2014 AAPM SUMMER SCHOOL
University of Vermont • Burlington, VT • June 22–26, 2014
SRS/SBRT/SABR:
Safely and Accurately Delivering
High-Precision, Hypofractionated Treatments

Radiobiological Effects of Hypofractionation: Unique Aspects of Tumor Response to High Dose Per Fraction Radiotherapy— SBRT as Ablative Therapy

Dr. Jimm Grimm, PhD

Holy Redeemer Hospital

with the support of 74 other physicians, physicists, and radiobiologists

Part 2 of 2

Conflict of Interest

- Dr. Grimm founded www.DiversiLabs.com and developed the DVH Evaluator (This conflict has been disclosed on the AAPM website since 2011)

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SRS/SBRT/SABR:
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WGSBRT

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Outline of Presentation

- Part 2
  - SBRT Lung TCP
    - A few hints about possible radiobiological explanations
  - NTCP for anatomical structures near Lung
  - SBRT Liver TCP

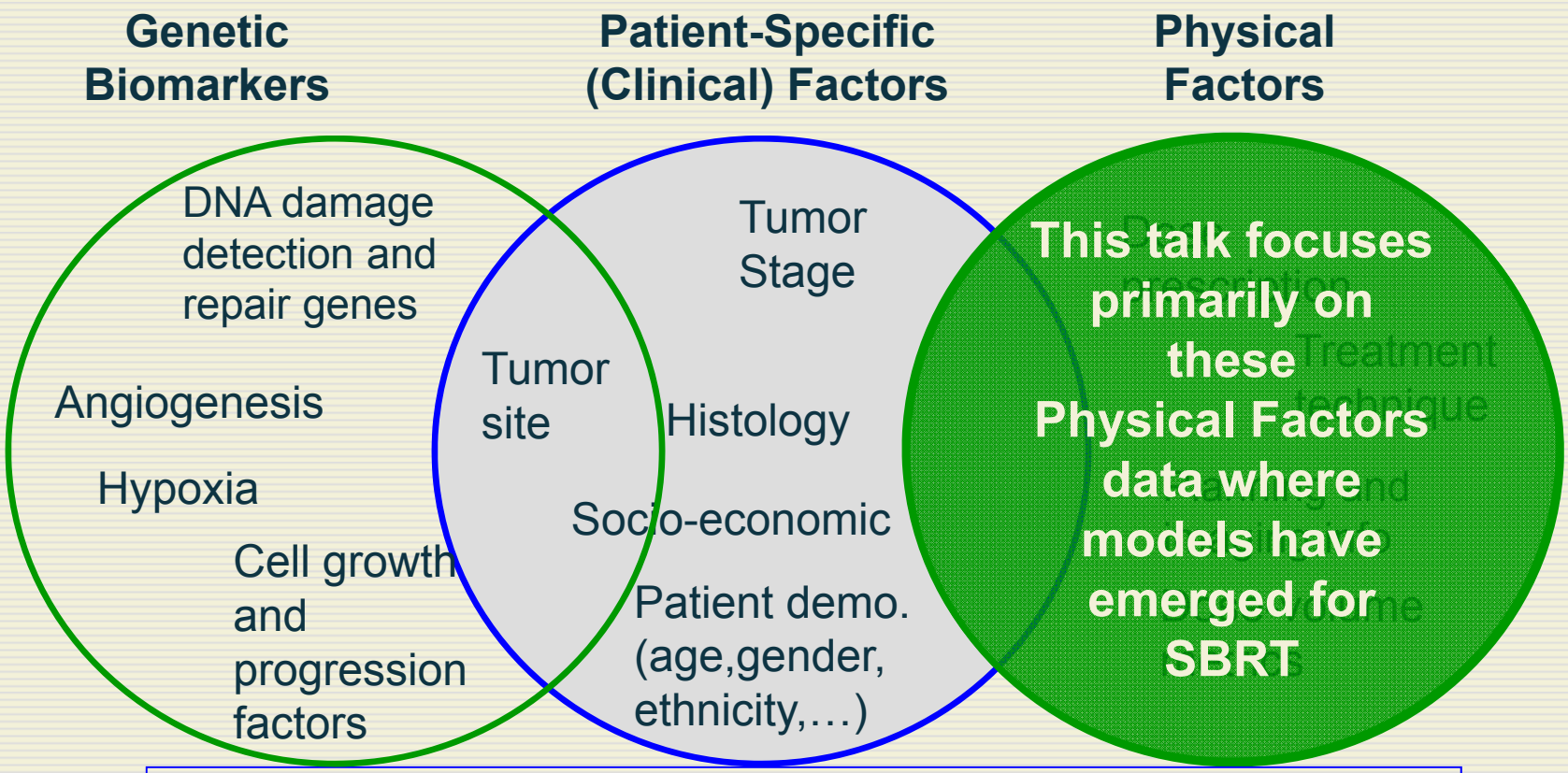
Learning Objectives

1. Common SBRT fractionation schemes and current evidence for efficacy
2. Evidence for normal tissue tolerances in hypofractionated treatments
3. Clinically relevant radiobiological effects at large fraction sizes

WGSBRT at AAPM Summer School

- WGSBRT is extensively reviewing all the SBRT literature
  - A bit too ambitious for one lecture at summer school
- Therefore, this presentation is just a sampling of the literature that we are reviewing
- We will consider a few key aspects here, but can't be as comprehensive as the whole project

- We will see the need for improved reporting standards

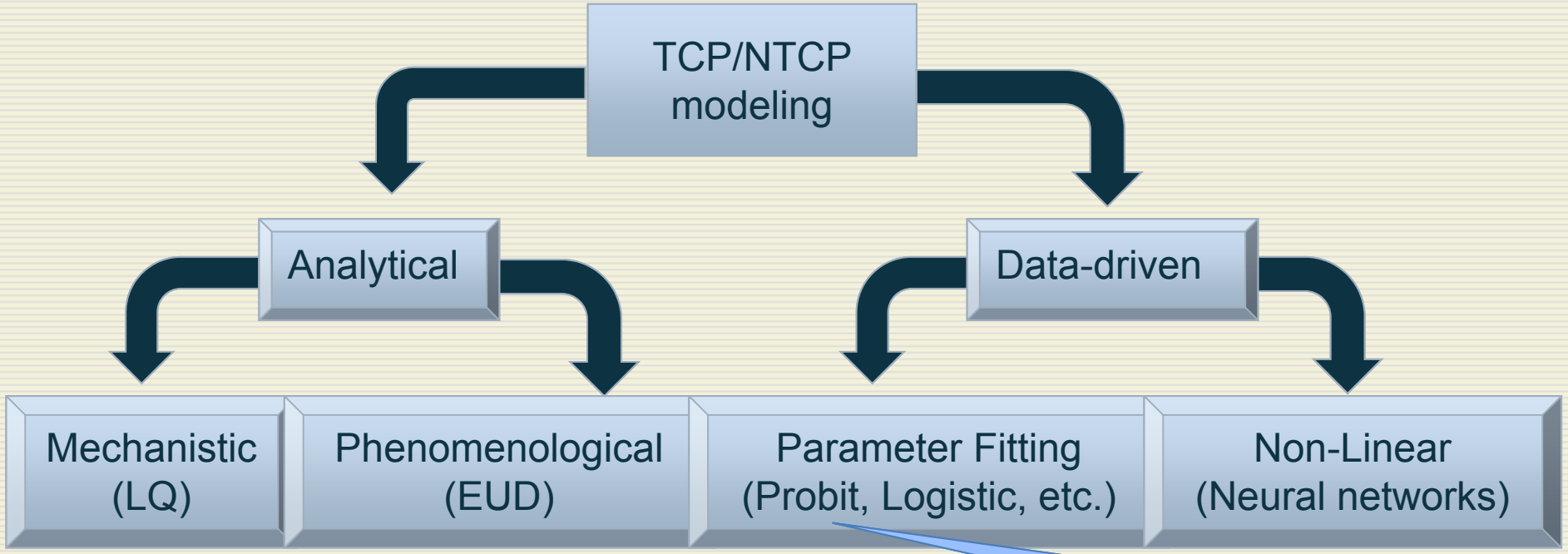


Treatment (RT, Chemo-RT)

Slide compliments of Dr. Issam El Naqa, PhD

Observed Outcome (TCP,NTCP, QoL, …)

TCP/NTCP Modeling Schemes



Slide compliments of Dr. Issam El Naqa, PhD

This talk focuses primarily on dose response models that have emerged for SBRT

Conventionally Fractionated Lung TCP, Martel 1999

- University of Michigan Medical Center
- 76 patients, non-small cell lung cancer
  - includes all patients treated from 1986 to1992 who have CT-based treatment plans that were evaluable for tumor dose information
- Daily fraction size of 1.8–2.0 Gy
- Isocenter doses ranging from 64 to 82 Gy (corrected)

Martel 1999 Logistic Model

$$TCP = \frac{1}{1 + (D_{50} / D)^{K}}$$

- D = isocenter dose
- D_{50} = isocenter dose needed to achieve a 50% probability of tumor control
- K = 4γ where γ = normalized slope at D_{50}

