Deconvolving Dose Response to Maximize Therapeutic Ratio

UC San Diego
RETHINKING MEDICAL PHYSICS

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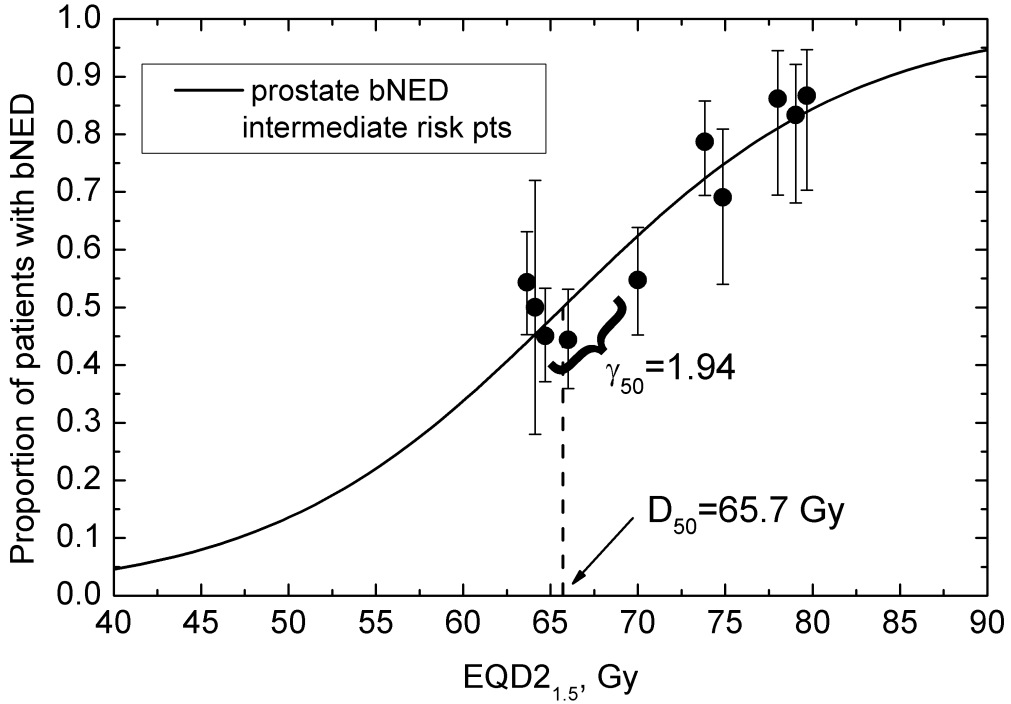
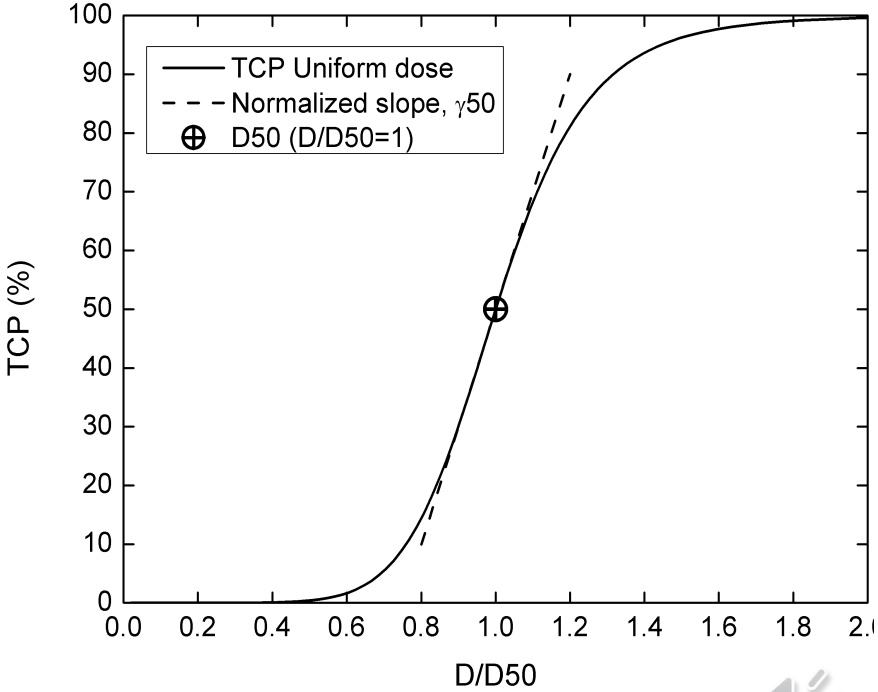
AAPM 2020

