The LQ Formulation – from Model to Practice in Prostate Cancer

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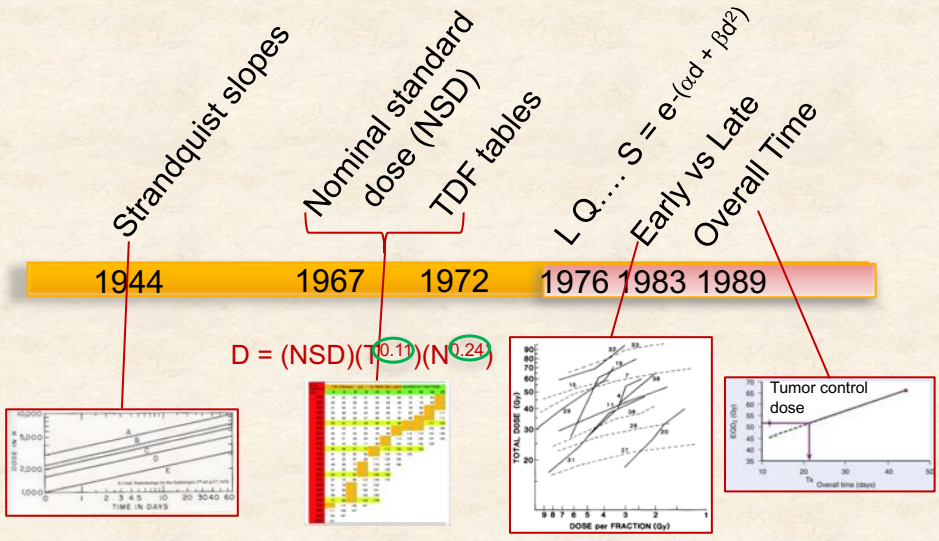
University of Wisconsin - Madison

In Honor of Jack Fowler

Radiobiological provocateur, innovator and teacher extraordinaire

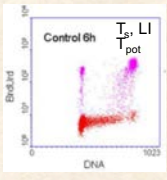
Models for fractionation and time



Jack's influence on models for fractionation and overall time

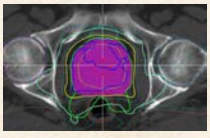
HDR Brachytherapy
- GYN; Breast

Proliferation
Normal tissue vs tumor response



H & N HyperFx

Prostate HypoFx

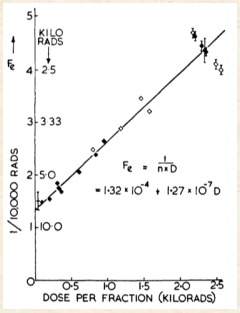


UW GYN HDR Brachytherapy Program
- Past and present Faculty -

* JACK FOWLER
* DOLORES BUCHLER
* BRUCE THOMADSEN
* JUDY STITT
* DAN PETEREIT
* BHUDATT PALIWAL
* RUPAK DAS
* SCOTT TANNEHILL

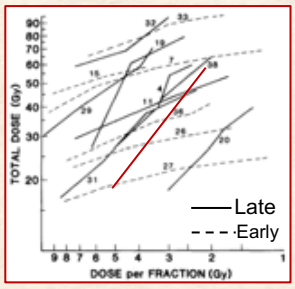
The Clinical Application of LQ to Prostate Cancer

Mouse skin rx



Douglas & Fowler 1976

Clinical data

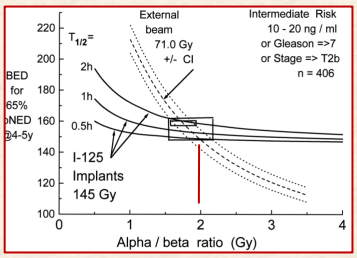


Thames, Withers
Peters,Fletcher: 1982
Barendsen, 1981

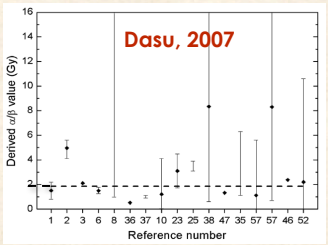
$E = \alpha D + \beta D d$

$1/D = \alpha/E + (\beta/E)\, d$

Prostate – Ext beam vs I-125



Duchesne, Peters, 1999
Brenner & Hall, 1999
Fowler, Chappell, Ritter, 2001



Outline:

- Why hypofractionation for prostate cancer?
  - Can hypofractionation be employed to improve the therapeutic ratio?
- What clinical hypofractionation trials have been completed or are underway?
- What are the potential benefits and pitfalls of extreme, so-called SBRT or SABR hypofractionation?
- What SBRT treatments are currently underway?