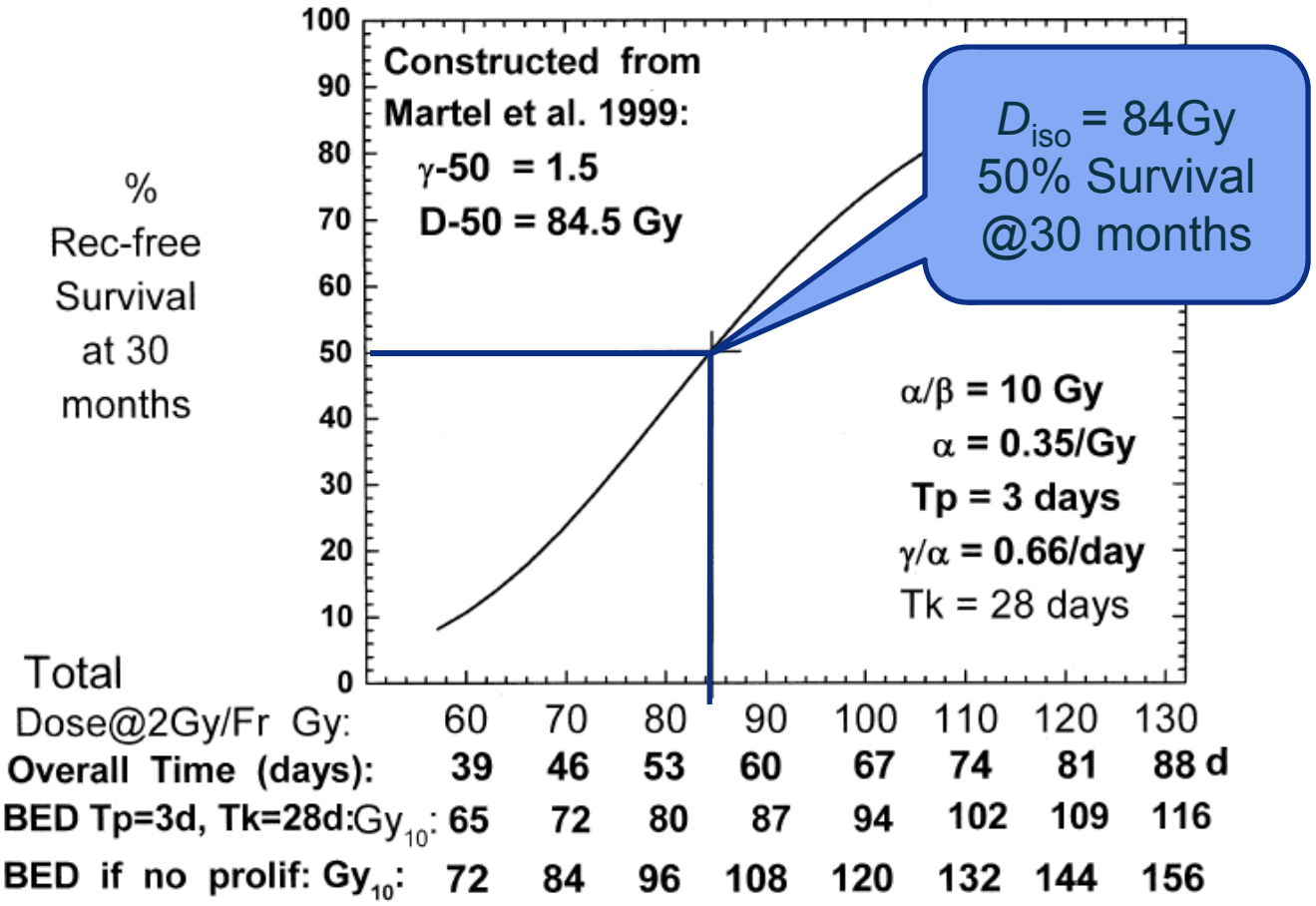


Figure from subsequent article:

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.

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 those 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, Scrimger 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.).

In the Martel 1999 NSCLC article, what isocenter dose was required to achieve 50% progression free survival at 30 months:

4%	1. 60 Gy
7%	2. 74 Gy
87%	3. 84 Gy
2%	4. 94 Gy
0%	5. 156 Gy

In the Martel 1999 NSCLC article, what isocenter dose was required to achieve 50% progression free survival at 30 months:

- Correct answer:

- 3. **84 Gy**

- Ref: **Martel MK, Ten Haken RK, Hazuka MB, Kessler ML, Strawderman M, Turrisi AT, Lawrence TS, Fraass BA, Lichter AS. Estimation of tumor control probability model parameters from 3-D dose distributions of non-small cell lung cancer patients. Lung Cancer. 1999 Apr;24(1):31-7.**

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Patient-Reported Quality of Life Outcomes Shed Light on Poor Survival in an RTOG Trial Evaluating Increased Radiotherapy Dose for Lung Cancer

Atlanta— Results of a quality of life (QOL) analysis presented today during a plenary session of the 2013 Annual Meeting of the American Society for Radiation Oncology (ASTRO) show that, at 3 months after the start of treatment, almost half of patients with stage III non-small cell lung cancer (NSCLC) who received a higher dose of radiotherapy (RT) with chemotherapy reported a clinically meaningful decline in QOL compared with less than a third of those who received a standard dose of radiation with chemotherapy.

$BED_{10} \geqslant 100Gy$
Onishi 2007

- 257 Patients from 14 Institutions in Japan
- Stage I NSCLC
- A total dose of 18 to 75 Gy at the isocenter in 1 to 22 fractions

TABLE 1. Patient Pretreatment Characteristics

Total cases: 257

Age: 39–92 yr (median, 74)
Performance status: PS 0, 109; PS 1, 103; PS 2, 39; PS 3, 6
Pulmonary chronic disease: 168 positive, 89 negative
Histology: 111 squamous cell, 120 adenocarcinoma, 26 other
Stage: 164 IA, 93 IB
Tumor diameter: 7–58 mm (median, 28)
Medical operability: 158 inoperable, 99 operable

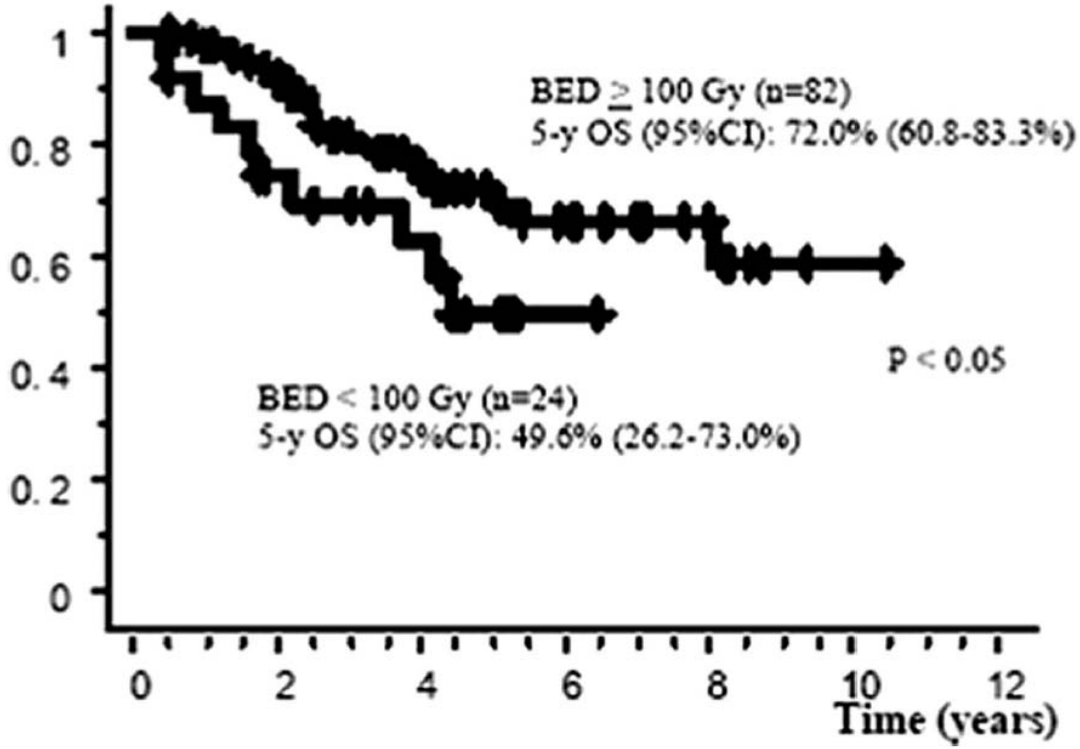


FIGURE 4. Overall survival rate in operable patients according to the biological effective dose (BED). OS, overall survival rate; CI, confidence interval.

Onishi H, Shirato H, Nagata Y, et al. Hypofractionated stereotactic radiotherapy (HypoFXSRT) for stage I non-small cell lung cancer: updated results of 257 patients in a Japanese multi-institutional study. J Thorac Oncol. 2007;2:S94-S100.

SBRT Lung TCP Guckenberger 2009

- 159 lesions in 124 patients
- 118 mets
- **CTV and PTV margin dose instead of isocenter dose**
- **Still compared to the 100Gy BED_{10} baseline**
- Median followup 14 month

Table 1. Patient and treatment characteristics

	Early-stage NSCLC	Pulmonary metastases
Patients (*n*)	40	84
Target volumes (*n*)	41	118
Age (y) Median (range)	70 (52–85)	64 (22–84)
Gender		
Male (*n*)	32	81
Female (*n*)	9	37
Karnofsky index (%) median/mean	70/77	90/89
Histology		
Unknown (*n*)	11	
Squamous cell carcinoma (*n*)	19	
Adenocarcinoma (*n*)	11	
Clinical target volume (cm^3) median (range)	29 (2–256)	8 (1–196)
Planning target volume (cm^3) median (range)	74 (11–384)	30 (3–343)
Target location		
Central (*n*)	6	16
Thoracic wall (*n*)	9	24
Peripheral (*n*)	26	78
Doses		
4-8 * 6–7 Gy to 65–80% (*n*)	6	2
3 * 10 Gy to 65% (*n*)	6	16
3 * 12–12.5 Gy to 65% (*n*)	23	38
1 * 26 Gy to 80% (*n*)	6	62
Follow-up (months) mean/median/ maximum	21/14/91	17/14/80

100Gy BED_{10}

- 100Gy is a round number that has been applied to both:
  - Isocenter dose
  - Margin dose

- Always check definitions!

