ON THE USE OF BIOMATHEMATICAL PRINCIPLES IN SBRT: UNDERSTANDING EFFICACY AND SAFETY

Wolfgang A. Tomé, PhD., FAAPM, FASTRO
Professor of Radiation Oncology
Professor of Neurology
Montefiore Einstein Comprehensive Cancer Center
Bronx, NY 10463

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- Research grants form the National Cancer Institute
- Research grants from Varian
- Research grants from Accuray
- Research grants from Chrysalis Biotherapeutics
- Research Collaboration agreements with Brainlab; MIM Software; Oncospace Inc.
- Member of the SAB of Archeus Technologies

Objectives:

- Once one steps outside the box of conventional fractionation how can one assess the potential efficacy/safety of a fractionation schedule for expected normal tissue complications and potential tumor effect.
- What distinguishes Prostate SBRT form other forms of SBRT such as Lung and Liver SBRT?
- Why are current prostate SBRT fractionation schedules safe and effective?

SBRT is about increasing the therapeutic window and widening the therapeutic index, by steepening the TCP curve and pushing the NTCP curve to the right.

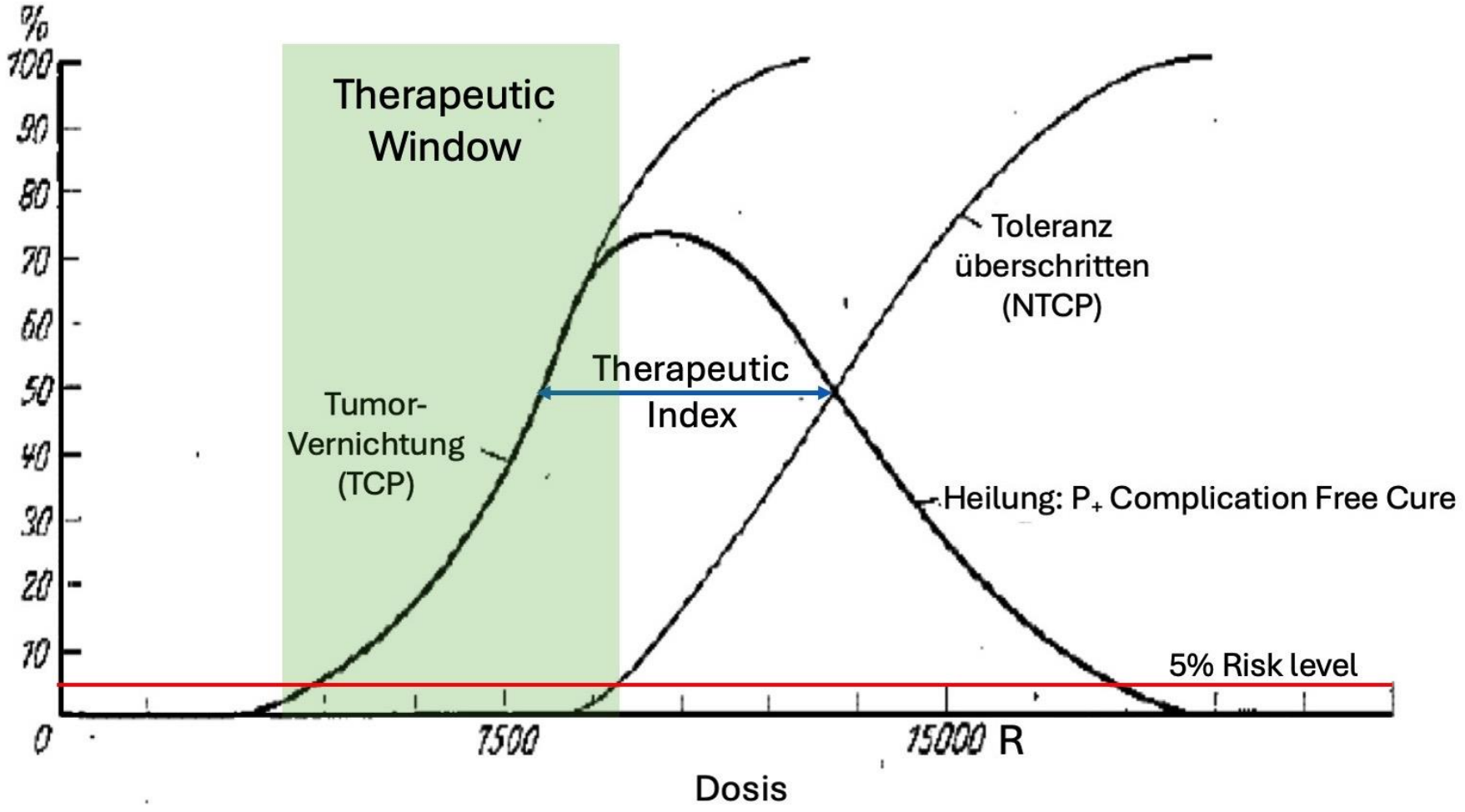


Figure 2.1: Sigmoid shaped dose response curves for TCP and NTCP. Adapted form Hermann Holthusen [Holthusen, Strahlentherapie, 1936; 57:254-69.]

The concept of Biological Effective Dose *(BED)*

The concept of Biological Effective Dose was introduced by Jack Fowler (BJR 1989; 62: 679-94). Fowler defined the BED as the total dose delivered in an infinite number of infinitesimally small doses per fraction (or at ultra low dose rate) that causes the same *Effect* (Cell Kill, *NTCP*, or *TCP*) as a given fractionation schedule.

$$BED = nd\left(1 + \frac{d}{\alpha/\beta}\right) - \frac{\lambda}{\alpha}(T - T_k)H(T - T_k)$$

In this expression, *n* denotes the number of fractions, *d* is the dose per fraction of the fractionation schedule considered, and the α/β-ratio in Gy has the usual meaning and is chosen appropriately for the endpoint studied. The proliferation correction term contains 3 parameters the proliferation rate λ, the overall treatment time T, and the kick-off time T_k (14-42 days). Since, BED values critically depend on the α/β-ratio they should be reported in $Gy_{\alpha/\beta}$ to allow for their proper interpretation.

Since SBRT schedules are usually delivered in $< T_k$ days implying that $H(T - T_k) = 0$, we have that the proliferation term is zero making such schedules more effective by steepening the dose response curve.

ELSEVIER

Int. J. Radiation Oncology Biol. Phys., Vol. 60, No. 4, pp. 1241–1256, 2004

0360-3016/04/$–see front matter

doi:10.1016/j.ijrobp.2004.07.691

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

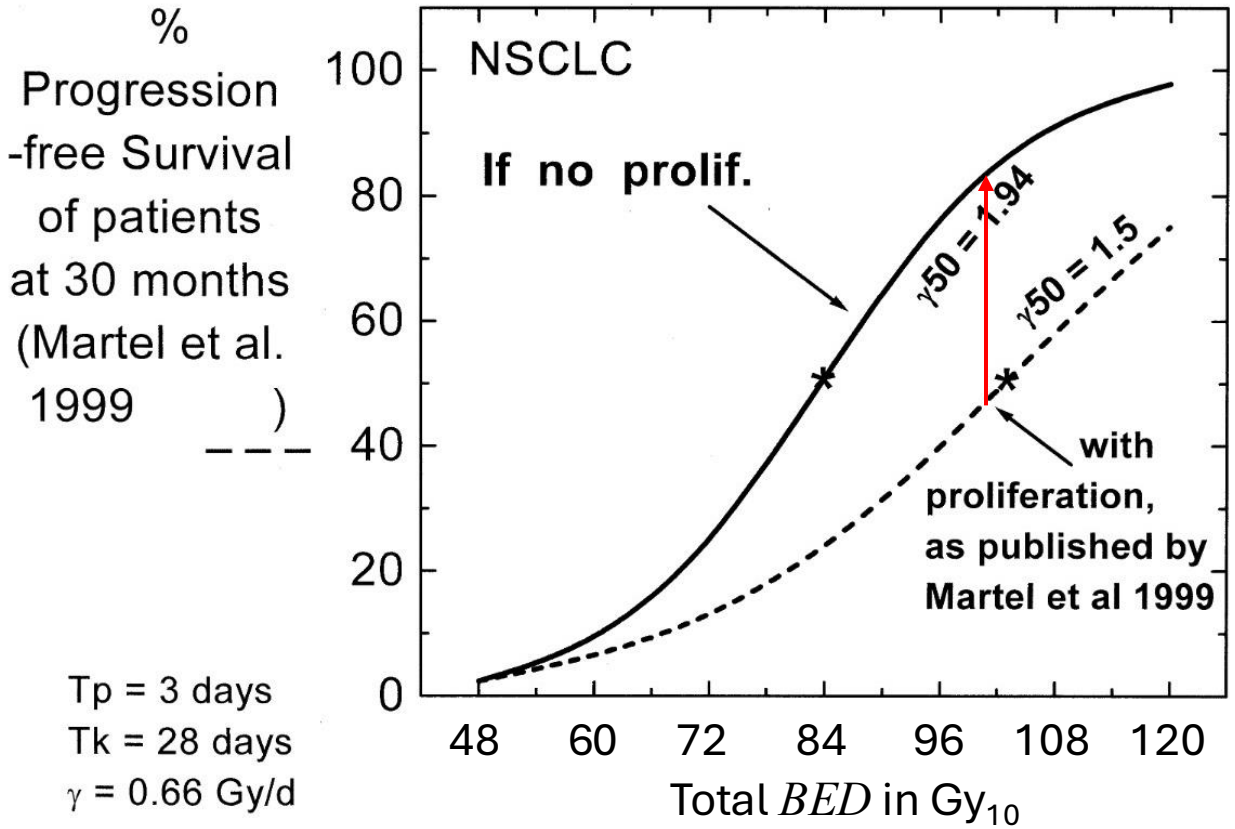


Fig. 2. Martel's curve with and without repopulation, and a calculated dose–response curve assuming no repopulation of tumor cells.

- If proliferation does not take place during therapy the dose response curve steepens significantly.
- Leading to a potential increase in LC at a BED =100Gy$_{10}$ of about 38%
- To achieve the maximal LC rate in lung SBRT a dose fraction schedule having a BED_{10} of minimally 100Gy$_{10}$ needs to be delivered.

P. Lee, B.W. Loo, T. Biswas, *et al.*
Local control following stereotactic body radiation therapy for stage I non-small cell lung cancer
Int J Radiat Oncol Biol Phys, 110 (1) (2021), pp. 160-171, 10.1016/j.ijrobp.2019.03.045

The Link Between BED and the Poisson Dose response Model

When describing Complication Probability (TCP or NTCP) using Poisson statistics it is clearly the probability of zero tumor/tissue stem cells surviving that is of interest, i.e.

$$CP = \frac{N^0}{0!}\exp(-N) = \exp(-N)$$

where N is the ***average number*** of surviving stem cells. For tumors N should be *as* small as possible, while for normal tissue it should be as large as possible. It is straightforward to show using the LQ model that the ***average number*** of surviving stem cells after *n* fractions of dose *d, is given by:*

$$N = N_o \prod_{i=1}^{n} SF(d) = N_o \left[SF(d)\right]^n = N_o \exp\left[-nd(\alpha + \beta d)\right]$$

Therefore, we find for the complication probability:

$$CP = \exp\{-N_0 \exp[-nd(\alpha + \beta d)]\} = \exp\left(-N_0 \exp\left\{-\alpha\left[nd\left(1 + \frac{d}{\alpha/\beta}\right)\right]\right\}\right)$$

Which is simply:

$$CP = \exp[-N_0 \exp(-\alpha\, BED)]$$

(Roberts &Hendry, Int. J. Radiat. Onc. Bio. Phys. 41: 689—699, 1998; 45: 1247-1257, 1999)

Draw back of the concept of Biological Effective Dose.

BED formalizes the conversion of doses delivered using any fractionation scheme to their biologically effective levels delivered at an Ultra Low Dose Rate, the only parameter needed for this conversion being the α/β- ratio for the endpoint studied. This is good for standardization purposes but means that the standard fractionation scheme to which all doses are converted is ULDR therapy, producing BED values that are very different to the doses used in typical external beam schedules.