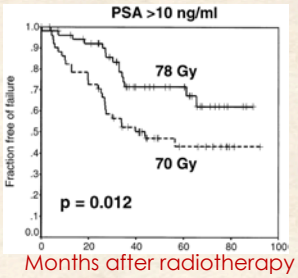
Localized Prostate Cancer: Available Treatment Modalities

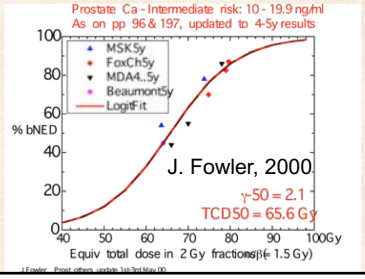
- Surveillance - (No Dose option)
- Radiotherapy: - Brachytherapy: LDR / HDR
  - High dose EBRT (IMRT)
  - Hypofractionation (incuding SBRT)
- Surgery: - Radical Retropubic
  - Laparoscopic / Robotic
- Cryosurgery
- HIFU

Dose Escalation - Rationale

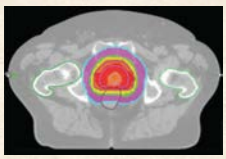
- Conventional radiation therapy (66-70 Gy) fails to achieve local control in many higher risk patients.
- Local failure can lead to the development of distant metastases.
- Dose escalation improves tumor control but at the risk of higher complications.

MD Anderson Randomized Trial
300 patients; 60 mo. median followup





Better treatment planning and delivery technology including image guidance



Dose escalation becomes feasible, but accomplished by increasing the number of radiation fractions, often to 40 or more.

<u>time, cost and resource intensive</u>

Does prostate cancer have therapeutically exploitable radiobiology that might allow a more efficient treatment?

- Slow proliferation
  - low labeling indices and long potential doubling times (Haustermans et. al., 1997)
  - long PSA doubling times often observed in new or failing patients
- A hypothesized low α/β ratio ~ 1.5 Gy
  - Implant versus external beam data

    (Duchene & Peters, 1999; Brenner and Hall,1999; Fowler, Ritter, Chappell, 2003; others)
  - HDR implant data (Brenner and Martinez)
  - External beam monotherapy data from different fraction arms

At the time, this was contrary to the prevailing belief that hyperfractionation was a potentially generally applicable approach for inproving therapeutic ratio.

Large fraction radiotherapy – "a dangerous and unsettling idea":

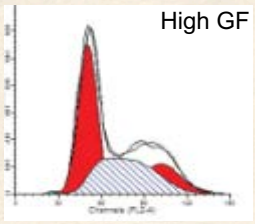
- Bates TD, Peters LJ. Dangers of the clinical use of the NSDformula for small fraction numbers. Br J Radiol 1975;48:773.
- Peters LJ, Withers HR. Morbidity from large dose fractions inradiotherapy. Br J Radiol 1980;53:170–171.
- Hatlevoll R, Host H, Kaalhus O. Myelopathy following radiotherapyof bronchial carcinoma with large single fractions: Aretrospective study. Int J Radiat Oncol Biol Phys 1983;9:41–44.
- Cox JD. Large-dose fractionation (hypofractionation). Cancer1985;55:2105–2111.

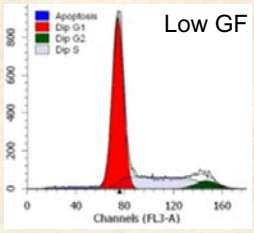
Mechanistic basis for prostate prostate hypofractionation?

Many tumors have higher growth fractions than late responding normal tissues.

Tumors with lower growth fractions may have better interfraction repair.

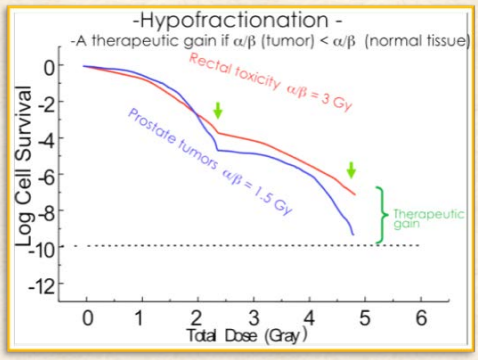
Prostate tumors often contain unusually small growth fractions (Haustermans, Begg, Fowler, 1997): T_{pot} >20 days