Guckenberger M, Heilman K, Wulf J, Mueller G, Beckmann G, Flentje M. Pulmonary injury and tumor response after stereotactic body radiotherapy (SBRT): results of a serial follow-up CT study. Radiother Oncol. 2007 Dec;85(3):435-42. Epub 2007 Nov 28. Erratum in: Radiother Oncol. 2008 Feb;86(2):293.

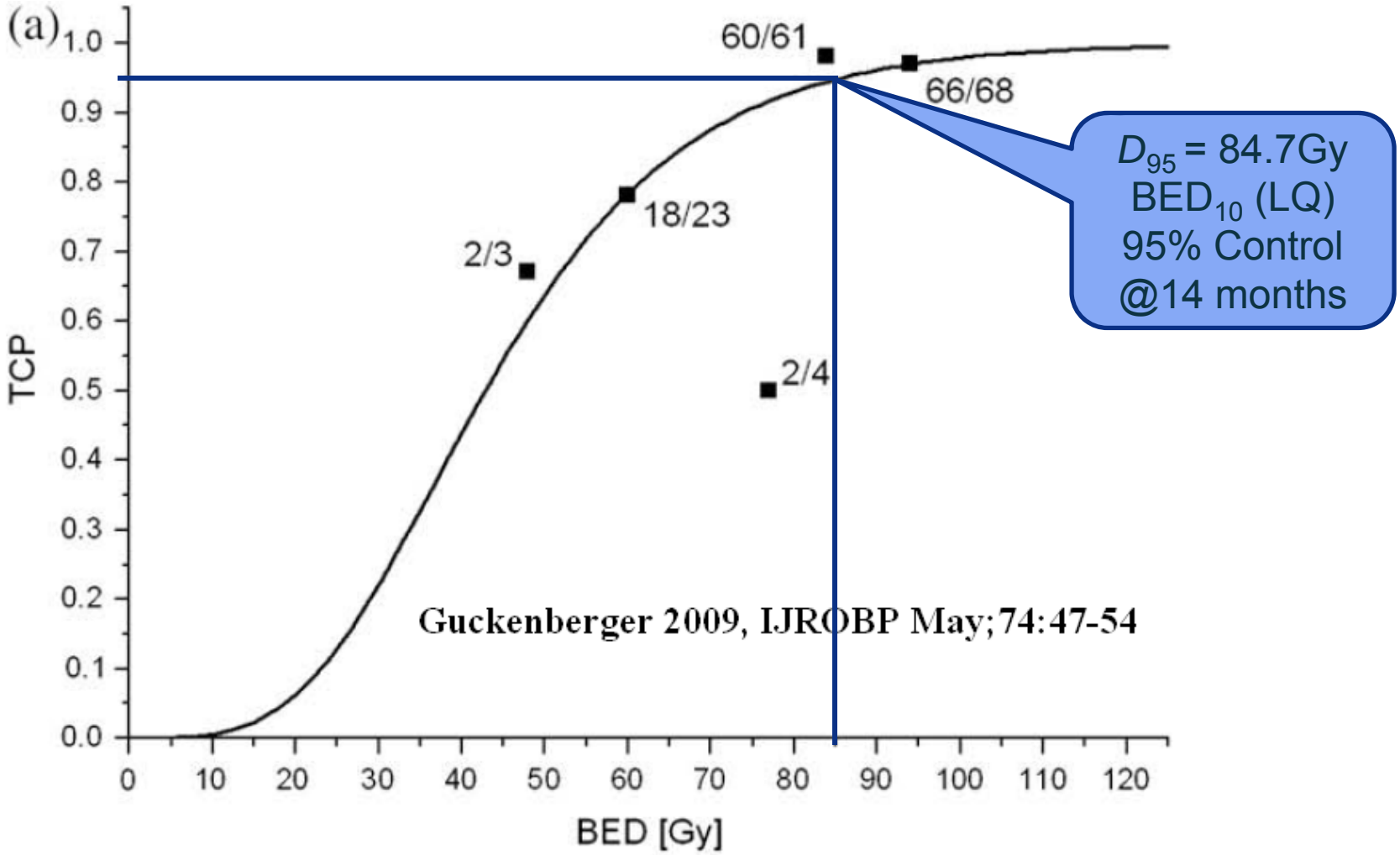


Fig 2a, D95 BED_{10} to 3D PTV

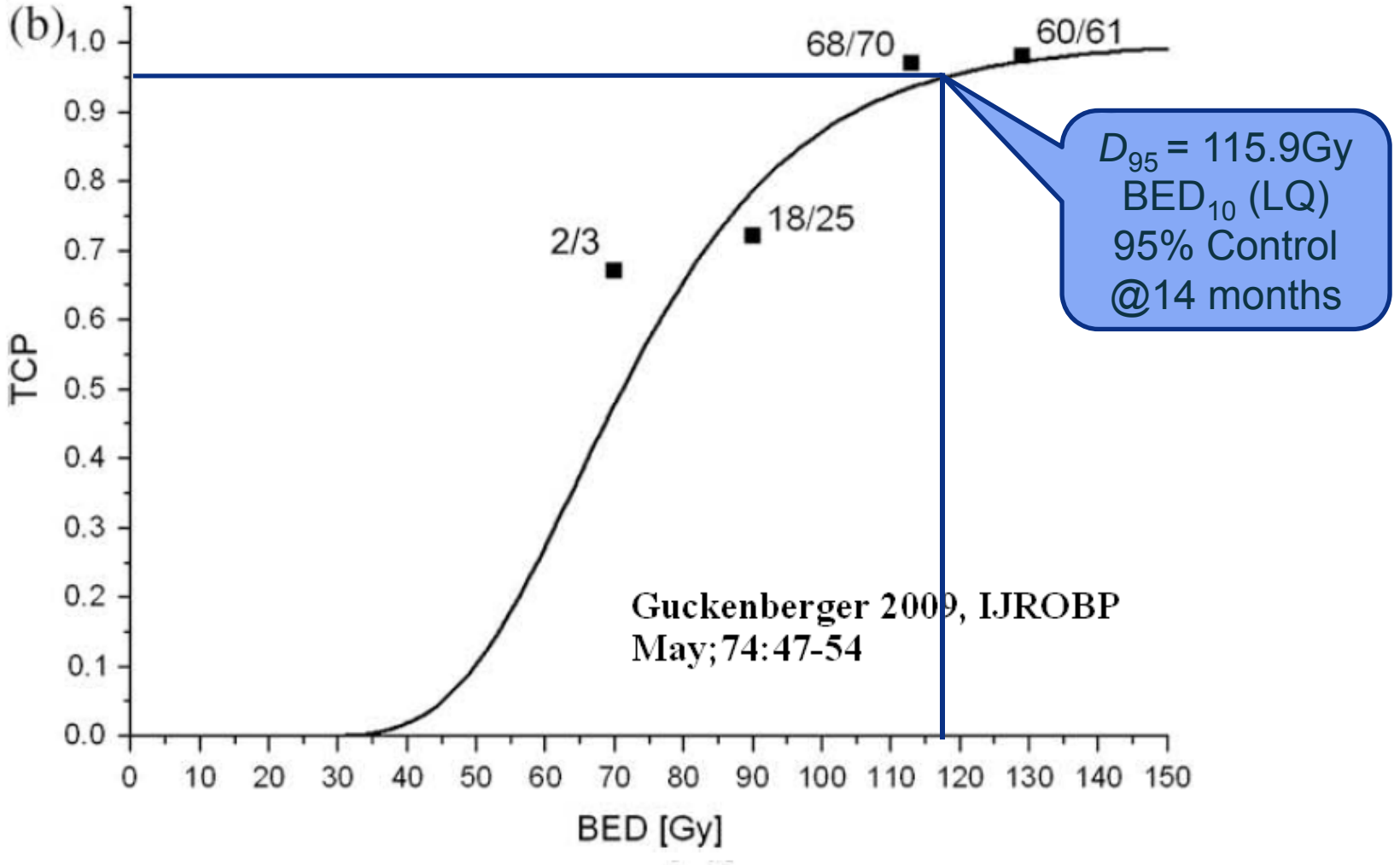


Fig 2b, D95 BED_{10} to 4D CTV

95% 14 Month Local Control

- 3D PTV: 84.7 Gy BED_{10} = 38Gy in 3 fractions
- 4D CTV: 115.9 Gy BED_{10} = 46Gy in 3 fractions

- CTV D95 is about 20% higher than PTV D95
- May want a bit higher dose for more durable LC
- Author conclusion: **"Doses of >100 Gy BED to the CTV based on 4D dose calculation resulted in excellent local control rates for image guided SBRT of primary early-stage NSCLC and pulmonary metastases."**

