


HyTEC Vision Papers: Rationale and Evidence for SBRT

Jimm Grimm, PhD



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100
"Make it the Best"
Abigail Geisinger
1827-1921
"Geisinger Quality – Striving for Perfection"

**AAPM 2019
San Antonio**


Conflict of Interest

Dr. Grimm designed and holds intellectual property rights to the

DVH Evaluator software tool

(www.DiversiLabs.com) which is an FDA-cleared product in commercial use, and which has been used for this analysis


Funding from Accuray, NovoCure



DVH EVALUATOR


FDA 510k Number K092928 Rx Only US Patents 9,019,307 & 9,192,782
www.DiversiLabs.com service@DiversiLabs.com
Soli Deo Gloria

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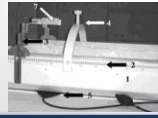
25 Years of SBRT




Leksell Lars. The stereotactic method and radiosurgery of the brain. *Acta Chir Scand.* **1951** Dec 13;102(4):316-9.



Lutz W. Winston KR, Maleki N. A system for stereotactic radiosurgery with a linear accelerator. *IJROBP.* **1988** Feb;14(2):373-81.



Lax I, Blomgren H, Nishund I, Svanström R. Stereotactic radiotherapy of malignancies in the abdomen. Methodological aspects. *Acta Oncol.* **1994** Jan;33(6):677-83.

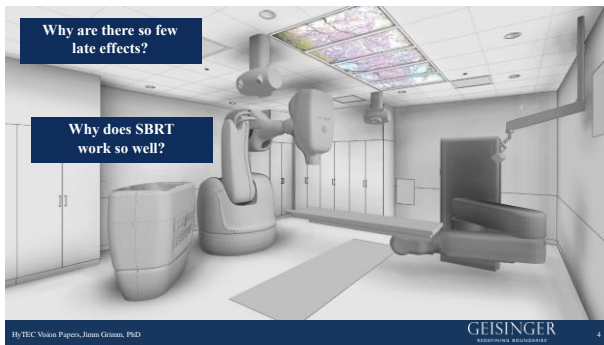


Adler J.R. Accuray, Inc. A Neurosurgical Business Case Study. *Cureus* 1(9):e1. "first CyberKnife patient treatment on June 6, **1994**"

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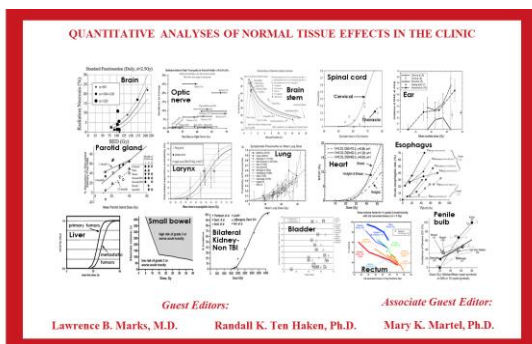
HyTEC:

Goals like QUANTEC for SBRT

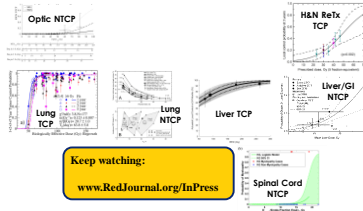
QUANTEC: Quantitative Analyses of Normal Tissue Effects in the Clinic

HyTEC: High Dose per Fraction, Hypofractionated Treatment Effects in the Clinic

HyTEC Vision Papers, James Geisinger, Ph.D. SBRT: Stereotactic Body Radiation Therapy GEISINGER RADIATION RESEARCH



HyTEC: High Dose per Fraction, Hypofractionated Treatment Effects in the Clinic



Keep watching:

www.RedJournal.org/InPress

Guest Editors:

Jimm Grimm, Ph.D. Ellen Yorke, Ph.D. Lawrence B. Marks, M.D.
Andrew Jackson, Ph.D. Brian D. Kavanagh, M.D. Jinyu Xue, Ph.D.

Today's Session:

Rationale and Evidence for SBRT

a.k.a. Why does SBRT work so well?

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HONOLULU, HAWAII

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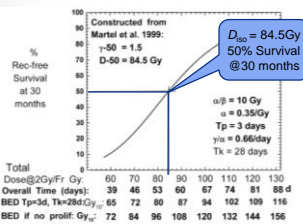


Fig. 1. Reconstruction of Martel et al.'s data from the dose escalation study in non-small-cell lung cancer at the University of Michigan (17). The plot is against total dose in 2 Gy fractions, given 5F per week. Scales below these doses show overall time in days, biologically effective dose (BED) as given allowing for repopulation, and equivalent BED if no repopulation occurred. (Reprinted from Mehta M, Scrimgeur R, Mackie R, et al., A new approach to dose escalation in non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2001;49:23-33, with permission of Elsevier Inc.)