Outline

- Dose-response for tumors and normal tissues
- Combining data from multiple sources
- Dose-response for population data
- Accounting for tumor/normal tissue properties
- Accounting for patient characteristics

TUMOUR CONTROL PROBABILITY (TCP) DOSE DEPENDENCE





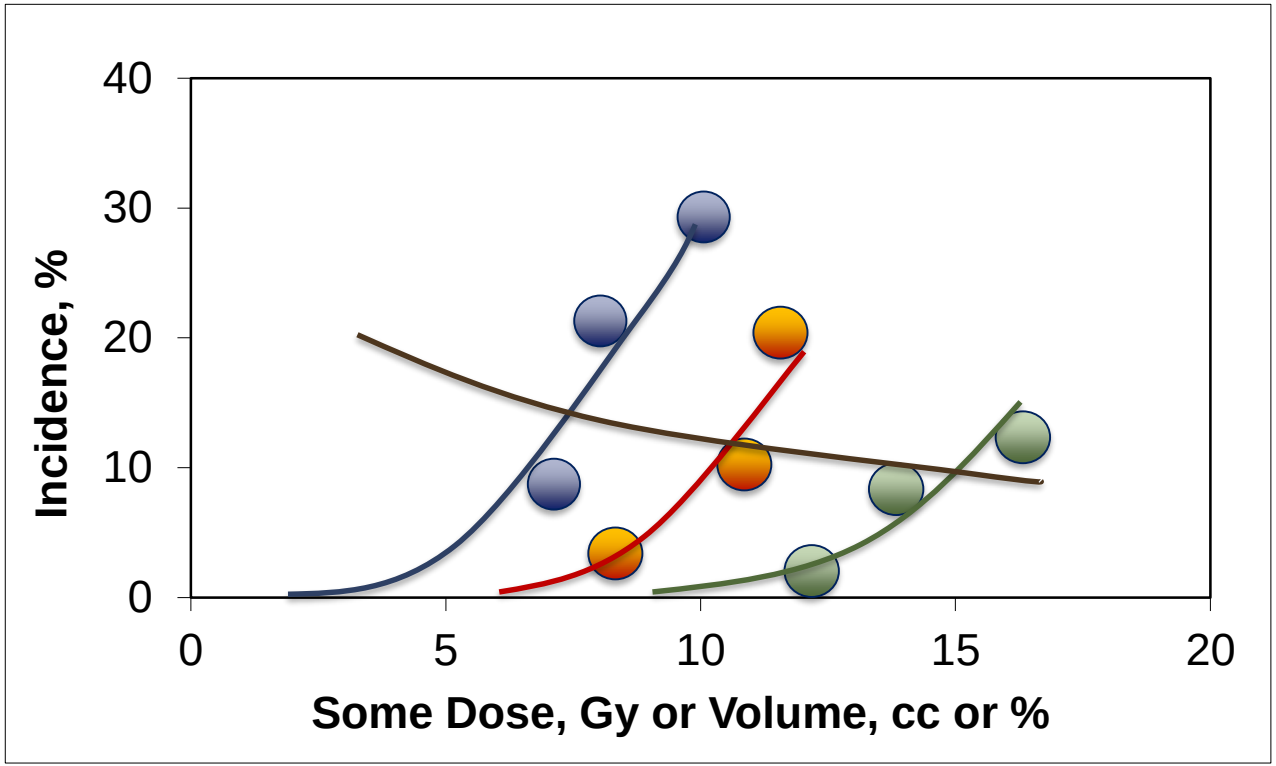
TCP: LOGISTIC EQUATION

Tumor site	Comment	Source	TCD_{50}, Gy	γ_{50}
Nasopharynx	T1-4	Bedwinek et al. 1980	61.59	3.38
Melanoma		Overgaard et al. 1986	49.84	0.99
Tonsil	N1-3	Perez et al. 1982	54.02	1.03