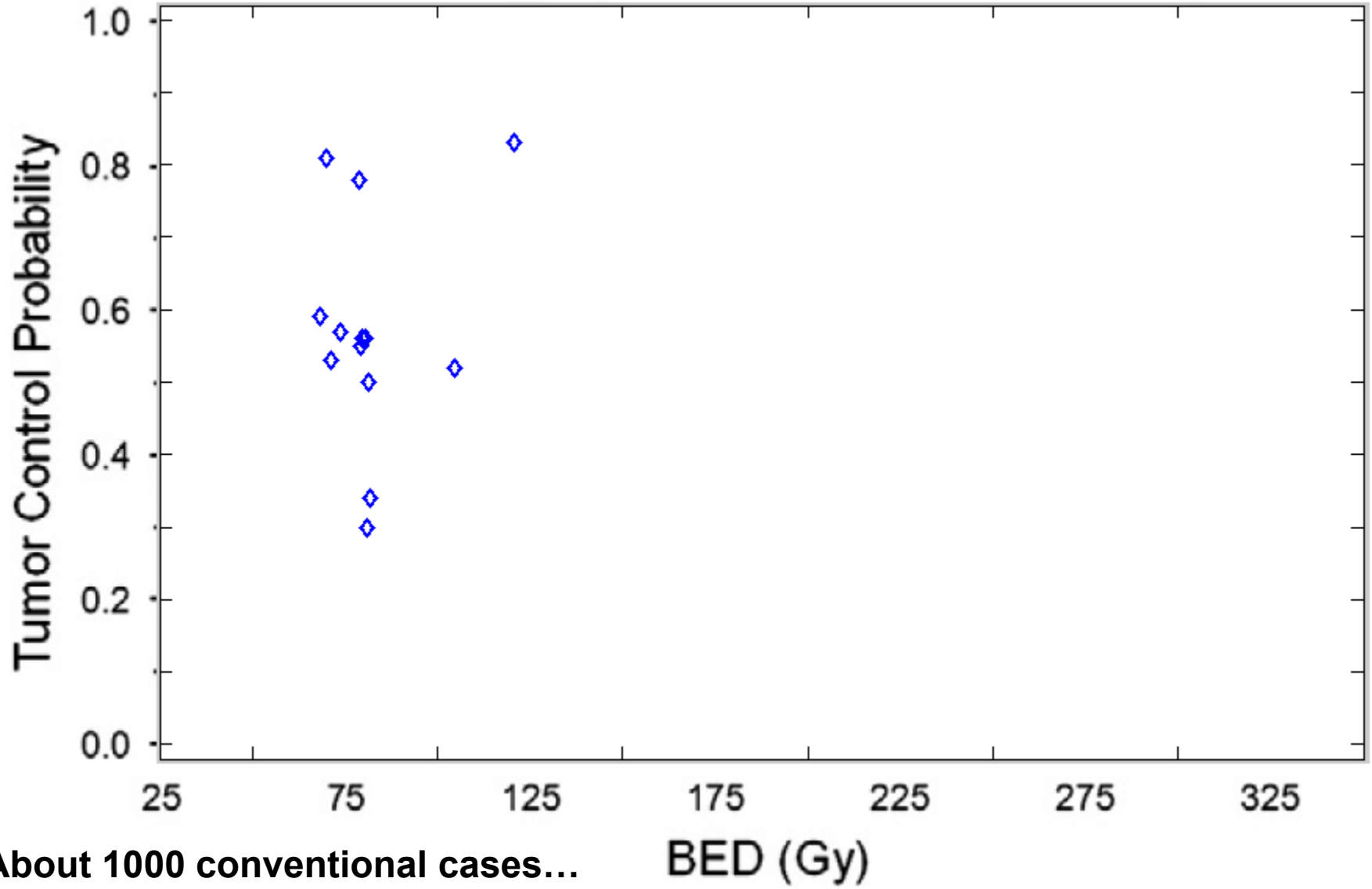
Mehta 2012 Pooled Analysis

- Stage I NSCLC
- 2-year followup required
- Data from 42 studies
  - **2696 total cases**
  - About **1000 conventional cases**
  - About **1500 SBRT cases**
  - Prescriptions converted to iso
- BED using LQ and USC
  - Least Squares fitting of
  - Logistic Model for both

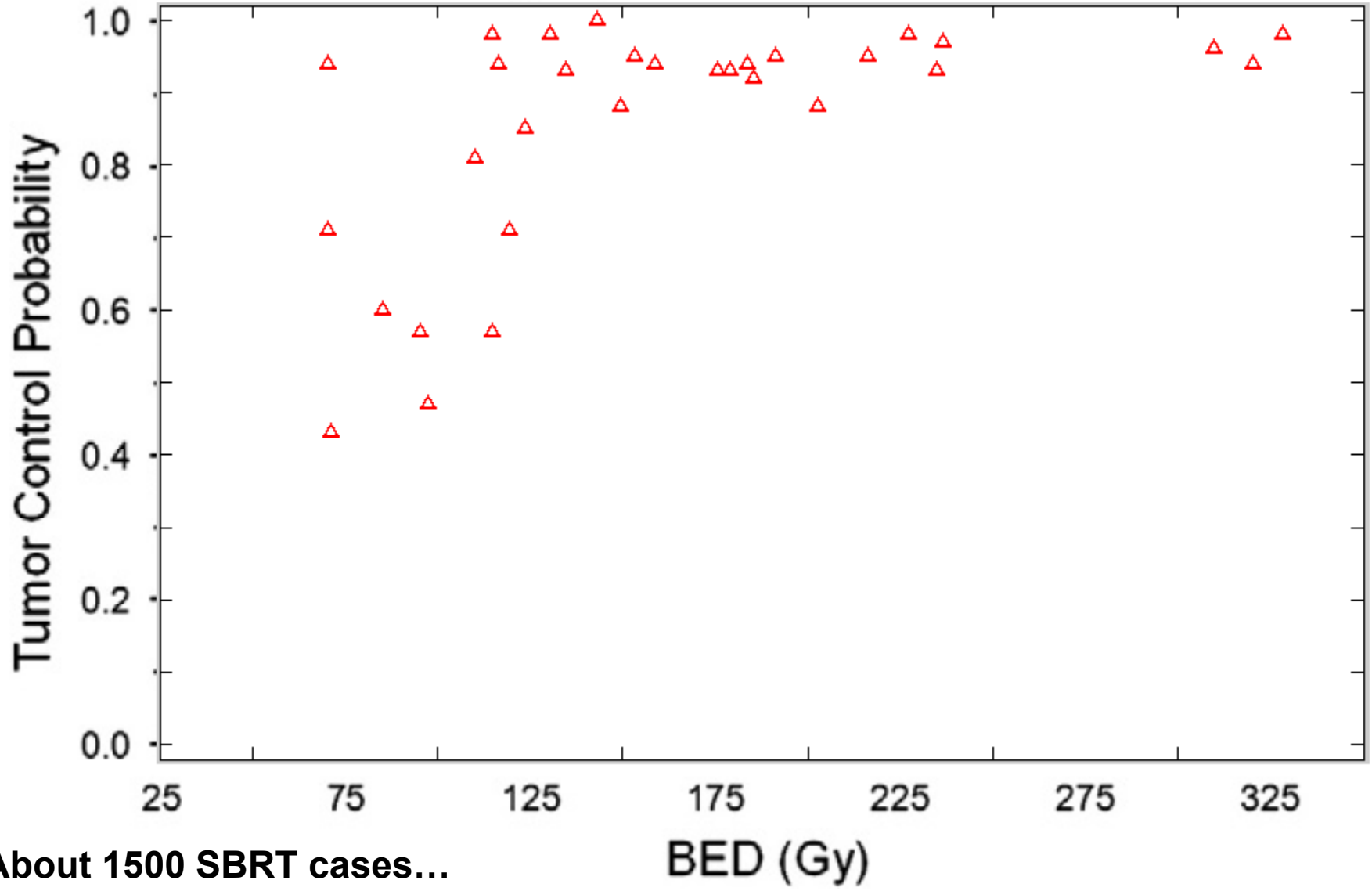
Table 3 Demographics, radiation therapy details, and tumor control

No. of patients	2696
Age, y	73 (22-95)
Histology	
Adenocarcinoma	704 (26%)
Squamous cell carcinoma	847 (31%)
NOS	1145 (42%)
T stage	
T1	1585 (56%)
T2	1128 (40%)
NOS	96 (3%)
Operable	
Yes	421 (14%)
No	2531 (86%)
RT technique	
3D-CRT	1046 (39%)
SBRT	1640 (61%)
Absolute dose range, Gy	
3D-CRT	48-102.9 (1.2-4 Gy/fx)
SBRT	20-66 (4.4-26 Gy/fx)
No. of fractions, range	
3D-CRT	12-49
SBRT	1-10
Median aBED, Gy	105.6
aBED range, Gy	59.6-286.6