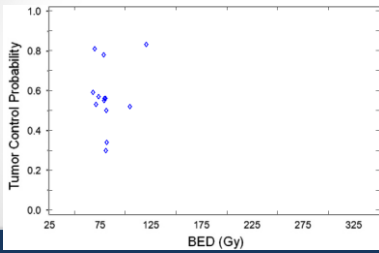
- Not easy to achieve high local control rates for lung tumors

Fowler JF, Tomé WA, Fenwick JD, Mehta MP.
A challenge to traditional radiation oncology.
Int J Radiat Oncol Biol Phys. 2004 Nov 15;60(4):1241-56.

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A pooled analysis of biological equivalent dose and local control, Stage 1 lung cancer

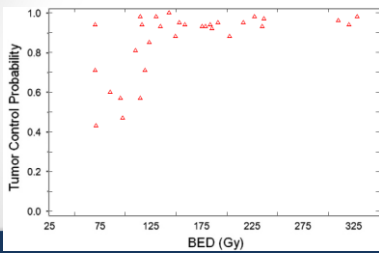


- About 1000 conventional cases...
- Mehta N, King CR, Agazaryan N, Steinberg M, Hua A, Lee P.
- Stereotactic body radiation therapy and 3-dimensional conformal radiotherapy for stage I non-small cell lung cancer: A pooled analysis of biological equivalent dose and local control.
- *Prac Radiat Oncol.* 2012 Oct; 2(4):288-295

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A pooled analysis of biological equivalent dose and local control, Stage 1 lung cancer

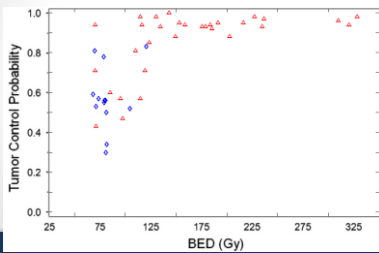


- About 1500 SBRT cases...
- Mehta N, King CR, Agazaryan N, Steinberg M, Hua A, Lee P.
- Stereotactic body radiation therapy and 3-dimensional conformal radiotherapy for stage I non-small cell lung cancer: A pooled analysis of biological equivalent dose and local control.
- *Prac Radiat Oncol.* 2012 Oct; 2(4):288-295

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A pooled analysis of biological equivalent dose and local control, Stage 1 lung cancer



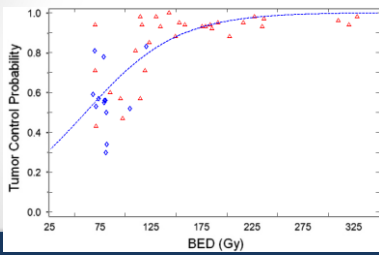
- About 2500 pooled cases...
- Mehta N, King CR, Agazaryan N, Steinberg M, Hua A, Lee P.
- Stereotactic body radiation therapy and 3-dimensional conformal radiotherapy for stage I non-small cell lung cancer: A pooled analysis of biological equivalent dose and local control.
- *Prac Radiat Oncol.* 2012 Oct; 2(4):288-295

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A pooled analysis of biological equivalent dose and local control, Stage 1 lung cancer

Dr. Percy Lee's group at UCLA



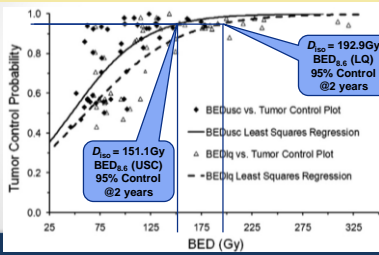
- Logistic Model, Linear Quadratic (LQ), $\alpha/\beta=8.6\text{Gy}$...
- Mehta N, King CR, Agazaryan N, Steinberg M, Hua A, Lee P.
- Stereotactic body radiation therapy and 3-dimensional conformal radiotherapy for stage I non-small cell lung cancer: A pooled analysis of biological equivalent dose and local control.
- Prac Radiat Oncol. 2012 Oct; 2(4):288-295

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A pooled analysis of biological equivalent dose and local control, Stage 1 lung cancer