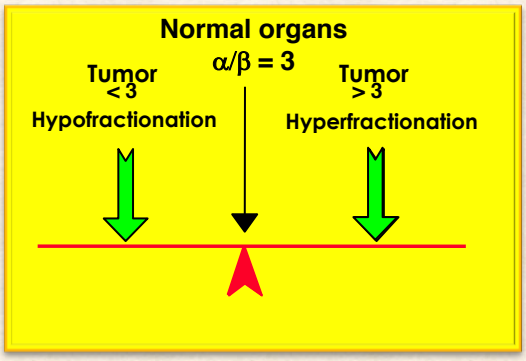




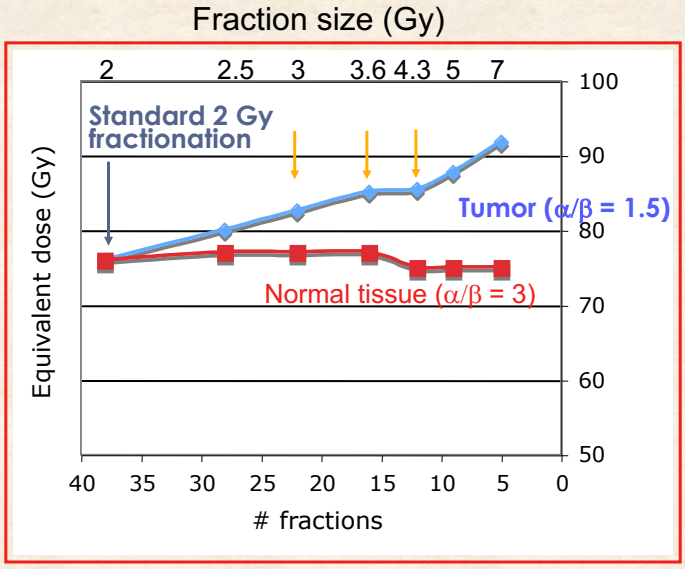
Rationale

High fraction-size sensitivity





Increasing Therapeutic Advantage with Increasing Hypofractionation



$$EQD_2 = nd \frac{\left(1 + \frac{d}{\alpha/\beta}\right)}{\left(1 + \frac{2}{\alpha/\beta}\right)}$$

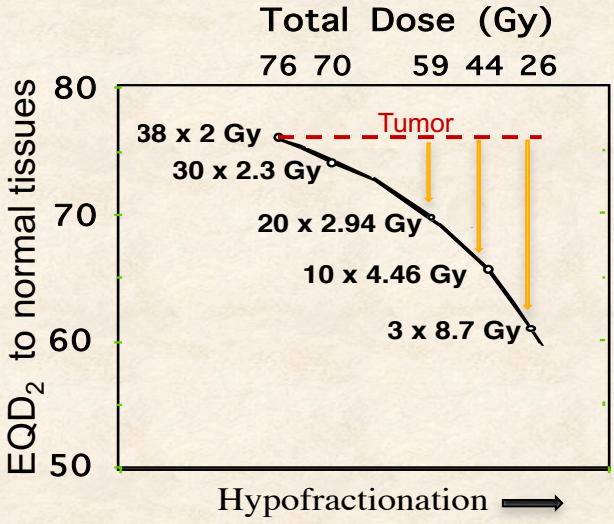
n = # fractions

d = fraction size

Prostate tumor α/β = 1.5

late tissue α/β = 3

Decrease normal tissue toxicity while maintaining constant tumor control.



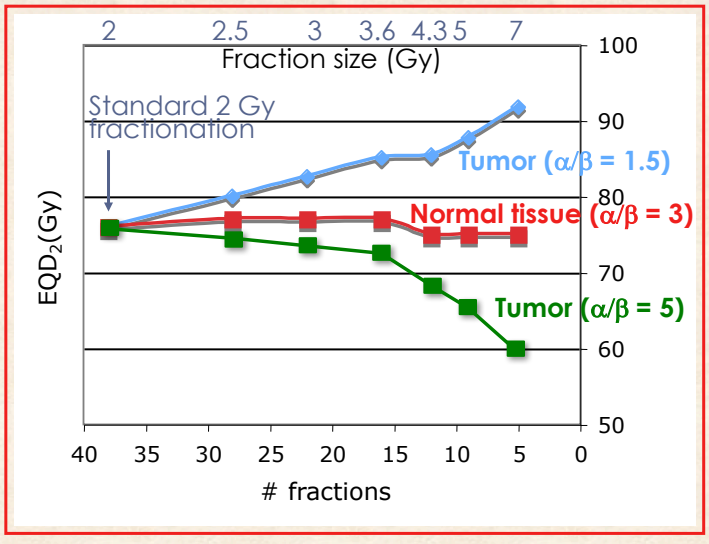
	α/β
Tumor	**1.5**
Normal	**3.0**

LQ and α/β Estimation Uncertainties

- α/β uncertainties: Large error bars
- Model uncertainties: Deviation from LQ at large fraction sizes…. differing tumor cell kill mechanisms, tumor vasculature
- Impact of tumor grade, ADT, proliferation
- Consequential late effects secondary to excessively short schedules
- Fewer fractions = reduced reoxygenation and cell cycle redistribution.

