# Modeling of Outcomes in RT

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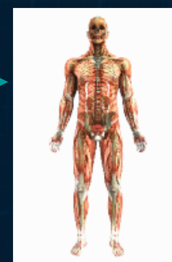
| Treatment | | Outcome |
|---|---|---|
| RT | | Local Control |
| Surgery | | Toxicity |
| Chemotherapy | | Progression |
| Hormone Therapy | | Mortality |
| Gene Therapy | | Quality of Life |
| Etc. | | Etc. |



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## Mechanistic or empirical modeling?

Mechanistically-based models have better cognitive and predictive potential…

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## Mechanistic or empirical modeling?

Data-based (empirical) models have a better practical value because of the infinite complexity of the underlying phenomena…

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## Mechanistic or empirical modeling?

There are no purely empirical or mechanistic models.

The distinction is only relative, reflecting the predominance of the empirical or mechanistic elements in a particular model.

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## Tolerance

- The capacity of an organ(ism) to tolerate unfavorable environmental conditions.

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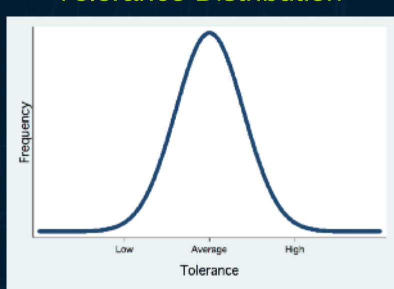
## Tolerance Distribution

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## Tolerance Dose

- The largest quantity of a substance, (radiologic or pharmacologic), that an (organ)ism can endure without exhibiting unfavorable or injurious effects.

