Altered Fractionation

Søren M. Bentzen, David Westerly, Hidefumi Aoyama

Departments of Human Oncology; Medical Physics; Biostatistics and Medical Informatics,
UW Paul P. Carbone Comprehensive Cancer Center, Madison, Wisconsin, USA

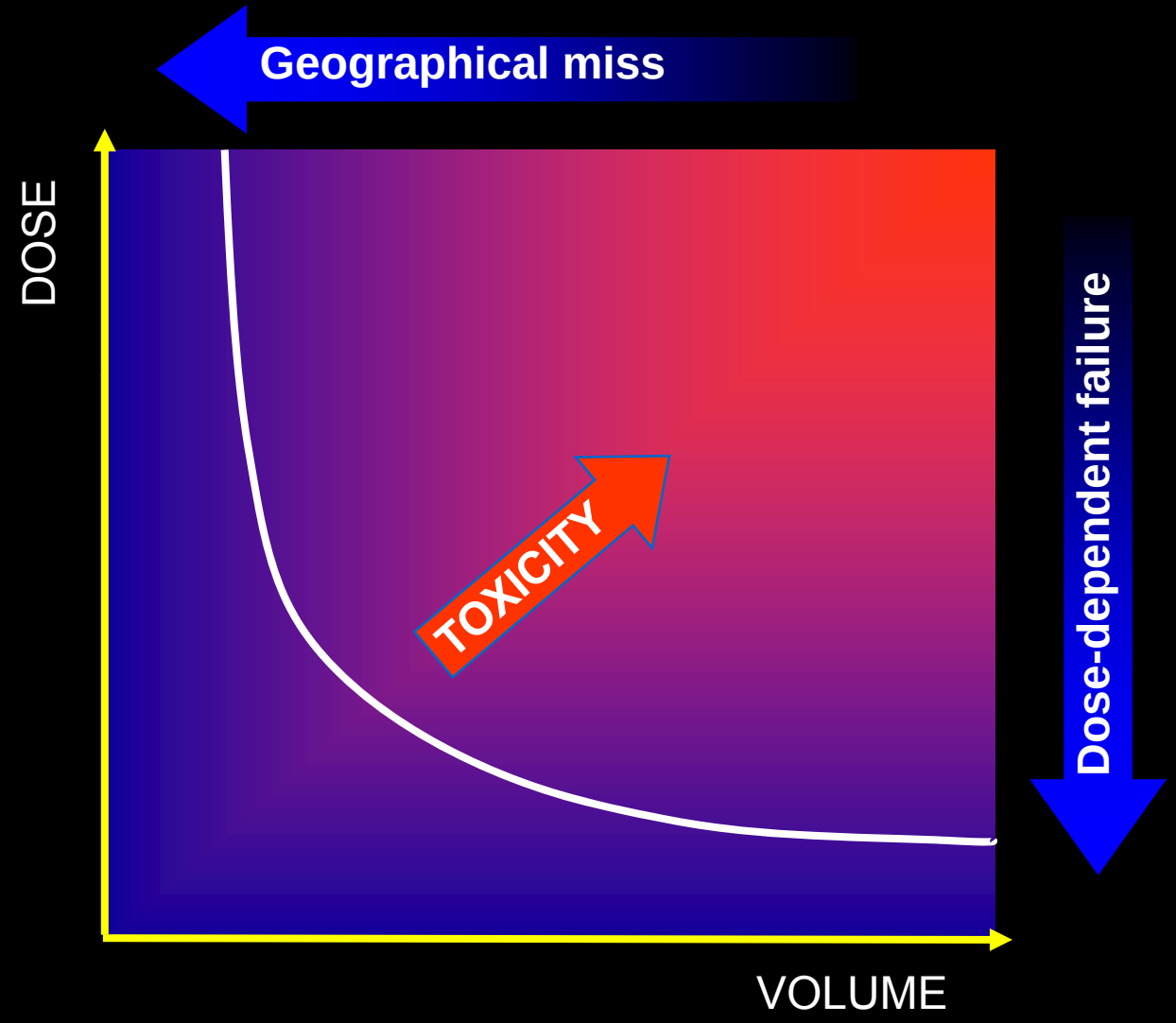
bentzen@humonc.wisc.edu

Radiation therapy is targeted therapy

- Absolute radioresistance does not exist: treatment failure occurs if and only if…
  - the biologically equivalent dose is not sufficiently high OR …
  - there is disease outside the high-dose volume

- Normal tissue toxicity arises in irradiated tissues only and shows a dose-volume relationship

The dose-volume trade-off



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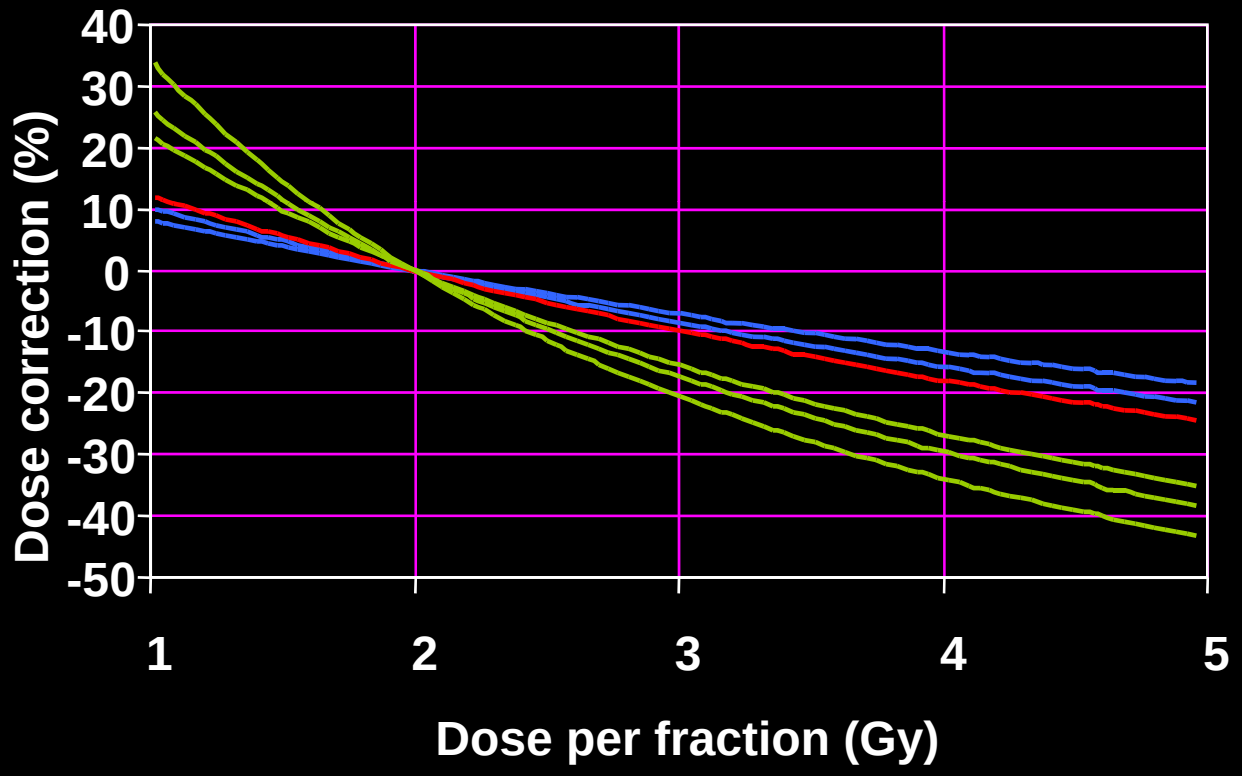
Fractionation sensitivity – human data



Moist desquamation
Erythema
SQCA head and neck
Telangiectasia
Frozen shoulder
Fibrosis