Dr. Percy Lee's group at UCLA



- 95% Local Control may be achievable!!!
- Mehta N, King CR, Agazaryan N, Steinberg M, Hua A, Lee P.
- Stereotactic body radiation therapy and 3-dimensional conformal radiotherapy for stage I non-small cell lung cancer: A pooled analysis of biological equivalent dose and local control.
- Prac Radiat Oncol. 2012 Oct; 2(4):288-295

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A pooled analysis of biological equivalent dose and local control, Stage 1 lung cancer

Dr. Percy Lee's group at UCLA

95% 2 Year Local Control

- USC: $151.1 \text{ Gy BED}_{8.6} = 22.6\text{Gy} \times 3 \text{ fractions}$
- LQ: $192.9 \text{ Gy BED}_{8.6} = 19.6\text{Gy} \times 3 \text{ fractions}$

$\approx 20\text{Gy} \times 3 \text{ fractions}$
Physical dose

- 95% Local Control may be achievable!!!
- Mehta N, King CR, Agazaryan N, Steinberg M, Hua A, Lee P.
- Stereotactic body radiation therapy and 3-dimensional conformal radiotherapy for stage I non-small cell lung cancer: A pooled analysis of biological equivalent dose and local control.
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'For NSCLC, then, it follows that there is no need to invoke a "new biology" to explain the high tumor control rates.'

International Journal of
Radiation Oncology
biology • physics

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Editorial

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. Brenner, PhD,[†] and David J. Carlson, PhD[‡]

*Department of Radiation Oncology, Stanford University School of Medicine, Stanford, California; [†]Center for Radiological Research, Columbia University Medical Center, New York, New York; and [‡]Department of Therapeutic Radiology, Yale University School of Medicine, New Haven, Connecticut

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'We disagree, however, that the data presented can support this conclusion.'

COMMENTS

Dose Escalation, Not "New Biology," Can Account for the Efficacy of Stereotactic Body Radiation Therapy With Non-Small Cell Lung Cancer



In Regard to Brown et al

To the Editor: With the increasing use of radiosurgery and stereotactic body radiation therapy (SBRT) in radiation oncology, there has been a growing need to understand the radiobiology contributing to the remarkably high tumor control rates seen with the large fraction sizes used. We therefore read with great interest the recent editorial by Brown et al regarding whether "New Biology" was needed to understand SBRT dose response in lung cancer (1), and

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fractionation regimens are not consistent with the hypothesis that they are drawn from the same BED-based function.

To further clarify SBRT tumor response, higher quality data, that is, data gathered in a more consistent and comprehensive fashion, will need to be collected and analyzed.

Shyam S. Rao, MD, PhD
Department of Radiation Oncology
Memorial Sloan-Kettering Cancer Center
New York, New York

Jung Han Oh, PhD
Andrew Jackson, PhD
Joseph O. Deasy, PhD
Department of Medical Physics
Memorial Sloan-Kettering Cancer Center
New York, New York

<http://dx.doi.org/10.1016/j.ijrobp.2014.03.027>

'clearly demonstrate that secondary cell death that is most likely caused by deterioration of the tumor physiology is involved in the response of tumors to high dose per-fraction SRS and SBRT.'

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BRIEF REPORT AND OPINION

Is Indirect Cell Death Involved in Response of Tumors to Stereotactic Radiosurgery and Stereotactic Body Radiation Therapy?



Chang W. Song, PhD,* Inhwan Park, BA,* L. Chinsoo Cho, MD,* Jianling Yuan, MD, PhD,* Kathryn E. Dusenbery, MD,* Robert J. Griffin, PhD,[†] and Seymour H. Levitt, MD*

*Department of Therapeutic Radiology-Radiation Oncology, University of Minnesota Medical School, Minneapolis, Minnesota; and [†]Department of Radiation Oncology, University of Arkansas for Medical Sciences, Little Rock, Arkansas

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RADIATION ONCOLOGY

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From: Jack Fowler

To: Deasy Ph.D. Joe; Michael Joiner; Jimm Grimm

Sent: Saturday, March 3, 2012 12:44 PM

Subject: High Dose-per-Fr Radiobiol

Dear Joe, Mike, Jimm, You've probably seen this already? Rad Res 2012;177:311-327. This new paper, by Chan Song, has the best discussion re high dose-per-fraction that I have ever seen, with his conclusion in Fig 7. I'll try and attach the pdf to this e-mail, but the copyright mechanisms might defeat me, so I put the actual ref first. do Please read the text! Best - Jack

The main advocate for the LQ model, showing interest in vascular damage!

