doubtful assumptions to questionable data…

Liversage 1971

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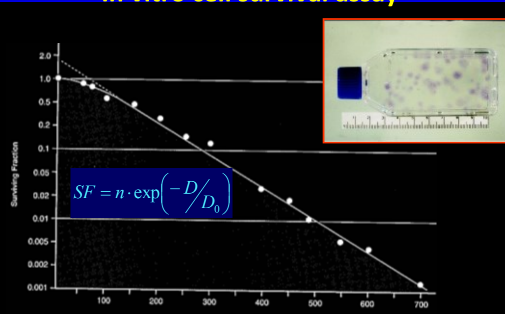
In vitro cell survival assay



$$SF = n \cdot \exp\left(-D/D_0\right)$$

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Puck & Marcus, *J Exp Med* 103: 653 (1956)

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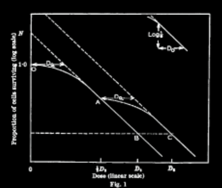
DOSE-EFFECT RELATIONSHIPS FOR RADIATION DAMAGE TO ORGANIZED TISSUES

By J. F. FOWLER
Department of Physics, St. Bartholomew's Hospital Medical College, Charterhouse Square, E.C.1
D. K. BEWLEY, R. L. MORGAN and J. ANN SILVESTER
Medical Research Council Cyclotron Unit, Hammersmith Hospital, W.12
AND
TIKVAH ALPER and SHIRLEY HORNSEY
Medical Research Council Experimental Radiopathology Research Unit, Hammersmith Hospital, London

WHEN a population of cells is exposed to ionizing radiation its ability to give rise to viable daughter cells is impaired, fewer and fewer cells retaining this ability (that is, 'surviving') as the dose is increased. ... dose necessary to give the same effect. It should be pointed out that if the fractions are ... all that the cell survival ... of the curve ...



The target cell hypothesis:

Biological effects of radiation in tumors and normal tissues are due to the depopulation of putative target cells. The (in vitro) dose-survival curve of these target cells governs the tissue response to fractionated radiation.

Fowler et al. *Nature* 199: 253 (1963)

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The target cell paradigm

"The object of treating a tumour by radiotherapy is to damage every single potentially malignant cell to such an extent that it cannot continue to proliferate"

Munro and Gilbert *BJR* 34: 246, 1961

"There are good reasons for believing that the primary effects of radiation on tissues are cell damage and cell depopulation in renewing populations. . ."

Thames and Hendry *Fractionation in Radiotherapy*, p.1, 1987

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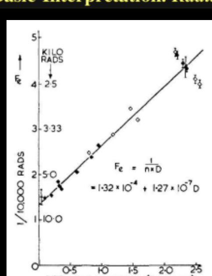
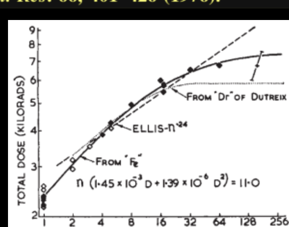
Douglas, B. G., and Fowler, J. F. The Effect of Multiple Small Doses of X Rays on Skin Reactions in the Mouse and a Basic Interpretation. *Radiat. Res.* 66, 401–426 (1976).





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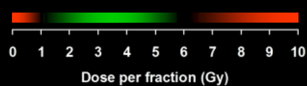
Equieffective doses – correcting for dose/fraction

D_{ref}, delivered under reference conditions, produce an equivalent effect with respect to a specific endpoint, as the dose D delivered with dose per fraction d.

$$D_{ref} = D \cdot \frac{d \cdot g + \alpha/\beta}{d_{ref} + \alpha/\beta}$$

Symbol
$EQD2_{\alpha/\beta}$
$EQD0_{\alpha/\beta}$

Range of applicability:



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Bentzen et al. R&O 105: 266 (2012)

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THE LQ WORLD

- Deliver the dose in the shortest possible time without exceeding early-responding tissue tolerance
  - This will improve tumor control because the time available for (accelerated) tumor cell proliferation is minimized
- Use as low dose per fraction as possible without prolonging overall treatment time
  - This will increase the biological effect on tumors relative to late-responding normal tissues