The Equivalent Dose in 2Gy fractions (EQD_2) or the Normalized Dose (NTD) concept

To remedy this situation Lebesque and Keus (Radiother. Oncol. 1991; 22: 45-55) introduced the Equivalent Dose (Normalized Dose) Concept. It is defined it as the total dose, given in 2 Gy fractions, that has the same biological effect as the actual treatment schedule under consideration. Therefore, EQD_2 given by:

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

Since, the value of EQD_2 critically depends on the α/β-ratio its value should be reported in $Gy_{\alpha/\beta}$ to allow for its proper interpretation. I.e. normal tissue EQD_2 *should be reported as* Gy_3 *, while for* tumors or rapidly proliferating normal tissue it should be reported as Gy_{10}. As was the case for BED one can link EQD_2 to the complication probability for a given EQD_2:

$$CP = \exp\left[-N_0 SF_2^{-\left(\frac{EQD_2}{2}\right)}\right]$$

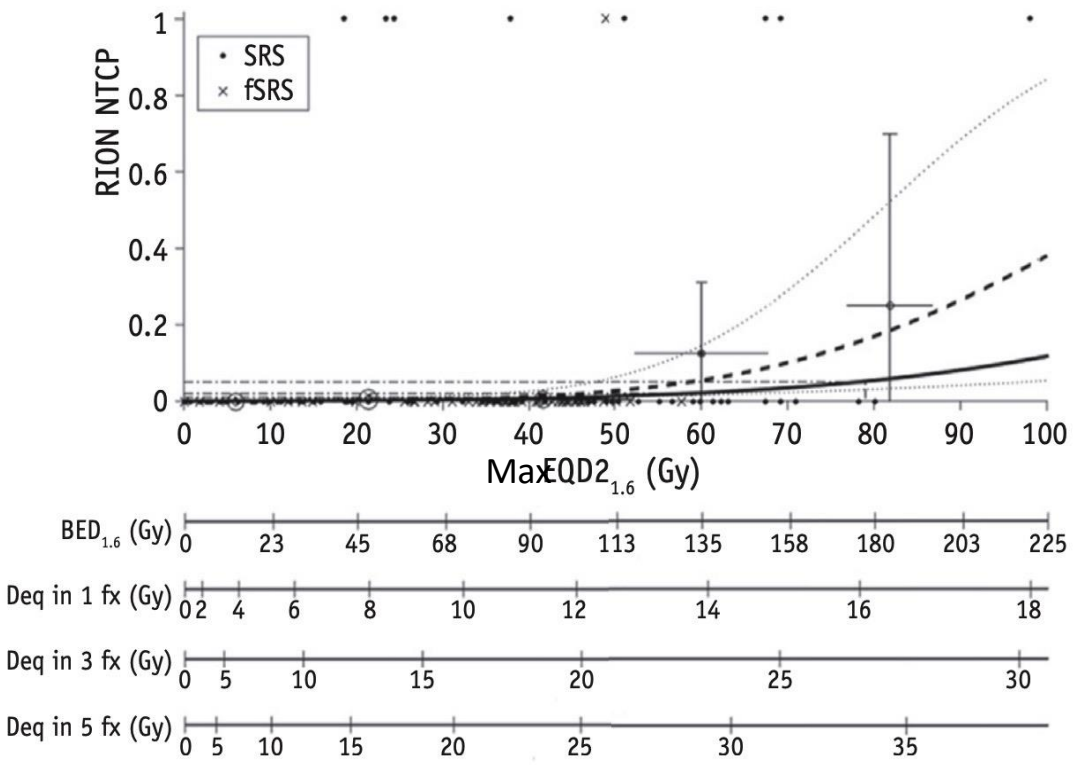
For organs that exhibit a mostly serial architecture the risk of incurring a complication is strongly influenced by high dose regions and hot spots, and therefore the maximum EQD_2 received by such an organ will strongly correlate with $NTCP$.

HyTEC Organ-Specific Paper

Single- and Multi-Fraction Stereotactic Radiosurgery Dose Tolerances of the Optic Pathways

Michael T. Milano, MD, PhD,* Jimm Grimm, PhD,† Scott G. Soltys, MD,‡ Ellen Yorke, PhD,§ Vitali Moiseenko, PhD,‖ Wolfgang A. Tomé, PhD,¶ Arjun Sahgal, MD,# Jinyu Xue, PhD,** Lijun Ma, PhD,†† Timothy D. Solberg, PhD,†† John P. Kirkpatrick, MD, PhD,‡‡ Louis S. Constine, MD,* John C. Flickinger, MD,§§ Lawrence B. Marks, MD,‖‖ and Issam El Naqa, PhD¶¶

Int J Radiation Oncol Biol Phys, Vol. 110, No. 1, pp. 87–99, 2021

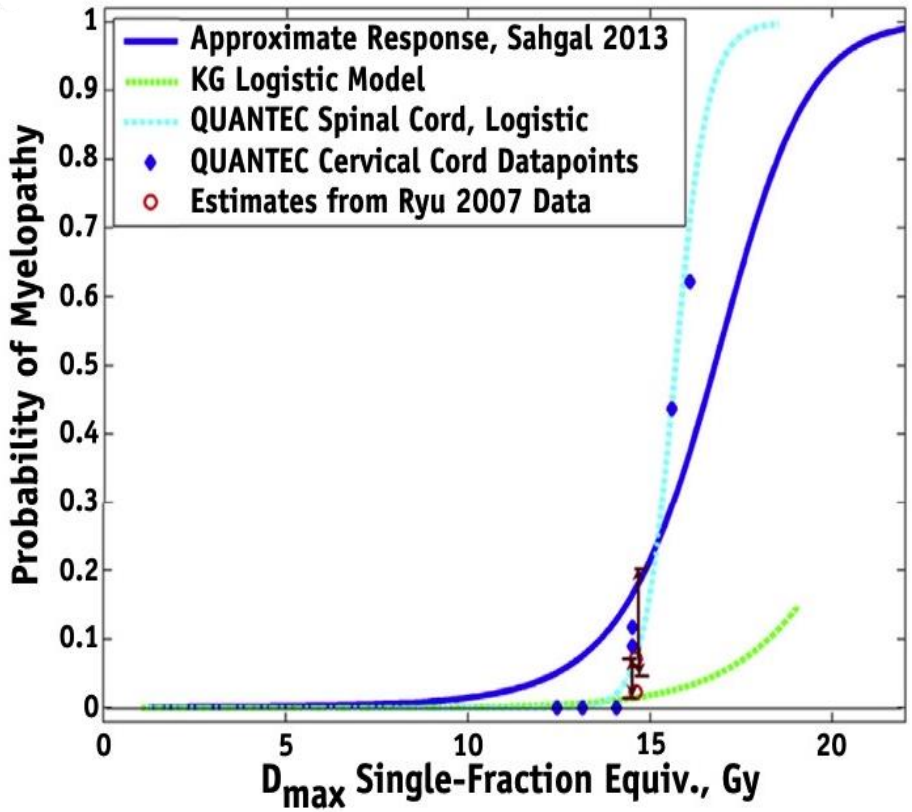


HyTEC Organ-Specific Paper: Spinal Cord

Spinal Cord Dose Tolerance to Stereotactic Body Radiation Therapy

Arjun Sahgal, MD,* Joe H. Chang, MBChB, PhD,* Lijun Ma, PhD,† Lawrence B. Marks, MD,‡ Michael T. Milano, MD, PhD,§ Paul Medin, PhD,‖ Andrzej Niemierko, PhD,¶ Scott G. Soltys, MD,# Wolfgang A. Tomé, PhD,** C. Shun Wong, MD,* Ellen Yorke, PhD,†† Jimm Grimm, PhD,‡‡ and Andrew Jackson, PhD††

Int J Radiation Oncol Biol Phys, Vol. 110, No. 1, pp. 124–136, 2021



The Mean Normalized Total Dose (NTD_{mean}) concept

While, for organs that exhibit a mostly parallel organization the risk for developing a complication depends on the dose distribution throughout the organ rather than the high dose to a small volume of the organ. Therefore, for parallel organs the mean dose received by the organ strongly correlates to $NTCP$. For this reason, one is interested in the mean NTD when considering parallel organs, which is defined as follows:

$$NTD_{mean} = \sum_{i=1}^{N_b} v_i \, NTD_i \quad \text{, where}$$

$$NTD_i = nd_i \frac{(\alpha/\beta + d_i)}{(\alpha/\beta + 2)} \quad \text{and} \quad \sum_{i=1}^{N_b} v_i = 1$$

Here N_b denotes the total number of dose bins in the differential DVH for the parallel organ under consideration, NTD_i denotes the NTD for the $i\text{-}th$ dose bin, n denotes the total number of fractions, d_i denotes the dose per fraction in the $i\text{-}th$ dose bin, and v_i denotes the partial volume associated with the $i\text{-}th$ dose bin.

NTCP model for the incidence of radiation pneumonitis based on NTD_{mean}

For partially irradiated lung, Kwa et al. (Int J. Radiat. Bio Phys 1998, 42 1-9) have described the use of the Lyman model in modeling the incidence of radiation induced pneumonitis in terms of NTD_{mean}. They proposed to use the following model to describe the incidence radiation induced pneumonitis:

$$NTCP = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{t} \exp(-x^2/2)dx + c,$$

with

$$t = \frac{NTD_{mean} - NTD_{50}}{m \; NTD_{50}}$$

where NTD_{50} is NTD that results in 50% probability for the incidence of radiation pneumonitis, the parameter m governs the slope of the dose response curve, and the parameter c describes a possible dose independent offset, i.e., the parameter c describes the possibility that radiation pneumonitis is induced even if the lung receives a very low NTD_{mean}.

Acta Oncologica, 2009; 48: 571–577

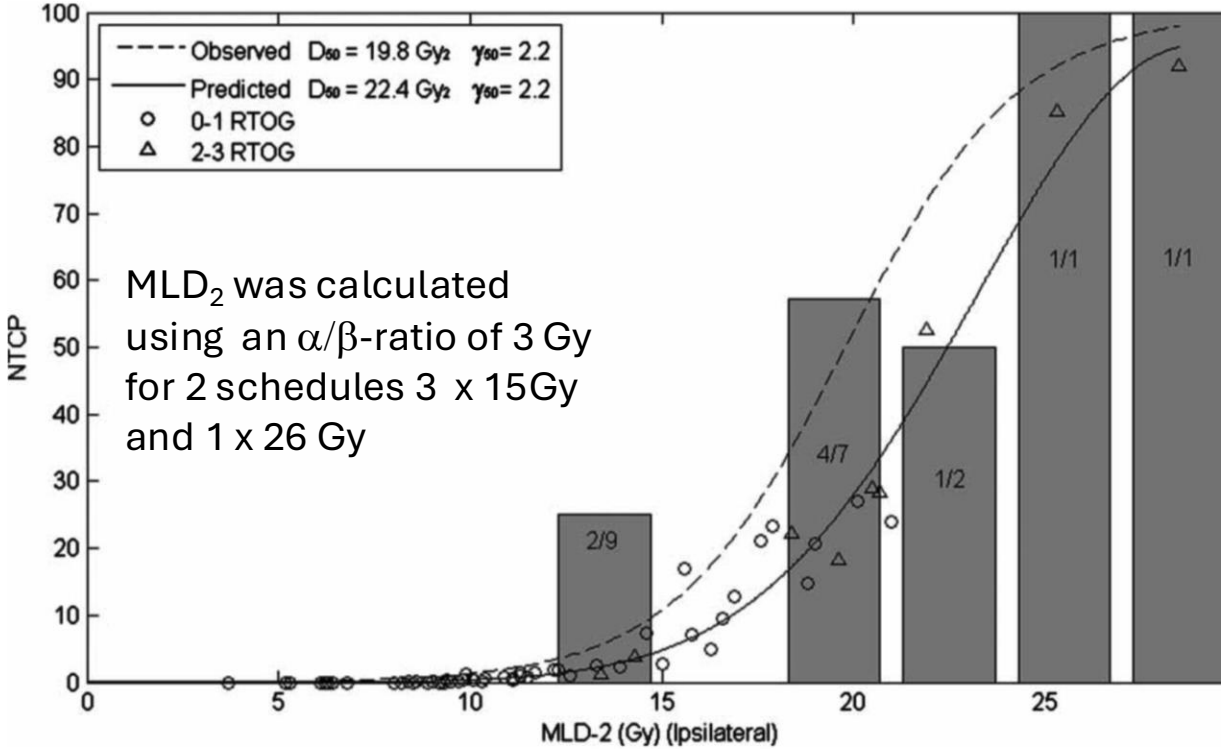
informa
healthcare

ORIGINAL ARTICLE

Dosimetric predictors of radiation-induced lung injury in stereotactic body radiation therapy