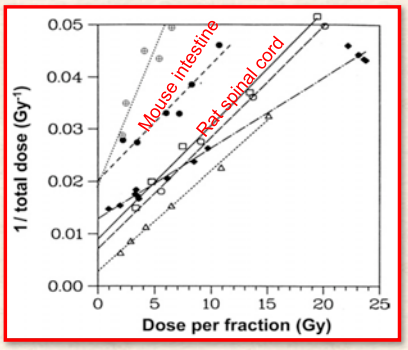
Tumor EQD_2 versus Hypofractionation

What would happen if α/β were higher than currently suspected?



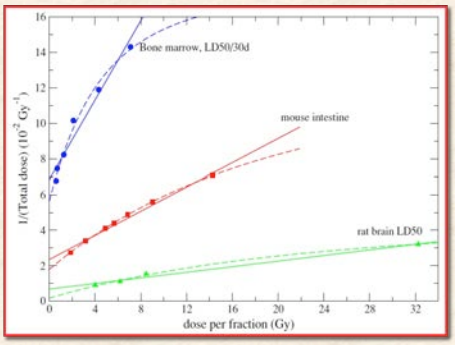
Does LQ remain valid at very large fraction sizes?

YES



As summarized by Brenner, Semin Radiat Oncol 18: 234 239 © 2008

NO



M Guerrero and Allen Li, Phys. Med. Biol. 49 (2004) 4825–4835

Less efficacy than predicted by LQ at large fraction sizes, approximated by a higher α/β.

LQ → **LQ-L**

The LQ Model -- Good Enough?

The LQ is unlikely to be mechanistically correct, but is probably adequate for moderate hypofractionation and perhaps with some modifications, for extreme hypofractionation

- Similar predictions to other mechanistic cell killing models
  - saturable repair, repair-misrepair, lethal-potentially lethal models
- Good agreement with most *in vitro* and *in vivo* laboratory fractionation experiments
- Is reasonably well validated, experimentally and theoretically, up to about 4-5 Gy/fraction and may be good enough at higher fraction sizes
- No catastrophes to date when the LQ model has been applied prudently in the clinic, but need cautious steps and adequate follow-up.

Brenner, Semin Radiat Oncol 18:234-239 © 2008

Jack's take:

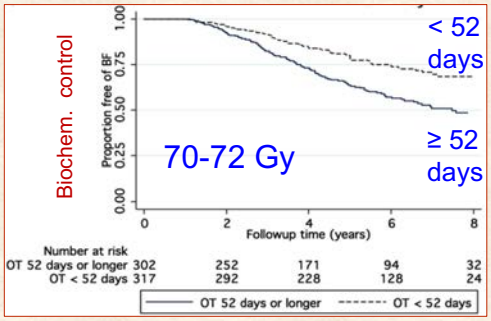
"What's a poor, confused prostate radiation oncologist to do? GO SIMPLE: Stay with LQ but perhaps adjust the alpha/beta upward as a compromise to best approximate both the low end and the high end of the fraction size spectrum."

Hypofractionated regimens are short. Standard fractionation regimens are long.....

so, does clonogen proliferation have a role?

Dose equivalent of proliferation (Gy/day)

Tumor	D_{prolif} (95% CI)
Various head and neck[23]	0.8 (0.5,1.1)
Tonsil[24]	0.73 (–,–)
Various[25]	0.64 (0.42,0.86)
Nonsmall cell lung[26]	0.45 (–,–)
Larynx[27]	0.74 (0.30,1.2)
Medulloblastoma[28]	0.52 (0.29,0.75)
Esophagus[29]	0.59 (0.18,0.99)



6% increase in biochemical failures for a one week increase in duration of treatment

Thames et al. Radiotherapy and Oncology 96 (2010) 6–12

Proliferation

$$EQD_2 = \frac{D(\alpha/\beta + d)}{(\alpha/\beta + 2)} - d_{prolif}\left(T - T_{delay}\right)$$

δ_{prolif} = 0.31 ± 0.056 Gy/d (95% CI 0.20-0.42).