Radiobiology thinking 1985

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Altered fractionation

- **Hyperfractionation:**
  - dose per fraction less than 1.8 Gy
- **Accelerated fractionation:**
  - rate of dose accumulation exceeds 10 Gy/week
- **Hypofractionation:**
  - dose per fraction exceeding 2.2 Gy

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Bentzen *Acta Oncol* 32: 259 (1993)

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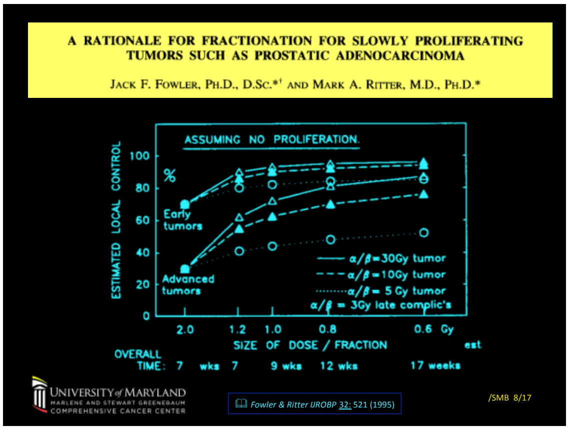
A RATIONALE FOR FRACTIONATION FOR SLOWLY PROLIFERATING TUMORS SUCH AS PROSTATIC ADENOCARCINOMA
JACK F. FOWLER, PH.D., D.SC.*† AND MARK A. RITTER, M.D., PH.D.*
ASSUMING NO PROLIFERATION.
ESTIMATED LOCAL CONTROL
%
100
80
60
40
20
0
Early tumors
Advanced tumors
α/β = 30Gy tumor
α/β = 10Gy tumor
α/β = 5 Gy tumor
α/β = 3Gy late complic's
2.0
1.2
1.0
0.8
0.6 Gy
SIZE OF DOSE / FRACTION
est
OVERALL TIME: 7 wks 7 9 wks 12 wks 17 weeks
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Fowler & Ritter IJROBP 32: 521 (1995)
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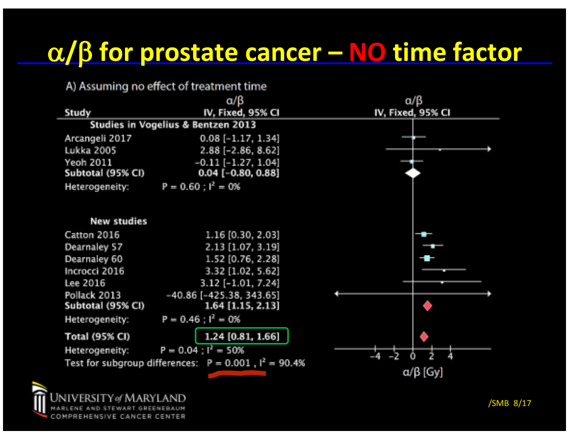
α/β for prostate cancer – NO time factor
A) Assuming no effect of treatment time
Study | α/β IV, Fixed, 95% CI | α/β IV, Fixed, 95% CI
Studies in Vogelius & Bentzen 2013
Arcangeli 2017 0.08 [−1.17, 1.34]
Lukka 2005 2.88 [−2.86, 8.62]
Yeoh 2011 −0.11 [−1.27, 1.04]
Subtotal (95% CI) 0.04 [−0.80, 0.88]
Heterogeneity: P = 0.60 ; I² = 0%
New studies
Catton 2016 1.16 [0.30, 2.03]
Dearnaley 57 2.13 [1.07, 3.19]
Dearnaley 60 1.52 [0.76, 2.28]
Incrocci 2016 3.32 [1.02, 5.62]
Lee 2016 3.12 [−1.01, 7.24]
Pollack 2013 −40.86 [−425.38, 343.65]
Subtotal (95% CI) 1.64 [1.15, 2.13]
Heterogeneity: P = 0.46 ; I² = 0%
Total (95% CI) 1.24 [0.81, 1.66]
Heterogeneity: P = 0.04 ; I² = 50%
Test for subgroup differences: P = 0.001 , I² = 90.4%
−4 −2 0 2 4
α/β [Gy]
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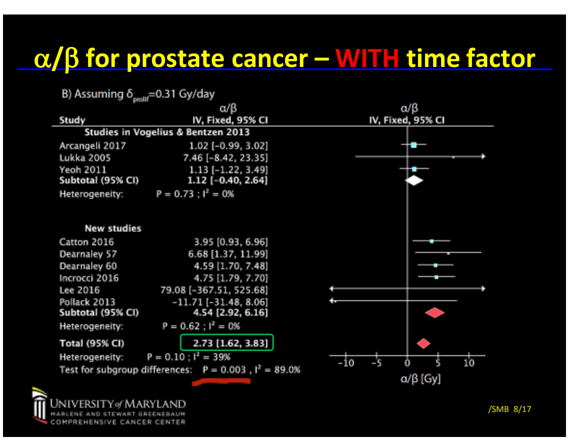
α/β for prostate cancer – WITH time factor
B) Assuming δ prolif =0.31 Gy/day
Study | α/β IV, Fixed, 95% CI | α/β IV, Fixed, 95% CI
Studies in Vogelius & Bentzen 2013
Arcangeli 2017 1.02 [−0.99, 3.02]
Lukka 2005 7.46 [−8.42, 23.35]
Yeoh 2011 1.13 [−1.22, 3.49]
Subtotal (95% CI) 1.12 [−0.40, 2.64]
Heterogeneity: P = 0.73 ; I² = 0%
New studies
Catton 2016 3.95 [0.93, 6.96]
Dearnaley 57 6.68 [1.37, 11.99]
Dearnaley 60 4.59 [1.70, 7.48]
Incrocci 2016 4.75 [1.79, 7.70]
Lee 2016 79.08 [−367.51, 525.68]
Pollack 2013 −11.71 [−31.48, 8.06]
Subtotal (95% CI) 4.54 [2.92, 6.16]
Heterogeneity: P = 0.62 ; I² = 0%
Total (95% CI) 2.73 [1.62, 3.83]
Heterogeneity: P = 0.10 ; I² = 39%
Test for subgroup differences: P = 0.003 , I² = 89.0%
−10 −5 0 5 10
α/β [Gy]
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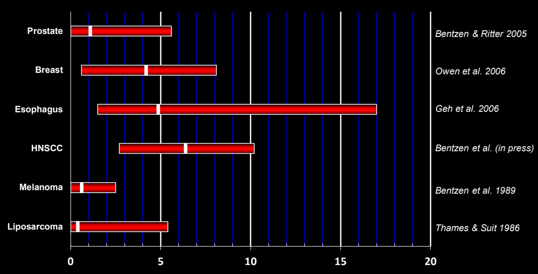
Human tumor fractionation sensitivity