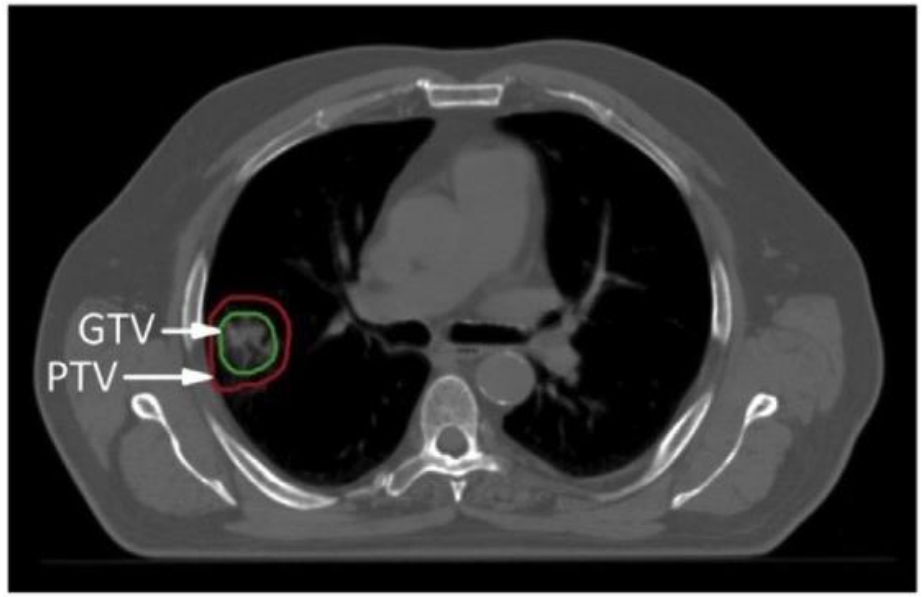
UMBERTO RICARDI[1], ANDREA RICCARDO FILIPPI[1], ALESSIA GUARNERI[1], FRANCESCA ROMANA GIGLIOLI[2], CRISTINA MANTOVANI[1], CHRISTIAN FIANDRA[1], SILVIA ANGLESIO[2] & RICCARDO RAGONA[1]

[1]*Department of Medical and Surgical Sciences, Radiation Oncology Unit, University of Torino, S. Giovanni Battista Hospital, Torino, Italy and* [2]*Medical Physics, S. Giovanni Battista Hospital, Via Genova, 3-10126 Torino, Italy*



The histogram shows the percentage of NRG grade 2-3 lung toxicity (the values in the bars indicated the number of patients with grade 2-3 toxicity over the total number of patients at risk at the MLD range.

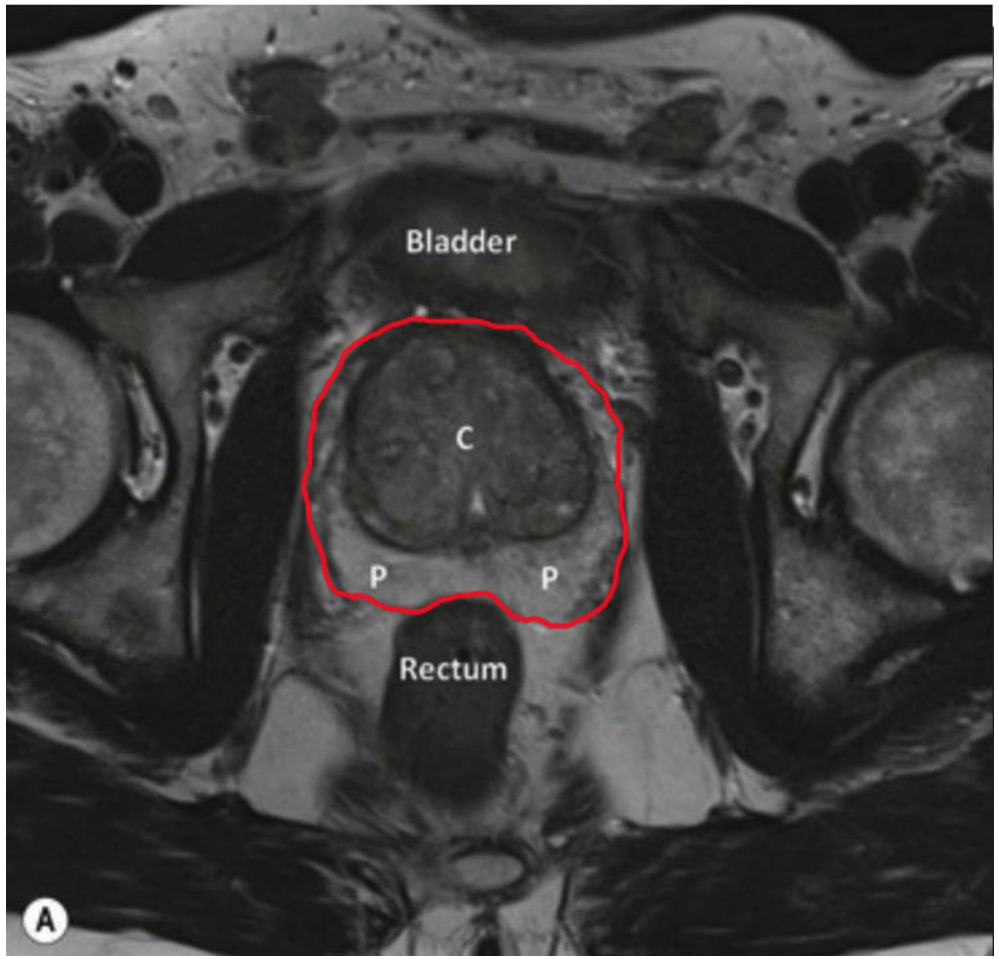
In Lung SBRT we have a tumor (the ultimate parallel structure) embedded in an organ at risk (lung) exhibiting a mostly parallel architecture. The same is true for Liver SBRT.



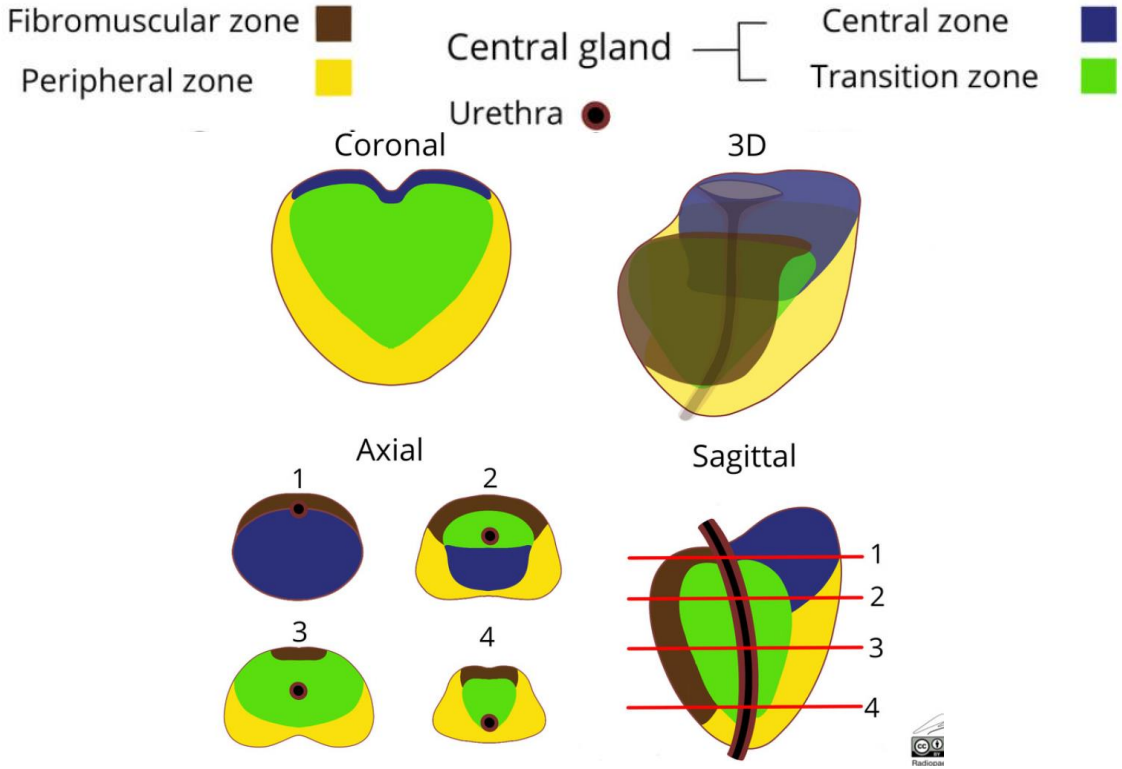
F-M Spring Kong, V Moiseenko, J Zhao, *et al.*
Organs at risk considerations for thoracic stereotactic body radiation therapy: What is safe for lung parenchyma?
Int J Radiat Oncol Biol Phys, 110 (2021), pp. 172-187

It therefore reasonable to ask if this also true for prostate SBRT?

Prostate SBRT: Surrounding Anatomy and the Anatomy of the Prostate



A. Axial T2-weighted MR image showing the prostate and its zonal anatomy. The peripheral zone (P) is shown as a crescent-shaped hyperintense structure; the central gland (C) is depicted as a structure with heterogeneous signal intensity. Downloaded from: https://radiologykey.com/prostate-2/



Downloaded from: https://radiopaedia.org/cases/prostate-anatomy?lang=us

Using multiparametric MR data form 90 patients Lee et al. found the following distribution of lesion location within the prostate:

- 35.2% in the Anterior Fibromuscular zone
- 5.6% in the Central zone
- 32.4% in the Peripheral zone
- 25.4% in the Transition zone

Lee, Carver, Feldmann, et al. Front. Oncol. 9 - 2019 | https://doi.org/10.3389/fonc.2019.00616

HyTEC Organ-Specific Paper: Abdomen and Pelvis

Prostate Stereotactic Body Radiation Therapy: An Overview of Toxicity and Dose Response

Kyle Wang, MD,* Panayiotis Mavroidis, PhD,* Trevor J. Royce, MD, MS, MPH,* Aaron D. Falchook, MD,† Sean P. Collins, MD, PhD,‡ Stephen Sapareto, PhD,§ Nathan C. Sheets, MD,* Donald B. Fuller, MD,‖ Issam El Naqa, PhD,¶ Ellen Yorke, PhD,# Jimm Grimm, PhD,**,†† Andrew Jackson, PhD,# and Ronald C. Chen, MD, MPH‡‡

**Department of Radiation Oncology, University of North Carolina, Chapel Hill, North Carolina; †Memorial Healthcare System, Pembroke Pines, Florida; ‡Department of Radiation Oncology, Georgetown University Hospital, Washington, DC; §Department of Medical Physics, Banner Health System, Phoenix, Arizona; ‖Genesis Healthcare Partners, San Diego, California; ¶Department of Machine Learning, Moffitt Cancer Center, Tampa, Florida; #Department of Medical Physics, Memorial Sloan Kettering Cancer Center, New York, New York; **Department of Radiation Oncology, Geisinger Health System, Danville, Pennsylvania; ††Department of Medical Imaging and Radiation Sciences, Thomas Jefferson University, Philadelphia, Pennsylvania; and ‡‡Department of Radiation Oncology, University of Kansas, Kansas City, Kansas*

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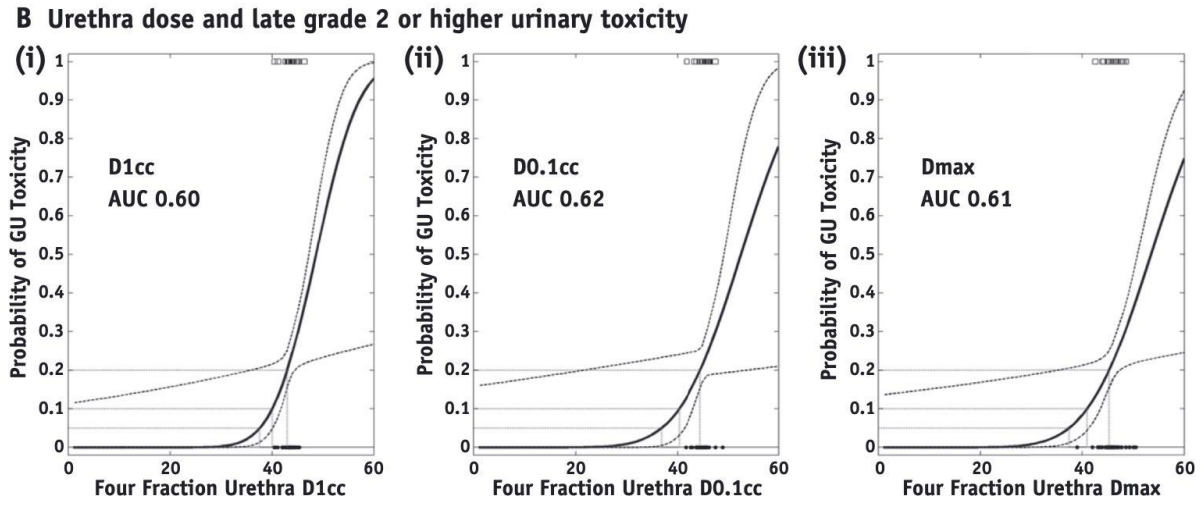
Int J Radiation Oncol Biol Phys, Vol. 110, No. 1, pp. 237–248, 2021