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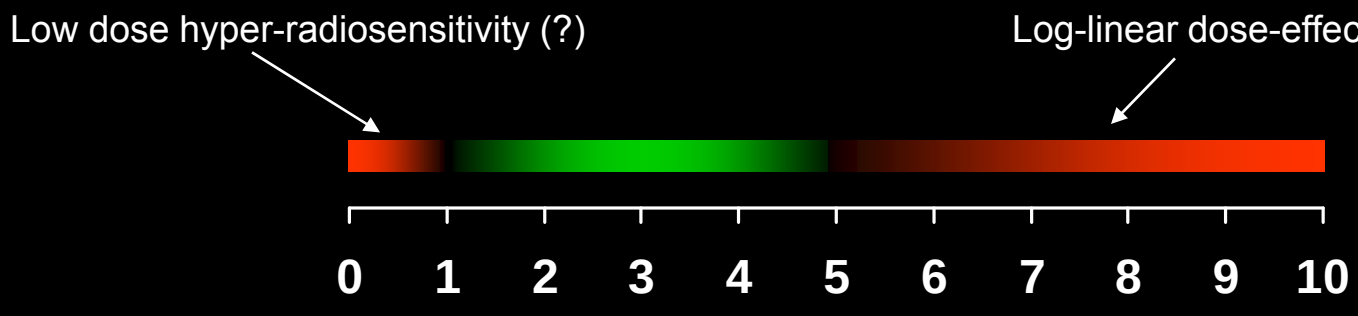
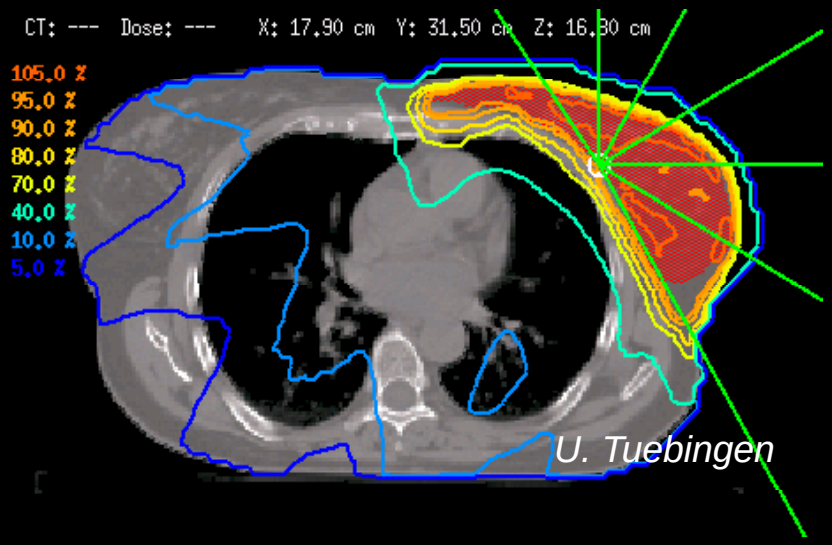
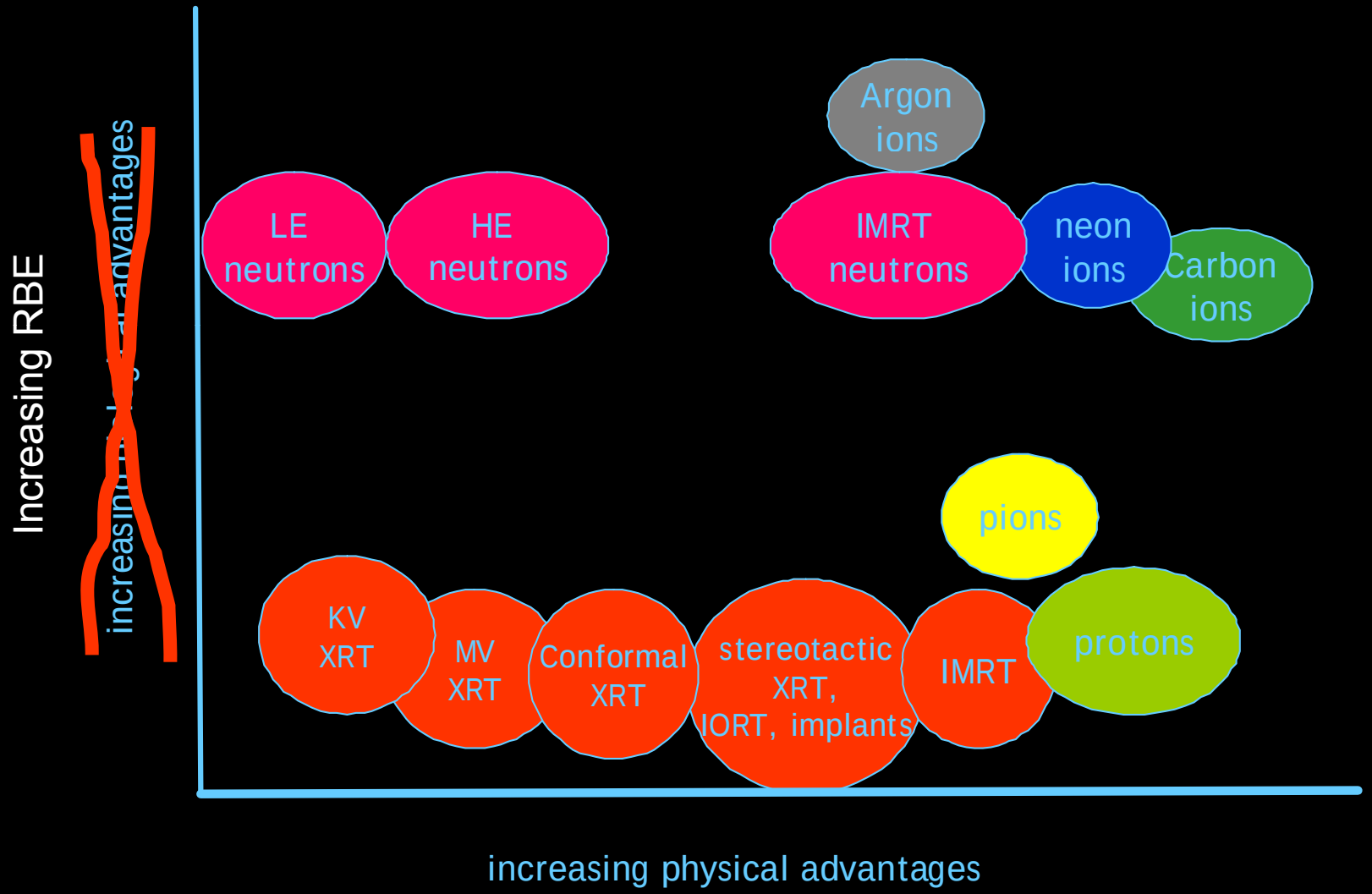
LQ-model: limits of applicability

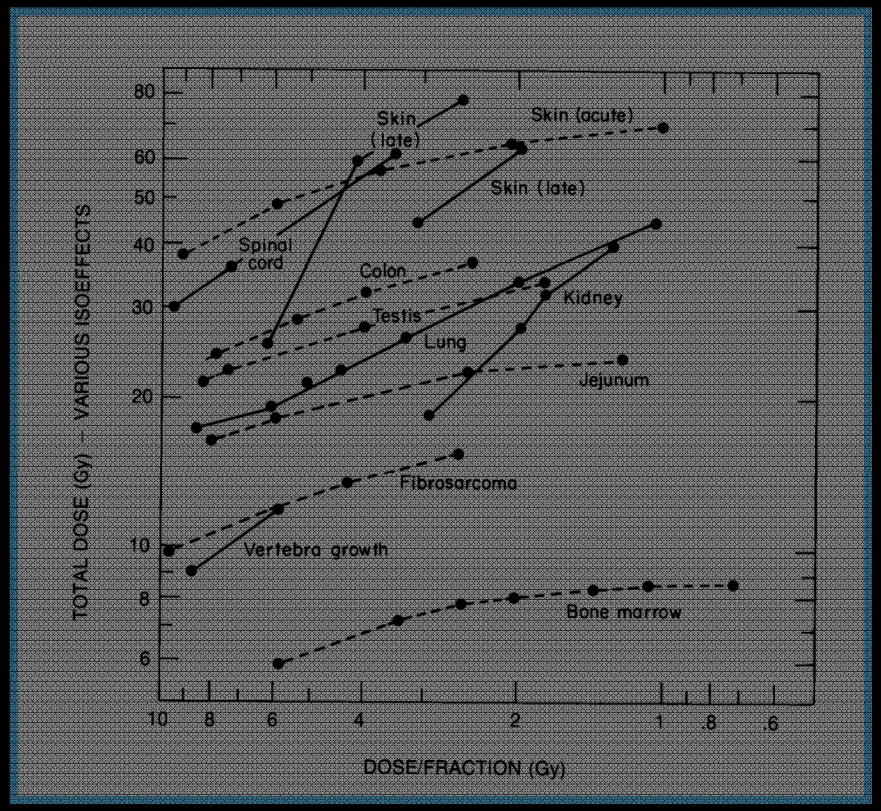


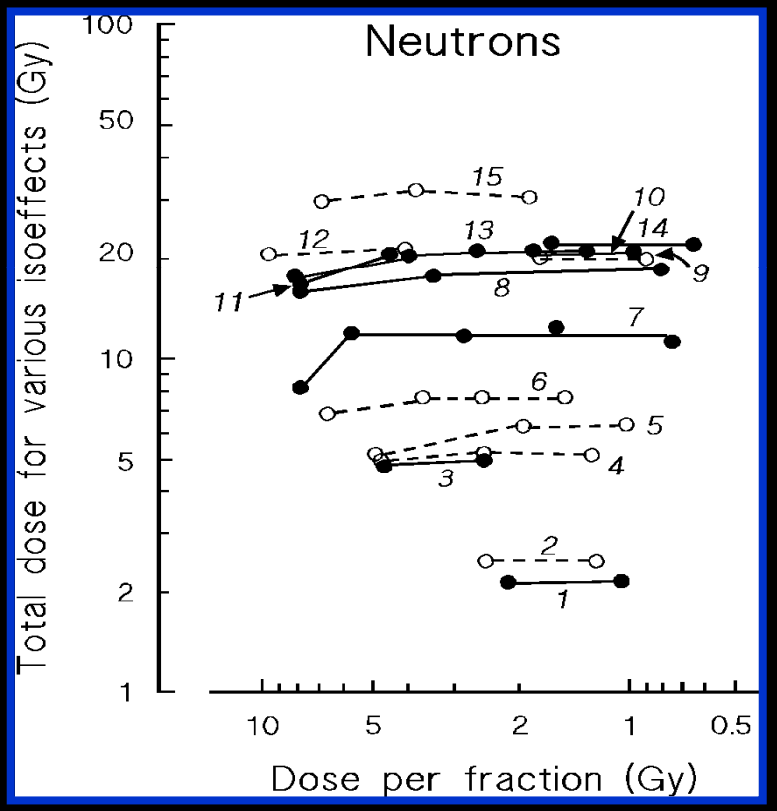


Dose-distribution *v* biological advantage



The “spaghetti” plot





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G.G.Steel: Basic Clinical Radiobiology, 3rd ed.