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RESEARCH ADVANCEMENT

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Rad Res
2012;177:
311-327

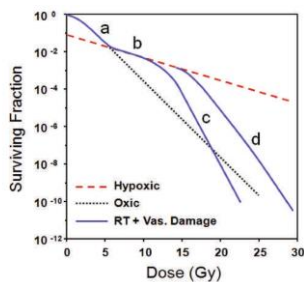


FIG. 7. Hypothetical cell death mechanism in the tumors

The main advocate for the LQ model, showing interest in vascular damage!

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From: Jimm Grimm

Date: Thu, 19 Jun 2014 18:28:29 -0700

To: WGSBRT

Subject: Re: Very interesting article: response to Brown

Hi!

The MSKCC editorial is in the July issue of Red Journal - see attached - with a reply by Brown, Carlson, and Brenner.

To me the irony is that by declaring 'there is no need to invoke a "new biology" to explain the high tumor control rates,' Brown et al. have sparked so much interest in studying that new biology.

The total number of photons delivered is generally lower in SBRT than in conventional fractionation and many of the tumor control rates have been very high, so regardless of whether the LQ model can fit or not, to me it is quite interesting to seek the underlying mechanisms. No matter what we believe, the truth is still the same - some day we will know for sure.

Thanks!

Jimm

No matter what we believe, the truth is still the same.
Seek the truth, and believe it!

Subject: Re: Very interesting article: response to Brown
 From: John R. Adler
 To: Dwight Heron, Jimm Grimm, Deasy J, 5 More...

Jun 20 at 7:05 PM



First they ignore you, then
 they laugh at you, then they
 fight you, then you win.

quotesapi.info Mahatma Gandhi

From: Dwight Heron
 To: Jimm Grimm, DeasyJ, WGSBRT
 Sent: Thursday, June 19, 2014 6:40:41 PM
 Subject: Re: Very interesting article: response to Brown

Amen brother. AMEN!

Now key people from all sides of the debate are
 •writing HyTEC papers together
 •presenting in this session together, and
 •beginning to understand all sides together...
 •We can all win together!!

A hint from AVM

- In the late 1960s, obliteration of arteriovenous malformation (AVM) demonstrated one of the first clinical successes of single fraction SRS.
- It is commonly observed that a single SRS treatment with only 15 to 25 Gy completely obliterates 80% to 90% of small AVMs, which implies that immature and abnormally formed vasculatures are radiosensitive.
 - HyTEC Vision Paper, Song et al. Indirect Cell Death. In-Press.
- Special thanks to Raymond Schulz for helping me to realize this – after Faiz Khan's Suntha lecture at Jefferson, on the way to the train station...

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 MEDICAL EDUCATION

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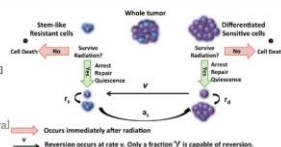
Radiation Therapy Dose Response Modeling and Optimization of Fractionation Schedules with Cancer Stem Cells

• Cancer stem cells (CSC) hypothesis

- Solid tumors are hierarchically organized to contain a small population of CSC along with non-stem differentiated cancer cells (DCC)^{[1][2]}

• CSC governs cancer progression

- Radio-resistant
- Higher proliferative capacity through self-renewal
- Irradiated DCCs reprogram to CSC



• Mathematical modeling and optimization with CSC

- Shown promise in describing the definitive treatment failure of Glioblastoma Multiforme and improved treatment outcome with hypofractionation for NSCLC^[4]
- Optimized dose fractionation with CSC models improved survival in mice^[5]

UCLA Health

[1] Reyes T et al. Nature 2001 [2] Clarke MF et al. Cancer Res 2006
 [3] Lagarde C et al. Stem Cells 2012 [4] Yu et al. UROBP 2014 [5] Leder et al. Cell 2014

1

**HyTEC Vision Papers:
Rationale and Evidence for SBRT**

Dr. Victoria Yu, PhD UCLA
Radiation therapy dose response modeling and optimization of fractionation schedules with cancer stem cells

Dr. Chang Song, PhD U Minnesota
Role of vascular damage and tumor microenvironment in the response of tumors to SBRT and SRS

Dr. David J. Carlson, PhD UPenn
Biological dose escalation and outcomes modeling in the era of stereotactic radiotherapy

Dr. Ariel Marciscano, MD MSKCC
Immunomodulatory Effects of SBRT: Preclinical Insights and Clinical Opportunities

Moderators: Dr. Jimm Grimm, PhD and Dr. Jinyu Xue, PhD