Dose response models for Urethra and Rectum



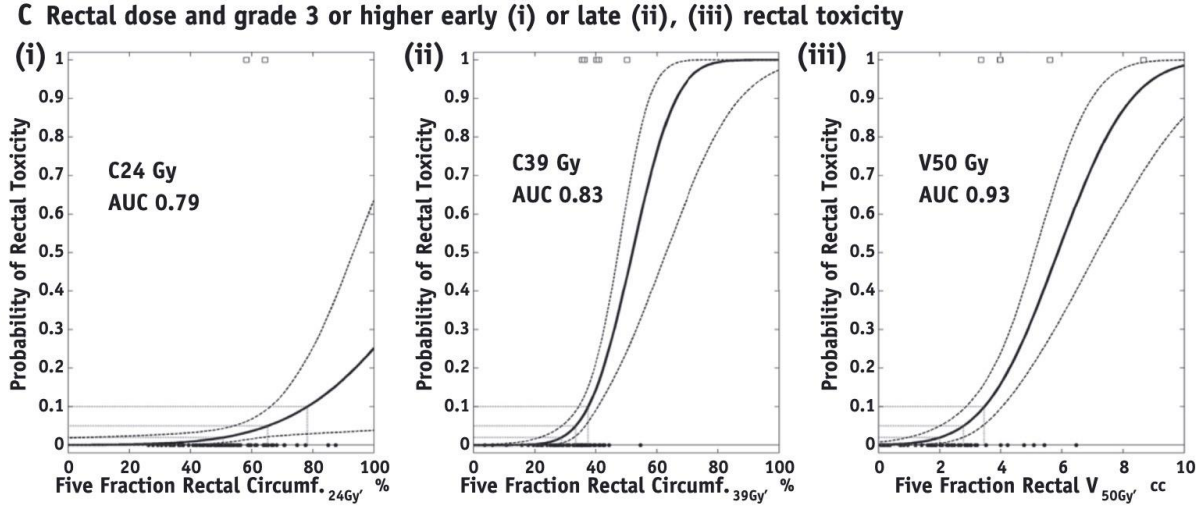


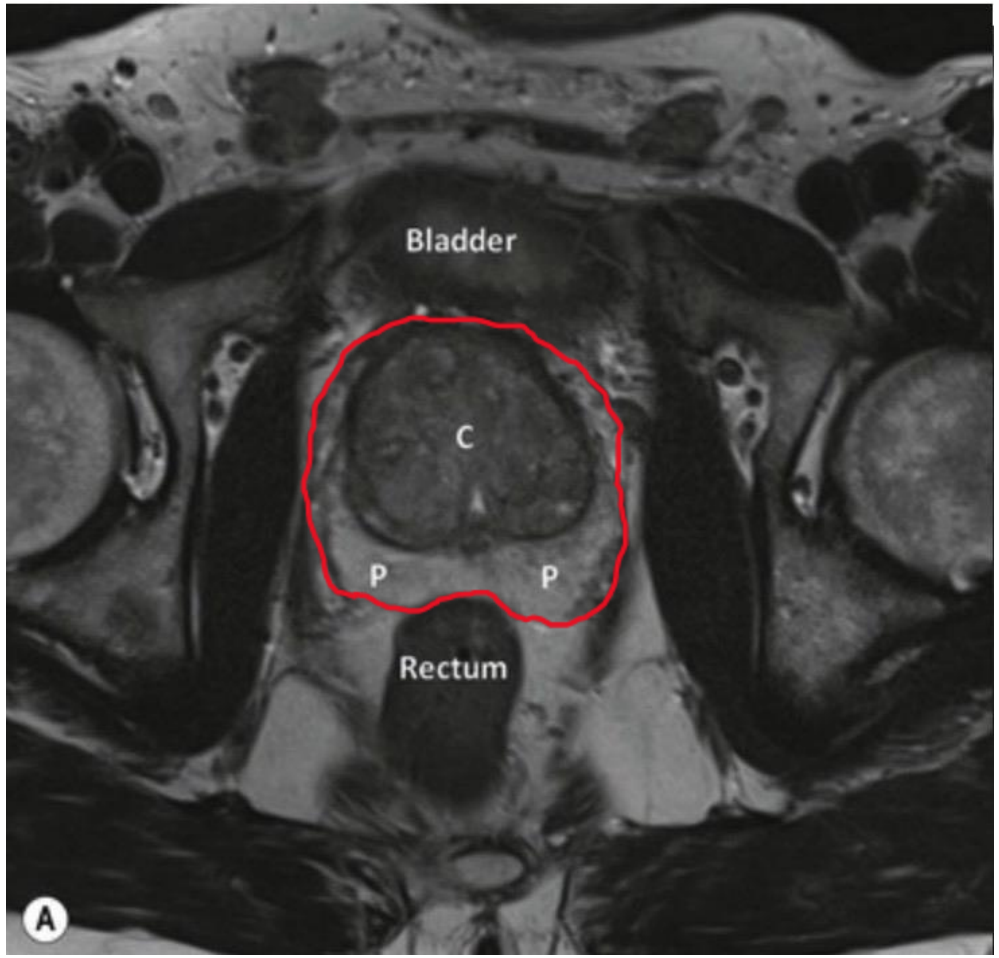
Fig. 1. (A) Five-fraction bladder dose and late urinary flare (Kole et al[29]). (i) Mean cumulative whole bladder dose-volume histogram for patients with (dashed line) and without (solid line) late urinary flare. (ii) Lyman-Kutcher-Burman model of the probability of late urinary flare versus bladder equivalent uniform dose. The figures in both panels were taken from the original publication. (B) Four-fraction urethra dose and late grade ≥2 urinary toxicity (Zhang et al[22]). Probit models of the

Wang et al. Int J Radiation Oncol Biol Phys, Vol. 110, No. 1, pp. 237–248, 2021

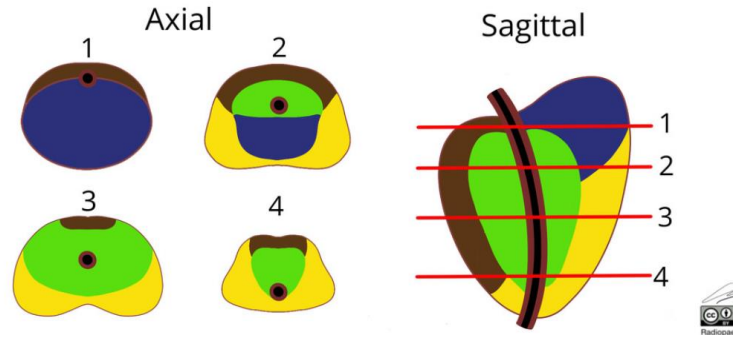
- Urethral complications seem to correlate with the maximum dose received by the urethra. Dose is shown as 4-fraction equivalent dose using an α/β-ratio of 3 Gy.
- From the complication curves one can see that a dose of 40 Gy in 4 fractions, or an $EQD_2 = 104\ Gy_3$, predicts for less than 10% in grade 2 or higher toxicity.
- While a dose of less than 38.5 Gy in 4 fractions, or an $EQD_2 = 97.21\ Gy_3$, predicts for a complication probability of about 5%

- Early Rectal complication are strongly governed by the fraction of rectal wall irradiated to 24 Gy in 5 fractions, or an $EQD_2 = 60.4\ Gy_3$.
- While late rectal complications are strongly governed by the fraction of rectal wall irradiated to 39 Gy in 5 fractions, or an $EQD_2 = 84.2\ Gy_3$ and the volume of rectum receiving a dose > 50 Gy.

Prostate SBRT: Surrounding Anatomy and the Anatomy of the Prostate



A. Axial T2-weighted MR image showing the prostate and its zonal anatomy. The peripheral zone (P) is shown as a crescent-shaped hyperintense structure; the central gland (C) is depicted as a structure with heterogeneous signal intensity. Downloaded from: https://radiologykey.com/prostate-2/



Downloaded from: https://radiopaedia.org/cases/prostate-anatomy?lang=us

Using multiparametric MR data form 90 patients Lee et al. determined the following distribution lesion location within the prostate:

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- 32.4% in the Peripheral zone
- 25.4% in the Transition zone

Lee, Carver, Feldmann, et al. Front. Oncol. 9 - 2019 | https://doi.org/10.3389/fonc.2019.00616

Unlike in Lung and Liver SBRT, in Prostate SBRT we have a serial organ at risk, the urethra, that is embedded in and runs through a tumor bearing organ (prostate). This means that achievable prescription doses will be limited by and need to respect the maximally tolerable dose for the urethra.

This yields the following implications for the safe delivery of prostate SBRT

Biomathematical Modeling implications for the safe delivery of prostate SBRT

- Dose to the rectum can be reduced by increasing the spacing between the rectum and the prostate using implantable perirectal spacers such as SpaceOAR Vue (Boston Scientific) or the Barrigel Spacer (Palette Life Sciences)
- Portion of rectal wall irradiated can be reduced by either using a rectal balloon or by safely reducing margins.
- Portion of the bladder being irradiated can be reduced by keeping the bladder comfortably full at each fraction or by safely reducing margins.
- Margins can be safely reduced using advanced RT delivery techniques such as real time motion management techniques combined with daily online adaptive radiotherapy.
- Since prostate lesions can occur in all zones of the prostate the entire gland should be treated to a tumor ablative dose.
- However, the urethra runs through the prostate and hence is the dose limiting organ in prostate SBRT dictating the maximum dose that can be safely delivered, namely an EQD_2 of approximately 97 Gy_3. The means the whole organ dose should not exceed an EQD_2 *dose of* 97 Gy_3 if delivered uniformly to entire prostate.

A low α/β –ratio for prostate cancer as a rational for prostate SBRT.

Int. J. Radiation Oncology Biol. Phys., Vol. 43, No. 5, pp. 1095–1101, 1999

0360-3016/99/$–see front matter

PII S0360-3016(98)00438-6

BIOLOGY CONTRIBUTION

FRACTIONATION AND PROTRACTION FOR RADIOTHERAPY OF PROSTATE CARCINOMA

DAVID J. BRENNER, D.SC.,* AND ERIC J. HALL, D.SC.*

Center for Radiological Research, Department of Radiation Oncology, Columbia University, New York, NY

Methods and Materials: We analyzed two mature data sets on radiotherapeutic tumor control for prostate cancer, one using EBRT and the other permanent seed implants, to extract the sensitivity to changes in fractionation of prostatic tumors. The standard linear-quadratic model was used for the analysis.
Results: Prostatic cancers appear significantly more sensitive to changes in fractionation than most other cancers. The estimated α/β value is 1.5 Gy [0.8, 2.2]. This result is not too surprising as there is a documented relationship between cellular proliferative status and sensitivity to changes in fractionation, and prostatic tumors contain exceptionally low proportions of proliferating cells.

Int. J. Radiation Oncology Biol. Phys., Vol. 50, No. 4, pp. 1021–1031, 2001

0360-3016/01/$–see front matter

PII S0360-3016(01)01607-8

BIOLOGY CONTRIBUTION

IS α/β FOR PROSTATE TUMORS REALLY LOW?

JACK FOWLER, D.SC., PH.D.,* RICK CHAPPELL, PH.D.,† AND MARK RITTER, M.D., PH.D.*

Departments of *Human Oncology and †Biostatistics, University of Wisconsin-Madison, Madison, WI

Results: The second method gave the definitive result of α/β = 1.49 Gy (95% CI 1.25–1.76) and $T_{½}$ = 1.90 h (95% CI 1.42–2.86 h). The first method gave a range from 1.4 to 1.9 Gy and showed that if mean or median dose were used instead of prescribed dose, the estimate of α/β would be substantially below 1 Gy. The third method, although based on early follow-up, was consistent with low values of α/β in the region of 2 Gy or below. The estimate for $T_{½}$ is the first value reported for prostate tumors *in situ*.