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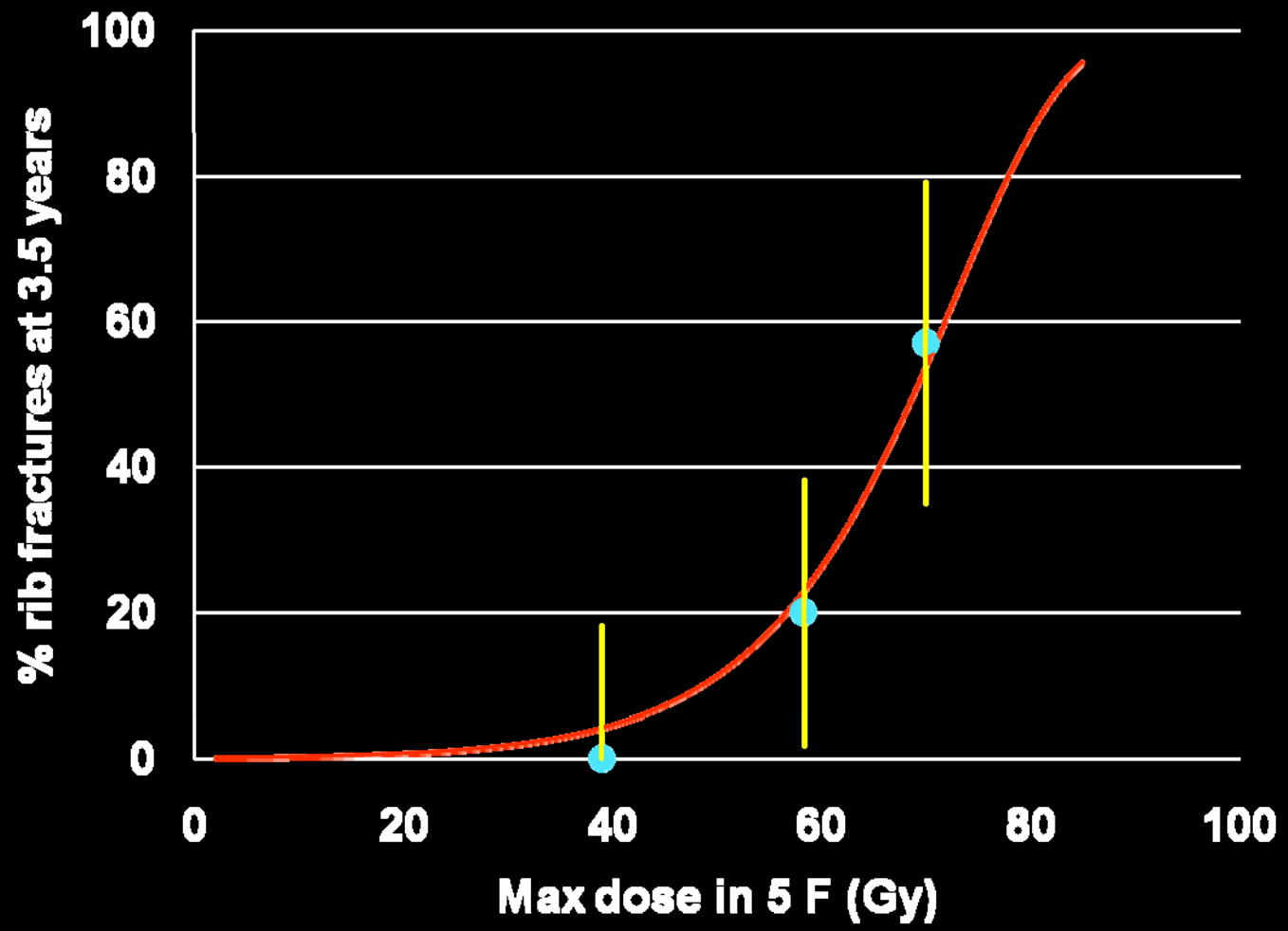
Rib fractures after SBRT



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Hodge et al. *(in preparation)*

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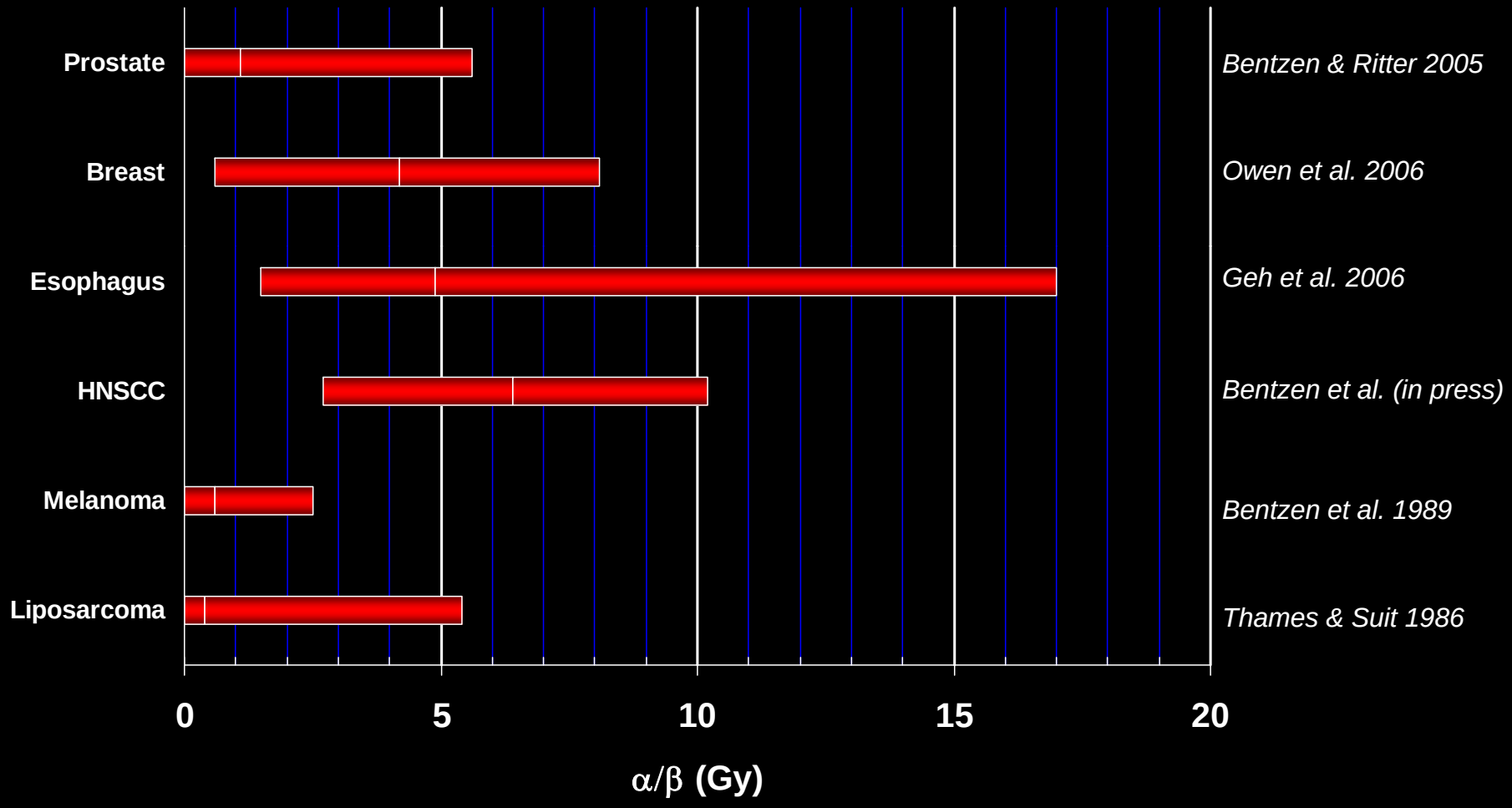
Human tumor fractionation sensitivity



Dose-fractionation effects cannot be analyzed without simultaneous consideration of dose distribution (and combined modalities)