Vogelius IR, Bentzen SM: Int J Radiat Oncol Biol Phys 85:89-94, 2013

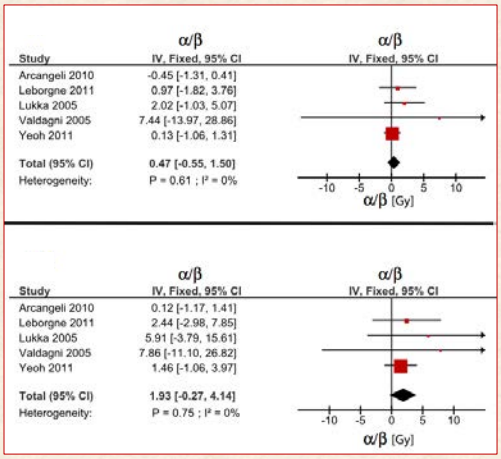
What is the value for T_{delay} ?

Thames T_{delay} ≥ 7 weeks
DeAmbrosia T_{delay} = 30-35 days.

Impact of modeling proliferation into alpha/beta estimates

without prolif.

with prolif



α/β

0.47 [-.55, 1.5]

1.93 [-.27, 4.14]

* assuming δ_{prolif} = 0.31 Gy/d

Vogelius IR, Bentzen SM:, 2013

Practical Time–Dose Evaluations, or How to Stop Worrying and Learn to Love Linear Quadratics

Jack F. Fowler

"This chapter is written mainly for those who say "I don't understand this α/β business – I can't be bothered with Linear Quadratic and that sort of stuff". Well, it might seem boring--depending on your personality--but it is easy, and it makes so many things in radiation therapy wonderfully and delightfully clear."

Technical Basis of Radiation Therapy: Practical Clinical Applications
edited by Seymour H Levitt, James A. Purdy, Carlos A. Perez, Philip Poortmans. Springer, 2012

10/31/89

Courtesy of Randy Jirtle, Duke University

Hypofractionation Trials: Schedules and Equivalent Doses

			Total Equivalent Dose in 2 Gy fractions (EQD_2)			Intermed. risk	≥ Grade 2 Late Toxicity (%)	
REFERENCE	No. PTS	Dose/fx size/# fxs	α/β = 1.5 (tumor)	α/β = 3 (late effects)	Med. F/U (mo.)	% bPFS	GI	GU
Livsey et al [22] Manchester	705	50 Gy/3.13 Gy/16 fx	66 Gy	61.3 Gy	60	56 (5 yr)	5	9
Akimoto et al [35] Gumma	52	69 Gy/3 Gy/23 fx	88.7 Gy	82.8 Gy	33	---	25	---
Tsuji et al [24] Chiba	201	66 GyE/2/3 GyE/20 fx (carbon ions)	90.5 Gy	83.1 Gy	30	97	2	6
Higgins et al [33] Edinburgh	300	52.5Gy/2.625Gy/20 fx	61.9 Gy	59.1 Gy	12	55	---	---
Soete et al [36] Jette, Belgium	36	56 Gy/3.5 Gy/16	80 Gy	72.8 Gy	----	---	---	---
Martin et al [29] Princess Margaret	92	60 Gy/3 Gy/20 fx	77.2 Gy	72 Gy	36	85	4	3
Kupelian et al [21, 37] Cleveland Clinic	770	70 Gy/2.5 Gy/28 fx	80 Gy	77 Gy	45	85	4.5	5.3
Ritter et al [28] Wisconsin	100 100 80 (active)	64.7 Gy/2.94Gy/22 fx 58.1 Gy/3.63Gy/16 fx 51.6 Gy/4.3Gy/12 fx	82.6 Gy 85.1 Gy 85.5 Gy	77 Gy 77 Gy 75 Gy	38 24 14	95	8.5	1
Lukka et al [23] NCIC	466 470	52.5/2.625 Gy/20 fx 66 Gy/2 Gy/33 fx	61.9 Gy 66 Gy	59.1 Gy 66 Gy	68	40	1.3	1.9
Yeoh et al [38] Adelaid	108 109	55 Gy/2.75 Gy/20 fx 64 Gy/2 Gy/32 fx	66.8 Gy 64 Gy	63.2 Gy 64 Gy	48	57.4 55.5	Alternate scoring	Alternate scoring
Pollack et al [39] Fox Chase	150 150	70.2 Gy/2.7Gy/26 fx 76 Gy/2 Gy/38 fx	84.2 Gy 76 Gy	80 Gy 76 Gy	---	---	---	---
RTOG www.rtog.org/members/protocols/0415/0415.pdf	Ongoing (to 1067 pts)	70 Gy/2.5 Gy/28 fx 73.8 Gy/1.8 Gy/41 fx	80 Gy 69.6 Gy	77 Gy 70.8 Gy	---	---	---	---
CHIP - MRC	Ongoing (to 2100 pts)	57 Gy/3 Gy/19 fx 60 Gy/3 Gy/20 fx	73.3 Gy 77.2 Gy	68.4 Gy 72 Gy	---	---	---	---