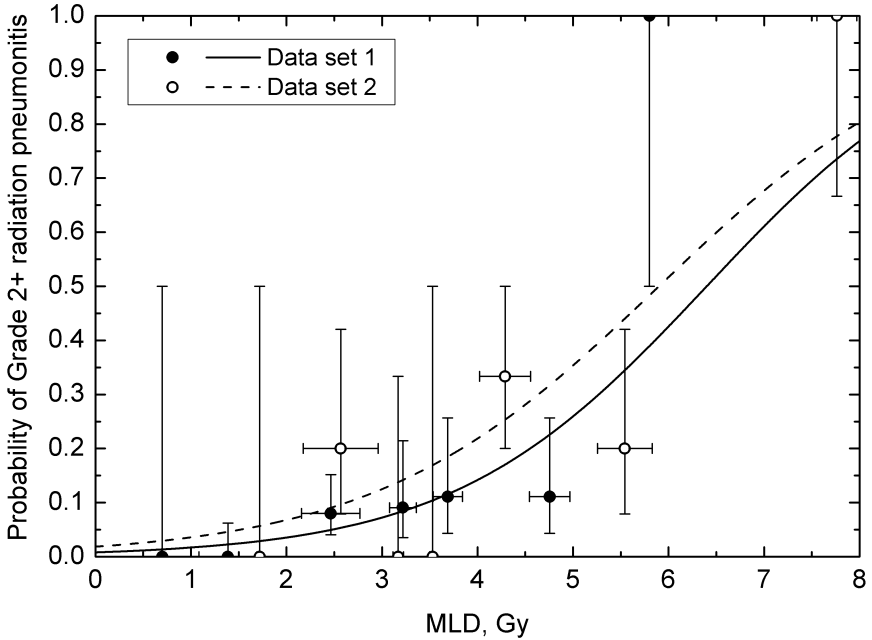
Tonsil: adding a 2 Gy fraction to Rx 66Gy, improves TCP from 71.4% to 74.4%

Significant dose escalation is required to achieve noticeable improvement in TCP

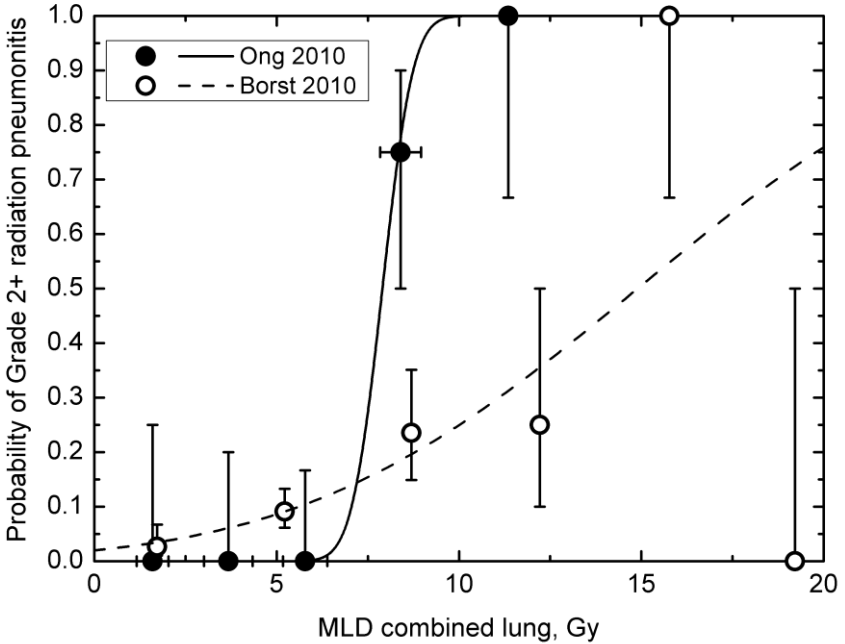
Hazard of combining data



Are guidelines transferrable?



Yamashita et al 2007
Okubo et al 2017



Kong et al IJROBP, in press (HyTEC paper)