Materials

Virtual clinical trial comparing

6MV IMRT *versus* tomotherapy *versus* proton therapy

15 patients

5 HCC	60 Gy/10F
5 NSCLC (3 IA, 2 IIIA)	70 Gy/35F
3 prostate	70 Gy/35F
2 skull base	50.4 Gy/28F

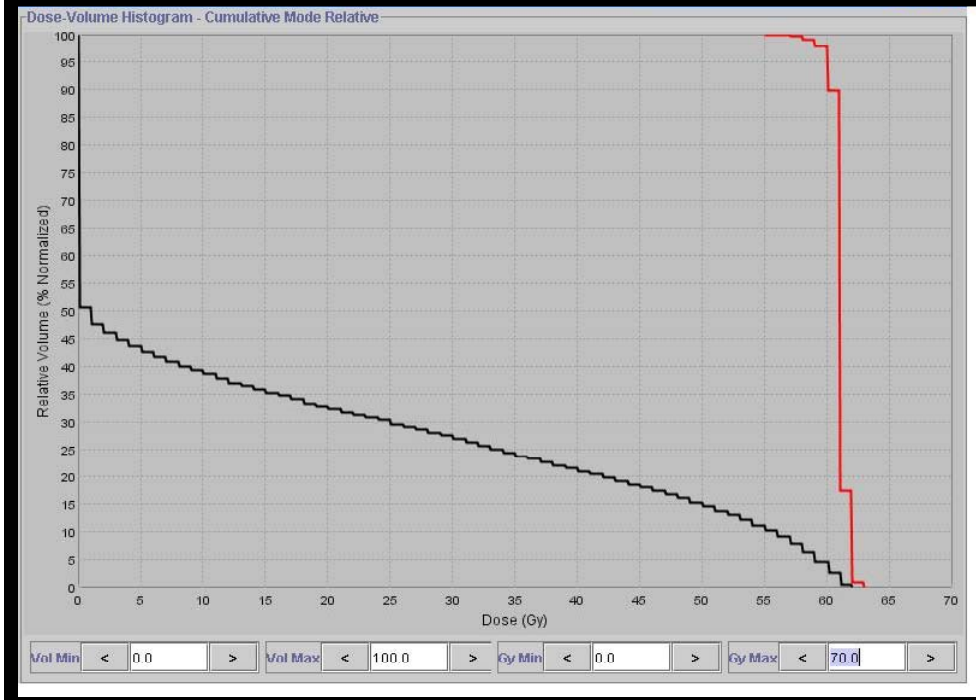
PI: Hidefumi Aoyama

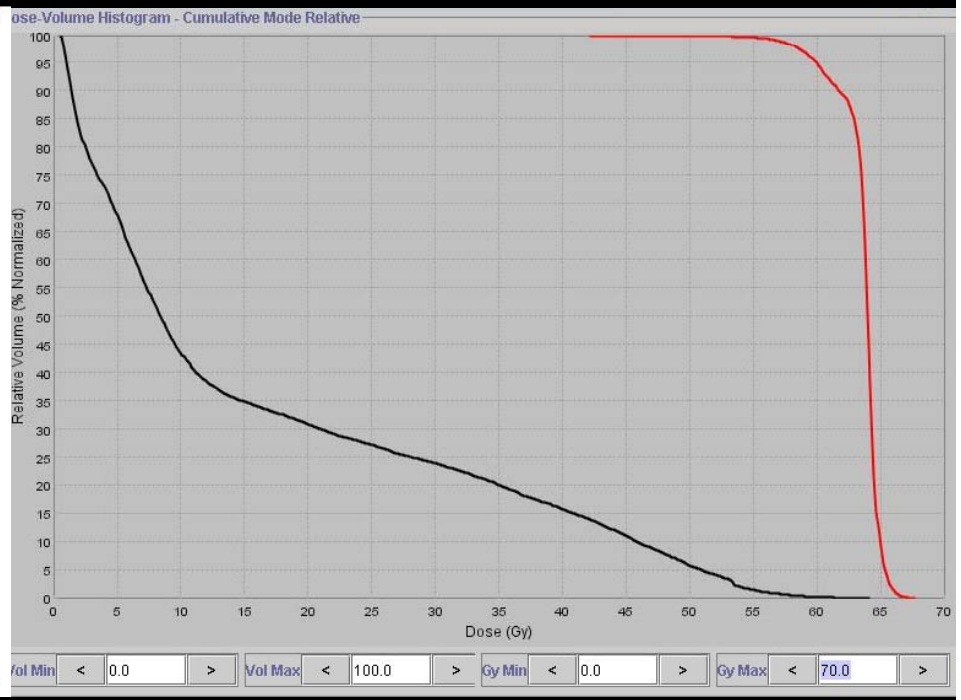
Results of liver cases

General trend in DVHs

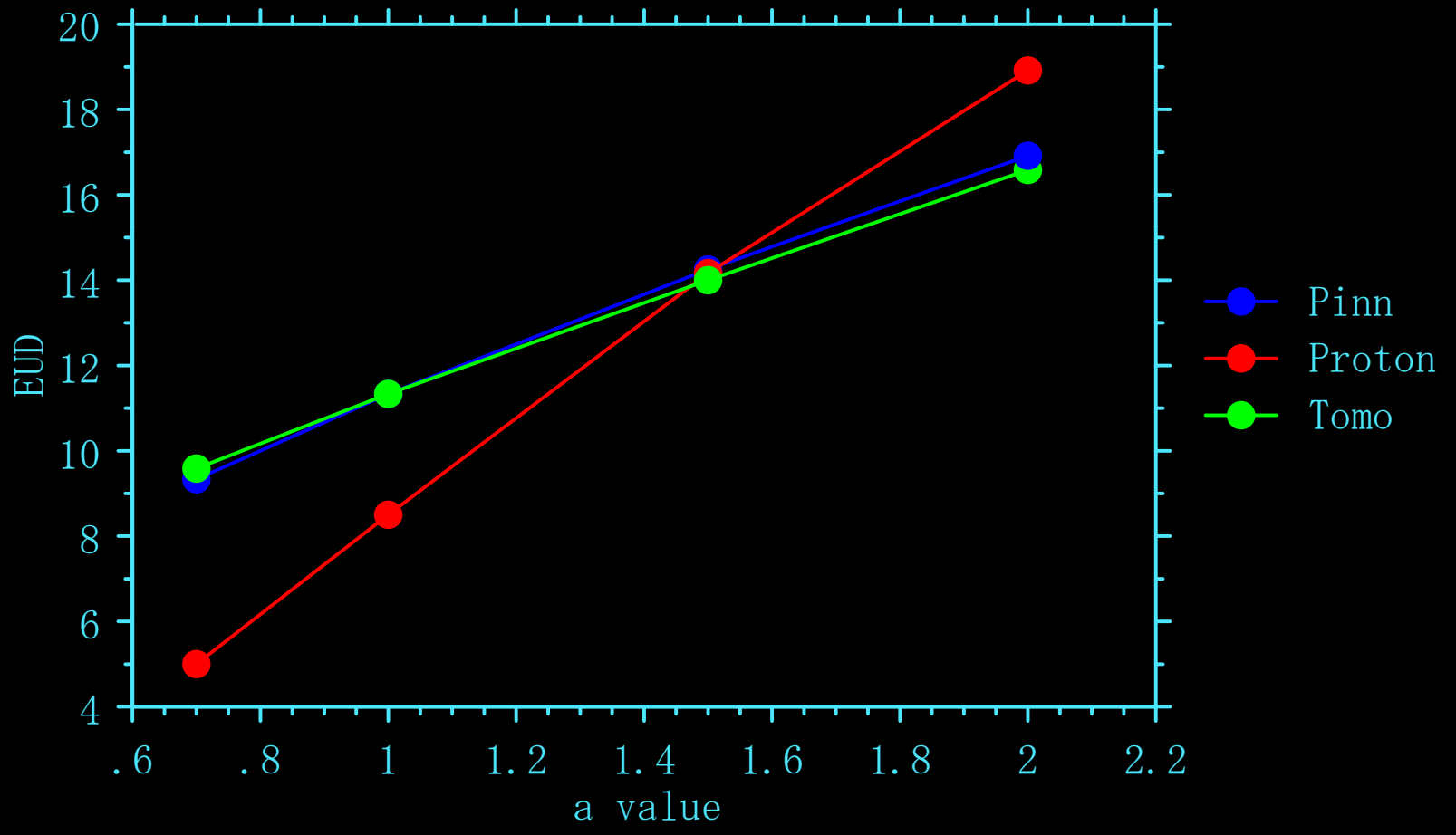
Tomotherapy reduced the high dose volume in normal liver.

Proton therapy reduced the low dose volume in normal liver.