A Phase I/II Trial of Increasingly Hypofractionated Radiation Therapy for Prostate Cancer

Investigators

Mark Ritter
Jack Fowler — **University of Wisconsin**
Rick Chappell
Jeffrey Forman — **Wayne State University**
Patrick Kupelian — **M.D. Anderson, Orlando**
Daniel Petereit — **Rapid City, S. Dakota**
Colleen Lawton — **Medical College of Wisconsin**

Acknowledgements

Data management: Nick Anger, Wendy Walker, Heather Geye

NIH-R01CA106835; PO1 CA106835

A Five Institution, Phase I/II Hypofractionation Trial

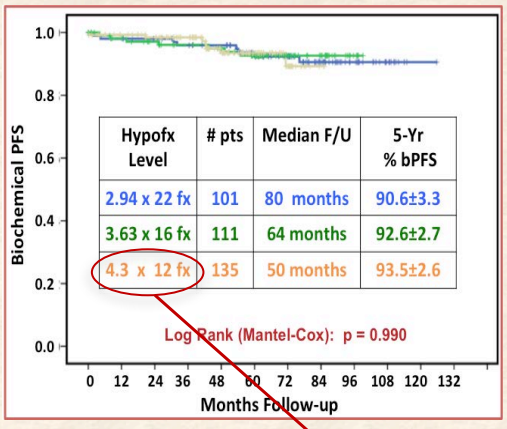
347 patients

Median follow-ups of 80, 64 and 50 months

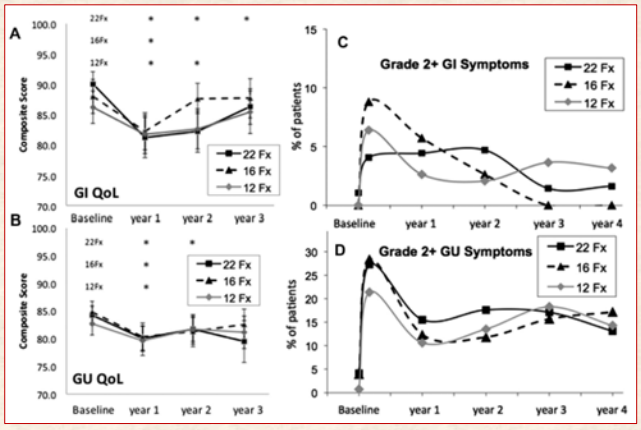
Fract. Level	# pts	Dose per Fx (Gy)	# Fxs	Total dose (Gy)	Tumor EQD_2 *alpha/beta* =1.5)
I	101	2.94	22	64.68	82.6
II	111	3.63	16	58.08	85.1
III	135	4.3	12	51.6	85.5