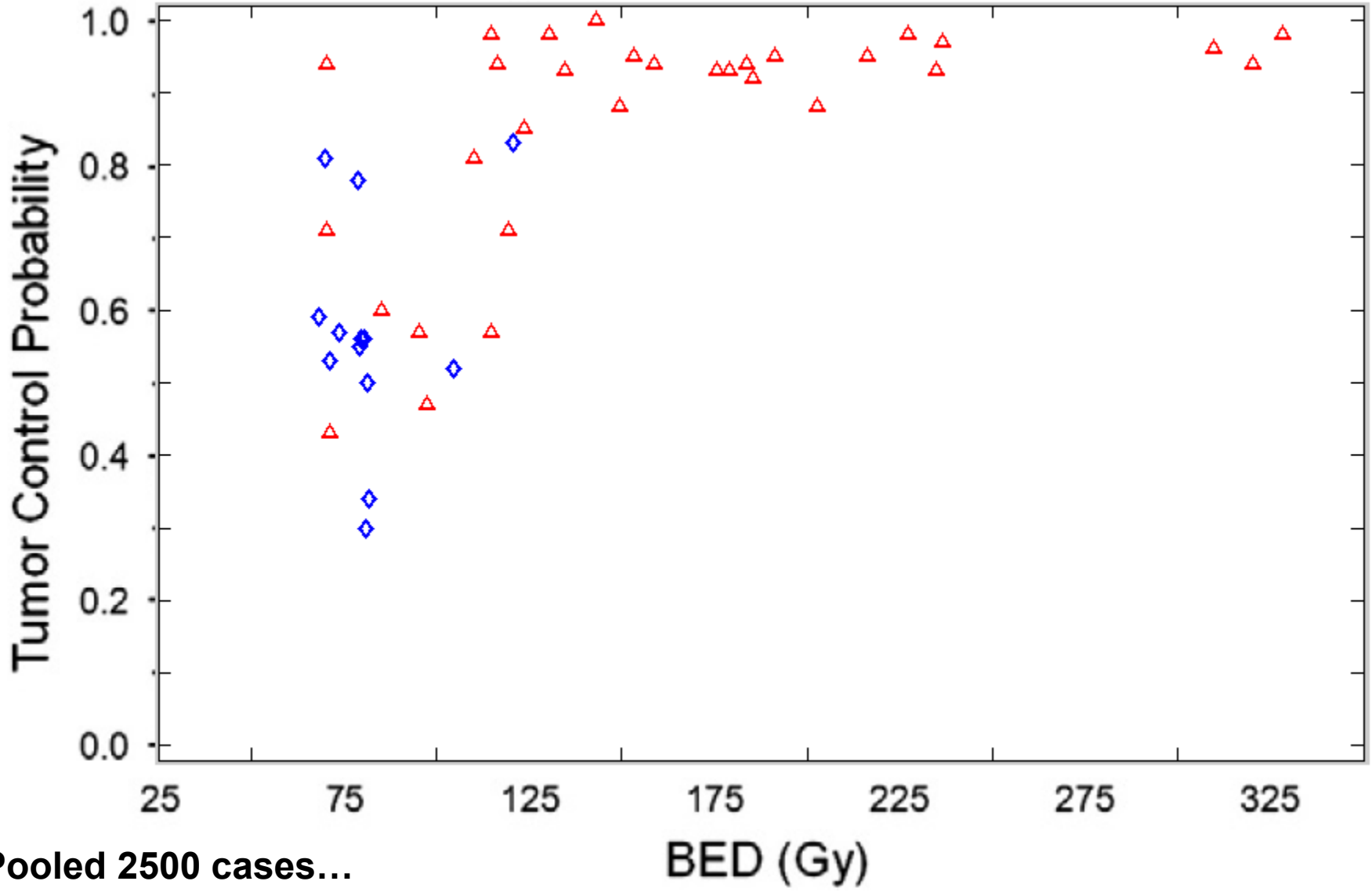
3D-CRT, 3-dimensional conformal radiation therapy; aBED, average biological effective dose; NOS, not otherwise specified; RT, radiation therapy; SBRT, stereotactic body radiation therapy.