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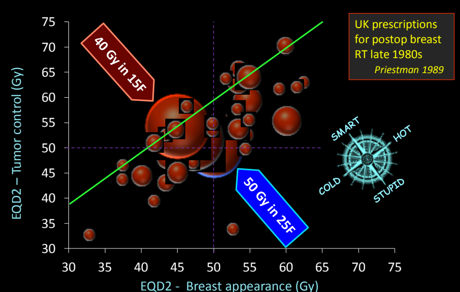
Therapeutic ‘ratio’ of breast RT schedules



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Bentzen & Yarnold *Clin Oncol (RCR)* 26: 599, 2014

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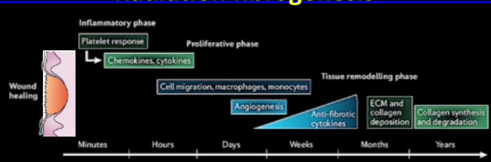
Radiation fibrogenesis



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Bentzen *Nature Rev Cancer* 6: 702 (2006)

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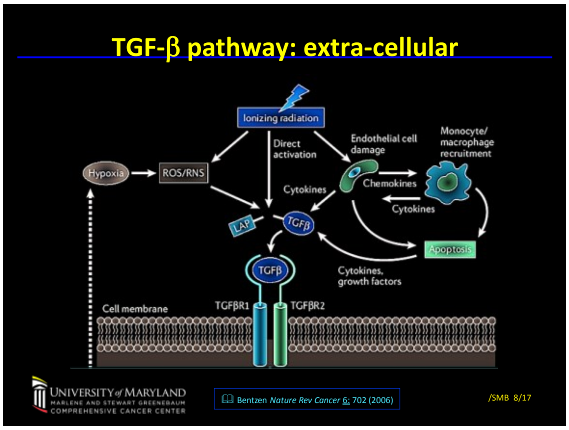
TGF-β pathway: extra-cellular
Ionizing radiation
Direct activation
Endothelial cell damage
Monocyte/ macrophage recruitment
Hypoxia
ROS/RNS
Cytokines
Chemokines
Cytokines
LAP
TGFβ
Apoptosis
TGFβ
Cytokines, growth factors
Cell membrane
TGFβR1
TGFβR2
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Bentzen Nature Rev Cancer 6: 702 (2006)
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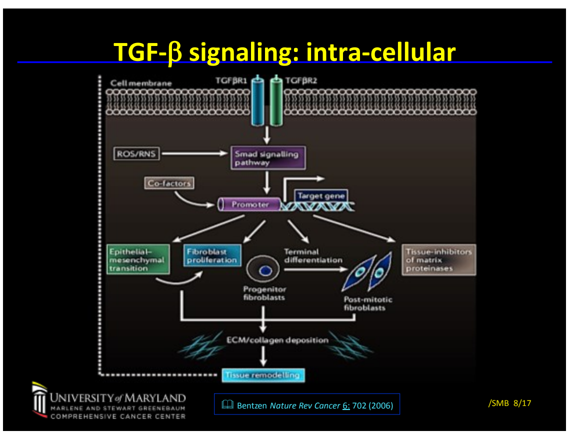
TGF-β signaling: intra-cellular
Cell membrane
TGFβR1
TGFβR2
ROS/RNS
Smad signalling pathway
Co-factors
Promoter
Target gene
Epithelial–mesenchymal transition
Fibroblast proliferation
Terminal differentiation
Tissue-inhibitors of matrix proteinases
Progenitor fibroblasts
Post-mitotic fibroblasts
ECM/collagen deposition
Tissue remodelling
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Bentzen Nature Rev Cancer 6: 702 (2006)
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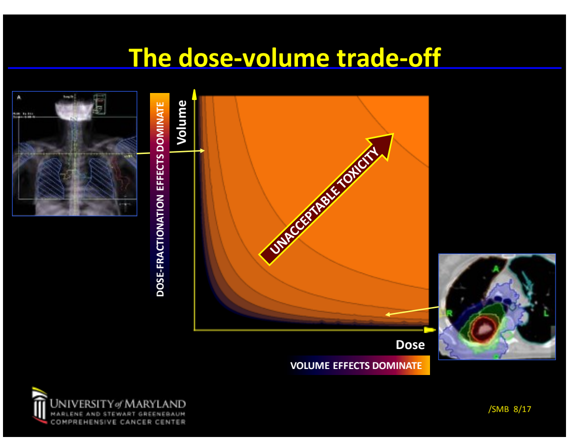
The dose-volume trade-off
DOSE-FRACTIONATION EFFECTS DOMINATE
Volume
UNACCEPTABLE TOXICITY
Dose