Predicted late toxicities equivalent to 76Gy in 2 Gy fractions

Biochemical PFS vs Hypofractionation Level

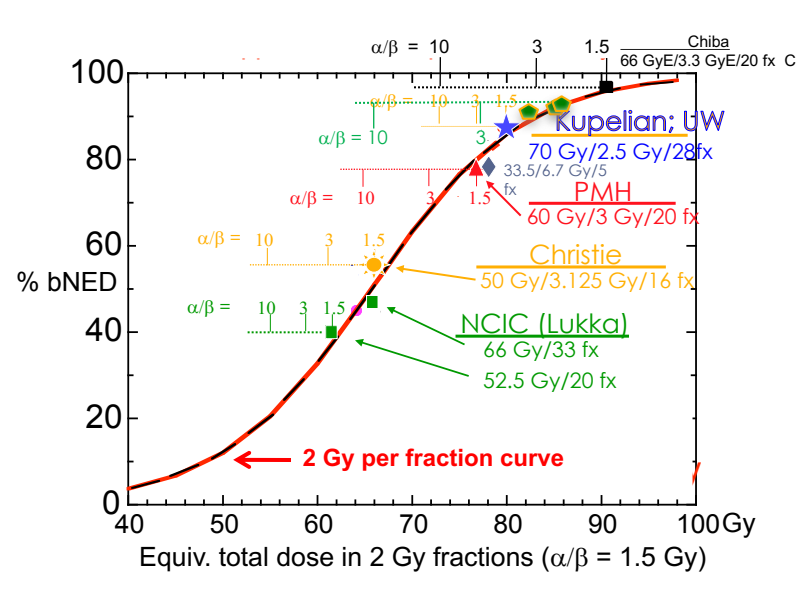


Quality of Life scores



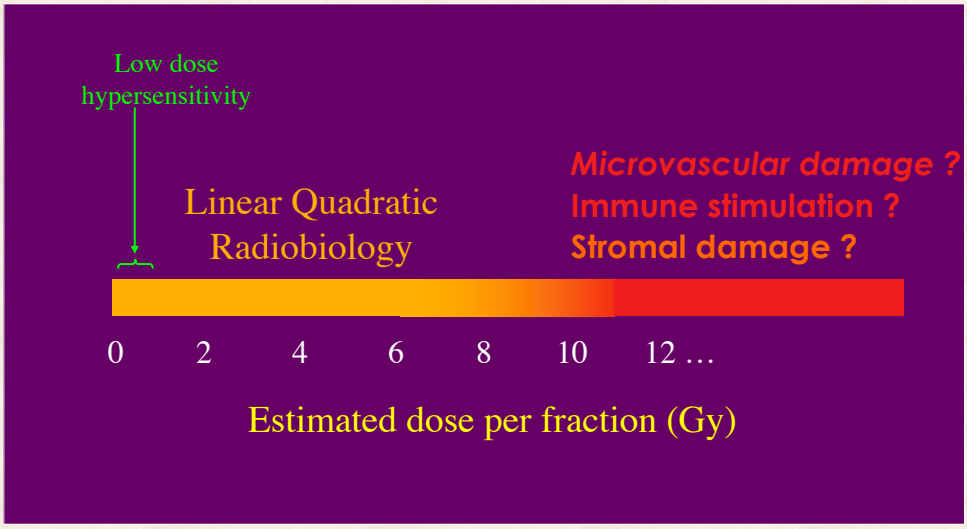
RTOG 0938: Randomized phase II: 4.3 Gy x 12 versus 7.25 Gy x 5 fractions

Dose response curve for % PSA control



If one assumes an α/β of 1.5, clinical outcomes match LQ predictions.

Hypofractionation



Stereotactic Body Radiation Therapy

SBRT Considerations

- Immobilization
- Image guidance
  - Motion
    - Interfraction
    - Intrafraction
      - Imaging-to-treatment interval
  - Respiration
    - prone versus supine
    - body fix or respiratory gating

HEALTH

The New York Times

Popular Prostate Cancer Therapy Is Short, Intense and Unproven.

By GINA KOLATA MARCH 20, 2017

Faster	5 treatments vs 40	√
Cheaper	$13,645 versus $21,023 (Medicare claims:Yu, 2014) $22,152 versus $35,431 (Hodges, 2012)	√
Better		?

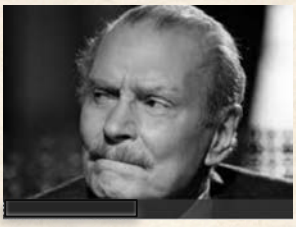
Selected prostate SBRT trials with more than minimal follow-up

Institution	Platform	Dose Fractionation	Median F/U years	Risk group	Pts	5-Year bDFS[a] (%)
Virginia Mason (71)	Gantry-based linac	6.7 Gy × 5	3.4	Low	40	90[b]
Stanford (73)	CyberKnife	7.25 Gy × 5	2.7	Low and low–intermediate	67	94
Stanford, Naples (79)	CyberKnife	7–7.25 Gy × 5	5	Low and low–intermediate	41	93
Winthrop Hospital (78)	CyberKnife	7–7.25 Gy × 5	6	Low	324	97
				Intermediate	153	91
San Bortolo (80)	CyberKnife	7 Gy × 5	3	Low, intermediate, and high	100	94
Pooled eight institutions (74)	CyberKnife	36–40 Gy in 4–5 fxs	3	Low	641	95
				Intermediate	334	84
				High	125	81
Katz and Kang (81)	CyberKnife	7–7.25 Gy × 5	5	High	97	68
Multi-institution (82)	CyberKnife	8 Gy × 5	3	Intermediate	137	97
Sunnybrook (76)	Gantry-based linac	7 Gy × 5	4.7 5	Low	84	97
Twenty-first century (77)	Gantry-based linac	8 Gy × 5	5	Low	98	99

Meier, Front. Oncol 2015

6 x 6 Gy 232 pts (1962 – 84). Olivier treated in 1967
(Similar to the 5 x 7.25 Gy regimen commoned today).
EQD2: 77.25 Gy vs. 90.75 Gy

Collins CD, Lloyd-Davies RW, Swan AV. Radical external beam radiotherapy for localised carcinoma of the prostate using a hypofractionation technique. Clin Oncol (R Coll Radiol) 1991;3:127–132.