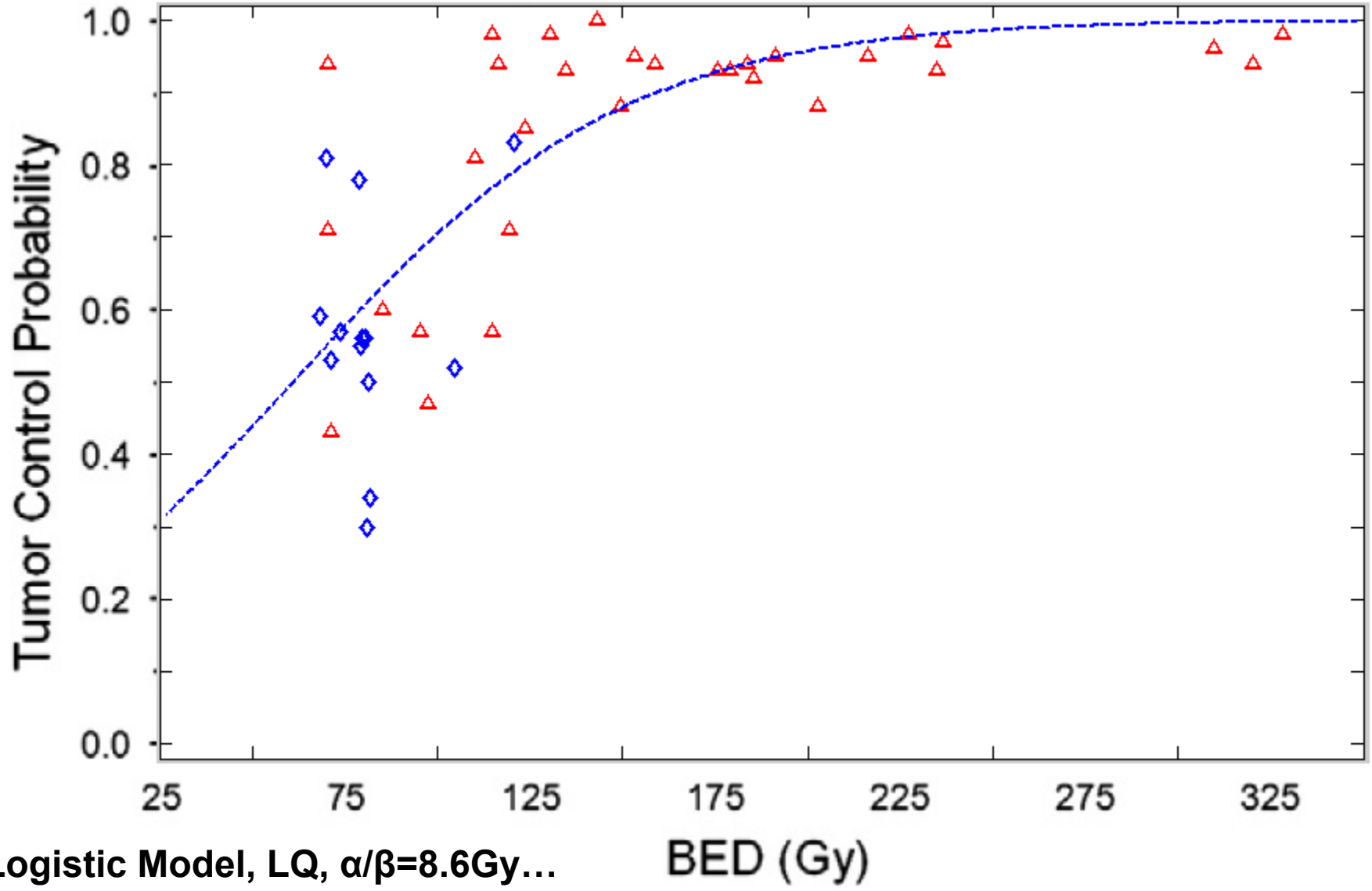
About 1000 conventional cases…



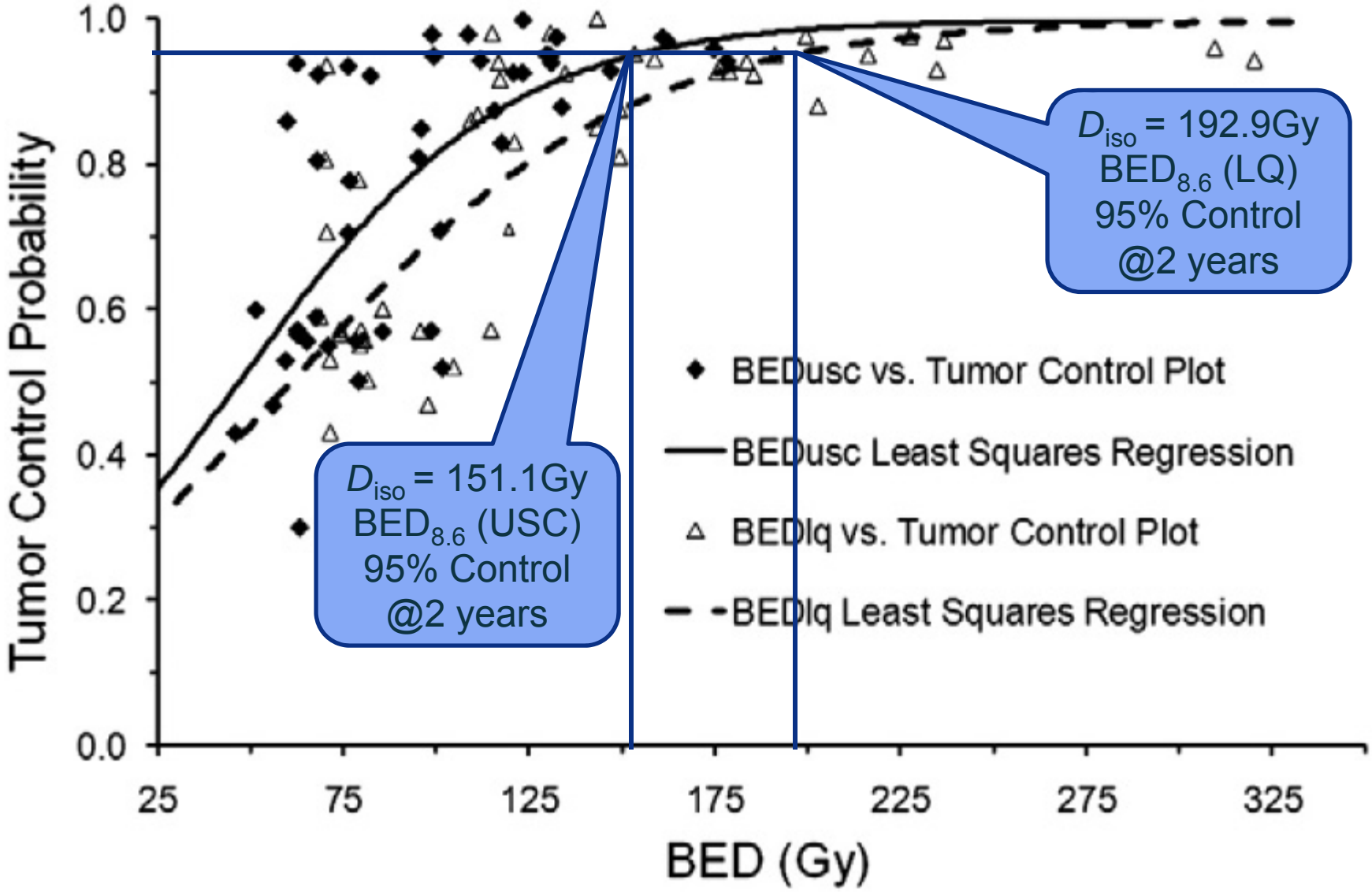
About 1500 SBRT cases…



Pooled 2500 cases…



Logistic Model, LQ, α/β=8.6Gy…


Tumor Control Probability
1.0
0.8
0.6
0.4
0.2
0.0
25
75
125
175
225
275
325
BED (Gy)
D_{iso} = 192.9Gy
$BED_{8.6}$ (LQ)
95% Control
@2 years
D_{iso} = 151.1Gy
$BED_{8.6}$ (USC)
95% Control
@2 years
BEDusc vs. Tumor Control Plot
BEDusc Least Squares Regression
BEDlq vs. Tumor Control Plot
BEDlq Least Squares Regression

95% 2 Year Local Control

- USC: 151.1 Gy $BED_{8.6}$ = 22.6Gy * 3 fractions
- LQ: 192.9 Gy $BED_{8.6}$ = 19.6Gy * 3 fractions

≈ 20Gy * 3 fractions
Physical dose

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.

According to the model in Mehta 2012, what prescription dose resulted in 95% local control at 2 years?

0% 1. 10Gy * 3 fractions

1% 2. 12Gy * 3 fractions

0% 3. 15Gy * 3 fractions

99% 4. 20Gy * 3 fractions

0% 5. 24Gy * 3 fractions

According to the model in Mehta 2012, what prescription dose resulted in 95% local control at 2 years?

- Correct answer
- 4. **20Gy * 3 fractions**
- Ref: **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.**
- **Caveats: dose calculation algorithm, isocenter versus margin dose, many other factors – see the next slide…**

Many Other Factors May Affect Outcomes

- Patient age, gender, smoking, comorbidities
- Gating/tracking/immobilization/delivery system
- Dose calculation algorithm/heterogeneity correct
- D95%, min dose, max dose, isodose, margin
- GTV size, CTV/ITV/PTV size
- Duration of each treatment
- Surgery, Chemotherapy or other treatments

Which of the following factors may affect outcomes?

1% 1. Patient gender

1% 2. Tumor size

1% 3. Operable/Inoperable

1% 4. Dose calculation algorithm

97% 5. All of the above

Which of the following factors may affect outcomes?

- Correct answer
- 5. **All of the above**
- Refs: **1) Matsuo Y, Shibuya K, Yasushi N, et al. Prognostic factors in stereotactic body radiotherapy for non-small-cell lung cancer Int J Radiat Oncol Biol Phys. 2011, 79:1104-11**
2) Latifi K, Oliver J, Baker R, Dilling TJ, Stevens CW, Kim J, Yue B, Demarco M, Zhang GG, Moros EG, Feygelman V. Study of 201 non-small cell lung cancer patients given stereotactic ablative radiation therapy shows local control dependence on dose calculation algorithm. Int J Radiat Oncol Biol Phys. 2014 Apr 1;88(5):1108-13.

Reporting Standards

- It is often hard to prove which factors are most significant because of lack of reported details
  - Dose per patient
  - PTV D95, GTV min dose, Isocenter dose, etc.
  - Explicitly state Endpoints
  - Supplemental electronic material can be used to share more detailed information
  - Too few events in each article – hard to combine them if the reporting isn't clear or if definitions vary too much

Why are reporting standards important?

1%	1.	Small numbers of events in individual series
2%	2.	Facilitates later analysis of clinical outcome data
1%	3.	Gets everyone speaking the same language
1%	4.	Not important; just pass peer-review
96%	5.	1, 2, and 3 are correct

Why are reporting standards important?

- Correct answer
- 5. **1, 2, and 3 are correct**
- Ref: **Jackson A, Marks LB, Bentzen SM, Eisbruch A, Yorke ED, Ten Haken RK, Constine LS, Deasy JO. The lessons of QUANTEC: recommendations for reporting and gathering data on dose-volume dependencies of treatment outcome. Int J Radiat Oncol Biol Phys. 2010 Mar 1;76(3 Suppl):S155-60.**

WGSBRT Thoracic TCP Group

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- **Wolfgang Tome, PhD**
- **Chang Song, PhD**
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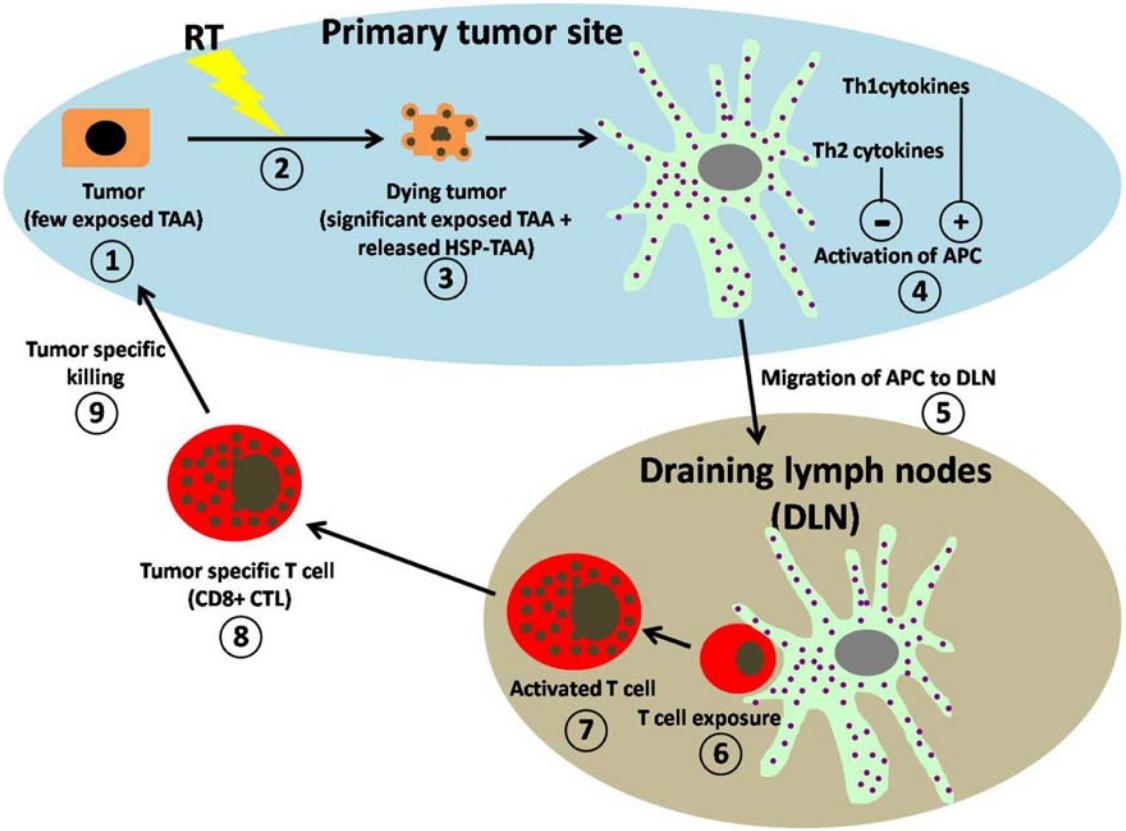
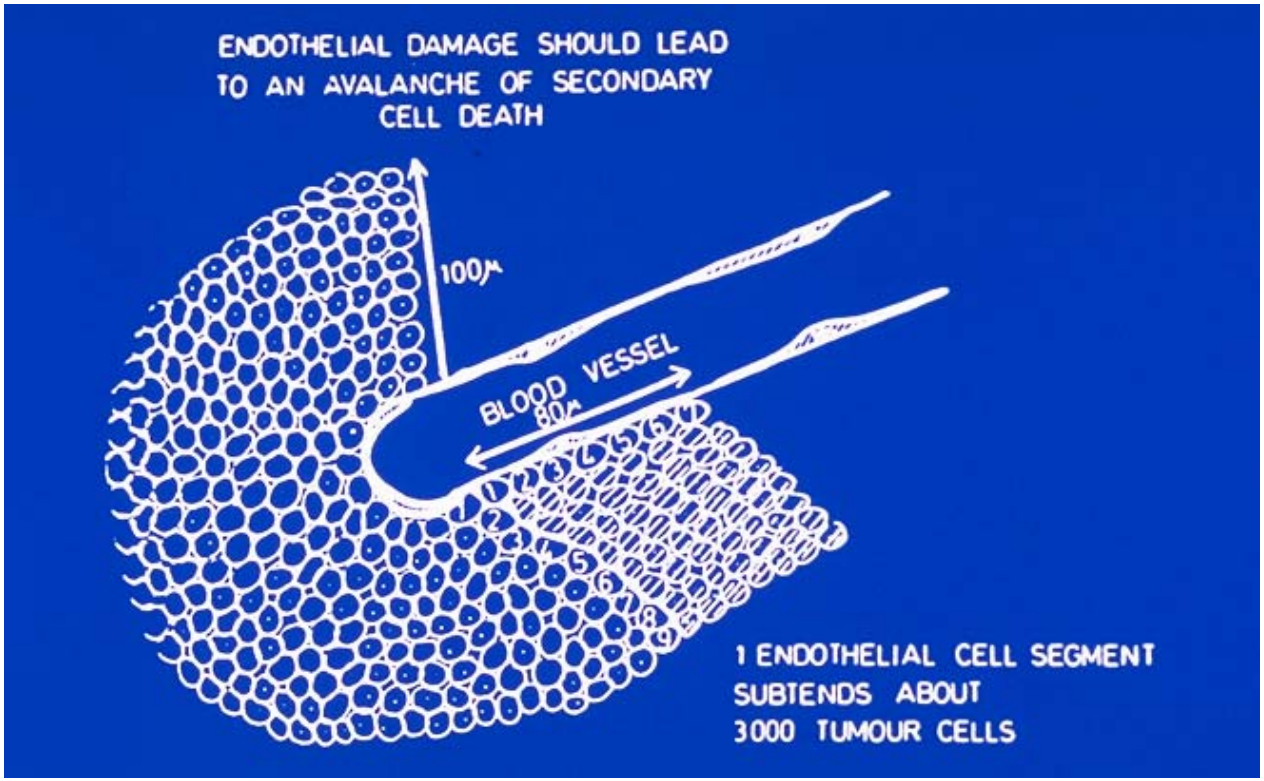
- Analyzing all this data and more
- Comparing BED models
- Comparing dose response models
- Multivariate analysis to determine which factors significantly affect outcomes