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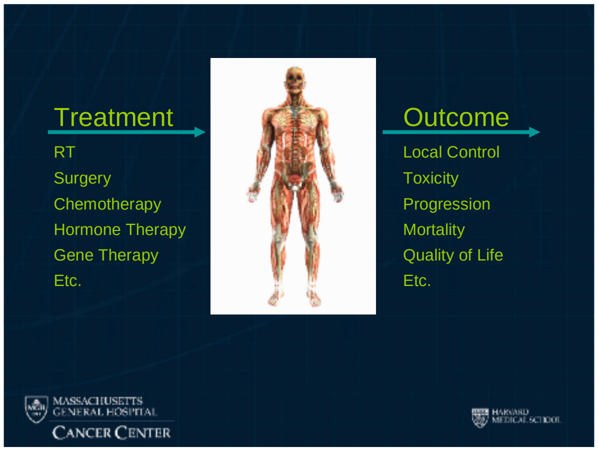
Treatment
RT
Surgery
Chemotherapy
Hormone Therapy
Gene Therapy
Etc.
Outcome
Local Control
Toxicity
Progression
Mortality
Quality of Life
Etc.
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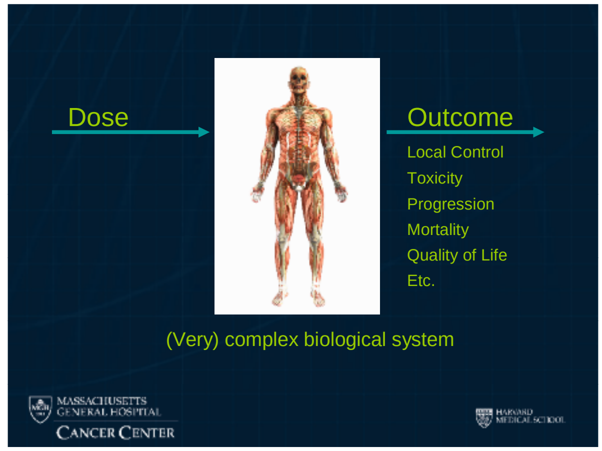
Dose
Outcome
Local Control
Toxicity
Progression
Mortality
Quality of Life
Etc.
(Very) complex biological system
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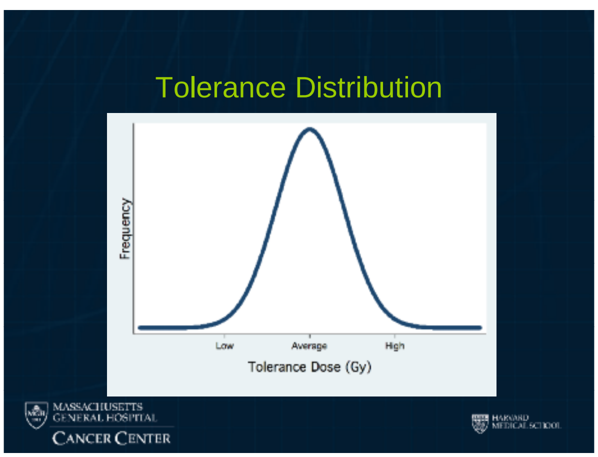
Tolerance Distribution
Frequency
Low
Average
High
Tolerance Dose (Gy)
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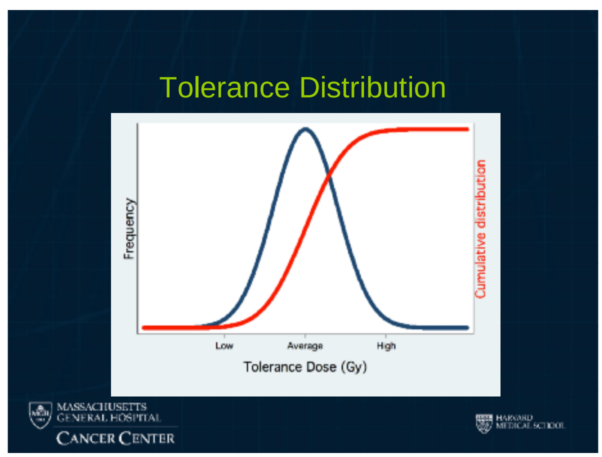
Tolerance Distribution
Frequency
Cumulative distribution
Low
Average
High
Tolerance Dose (Gy)
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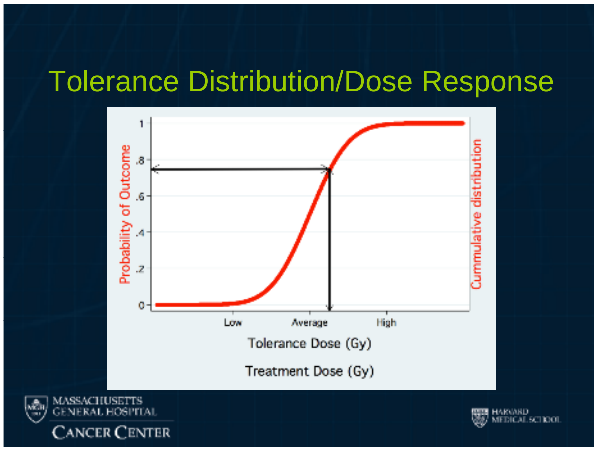
Tolerance Distribution/Dose Response
Probability of Outcome
Cummulative distribution
1
.8
.6
.4
.2
0
Low
Average
High
Tolerance Dose (Gy)
Treatment Dose (Gy)
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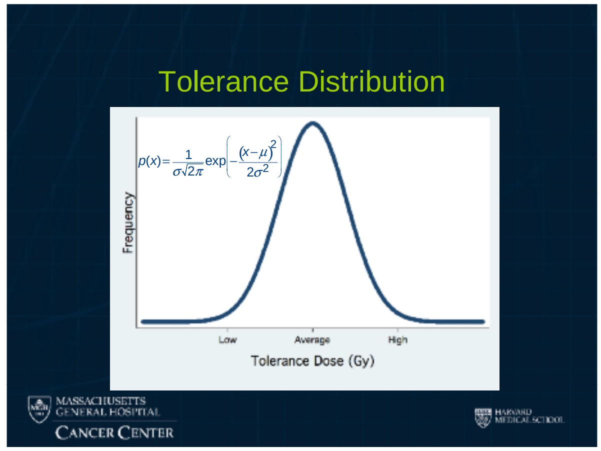
Tolerance Distribution
$p(x)=\frac{1}{\sigma\sqrt{2\pi}}\exp\left(-\frac{(x-\mu)^2}{2\sigma^2}\right)$
Frequency
Low
Average
High
Tolerance Dose (Gy)
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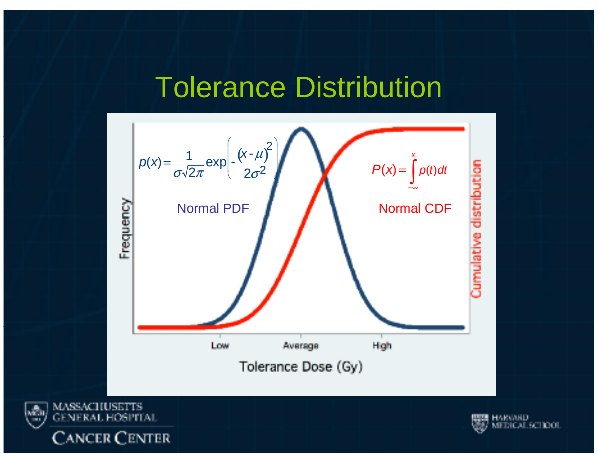
Tolerance Distribution
$p(x)=\frac{1}{\sigma\sqrt{2\pi}}\exp\left(-\frac{(x-\mu)^2}{2\sigma^2}\right)$
Normal PDF
$P(x)=\int_{-\infty}^{x} p(t)dt$
Normal CDF
Frequency
Cummulative distribution
Low
Average
High
Tolerance Dose (Gy)
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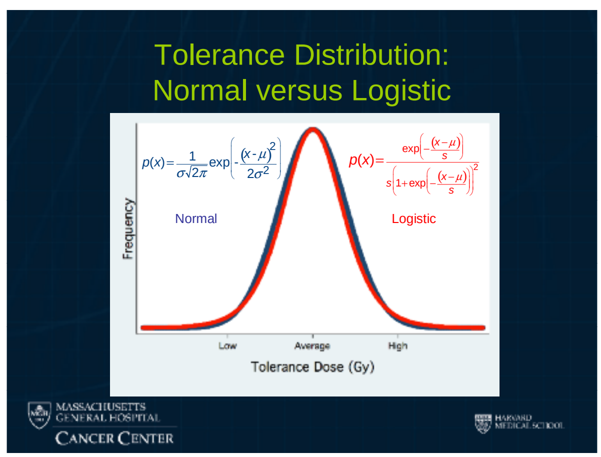
Tolerance Distribution:
Normal versus Logistic
$p(x)=\frac{1}{\sigma\sqrt{2\pi}}\exp\left(-\frac{(x-\mu)^2}{2\sigma^2}\right)$
Normal
$p(x)=\frac{\exp\left(-\frac{(x-\mu)}{s}\right)}{s\left(1+\exp\left(-\frac{(x-\mu)}{s}\right)\right)^2}$
Logistic
Frequency
Low
Average
High
Tolerance Dose (Gy)
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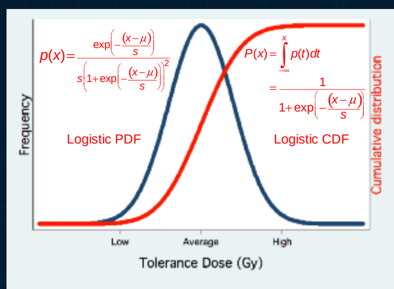
## Logistic Tolerance Distribution