VOLUME EFFECTS DOMINATE
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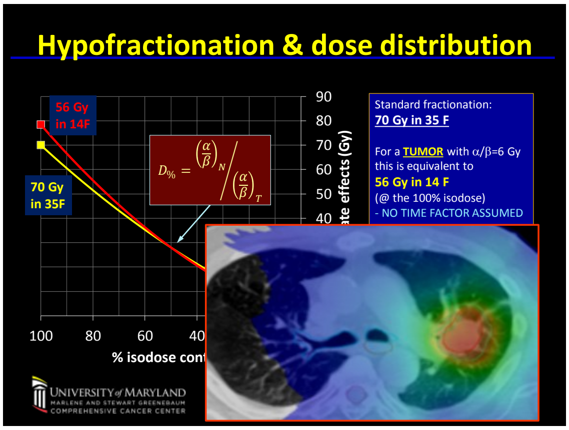
Hypofractionation & dose distribution
56 Gy in 14F
70 Gy in 35F
90
80
70
60
50
40
ate effects (Gy)
100
80
60
40
% isodose cont
Standard fractionation:
70 Gy in 35 F
For a TUMOR with α/β=6 Gy this is equivalent to
56 Gy in 14 F
(@ the 100% isodose)
- NO TIME FACTOR ASSUMED
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Critical Review
The Tumor Radiobiology of SRS and SBRT: Are More Than the 5 Rs Involved?
J. Martin Brown, PhD
BIOLOGY CONTRIBUTION
A CHALLENGE TO TRADITIONAL RADIATION ONCOLOGY
JACK F. FOWLER, PH.D., D.SC., WOLFGANG A. TOMÉ, PH.D., JOHN D. FENWICK, PH.D., AND MINESH P. MEHTA, M.D.
Department of Human Oncology, Medical School of the University of Wisconsin, Madison, WI
Dose Escalation, Not "New Biology," Can Account for the Efficacy of Stereotactic Body Radiation Therapy With Non-Small Cell Lung Cancer
J. Martin Brown, PhD, David J. Carlson, PhD
Tumor Response to Radiotherapy Regulated by Endothelial Cell Apoptosis
Monica Garcia-Barros, Francois Paris, Carlos Cordon-Cardo, David Lyden, Shahin Rafii, Adriana Haimovitz-Friedman, Zvi Fuks, Richard Kolesnick
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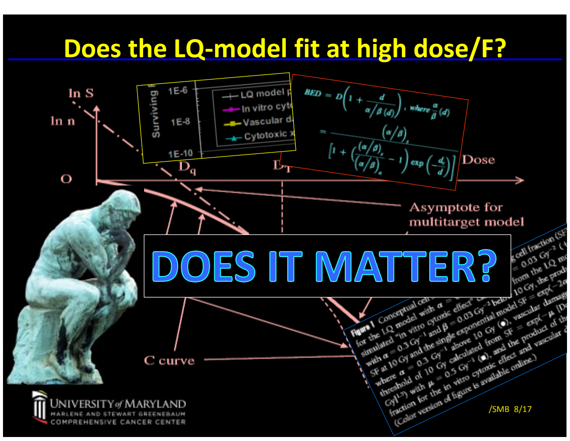
Does the LQ-model fit at high dose/F?
ln S
ln n
O
Dq
DT
Dose
Asymptote for multitarget model
C curve
LQ model
In vitro cyt
Vascular d
Cytotoxic
Surviving
1E-6
1E-8
1E-10
DOES IT MATTER?
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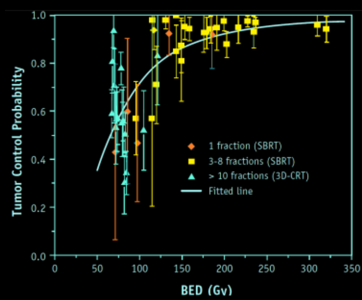
Does one (LQ-) size fit all?