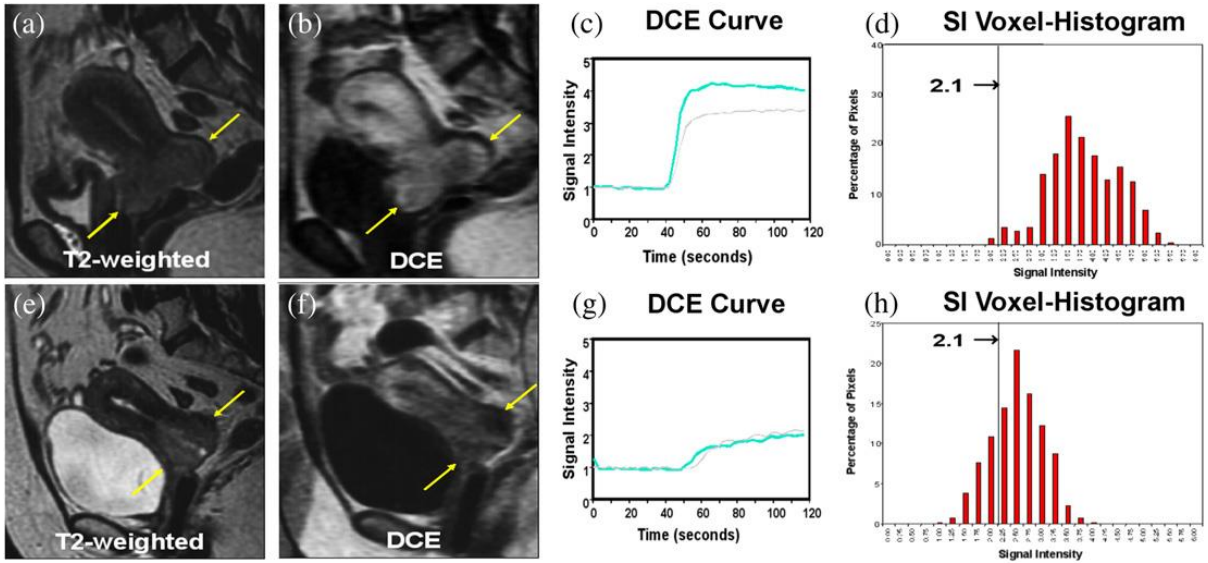
Factors in play

- Patient selection
- Target volume definition
- OAR delineation
- Dose calculation
- Toxicity scoring
- Patient-to-patient variation

Factors in play

- Factors to broadly classify patients (stage)
- Factors which modify response to radiation (hypoxia, fast repopulation)
- Intrinsic radiosensitivity

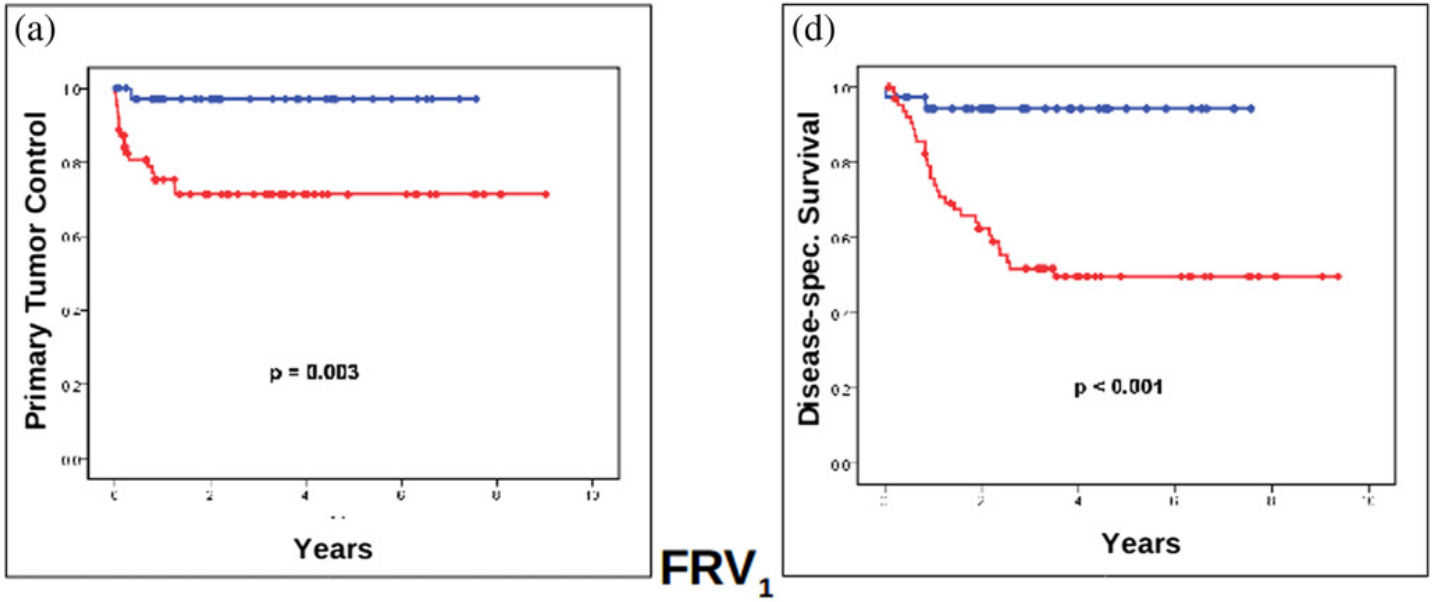
Imaging for hypoxia



Cervical cancer pts, a-d: poor outcome expected; e-f: excellent outcome expected. Dynamic contrast-enhanced-MRI performed 2 weeks after (b and f) commencement of RT show good perfusion (b), e-h poor perfusion (f). Patient a-d disease-free 10+ years, patient e-h 6 months after RT.