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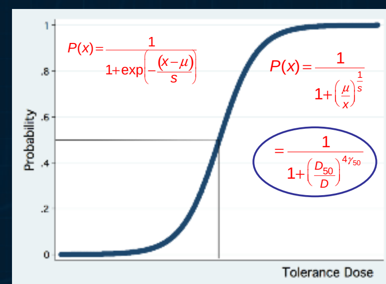
## Logistic Response Model

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## Logistic Response Model

$$P(D)=\frac{1}{1+\left(\frac{D_{50}}{D}\right)^{4\gamma_{50}}}$$

$D_{50}, \gamma_{50}$ - parameters describing distribution of tolerance

$$\gamma_{50}=\frac{\pi}{4\sqrt{3}\sigma}$$

$D$ - variable describing treatment

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## Logistic Response Model

$$P(D)=\frac{1}{1+\left(\frac{D_{50}}{D}\right)^{4\gamma_{50}}}$$

Response depends on several treatment and patient factors:

- fractionation
- spatial dose heterogeneity
- hypoxia
- risk factors (age, gender, race, smoking, diabetes, genetics)
- etc

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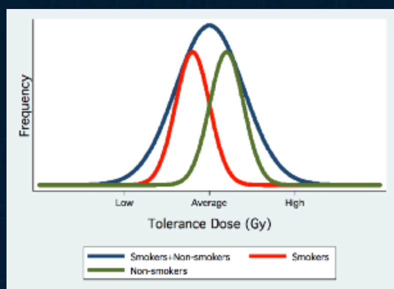
## Tolerance Distribution

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## Logistic Response Model

$$P(D)=\frac{1}{1+\left(f(\text{smoking})\frac{D_{50}}{D}\right)^{4\gamma_{50}}}$$

$$=\frac{1}{1+\left(\frac{0.5D_{50}}{D}\right)^{4\gamma_{50}}}$$

Average tolerance of smokers is half the tolerance of non-smokers

$$=\frac{1}{1+\left(\frac{D_{50}}{2D}\right)^{4\gamma_{50}}}$$

"Effective" dose for an average smokers is twice the dose for an average non-smokers

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## Logistic Response Model

$$P(D)=\frac{1}{1+\left(f(\text{dose-per-fraction})\frac{D_{50}}{D}\right)^{4\gamma_{50}}}$$

$$D_{50}(d)=D_{50}(d_{ref})\frac{\frac{\alpha}{\beta}+d_{ref}}{\frac{\alpha}{\beta}+d}$$