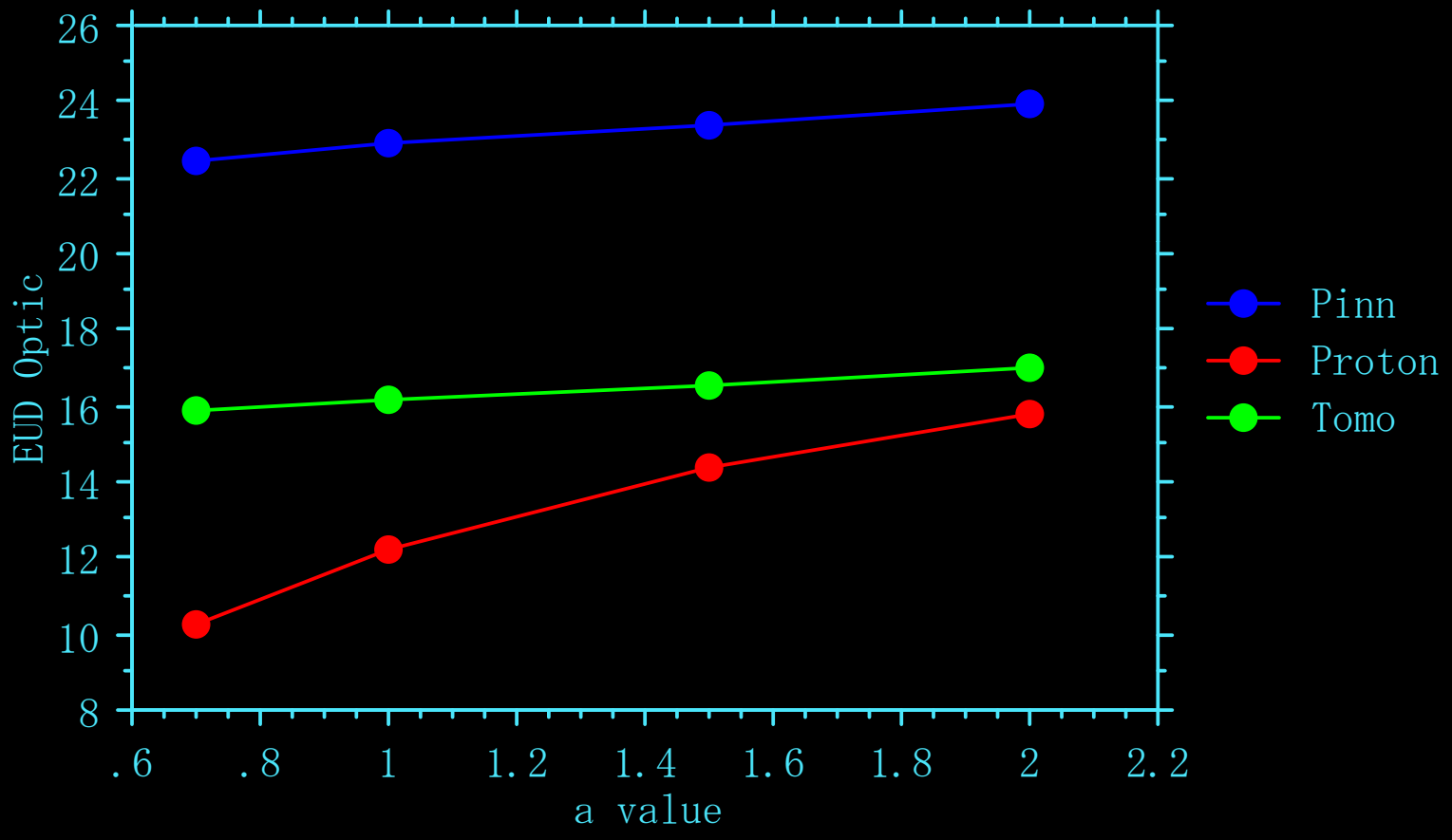




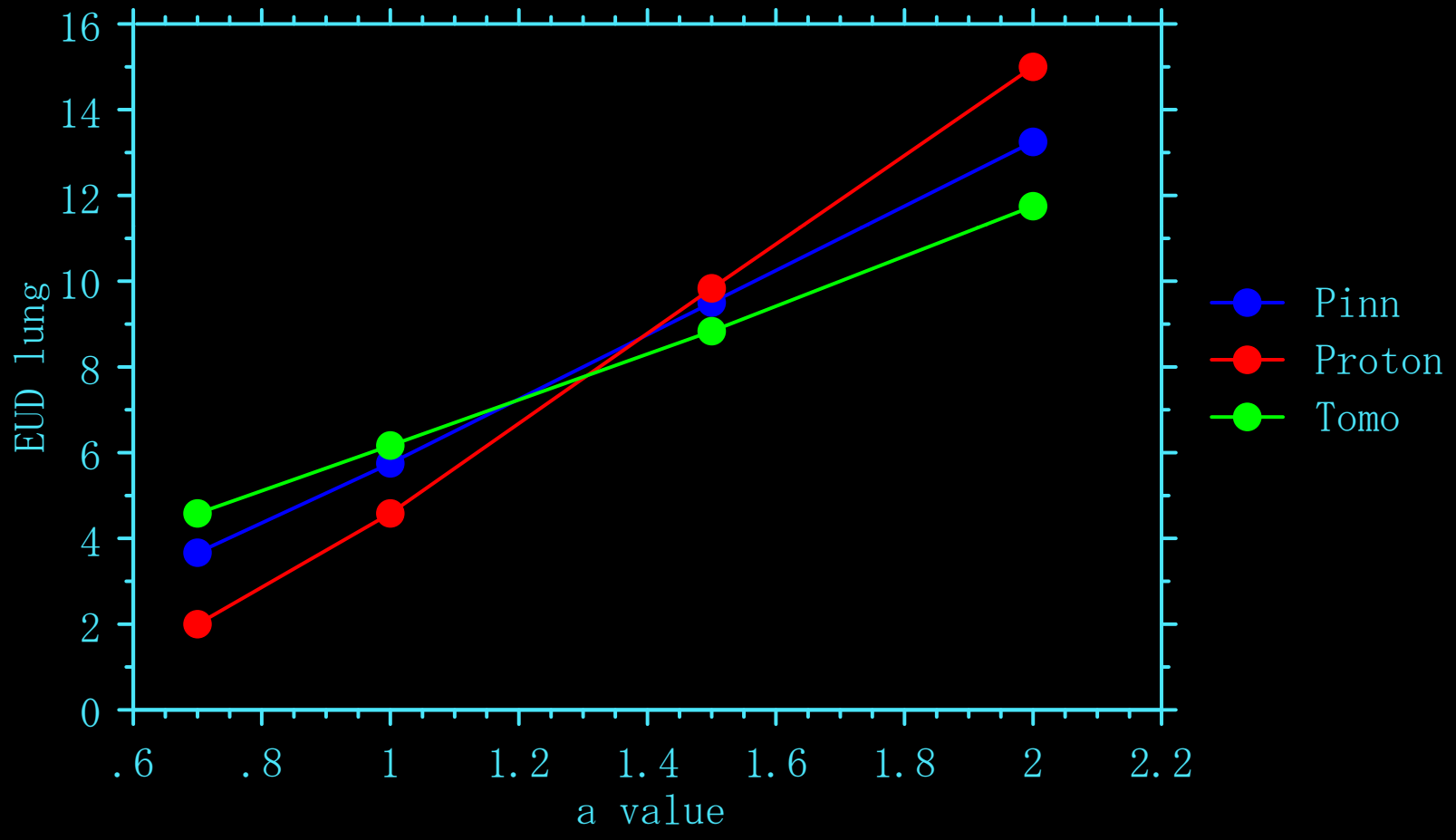
Hepato-cellular carcinoma



Skull base tumors: EUD for optic chiasm



NSCLC



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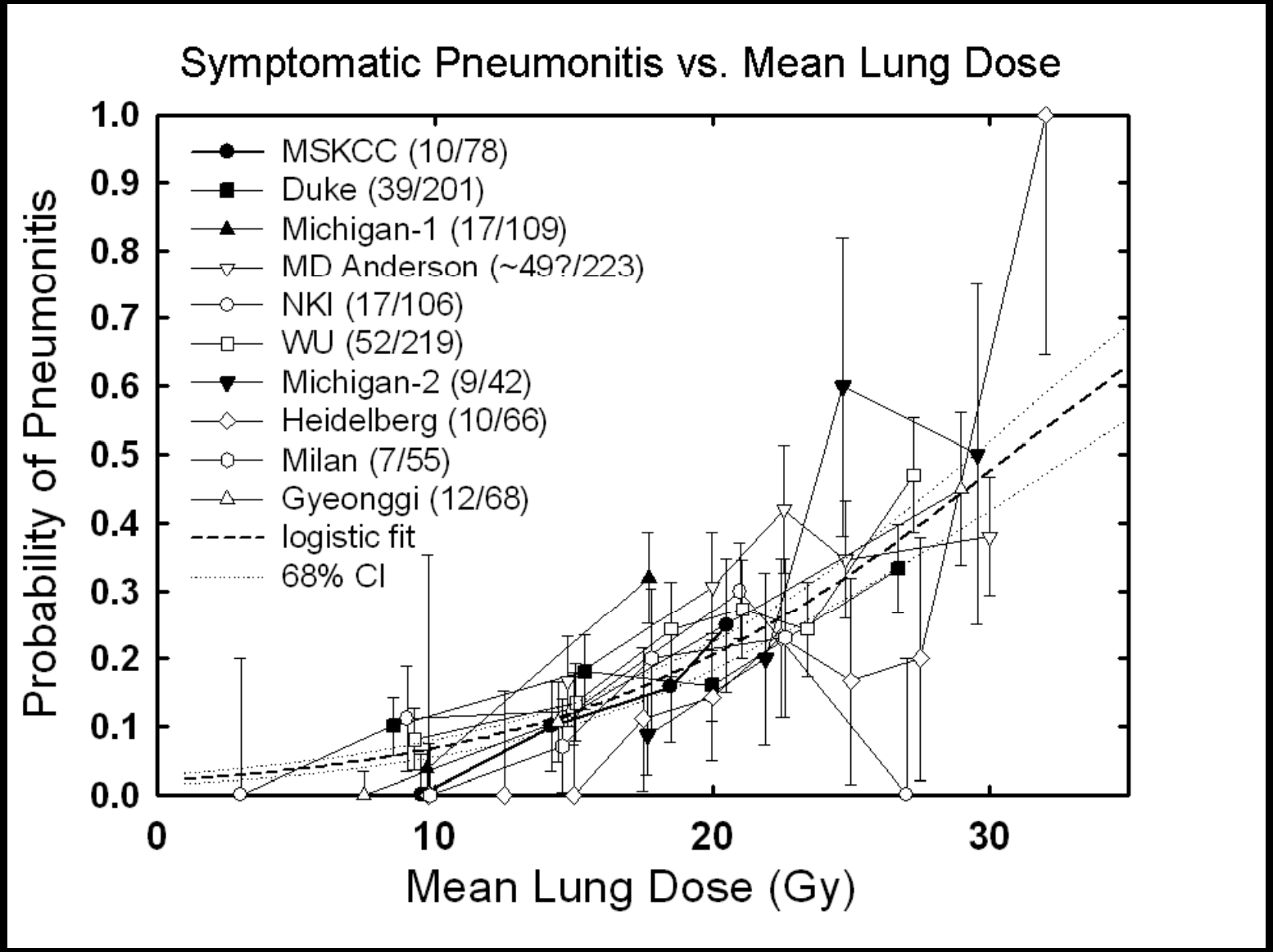
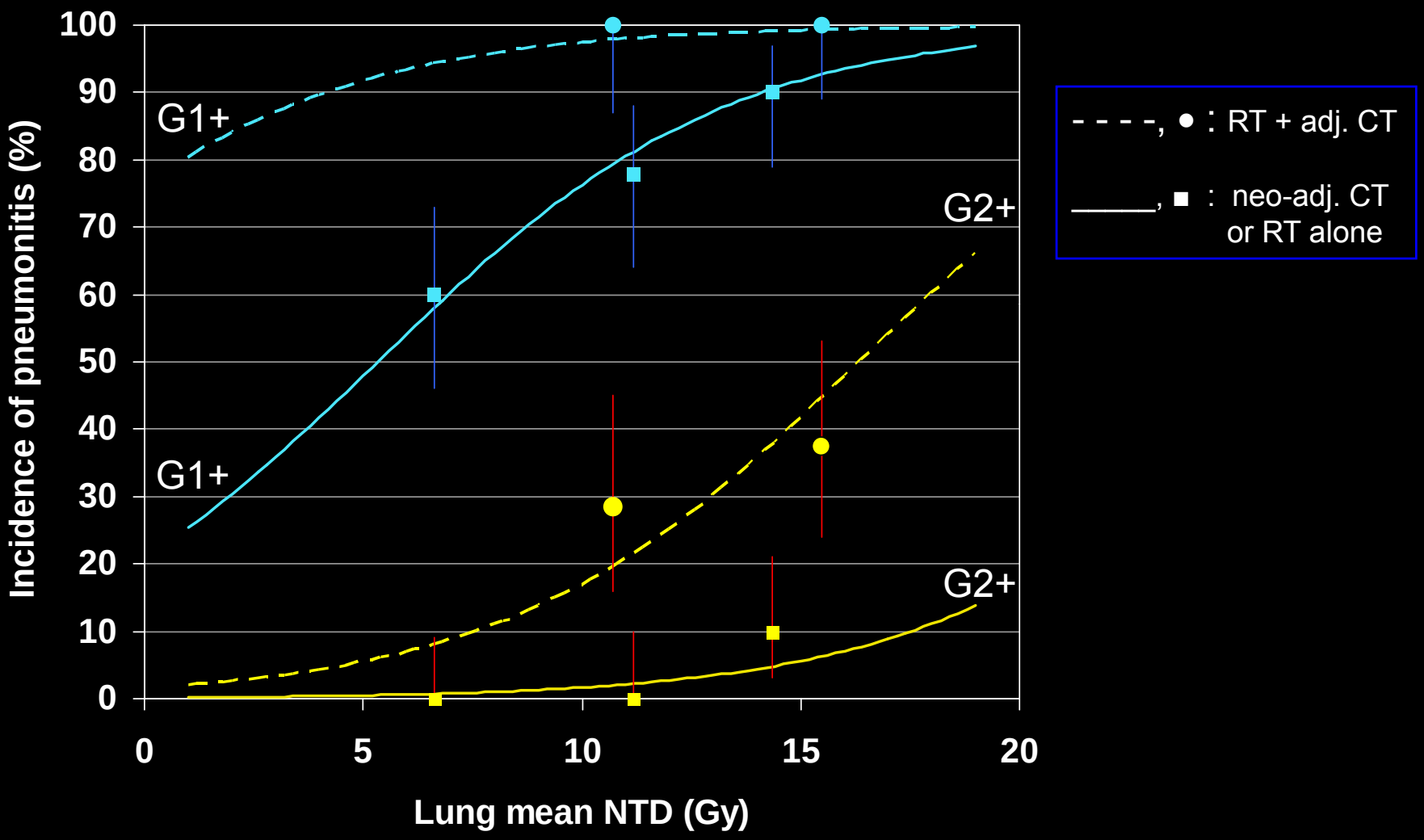

Symptomatic Pneumonitis vs. Mean Lung Dose
Probability of Pneumonitis
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
10
20
30
Mean Lung Dose (Gy)
MSKCC (10/78)
Duke (39/201)