Int. J. Radiation Oncology Biol. Phys., Vol. 52, No. 1, pp. 3–5, 2002

0360-3016/02/$–see front matter

PII S0360-3016(01)02665-7

EDITORIAL

THE PROSPECTS FOR NEW TREATMENTS FOR PROSTATE CANCER

JACK F. FOWLER, D.SC., PH.D.,* RICK J. CHAPPELL, PH.D.,† AND MARK A. RITTER, M.D., PH.D.*

Departments of *Human Oncology and †Biostatistics and Medical Informatics, University of Wisconsin-Madison, Madison, WI

If, however, the prostate tumor α/β is significantly lower than that for the critical normal tissues, for example 1.5 Gy versus 3 Gy for rectal complications, then two obvious strategies arise. First, we could aim for equal tumor effect and underdosing of normal tissues. Second, we could aim for equal late complications and more effect on tumor destruction. Examples are given below, and they show dramatic gains by both strategies. The least we can expect is

Int. J. Radiation Oncology Biol. Phys., Vol. 56, No. 4, pp. 1093–1104, 2003

0360-3016/03/$–see front matter

doi:10.1016/S0360-3016(03)00132-9

CLINICAL INVESTIGATION Prostate

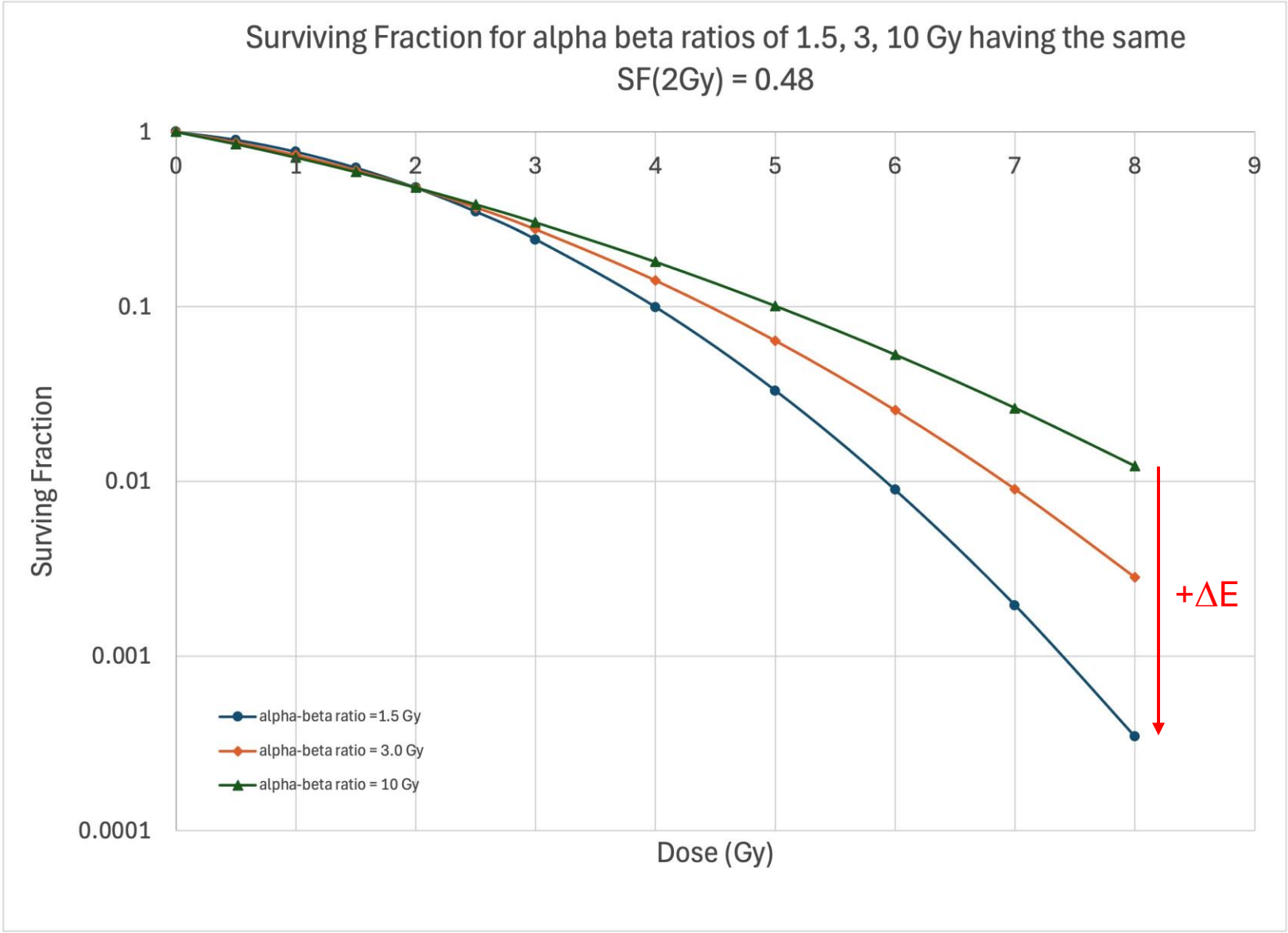
WHAT HYPOFRACTIONATED PROTOCOLS SHOULD BE TESTED FOR PROSTATE CANCER?

JACK F. FOWLER, D.SC., PH.D.,* MARK A. RITTER, M.D., PH.D.,* RICK J. CHAPPELL, PH.D.,† AND DAVID J. BRENNER, D.SC., PH.D.‡

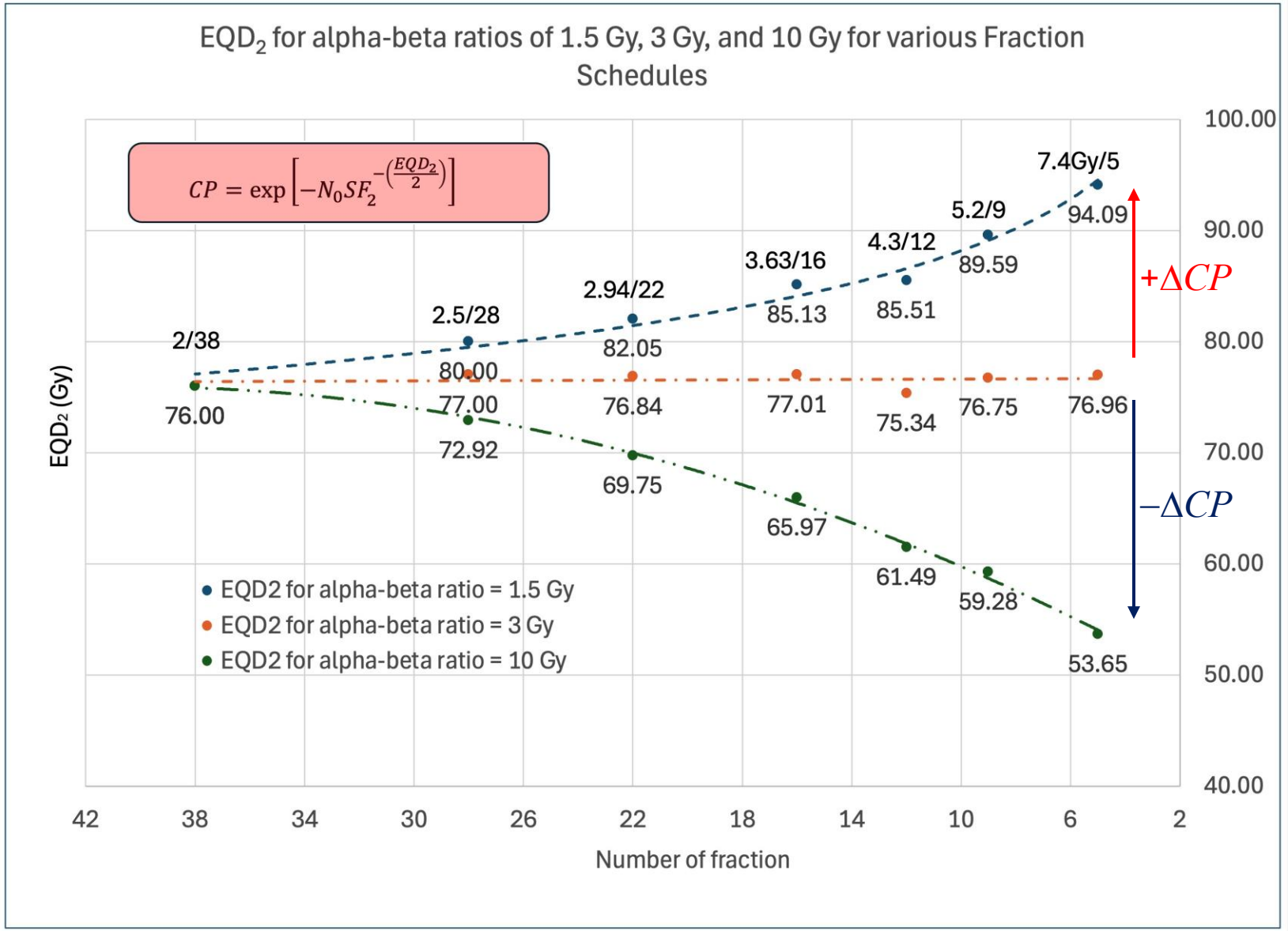
Departments of *Human Oncology and †Biostatistics and Medical Informatics, University of Wisconsin-Madison, Madison, WI; ‡Center for Radiological Research, Columbia University, New York, NY

Methods and Materials: Using standard linear-quadratic (LQ) modeling, a set of hypofractionated protocols can be designed in which a series of dose steps is given, each step of which keeps the late complications constant in rectal tissues. This is done by adjusting the dose per fraction and total dose to maintain a constant level of late effects. The effect on tumor control is then investigated. The resulting estimates are theoretical, although based on the best current modeling with α/β parameters, which are discussed thoroughly.

What are the radiobiological implications of a low α/β –ratio for prostate cancer



What are the biomathematical modeling implications of a low α/β –ratio for prostate cancer



Three of these fractionation schedules 2.94 Gy/22, 3.63 Gy/16, and 4.3 Gy/12 have been tested in a prospective Phase I/II multi-institutional clinical trial in low and intermediate risk prostate cancer. The results of which were published in 2020.

Practical Radiation Oncology® (2020) 10, 345-353

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Basic Original Report

A Prospective Multi-Institutional Phase I/II Trial of Step-Wise Dose-per-Fraction Escalation in Low and Intermediate Risk Prostate Cancer

Mark A. Ritter, MD, PhD,[a,*] Patrick A. Kupelian, MD,[b] Daniel G. Petereit, MD,[c] Colleen A. Lawton, MD,[d] Nick Anger, BS,[a] Heather Geye, MS,[a] Richard J. Chappell, PhD,[e] and Jeffrey D. Forman, MD[f]

[a]*Department of Human Oncology, University of Wisconsin Carbone Cancer Center, Madison, Wisconsin;* [b]*UCLA Medical Center, Los Angeles, California;* [c]*John T. Vucurevich Cancer Center Institute, Rapid City, South Dakota;* [d]*Medical College of Wisconsin, Milwaukee, Wisconsin;* [e]*Department of Biostatistics and Medical Informatics and Department of Statistics, University of Wisconsin, Madison, Wisconsin; and* [f]*Karmanos Cancer Institute, Detroit, Michigan*

Received 24 January 2020; revised 6 February 2020; accepted 9 February 2020

Abstract

Purpose: This phase I/II, multi-institutional trial explored the tolerance and efficacy of stepwise increasing hypofractionation (HPFX) radiation therapy regimens for fraction sizes up to 4.3 Gy in localized prostate cancer.

Methods and Materials: Three escalating dose-per-fraction schedules were designed to yield similar predicted tumor control while maintaining equivalent predicted late toxicity. HPFX levels I, II, and III were carried out sequentially and delivered schedules of 64.7 Gy/22 fx/2.94 Gy, 58.08 Gy/16 fx/3.63 Gy, and 51.6 Gy/12 fx/4.3 Gy, respectively with next level escalations contingent upon acceptable gastrointestinal (GI) toxicity. The primary endpoints were biochemical control and toxicity.

Results: A total of 347 patients were recruited by 5 institutions with 101, 111, and 135 patients treated on HPFX levels I, II, and III with median follow-ups of 100, 85.5, and 61.7 months, respectively (83.2 months combined). The National Comprehensive Cancer Network low- or intermediate-risk group distribution was 46% and 54%, respectively. Sixteen percent of patients, primarily intermediate risk, received 6 months of androgen deprivation therapy. The 8-year nadir + 2 actuarial biochemical control rates for HPFX levels I, II, and III were 91.1% ± 3.0%, 92.7% ± 2.7%, and 88.5% ± 4.6%, respectively (Kaplan-Meier log rank, 0.903). Among clinical covariates, only Gleason score reached near significance in multivariate analysis ($P = .054$). Twenty-six patients failed biochemically (crude incidence of 7.5%), and there were 5 cause-specific deaths. GI and genitourinary toxicities were acceptable and similar across the 3 HPFX levels. The combined actuarial cumulative incidence of grade 2+ GI and genitourinary toxicities at 7 years were 16.3% ± 2.1% and 22.1% ± 2.4%, respectively.