Mayr et al. 2012

Imaging for hypoxia

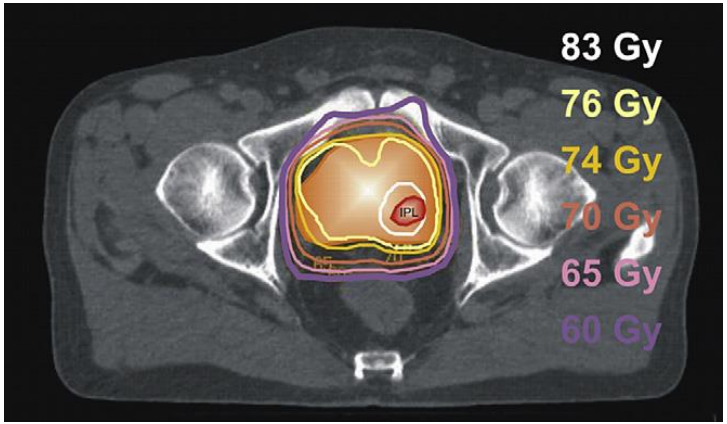


Cervical cancer pts, Dynamic contrast-enhanced-MRI performed prior to treatment.

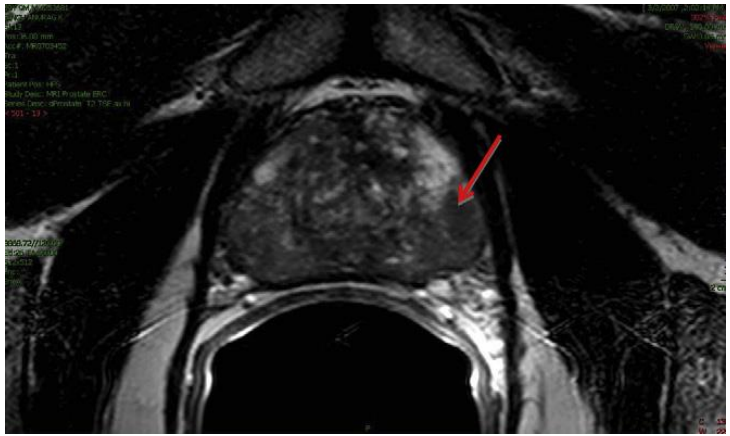
Mayr et al. 2012

Prostate cancer RT: SIB for IPL

Fonteyne et al. 2008, MRI/MRS - defined IPL, boost to IPL using fixed gantry IMRT