Rao et al. *IJROBP* 89: 692 (2014)

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The Fowler Phenomenon – Jack's legacy

1925-2016

Thank you, Jack.

It was a great privilege to know you and to work in the same field as you.

You made all of us better scientists.

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THANK YOU!

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Ellis's assumptions (1967)

i. "The healing of skin epithelium depends on the condition of the underlying connective tissue stroma"

ii. "Apart from bone and brain, connective tissues throughout the body are similar"

iii. "Within and around a malignant tumour normal connective tissue elements make up the stroma"

"Therefore apart from bone and brain, the tumour dose limited by the normal tissue tolerance dose, could be based on skin tolerance"

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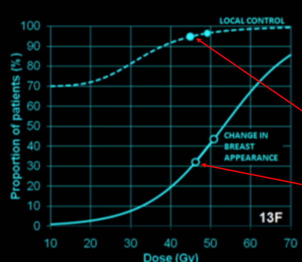
Special consideration – subclinical breast cancer



Clinical outcome data from 1487 patients in the two 13F test arms of the START A trial

Lancet Oncol 9: 331 (2008)

γ_{eff} = 0.2

γ_{30} = 1.7

…without adjusting for age, chemotherapy, tamoxifen, breast size, and surgical deficit

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Yarnold, Bentzen et al. *IJROBP* 79: 1 (2011)