Conclusions: HPFX employing fraction sizes extending into the 3.6 to 4.3 Gy/fraction range can be delivered with excellent oncologic outcomes. Such schedules, positioned between moderate and ultra-HPFX, may provide additional options for patients wishing to avoid prolonged treatment schedules associated with conventionally fractionated radiation therapy for prostate cancer.

In this trial 8-year nadir + 2 ng/mol actuarial biochemical control rates for HPFX levels I, II, and III were 91.1% ± 3.0%, 92.7% ± 2.7%, and 88.5% ± 4.6%, respectively

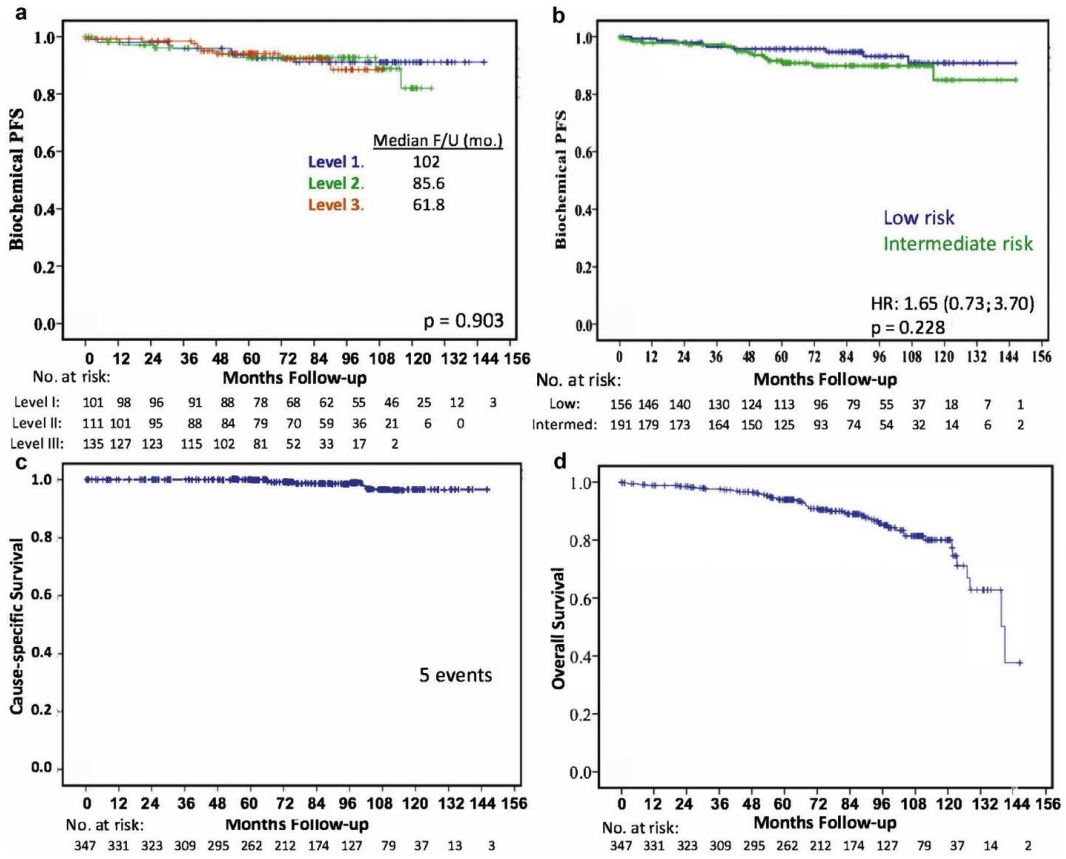

Figure 1 Biochemical control versus (a) fractionation level or (b) risk group. Cause-specific survival (c) and overall survival (d) are shown for combined hypofractionation (HPFX) levels.

Gastrointestinal and genitourinary toxicities were acceptable and similar across the 3 HPFX levels. The combined actuarial cumulative incidence of grade 2+ GI and GU toxicities at 7 years were 16.3% ± 2.1% and 22.1% ± 2.4%, respectively.

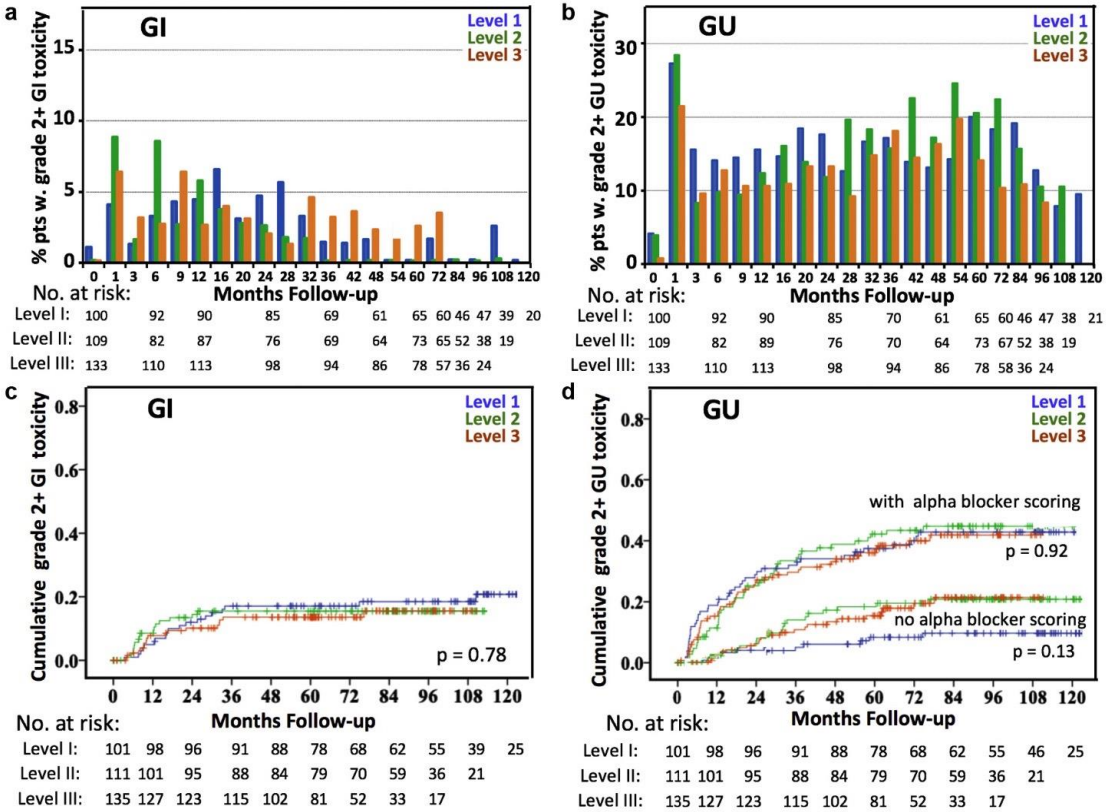

Figure 2 Prevalence (a, b) and cumulative incidence (c, d) of grade 2+ gastrointestinal (GI) (a,c) and genitourinary (GU) (b, d) toxicity versus time and fractionation level. The GU cumulative toxicity is shown with or without including alpha blocker initiation as a grade 2 toxicity.

HyTEC Organ-Specific Paper: Abdomen and Pelvis

Tumor Control Probability Modeling and Systematic Review of the Literature of Stereotactic Body Radiation Therapy for Prostate Cancer

Trevor J. Royce, MD, MS, MPH,* Panayiotis Mavroidis, PhD,* Kyle Wang, MD,* Aaron D. Falchook, MD,† Nathan C. Sheets, MD,* Donald B. Fuller, MD,‡ Sean P. Collins, MD, PhD,§ Issam El Naqa, PhD,‖ Daniel Y. Song, MD,¶ George X. Ding, PhD,# Alan E. Nahum, PhD,** Andrew Jackson, PhD,†† Jimm Grimm, PhD,‡‡,§§ Ellen Yorke, PhD,†† and Ronald C. Chen, MD, MPH‖‖

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Results: Twenty-five published cohorts were identified for inclusion, with a total of 4821 patients (2235 with low-risk, 1894 with intermediate-risk, and 446 with high-risk disease, when reported) treated with a variety of dose/fractionation schemes, permitting dose-response modeling. Five studies had a median follow-up of more than 5 years. Dosing regimens ranged from 32 to 50 Gy in 4 to 5 fractions, with total BED ($\alpha/\beta = 1.5$ Gy) between 183.1 and 383.3 Gy. At 5 years, we found that in patients with low-intermediate risk disease, an equivalent doses of 2 Gy per fraction (EQD2) of 71 Gy (31.7 Gy in 5 fractions) achieved a TCP of 90% and an EQD2 of 90 Gy (36.1 Gy in 5 fractions) achieved a TCP of 95%. In patients with high-risk disease, an EQD2 of 97 Gy (37.6 Gy in 5 fractions) can achieve a TCP of 90% and an EQD2 of 102 Gy (38.7 Gy in 5 fractions) can achieve a TCP of 95%.

Conclusions: We found significant variation in the published literature on target delineation, margins used, dose/fractionation, and treatment schedule. Despite this variation, TCP was excellent. Most prescription doses range from 35 to 40 Gy, delivered in 4 to 5 fractions. The literature did not provide detailed dose-volume data, and our dosimetric analysis was constrained to prescription doses. There are many areas in need of continued research as SBRT continues to evolve as a treatment modality for prostate cancer, including the durability of local control with longer follow-up across risk groups, the efficacy and safety of SBRT as a boost to intensity modulated radiation therapy (IMRT), and the impact of incorporating novel imaging techniques into treatment planning.

Result of TCP modeling for these 25 patient cohorts

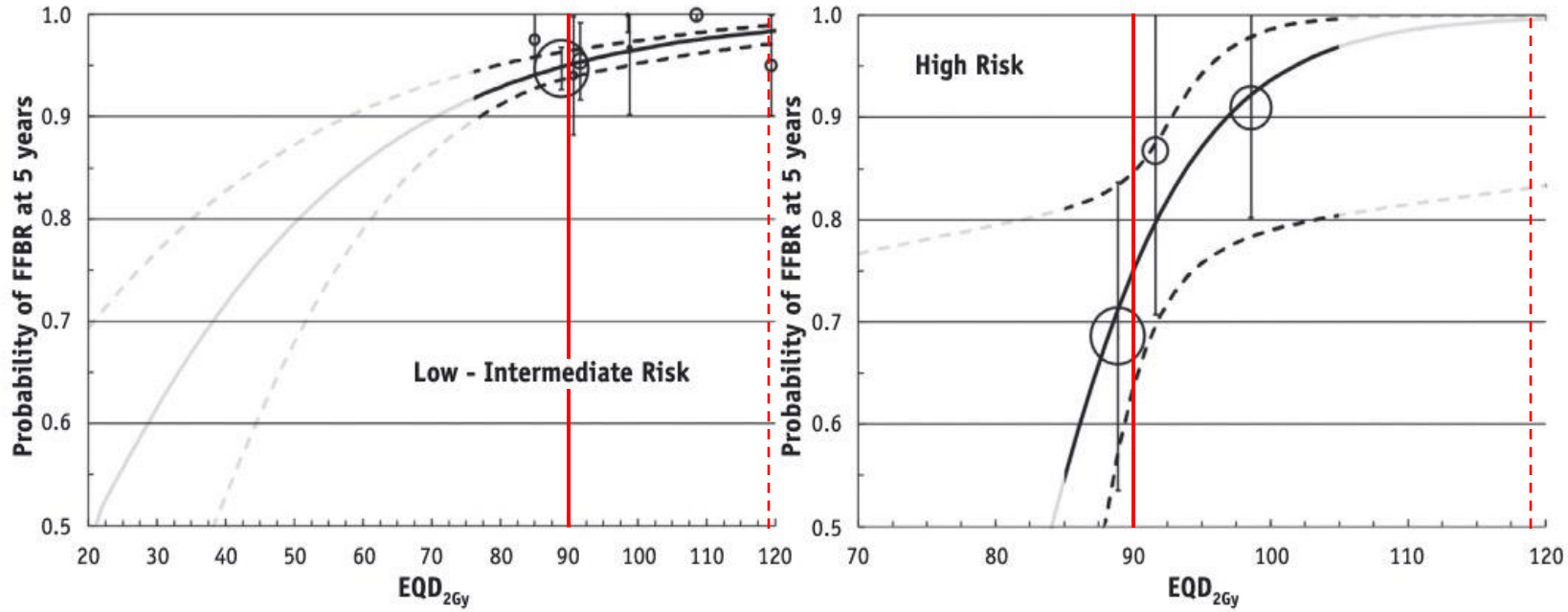

Fig. 1. The dose response curves of the Poisson prostate tumor control probability model for the low-intermediate risk (left) and high-risk (right) patient cohorts having at least 5 years for follow-up postradiation. The dashed lines indicate the 95% confidence intervals (CIs) of the curves. The dose-response data of each patient cohort are plotted in the form of open circles, whose size is proportional to the size of the patient cohort from each study relative to the size of the overall risk cohort; 95% CI error bars are shown. The plot for the low-intermediate risk patients was based on data from 9 studies* (1069 patients)[37,42,46-48,60-62]; the plot for the high-risk patients was based on 3 studies (85 patients).[48,61,62] (*One study is not shown in the plot because it lies outside the x-axis dose range.[42]) The error bars were calculated assuming a binomial distribution of the data. The reviewed studies did not include equivalent prescription doses less than approximately 80 Gy, represented by the faded regions of the curves; therefore, these regions are only suggestive in the model, and clinical FFBR conclusions should not be made in these regions that extend beyond the available data. *Abbreviation:* FFBR = freedom from biochemical relapse.