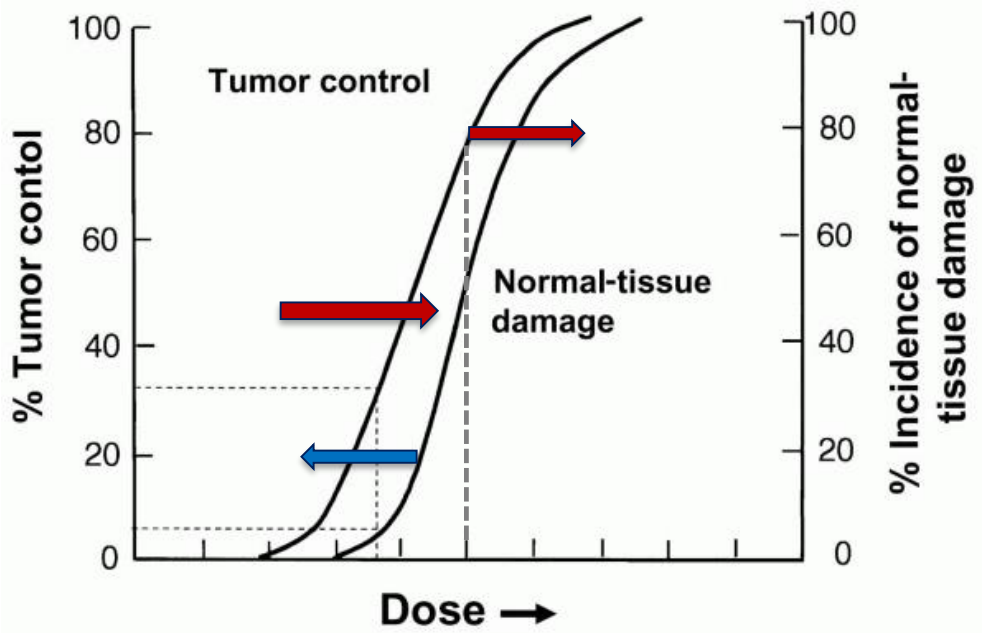


Housri et al. 2011, MRI/MRS - defined IPL



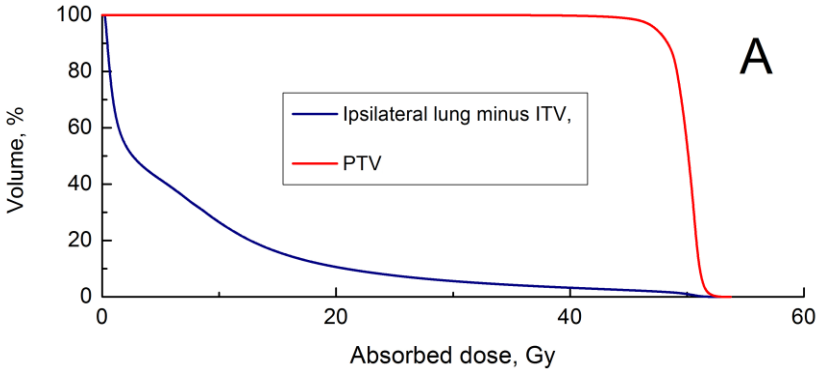
Fist and conceptually the simplest solution which may work is: if there is a problem – let's boost it. Prostate cancer prescribed dose currently 78Gy/39 fx or 81Gy/45 fx.