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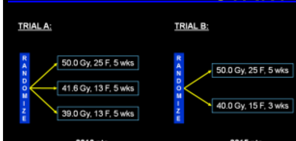
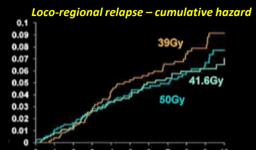
START @ 10

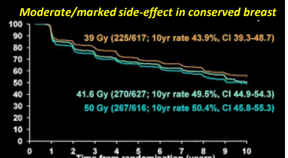


- Median F-U: 10 years
- Change in breast appearance
  - α/β=3.1 Gy (95% CI 2.0–4.2 Gy)
- Tumor relapse
  - α/β = 3.5 Gy (95% CI 1.2 – 5.7 Gy)
- Radiobiol. modeling in progress

Loco-regional relapse – cumulative hazard



Moderate/marked side-effect in conserved breast



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Haviland et al. *Lancet Oncol* 14: 1086 (2013)

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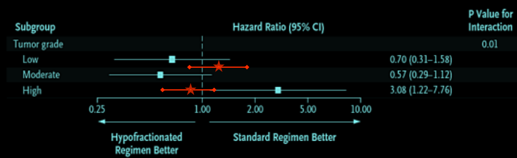
Relative contraindications for hypoFx?

OCOG (N=1234)



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Whelan et al. *NEJM* 362: 513 (2010)
Haviland, Yarnold, Bentzen *NEJM* 362: 1843 (2010)

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UK FAST-FORWARD trial

RANDOMIZE

- 40 Gy, 15F, 3 wks
- 27 Gy, 5F, 1 wk
- 26 Gy, 5F, 1 wk

- Target accrual: 4,000 women with early breast cancer randomized 1:1:1
- Primary endpoints and statistical design:
  - Tumor control: 80% power to exclude an increase in local relapse at 5 years from 2% to 3.6% (1-sided P = 0.025)
  - Tumor control (II): 80% power to exclude a 1.3% increase in 5-year local relapse in the two test arms combined
  - Breast shrinkage: 2196 patients will provide 80% power to detect an 8% increase in 5-year late toxicity (assuming 35% incidence in control arm)

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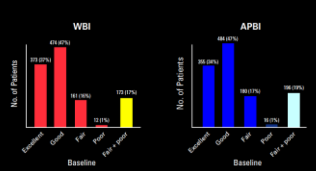
Cosmetic results from RAPID trial

- Open 2006–2011
- 2,135 women randomly assigned to 3D-CRT APBI or WBI
  - 38.5 Gy in 10 fractions twice daily vs.
  - 42.5 Gy in 16 or 50 Gy in 25 daily fractions
- Median follow-up was 36 months



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Olivotto et al. *JCO* 31: 4038 (2013)

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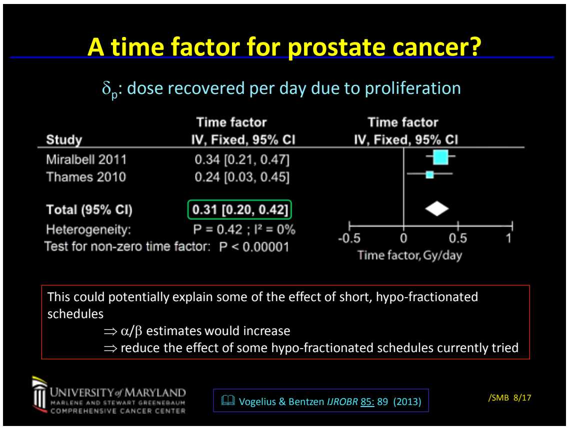
A time factor for prostate cancer?
δp: dose recovered per day due to proliferation
Study
Time factor IV, Fixed, 95% CI
Time factor IV, Fixed, 95% CI
Miralbell 2011 0.34 [0.21, 0.47]
Thames 2010 0.24 [0.03, 0.45]
Total (95% CI) 0.31 [0.20, 0.42]
Heterogeneity: P = 0.42 ; I² = 0%
Test for non-zero time factor: P < 0.00001
-0.5 0 0.5 1
Time factor, Gy/day
This could potentially explain some of the effect of short, hypo-fractionated schedules
⇒ α/β estimates would increase
⇒ reduce the effect of some hypo-fractionated schedules currently tried
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Vogelius & Bentzen IJROBR 85: 89 (2013)
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