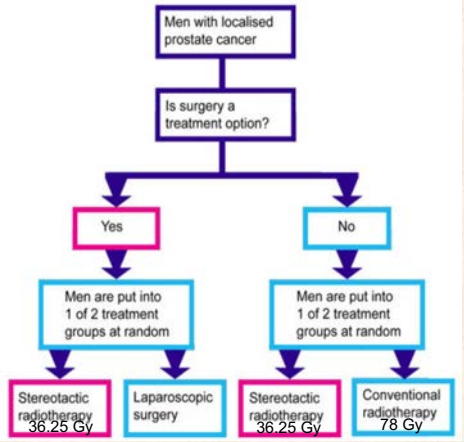


Cottrell J. Laurence Olivier. Englewood Cliffs, NJ: Prentice-Hall; 1975. p. 352.

RANDOMIZED SBRT TRIALS

	SBRT Arm		Arm 2
Widmark:	42.7 at 6.1 Gy 7 fractions	vs	78 Gy at 2 Gy 39 fractions
RTOG 0938:	36.25 at 7.25 Gy 5 fractions	vs	51.6 at 4.3 Gy 12 fractions
U. Miami	36.25 at 7.25 Gy 5 fractions	vs	70.2 at 2.7 Gy 26 fractions

PACE trial (UK)
(1,700 patients)

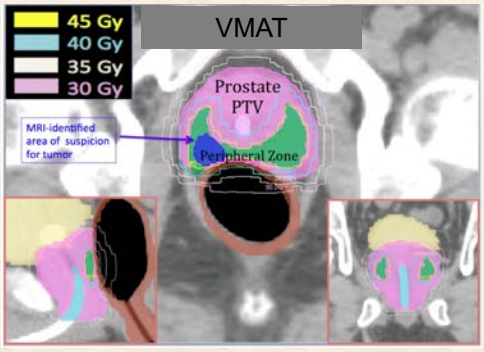


A UW Phase I/II Trial of Stereotactic Body Radiotherapy (SBRT) for Prostate Cancer with a Simultaneous Integrated Boost to MRI-identified Intraprostatic Tumors(NCT02470897)

Prostate MRI
Identify prostate borders, tumor(s), urethra

Planning CT
target and normal organ contours on CT/MRI fusion

- 8 Gy for 5 fractions delivered every other week day; IMRT/IGRT except to exclusion zone and MRI-identified intra-prostatic cancers
- Exclusion zone: Urethra, adjacent bladder and rectal borders constrained to 7.25 Gy per fraction (or 8 Gy to any region overlapping with an MRI-detected tumor.
- **Tumor SIB volume:** MRI-identified, lesions simultaneously boosted up to to 9 Gy per Fx (8 Gy/Fx if overlapping exclusion zone)

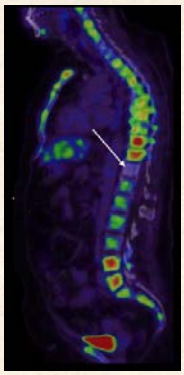


Newer research directions in the management of prostate cancer

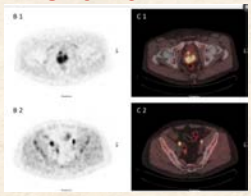
Imaging

- improved staging;
- ablation of oligomets

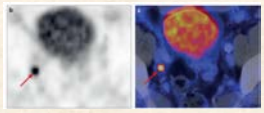
NaF PET



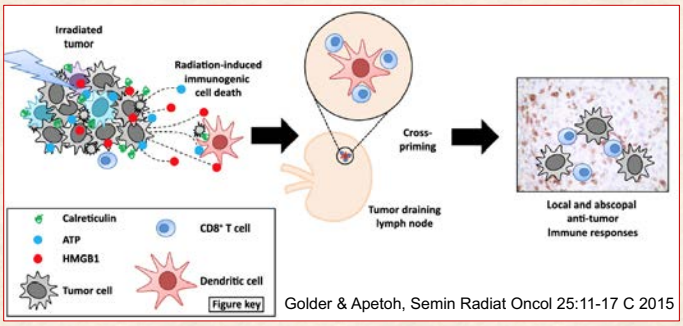
Choline-PET



PSMA-PET



Immuno-radiation therapy



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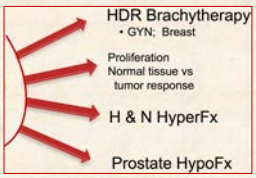
Jack's Legacy



- Profound and continuing impact on the field of Radiation Oncology and on countless research careers.
- A kind, generous and enthusiastic mentor to many, myself included.
- Contagious enthusiasm for research and for life.

May 2006