Concept of therapeutic ratio



Hall & Giaccia, 2006

Relationship between tumor control and normal tissue toxicity



Yorke et al. 2018

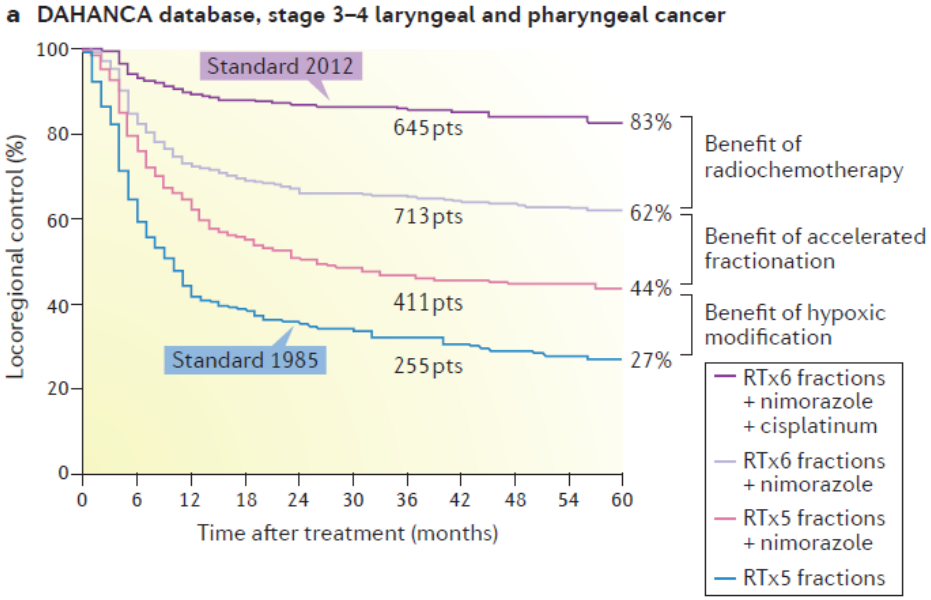
Head and neck cancer

1980s: locoregional control ~30%

Present: locoregional control ~70-80%

“stage migration”, chemo, imaging, targeting, fractionation

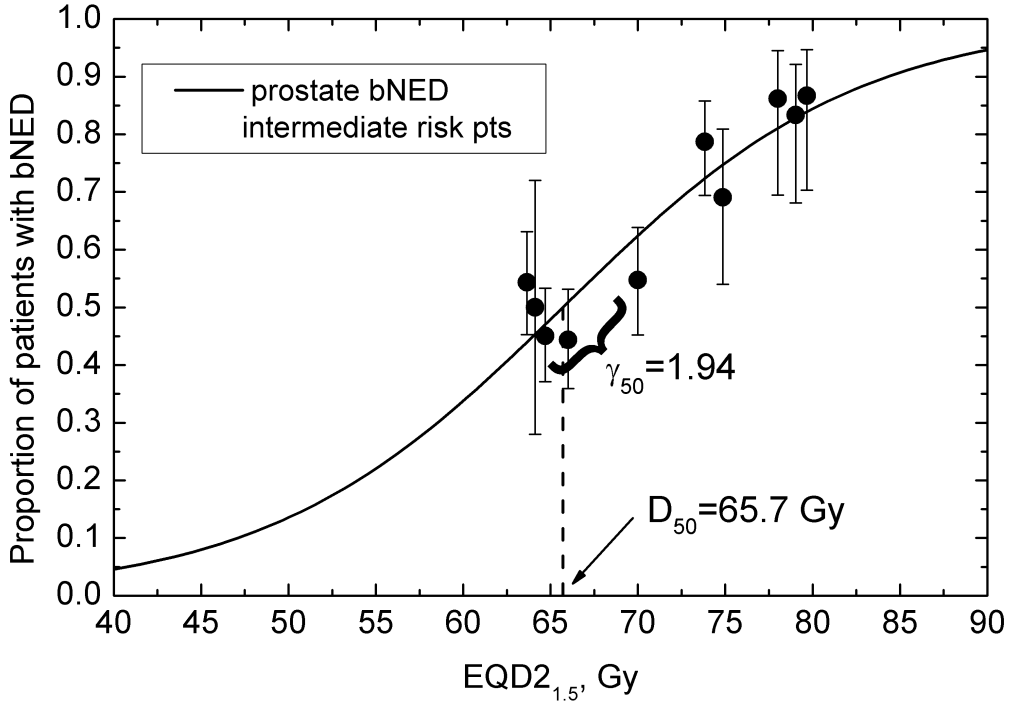
Baumann 2016

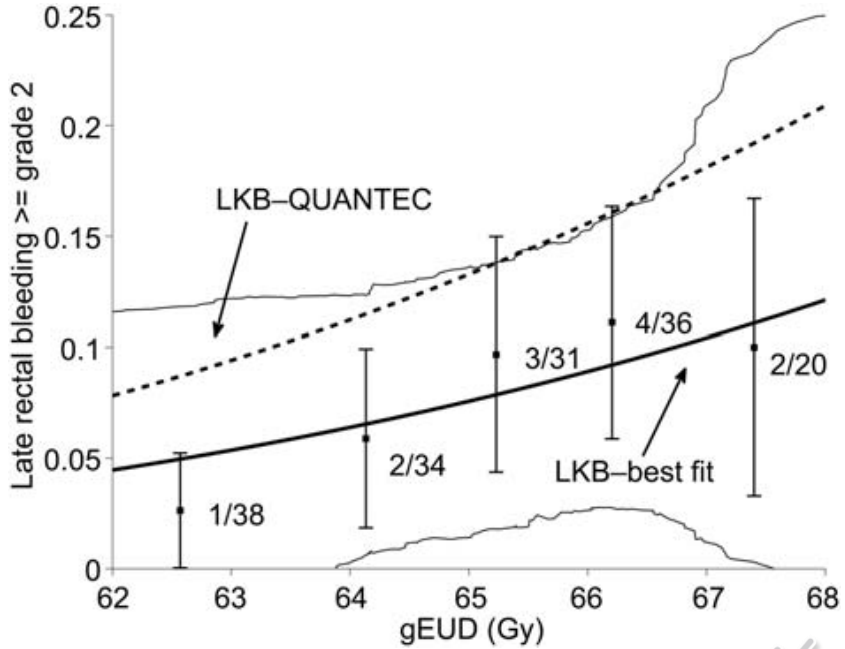


DAHANCA Trial (Denmark, Overagaard et al.)