Michigan-1 (17/109)
MD Anderson (~49?/223)
NKI (17/106)
WU (52/219)
Michigan-2 (9/42)
Heidelberg (10/66)
Milan (7/55)
Gyeonggi (12/68)
logistic fit
68% CI

Pneumonitis – Lung bin protocol



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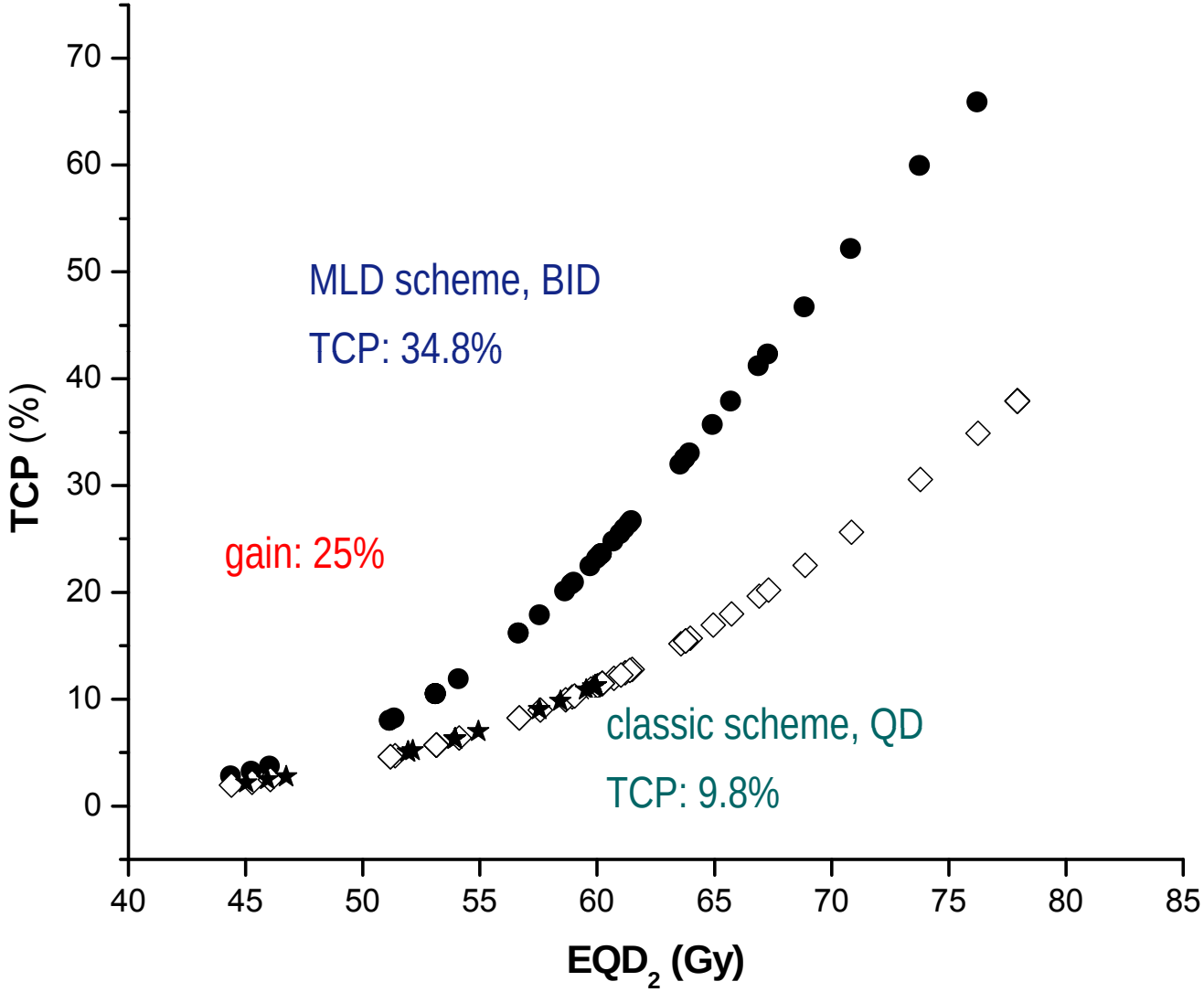
Adkison et al. *Technol Can Res Treat* 7: 441 (2008)

Step 4: Is individualized accelerated radiation possible by using selective mediastinal irradiation and dose prescription on the basis of the MLD? (NCT00573040).