Possible Radiobiological Explanations: Immunogenic Response



Kaur P, Asea A. Radiation-induced effects and the immune system in cancer. Front Oncol. 2012 Dec 17;2:191.

Possible Radiobiological Explanations: Vascular Damage



J. Denekamp, Acta Radiologica Oncol, 23, p217, 1984
C. Song, Rad Res, 177, p323, 2012

Single Endothelial Cell?

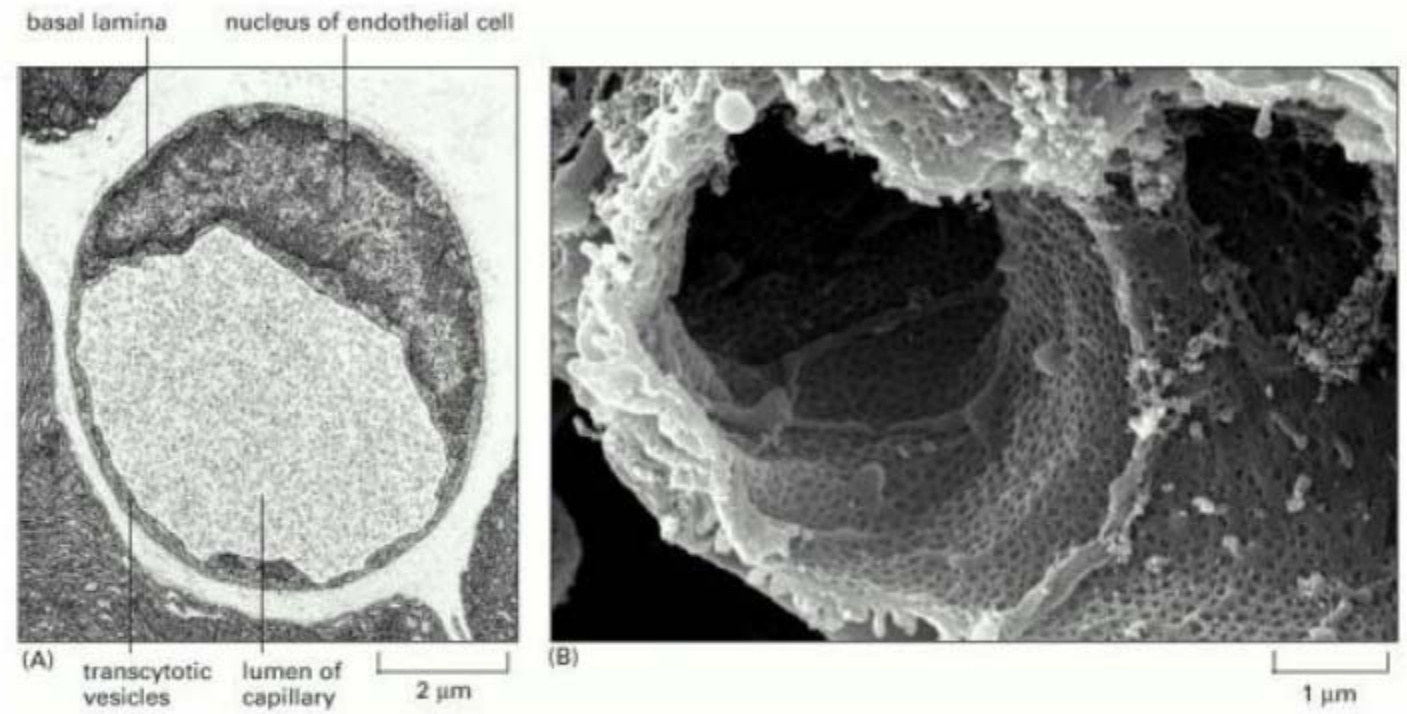


Figure 22-23 Capillaries

(A) Electron micrograph of a cross section of a small capillary in the pancreas. The wall is formed by a single endothelial cell surrounded by a basal lamina.

Alberts B, Johnson A, Lewis J, Raff M, Roberts K, Walter P. Molecular Biology of the Cell. 4th edition. New York: Garland Science; 2002

Thoracic NTCP

- Example: Rib Fractures / Chestwall Pain

Much Data Exists Regarding Rib / Chestwall Tolerance for SBRT

- **Dunlap 2010:** Dunlap NE, Cai J, Biedermann GB, Yang W, Benedict SH, Sheng K, Schefter TE, Kavanagh BD, Larner JM. Chest Wall Volume Receiving >30 Gy Predicts Risk of Severe Pain and/or Rib Fracture After Lung Stereotactic Body Radiotherapy. Int J Radiat Oncol Biol Phys. 2010 Mar 1;76(3):796-801. Epub 2009 May 8.
- **Pettersson 2010:** Pettersson N, Nyman J, Johansson KA. Radiation-induced rib fractures after hypofractionated stereotactic body radiation therapy of non-small cell lung cancer: a dose- and volume-response analysis. Radiother Oncol. 2009 Jun;91(3):360-8. Epub 2009 May 4.
- **Welsh 2011:** Welsh J, Thomas J, Shah D, Allen PK, Wei X, Mitchell K, Gao S, Balter P, Komaki R, Chang JY, Obesity Increases the Risk of Chest Wall Pain from Thoracic Stereotactic Body Radiation Therapy, Int J Radiat Oncol Biol Phys. 2011 Sep 1;81(1):91-6.
- **Tome 2011:** Tome WA, Hodge CW, Mehta MP, Bentzen SM. Incidence of rib fractures after stereotactic body radiotherapy for peripheral lung lesions: clinical experience and dose response estimation. JRSBRT. 2011;1(2):155-61.
- **Bongers 2011:** Bongers EM, Haasbeek CJ, Lagerwaard FJ, Slotman BJ, Senan S. Incidence and risk factors for chest wall toxicity after risk-adapted stereotactic radiotherapy for early-stage lung cancer. J Thorac Oncol. 2011 Dec;6(12):2052-7.
- **Stanic 2011:** Stanic S, Boike TP, Rule WG, Timmerman RD. Rib fracture following stereotactic body radiotherapy: a potential pitfall. Clin Nucl Med. 2011 Nov;36(11):e168-70.
- **…**

Much Data Exists Regarding Rib / Chestwall Tolerance for SBRT

- …
- **Stephans 2012:** Stephans KL, Djemil T, Tendulkar RD, Robinson CG, Reddy CA, Videtic GM. Prediction of chest wall toxicity from lung stereotactic body radiotherapy (SBRT). Int J Radiat Oncol Biol Phys. 2012 Feb 1;82(2):974-80.
- **Mutter 2012:** Mutter RW, Liu F, Abreu A, Yorke E, Jackson A, Rosenzweig KE. Dose-volume parameters predict for the development of chest wall pain after stereotactic body radiation for lung cancer. Int J Radiat Oncol Biol Phys. 2012 Apr 1;82(5):1783-90.
- **Creach 2012:** Creach KM, El Naqa I, Bradley JD, Olsen JR, Parikh PJ, Drzymala RE, Bloch C, Robinson CG. Dosimetric predictors of chest wall pain after lung stereotactic body radiotherapy. Radiother Oncol. 2012 Jul;104(1):23-7.
- **Taremi 2012:** Taremi M, Hope A, Lindsay P, Dahele M, Fung S, Purdie TG, Jaffray D, Dawson L, Bezjak A. Predictors of radiotherapy induced bone injury (RIBI) after stereotactic lung radiotherapy. Radiat Oncol. 2012 Sep 17;7:159.
- **Asai 2012:** Asai K, Shioyama Y, Nakamura K, Sasaki T, Ohga S, Nonoshita T, Yoshitake T, Ohnishi K, Terashima K, Matsumoto K, Hirata H, Honda H. Radiation-Induced Rib Fractures After Hypofractionated Stereotactic Body Radiation Therapy: Risk Factors and Dose-Volume Relationship. Int J Radiat Oncol Biol Phys. 2012 Nov 1;84(3):768-73.
- **Many more still coming…**