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Summary: Recommended dose constraints for the safe delivery of prostate SBRT

Table 4 Examples of dose constraints used in the authors' institutions and on clinical trials

	Georgetown* (35-36.25/5 fx, for 2 wk)	UNC (NCT 00643617)* (38 Gy/4 fx for 4 d)	RTOG 0938[55] (36.25 Gy/5 fx for 2.5 wk)	NRG GU-005[56] (36.25 Gy/5 fx for 2.5 wk)
PTV	≤125% prescription dose		D0.03cc ≤8.78 Gy (Linac)	Dmax ≤38.78 Gy
	91 $Gy_{1.5}$ < EQD_2 ≤ 136.7 $Gy_{1.5}$	EQD_2 = 119 $Gy_{1.5}$	D0.03cc ≤43.5 Gy	Max EQD_2 ≤ 103 $Gy_{1.5}$
	74 Gy_3 < EQD_2 ≤ 109.31 Gy_3	EQD_2 = 95 Gy_3	(CyberKnife)	Max EQD_2 ≤ 84Gy_3
Prostatic urethra	V42 Gy ≤0.03 cc	Dmax <40 Gy	D0.03cc ≤38.78 Gy	D0.03cc ≤38.78 Gy
	EQD_2= 96 Gy_3	EQD_2 < 104 Gy_3	0.03cc EQD_2 ≤ 84.42 Gy_3	0.03cc EQD_2 ≤ 84.42 Gy_3
Bladder	V37Gy ≤5 cc	Dmax <45.6 Gy	D1cc ≤38.06 Gy	D0.03cc ≤38.06 Gy
	EQD_2= 77 Gy_3	D10cc <41.8 Gy	D10% ≤32.63 Gy	D10% ≤18.12 Gy
		Max EQD_2 < 131 Gy_3	D50% ≤18.13 Gy	0.03cc EQD_2 ≤ 80.56 Gy_3
Rectum	V36 Gy ≤1 cc	Dmax <38 Gy	D1cc ≤38.06 Gy	D0.03cc ≤38.06 Gy
	EQD_2= 73 Gy_3	Max EQD_2 < 80.5 Gy_3	D3cc ≤34.4 Gy	D3cc ≤34.4 Gy
			D10% ≤32.63 Gy	D10% ≤32.63 Gy
			D20% ≤29 Gy	D20% ≤29 Gy
			D50% ≤18.13 Gy	D50% ≤18.13 Gy
Penile bulb	V29.5 Gy ≤3 cc		Dmax ≤36.25 Gy	D0.03cc ≤36.25 Gy
			D3cc ≤20 Gy	D3cc ≤19.9 Gy

Abbreviations: fx = fractions; OAR = organ at risk; PTV = planning target volume; RTOG = Radiation Therapy Oncology Group; UNC = University of North Carolina.

Bladder and rectum volumes are defined as solid organs. For RTOG 0938 and NRG GU-005, the rectum is defined as extending 15 cm from the anus or to the rectosigmoid flexure.

* Dosimetric parameters currently used at authors' institutions.

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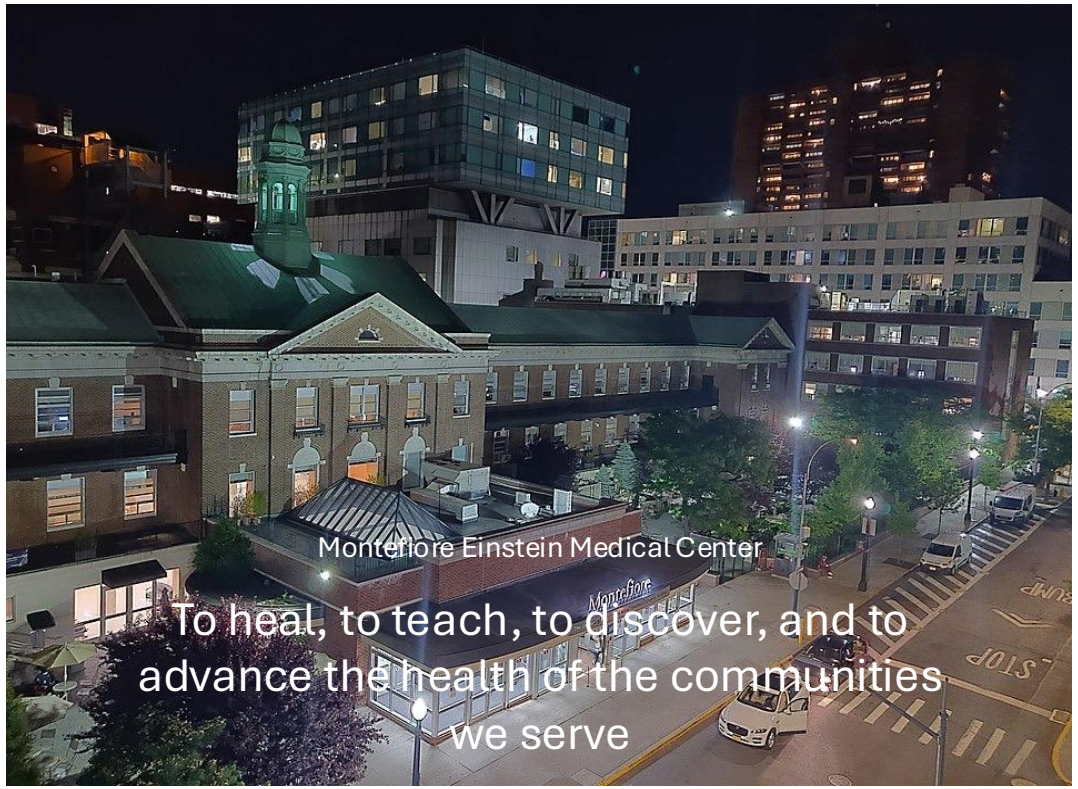
Biomathematical Modeling implications for the safe delivery of prostate SBRT

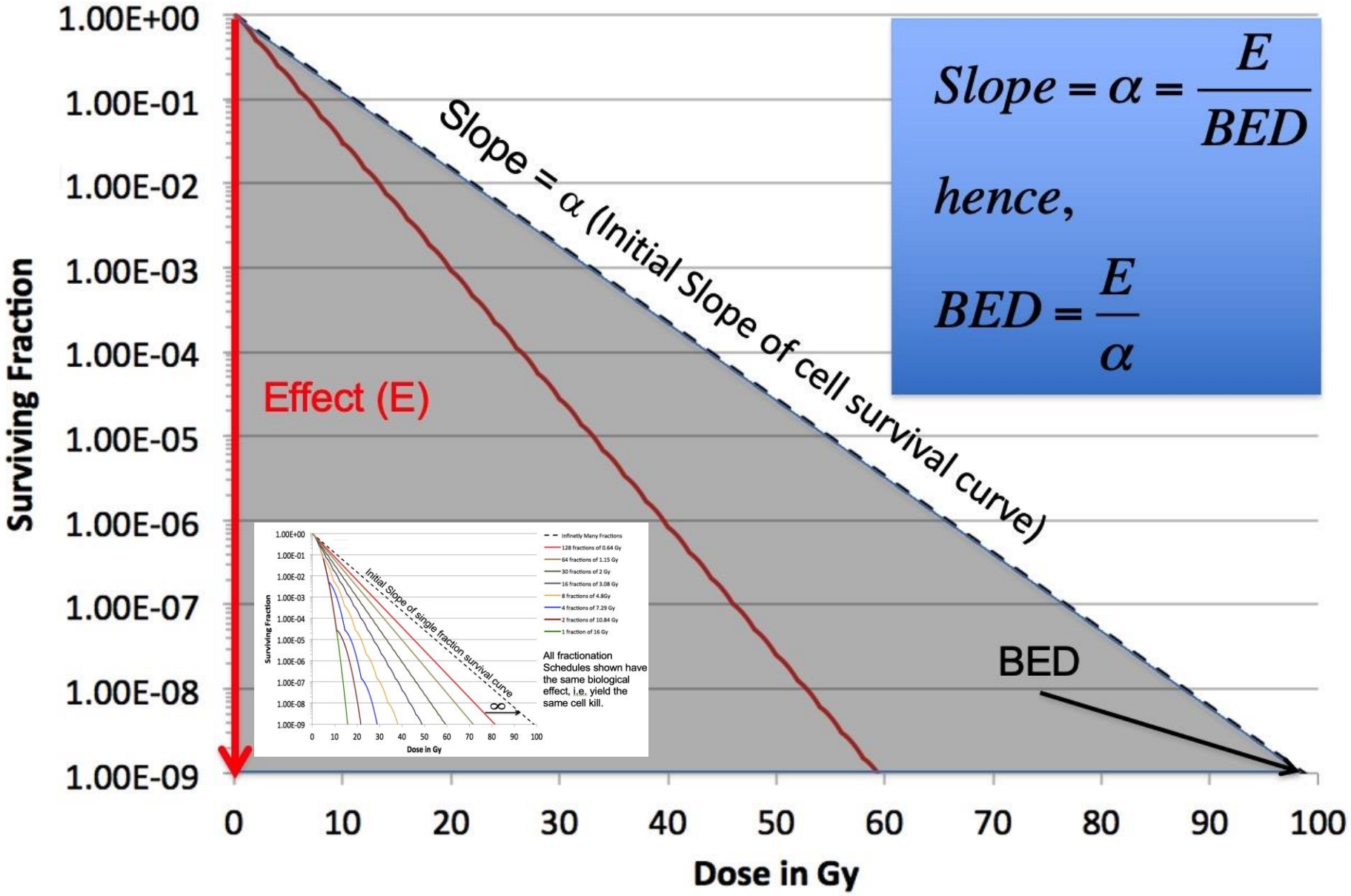
- Dose to the rectum can be reduced by increasing the spacing between the rectum and the prostate using implantable perirectal spacers such as SpaceOAR Vue (Boston Scientific) or the Barrigel Spacer (Palette Life Sciences)
- Portion of rectal wall irradiated can be reduced by either using a rectal balloon or by safely reducing margins.
- Portion of the bladder being irradiated can be reduced by keeping the bladder comfortably full at each fraction or by safely reducing margins.
- Margins can be safely reduced using advanced RT delivery techniques such as real time motion management techniques combined with daily online adaptive radiotherapy.
- Since prostate lesions can occur in all zones of the prostate, the entire gland should be treated to a tumor ablative dose.
- However, the urethra runs through the prostate and hence is the dose limiting organ in prostate SBRT dictating the maximum dose that can be safely delivered, namely an EQD_2 of approximately 97 Gy_3. This means means whole organ dose should not exceed this EQD_2 level if delivered uniformly to the entire prostate. Indicating that current prescription doses in 4 or 5 fractions should not be increased beyond that EQD_2 *level (36.25 Gy/5fx* $\equiv$ *74.3*Gy_3*; 38Gy/4fx* $\equiv$ *95*Gy_3*)*. However, conformal avoidance of the urethra can be considered if the resulting treatment plan can be safely delivered using real time motion management techniques.

Thank you for your attention.