Phase II trial.

De Ruysscher et al. ESTRO 27, 2008

Background . Isotoxic irradiation to a target MLD may lead to the best local tumor control rates vs. toxicity



van Baardwijk et al. Int J Radiat Oncol Biol Phys 2008 ("in silico")
van Baardwijk et al. Int J Radiat Oncol Biol Phys 2008 (Phase I)

Phase II trial: Radiotherapy

- GTV: primary tumor and the initially PET-positive mediastinal lymph nodes *(not anatomical areas)* or to the pathological positive nodes to the following MLD:

  MLD=19 Gy when FeV1 and DLCO > 50 %

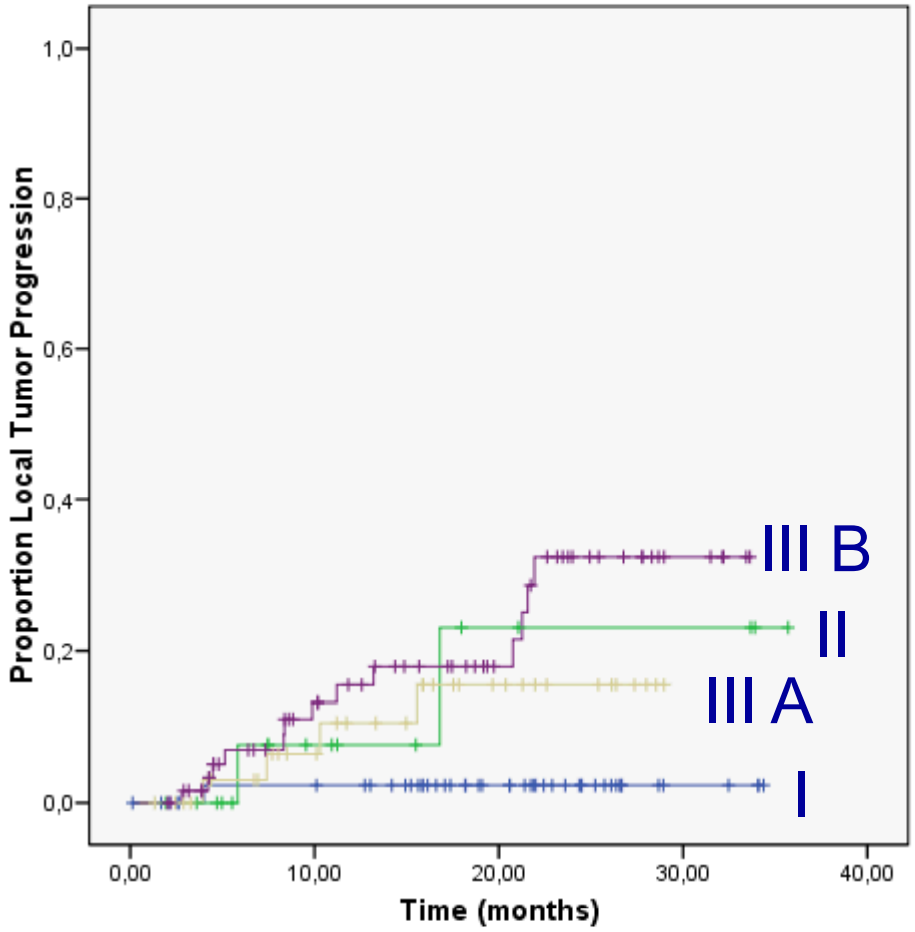
  MLD=15 Gy when FeV1 and/ or DLCO 40-49 %

  MLD=10 Gy when FeV1 and/or DLCO < 40 %

Results

- Median radiation dose: 63.1 ± 13.9 Gy (5.4-79.2)
- Median fractions: 34.8 ± 8.5 (3-44)
- Median overall treatment time: 25.5 ± 7.2 days (2-69)
- Median MLD: 13.6 ± 4.5 Gy (2.4-19.9)
- Median spinal cord dose (Dmax): 37.6 ± 17.3 Gy (0.7-58.4)
- Median follow-up: 24.5 ± 5.6 months (13.3-34.4)

Local Tumor Progression per stage



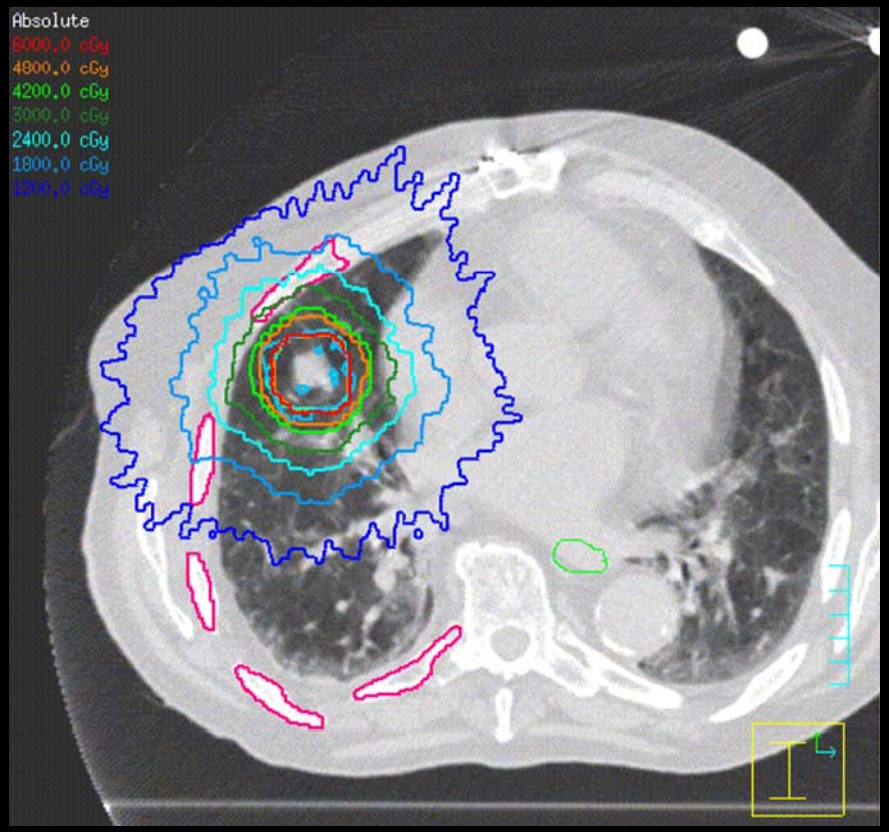
I: 2.3 %

II: 23.2 %

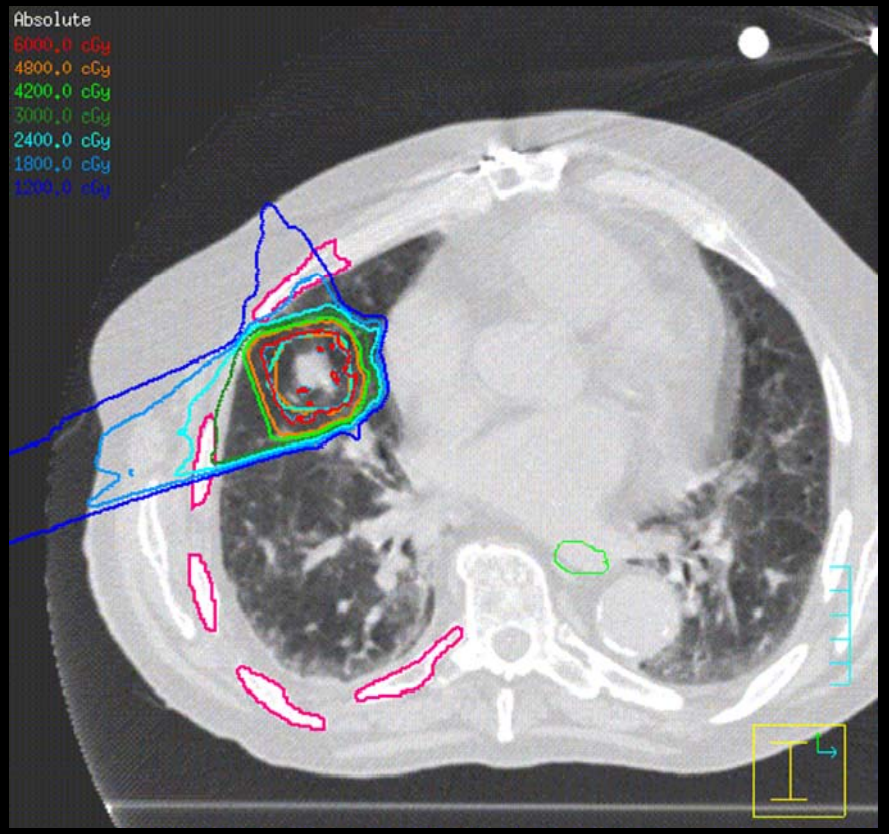
IIIA: 15.5 %

IIIB: 32.4 %

Tomotherapy



Proton - SS



NSCLC: reduced #F (iso-MLD)