Pettersson 2009

- One of the first articles published on the topic actually has enough data to get almost a complete set of dose tolerance limits

- Linac based SBRT
- Individual Ribs

Pettersson 2009 G1-3 Rib Tolerance Patient Characteristics

- 68 patients, inoperable, stage I, NSCLC
- 33 patients with complete treatment records and radiographic follow-up exceeding 15 months (median: 29 months)
- 13 fractures were found in 7 patients (of 81 ribs)
- Did not generally heal
- Most of the rib fractures radiographic only; not a great deal of pain

Pettersson 2009 G1-3 Rib Tolerance Treatment Characteristics

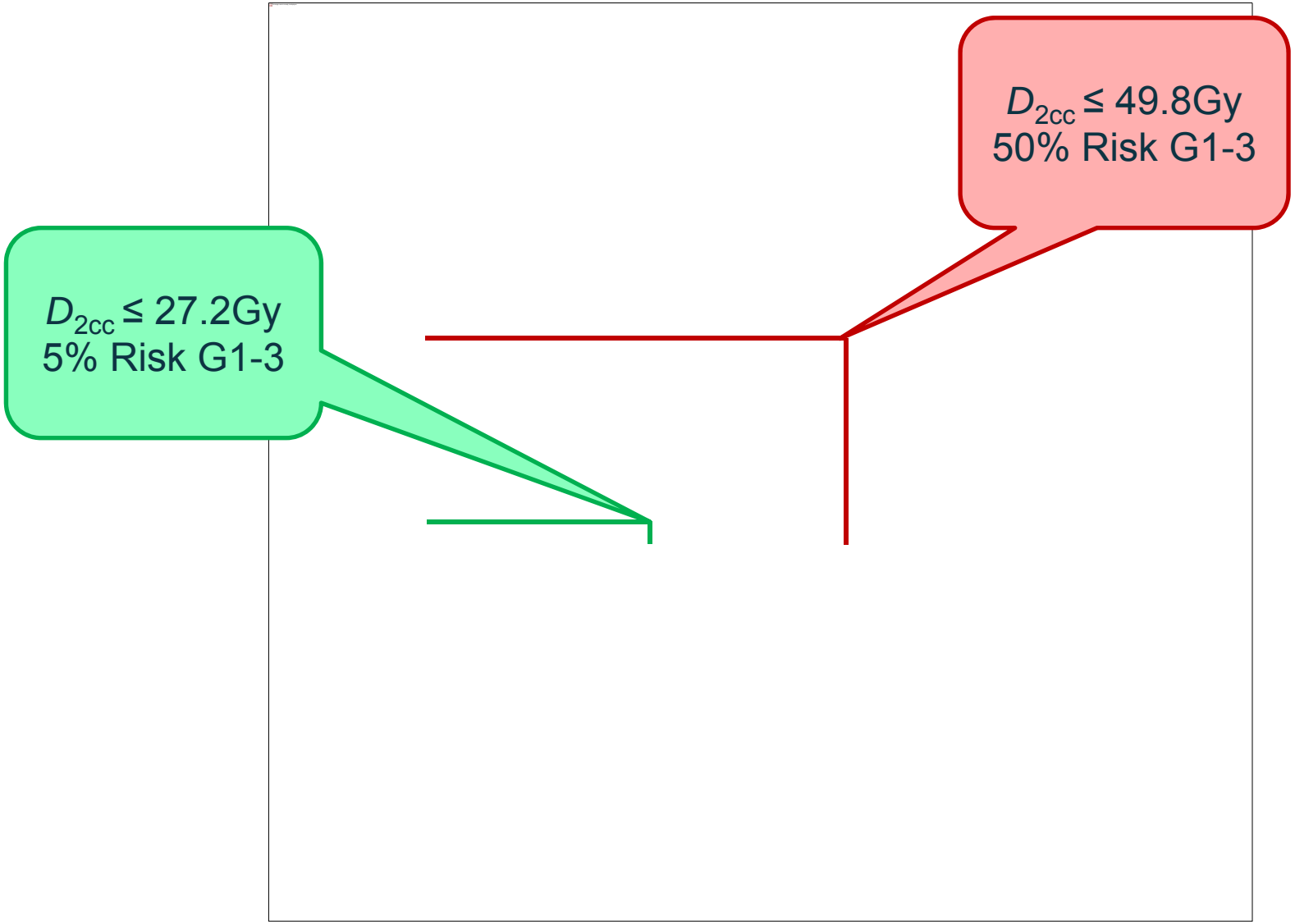
- 45 Gy in 3 fractions
- α/β=3 Gy, LQ model is “built into” logistic dose response model
- Elekta Body Frame
- Cadplan 6.4.7 or Eclipse 7.2.24, Varian
- Pencil beam convolution algorithm using the modified Batho method for inhomogeneity correction

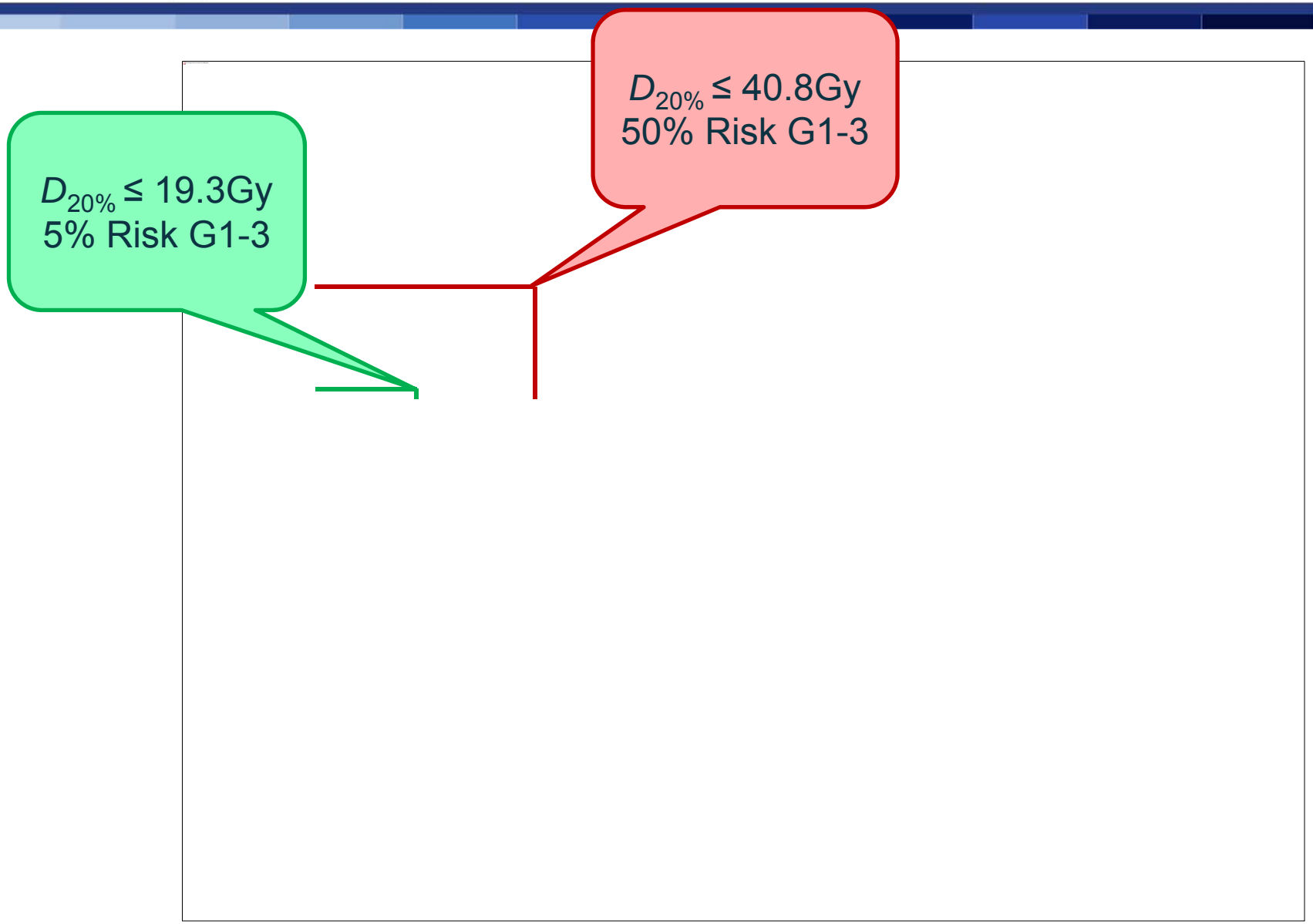
Endpoint

- "most of the rib fractures were only detected radiographically"
- "some patients had a long lasting moderate pain with need for analgesics"

- Would be CTCAE Grade 1-2, or maybe 1-3
  - Mostly Grade 1

National Cancer Institute. Common Terminology Criteria for Adverse Events, version 3.0.2006. Available at: http://ctep.cancer.gov/reporting/ctc.html.


$D_{2cc} \leq 49.8Gy$
50% Risk G1-3
$D_{2cc} \leq 27.2Gy$
5% Risk G1-3


$D_{20\%} \leq 40.8$Gy
50% Risk G1-3
$D_{20\%} \leq 19.3$Gy
5% Risk G1-3