Extra Slides

Biologically Effective Dose (BED)



Normal Tissue DVH-Reduction using generalized EUD

Rancatti et al. (Radiotherapy and Oncology 2004;73:21-32) have proposed a normal tissue DHV reduction schema that is based on generalized EUD (gEUD) and this is equivalent to the Kutcher-Burman DVH reduction schema. Niemierko has defined generalized EUD as:

$$gEUD = \left(\sum_i v_i D_i^{1/n} \right)^n$$

Recall that in the Kutcher-Burman DVH reduction formalism the final NTCP formula is given by:

$$NTCP(D_{ref}, v_{eff}) = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{t} \exp\left(-\frac{u^2}{2}\right) du$$

$$t = \frac{D_{ref} - D_{50}(v_{eff})}{m D_{50}(v_{eff})}; \qquad D_{50}(v_{eff}) = D_{50}(1) v_{eff}^{-n}$$

Normal Tissue DVH-Reduction using generalized EUD

Using this we can write t as follows:

$$t = \frac{D_{ref} v_{eff}^{n} - D_{50}(1)}{m D_{50}(1)}$$

Now let us look at the expression $D_{\max} v_{eff}^{n}$:

$$D_{ref} v_{eff}^{n} = D_{ref} \left(\sum_i v_i \left(\frac{D_i}{D_{ref}} \right)^{\frac{1}{n}} \right)^n = \left(\sum_i v_i D_{ref}^{\frac{1}{n}} \left(\frac{D_i}{D_{ref}} \right)^{\frac{1}{n}} \right)^n = \left(\sum_i v_i D_i^{\frac{1}{n}} \right)^n = gEUD,$$

where n is the volume effect parameter of the Lyman model.

Normal Tissue DVH-Reduction using generalized EUD

Therefore, the NCTP for an inhomogeneously irradiated volume in terms of *gEUD* becomes:

$$NTCP(gEUD) = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{t} \exp\left(-\frac{u^2}{2}\right) du$$

$$t = \frac{gEUD - D_{50}(1)}{mD_{50}(1)}; \qquad gEUD = \left(\sum_i v_i D_i^n\right)^{\frac{1}{n}}; \text{ where } n \text{ is the volume effect parameter}$$

This is a very natural expression of NTCP for an inhomogeneously irradiated volume. Note, that n here is not used in the way defined by Niemierko, but is the volume effect parameter of the Lyman model.

Proof that: $\exp(-\alpha\, BED) = SF_2^{-\left(\frac{EQD_2}{2}\right)}$

$$-\alpha\, BED = -\alpha\left(1+\frac{2}{\alpha/\beta}\right)\frac{BED}{1+\frac{2}{\alpha/\beta}} = -\alpha\left(1+\frac{2}{\alpha/\beta}\right)EQD_2$$

$$-\alpha\, BED = -\frac{1}{2}(\alpha 2+\beta 2^2)EQD_2 = -\frac{1}{2}EQD_2 \ln(SF_2), \text{ where } SF_d = \exp[-(\alpha d+\beta d^2)]$$

$$-\alpha\, BED = \ln\left(SF_2^{-\frac{1}{2}EQD_2}\right)$$

$$\exp(-\alpha\, BED) = SF_2^{-\left(\frac{EQD_2}{2}\right)}$$

What is known about α/β–ratios from Animal and Human Clinical Data:

- The α/β–ratio is **large** for **rapid turnover tissues**
- The α/β–ratio is **small** for **low turnover tissues**
- The α/β–ratio is **less variable** than α or β separately
- The α/β–ratio is the **dose** at which α-damage equals β-damage:

$$\alpha d = \beta d^2 \square \quad d = \frac{\alpha}{\beta}$$

Animal data for the α/β–ratio for a variety of rapid turnover (early) responding and low turnover (late) responding tissues

GG Steel [Ed]. ***Basic Clinical Radiobiology 1997.*** Arnold (London) & OUP (NY).

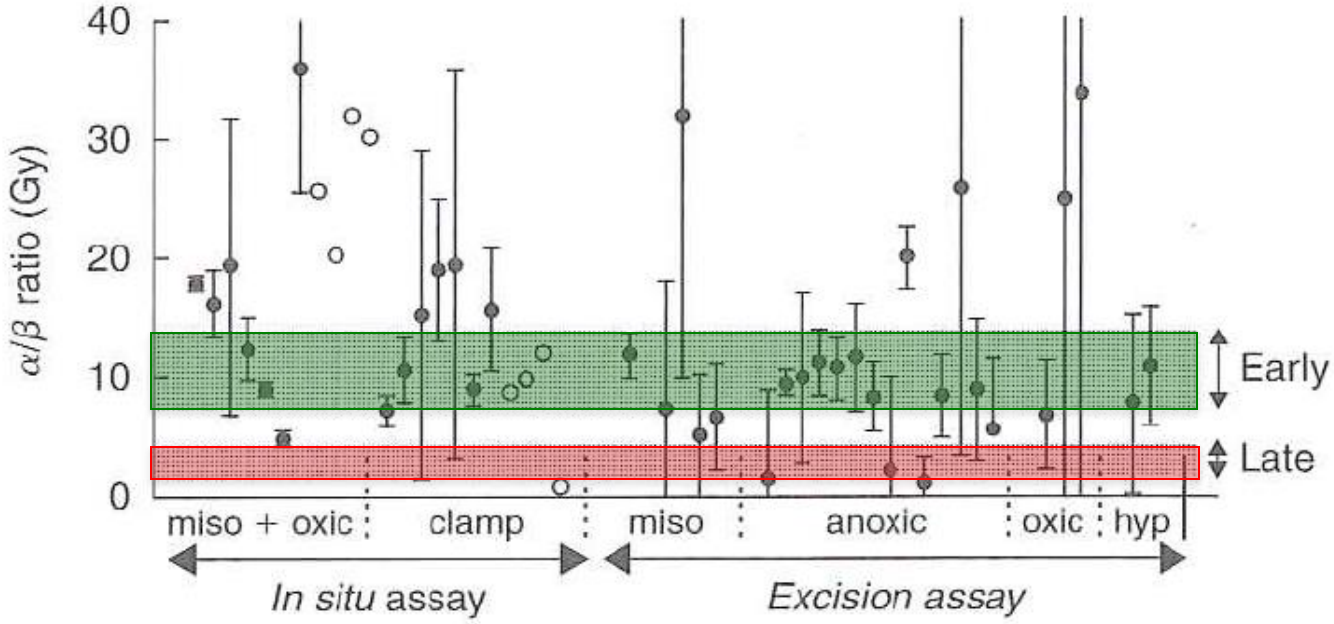
Table 13.1 Values for the α/β ratio for a variety of early- and late-responding normal tissues in experimental animals ANIMALS

Early reactions	α/β	References
Skin		
Desquamation	9.1 – 12.5	Douglas and Fowler (1976)
	8.6 – 10.6	Joiner *et al* (1983)
	9 – 12	Moulder and Fischer (1976)
Jejunum		
Clones	6.0 – 8.3	Withers *et al* (1976)
	6.6 – 10.7	Thames *et al* (1981)
Colon		
Clones	8 – 9	Tucker *et al* (1983)
Weight loss	9 – 13	Terry and Denekamp (1984)
Testis		
Clones	12 – 13	Thames and Withers (1980)
Mouse lethality		
30 d	7 – 10	Kaplan and Brown (1952)
30 d	13 – 17	Mole (1957)
30 d	11 – 26	Paterson *et al* (1952)
Tumour bed		
45 d	5.6 – 6.8	Begg and Terry (1984)

Late reactions	α/β	References
Spinal cord		
Cervical	1.8 – 2.7	van der Kogel (1979)
Cervical	1.6 – 1.9	White and Hornsey (1978)
Cervical	1.5 – 2.0	Ang *et al* (1983)
Cervical	2.2 – 3.0	Thames *et al* (1988)
Lumbar	3.7 – 4.5	van der Kogel (1979)
Lumbar	4.1 – 4.9	White and Hornsey (1978)
	3.8 – 4.1	Leith *et al* (1981)
	2.3 – 2.9	Amols, Yuhas (quoted by Leith *et al*, 1981)
Colon		
Weight loss	3.1 – 5.0	Terry and Denekamp (1984)
Kidney		
Rabbit	1.7 – 2.0	Caldwell (1975)
Pig	1.7 – 2.0	Hopewell and Wiernik (1977)
Rats	0.5 – 3.8	van Rongen *et al* (1988)
Mouse	1.0 – 3.5	Williams and Denekamp (1984 a,b)
Mouse	0.9 – 1.8	Stewart *et al* (1984 a)
Mouse	1.4 – 4.3	Thames *et al* (1988)
Lung		
LD_{50}	4.4 – 6.3	Wara *et al* (1973)
LD_{50}	2.8 – 4.8	Field *et al* (1976)
LD_{50}	2.0 – 4.2	Travis *et al* (1983)
Breathing rate	1.9 – 3.1	Parkins and Fowler (1985)
Bladder		
Frequency, capacity	5 – 10	Stewart *et al* (1984b)

α/β values are in grays.
From Fowler (1989); for references, see the original. BJR 62: 679-694 (1989)

α/β–ratios for experimental tumors in rats and mice



Values of the α/β-ratio for experimental tumors determined under a variety of conditions of oxygenation. The stripped areas indicate the range of values for rapid turnover and low turnover normal tissues. Williams, Denekamp, Fowler (1985) Int J. Radiat Oncol Biol Phys 11:87-96.

- "Miso & Oxic: Values calculated from data obtained under fully radiosensitized conditions (plotted directly)
- Clamp, Anoxic, & Hypoxic: Values calculated from data obtained under hypoxic conditions (plotted after dividing by an assumed ratio OER_{HD}^2 / OER_{LD} of 2.7, see the scaling law at end of lecture 3)
- Nota Bene: Tumors respond to irradiation in the same way as rapid turnover tissues do.

Human data for the α/β–ratio for a variety of rapid turnover (early) responding and low turnover (late) responding tissues

GG Steel [Ed]. ***Basic Clinical Radiobiology 1997.*** Arnold (London) & OUP (NY).

HUMAN

Table 13.2 *α/β* ratios for human normal tissues NORMAL TISSUES

Tissue/organ	End-point	*α/β* (Gy)	95% conf. lim. (Gy)	Reference
Early reactions EARLY				
Skin	Erythema	8.8	[6.9; 11.6]	Turesson and Thames, 1989
	Erythema	12.3	[1.8; 22.8]	Bentzen *et al*, 1988
	Desquamation	11.2	[8.5; 17.6]	Turesson and Thames, 1989
Oral mucosa	Mucositis	9.3	[5.8; 17.9]	Denham *et al*, 1995
	Mucositis	15	[-15; 45]	Rezvani *et al*, 1991
	Mucositis	~8	N/A	Chogule and Supe, 1993
Late reactions LATE				
Skin/vasculature	Telangiectasia	2.8	[1.7; 3.8]	Turesson and Thames, 1989
	Telangiectasia	2.6	[2.2; 3.3]	Bentzen *et al* 1990
	Telangiectasia	2.8	[–0.1; 8.1]	Bentzen and Overgaard, 1991
Subcutis	Fibrosis	1.7	[0.6; 2.6]	Bentzen and Overgaard, 1991
Muscle/vasculature/ cartilage	Impaired shoulder movement	3.5	[0.7; 6.2]	Bentzen *et al*, 1989
Nerve	Brachial plexopathy	<3.5*	N/A	Olsen *et al*, 1990
	Brachial plexopathy	~2	N/A	Powell *et al*, 1990
	Optic neuropathy	1.6	[–7; 10]	Jiang *et al*, 1994
Spinal cord	Myelopathy	<3.3	N/A	Dische *et al*, 1981
Eye	Corneal injury	2.9	[–4; 10]	Jiang *et al*, 1994
Bowel	Stricture/perforation	3.9	±0.7	Deore *et al*, 1993
Lung	Pneumonitis	3.3	±1.5	van Dyk *et al*, 1989
	Fibrosis (radiological)	3.1	[-0.2; 8.5]	Dubray *et al*, 1995
Head and neck	Various late effects	3.5	±1.2	Rezvani *et al*, 1991
Supraglottic larynx	Various late effects	3.8	[0.8; 14]	Maciejewski *et al*, 1986
Oral cavity + oroph.	Various late effects	0.8	[–0.6;2.5]	Maciejewski *et al*, 1990

α/β–ratios from human clinical tumor data

Tumor α/β values from clinical data

Tissue	α/β (Gy)	Authors
Vocal cord	>9.9	Harrison '88
Larynx	25-35	Maciejewski '88
"	15	" '93
Oral cavity	>6-10	Byhardt '77
Oropharynx	13-19	Rezvani '93
Oropharynx	50-∞	Chappell,Fowler'95
Larynx	50-∞	Roberts, Hendry,98
Lung (NSC)	50-90	Cox et al '87
Cervix Ut	>13.9	Watson '78
Skin Ca	8.5(5-11)	Trott '84
Melanoma	0.6(-1-2.5)	Bentzen '89
Liposarcoma	0.4(-1.4-5)	Thames, Suit '86
AdenoCa	<4.6	Notter&Turesson
Prostate	1.5(.8-2.2)	Brenner, Hall '99
Prostate	1.5(1.3-1.7)	Fowler,Chappell, Ritter '01

See also Animal Tumors: Williams, Dene-kamp & Fowler IJROBP 10:1703; '84