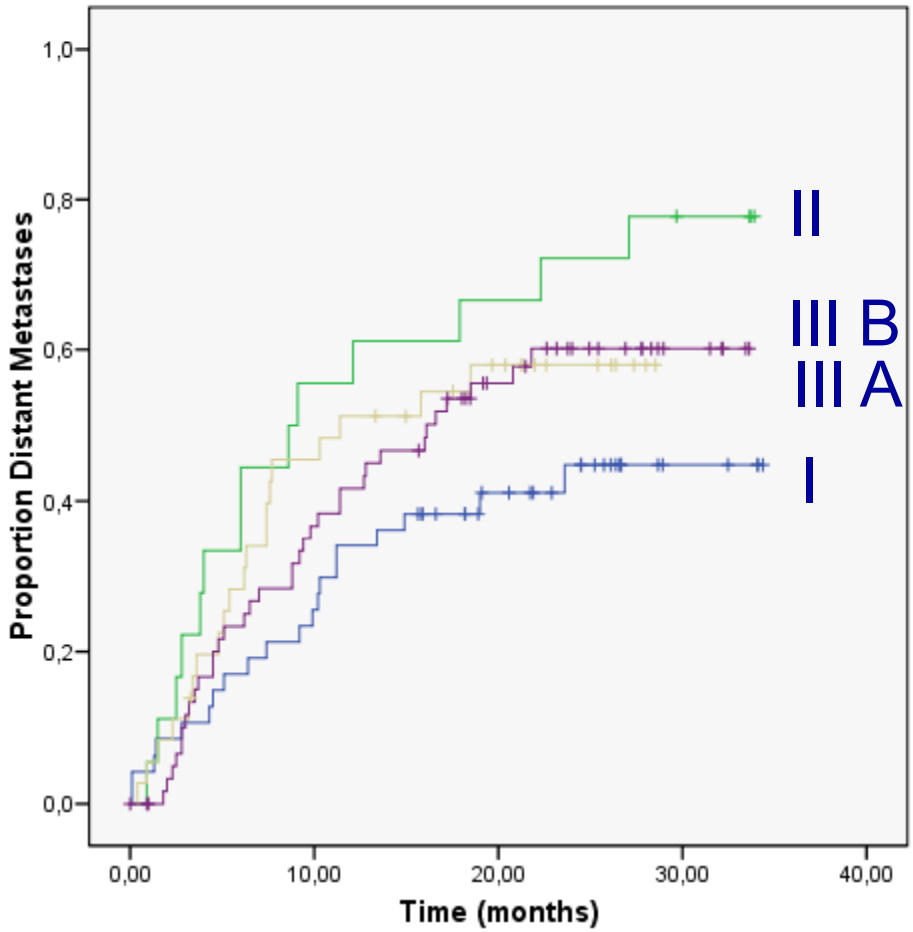
Dose limiting toxicity: symptomatic pneumonitis
α/β= 3.3 Gy

Reduce number of fractions until iso-MLD reached

CAVEATS

- No consideration of
  - proliferation – may not be too important
  - hypoxia – important??
  - other Organs at Risk – surely important
  - motion and margins
- Iso-dose contours and DVH's are not surrogate endpoints – not even after having been passed through a TCP/NTCP model
- Clinical benefit is more than local control

Distant Metastases per stage



I: 44.8 %

II: 77.8 %

IIIA: 58.0 %

IIIB: 60.0 %

Lung Ca Treatment Philosophy Needs a Massive Bailout!

Site	1976	1982	1994	2001	2008	Δ (30 yr)
Prostate	67	73	93	99	99	22 %
Breast	75	76	85	88	89	13 %
Colon	50	55	63	64	66	16 %
Lung	**12**	**13**	**14**	**15**	**16**	**4 %**

5-yr Survival

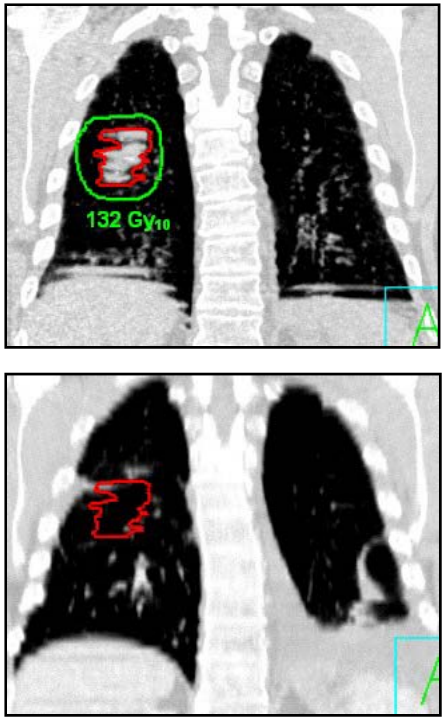
Landis. Ca: Cancer Statistics. 2008; online

"High-dose" RT →

Sequential CRT →

Concurrent CRT →

Targeted Drugs →

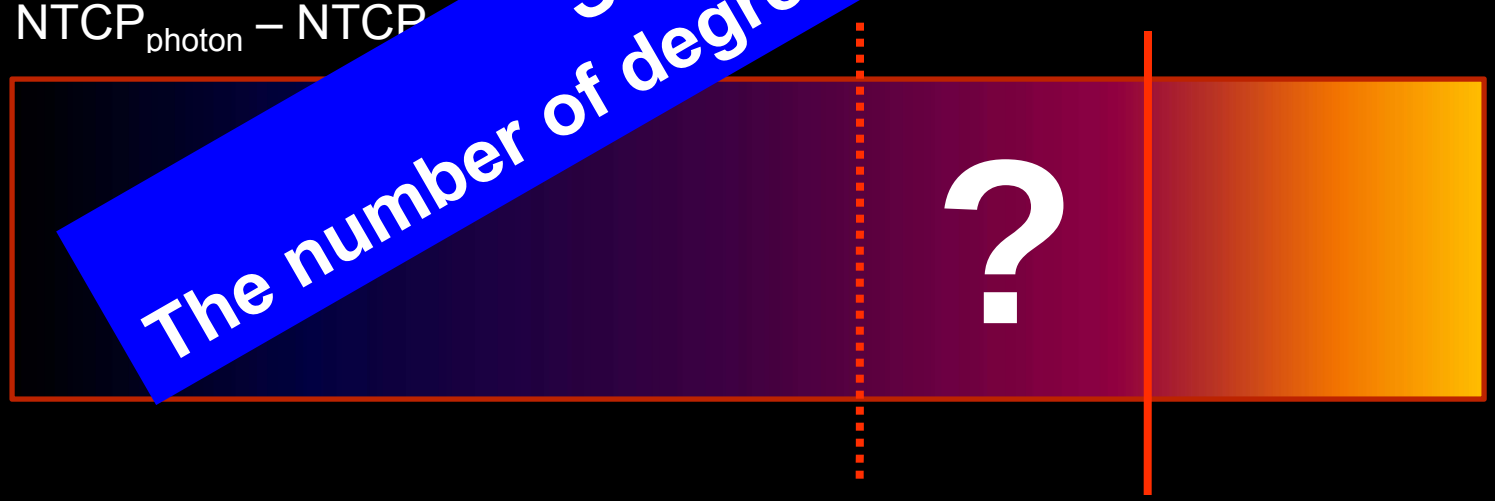


Future Solutions?

- Prevention
- Early diagnosis and treatment

Randomizing protons versus photons

- Equipoise
  - Collective and Individual equi… …uman)
  - What if $NTCP_{proton}$ << N…



Scientific utility?
The number of degrees of freedom is too high!

Bentzen *R&O* 86: 142 (2008)

IMRT "marginal medicine"….?

For instance, men with early stage prostate cancer who choose radiation therapy might have no co-payment for 3-dimensional conformal radiation but might have to cover the marginal cost if they want more expensive intensity-modulated radiation therapy. Value-based co-payments would promote high-value interventions and discourage use of marginal medicine. It w[illegible]

📖 Emanuel and Fuchs, *JAMA* 299: 2789 (2008)

Steepness of DR curve: fixed # fractions

Assuming the validity of the LQ-model, the following relationship holds up at any response level and irrespective of the exact mathematical form of the dose-response model

$$\gamma_N = \gamma_d \cdot \frac{\alpha/\beta + 2 \cdot d_r}{\alpha/\beta + d_r}$$

Bentzen *Acta Oncologica* 44: 825, 2005

The required accuracy in RT

- Random errors ~ $\frac{1}{\sqrt{N}}$
- Major mis-administrations ~ $\frac{1}{N}$
- Systematic dosimetric errors ~ γ_N
- Precision in dose/F prescription ~ γ_N
- Required accuracy increases with descreasing fraction number

Thanks!

/SMB