Adjusting tolerance to current dose per fraction (per LQ model)

$$D(d_{ref})=D\frac{\frac{\alpha}{\beta}+d}{\frac{\alpha}{\beta}+d_{ref}}$$

Adjusting dose to current dose per fraction (per LQ model)

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## Logistic Response Model

$$P(D)=\frac{1}{1+\left(f(\text{dose inhomogeneity})\frac{D_{50}}{D}\right)^{4\gamma_{50}}}$$

$D\rightarrow\{D_i\}$ Volumetric dose distribution

$$EUD(\{D_i\};a)=\left(\frac{1}{N}\sum_{i=1}^{N}D_i^a\right)^{\frac{1}{a}}$$

*EUD* - Equivalent Uniform Dose

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## Logistic Response Model

$$P(D) = \frac{1}{1 + \left( f\,(\text{dose inhomogeneity}) \frac{D_{50}}{D} \right)^{4\gamma_{50}}}$$

$$P(\{D_i\}) = \frac{1}{1 + \left( \frac{D_{50}}{EUD(\{D_i\})} \right)^{4\gamma_{50}}}$$

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## EUD - Equivalent Uniform Dose

EUD is that dose which, if applied uniformly to the whole structure/organ, would lead to the same clinical consequences as would be obtained using the non-uniform dose distribution of interest.

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## EUD - Equivalent Uniform Dose

45Gy | 60Gy

30 fractions

$EUD(\{45, 60\}; a = 3) \approx 54\text{Gy}$

(in 30 fractions)

---

45Gy | 60Gy

20 fractions

$EUD(\{45, 60\}; a = 3) \approx 54\text{Gy}$

(in 20 fractions)

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## EUD - Equivalent Uniform Dose

45Gy | 60Gy

30 fractions

$$EUD_{30} = EUD_{20} \frac{\frac{\alpha}{\beta} + \frac{EUD_{20}}{20}}{\frac{\alpha}{\beta} + \frac{EUD_{20}}{30}}$$

45Gy | 60Gy

20 fractions

$$= 54\text{Gy} \frac{2 + \frac{54}{20}}{2 + \frac{54}{30}} \approx 54\text{Gy} * 1.24 \approx 67\text{Gy}$$

$$EUD = \begin{cases} 54\text{Gy in 20 fractions} \\ 67\text{Gy in 30 fractions} \end{cases}$$

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## EUD - Equivalent Uniform Dose


30 fractions

$$EUD_{20} = EUD_{30} \frac{\frac{\alpha}{\beta} + \frac{EUD_{30}}{30}}{\frac{\alpha}{\beta} + \frac{EUD_{30}}{20}}$$


20 fractions

$$= 54Gy \frac{2 + \frac{54}{30}}{2 + \frac{54}{20}} \approx 54Gy * 0.81$$

$$\approx 44Gy$$



## Logistic Response Model (multivariable)

$$P(\{D_i\}, hypofractionation, sex, genetic\ profile, race, chemo, age, hypoxia, etc.) =$$

$$= \frac{1}{1 + \left(F \frac{D_{50}}{EUD}\right)^{4\gamma_{50}}}$$

$$F = \prod_k f_k$$



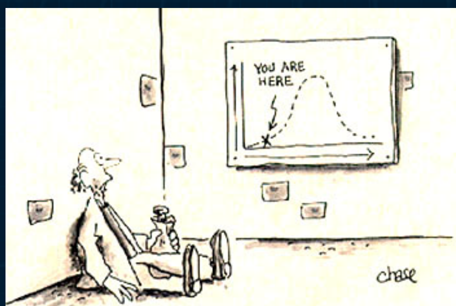
## Closing remarks

- The biology of tumors and normal tissues is too complex to allow biological/mechanistic modeling of RT outcomes "from first-principle".
- The outcomes depend on several known (and unknown, and possibly unknowable) factors in non-linear fashion.
- Non-linearity of response to treatment coupled with incompleteness of our models of outcomes may cause serious bias in estimates of model parameters and their errors.



## Closing remarks

- Better outcomes of RT will strongly depend on treatment individualization/optimization made possible by more reliable models of outcomes.
- Models of outcome need to combine data-driven phenomenology with radiobiological considerations.
- The ultimate measure of model's usefulness is the level of agreement of the model's predictions with a wide range of the corresponding clinical data.

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## Phenomenology

- A body of knowledge which relates empirical observations of phenomena to each other, in a way which is consistent with fundamental theory, but is not directly derived from theory.

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