DKDT (Germany, Linge et al; Lohaus et al)

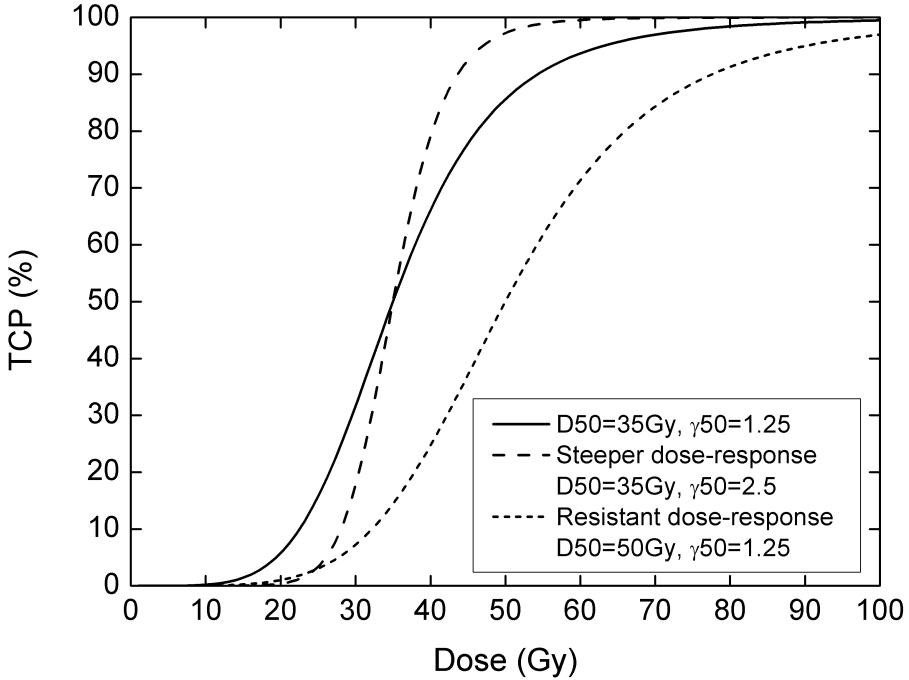
TUMOUR CONTROL PROBABILITY: POPULATION-BASED vs STRATIFIED

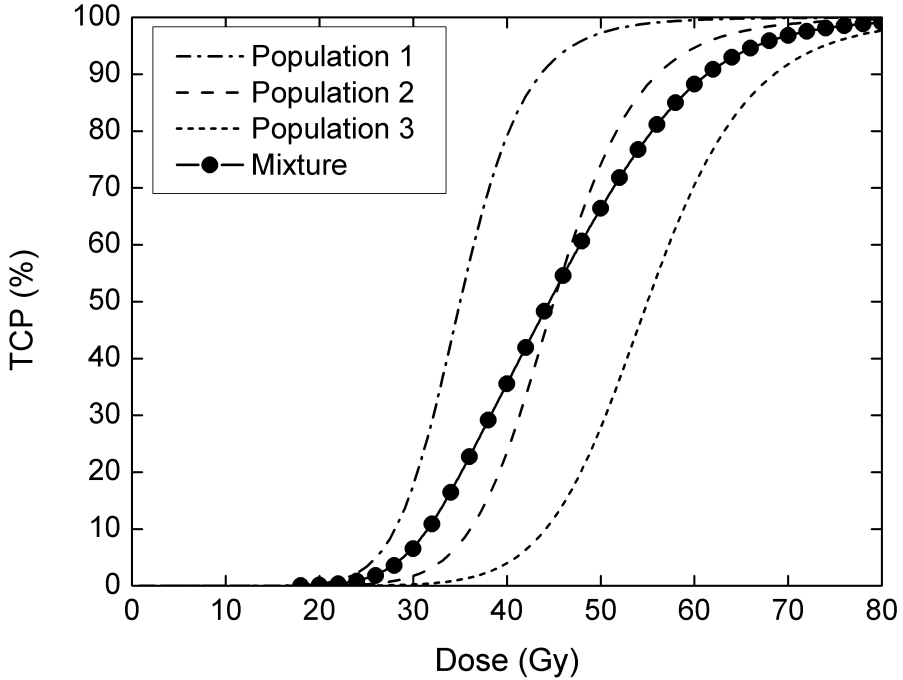




Liu et al. 2010

TUMOUR CONTROL PROBABILITY: POPULATION-BASED vs STRATIFIED





Yorke et al. 2018 Can we filter out each population?

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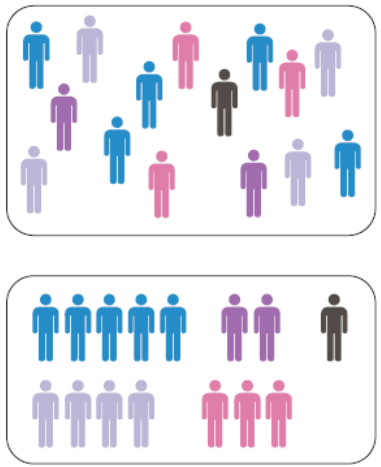
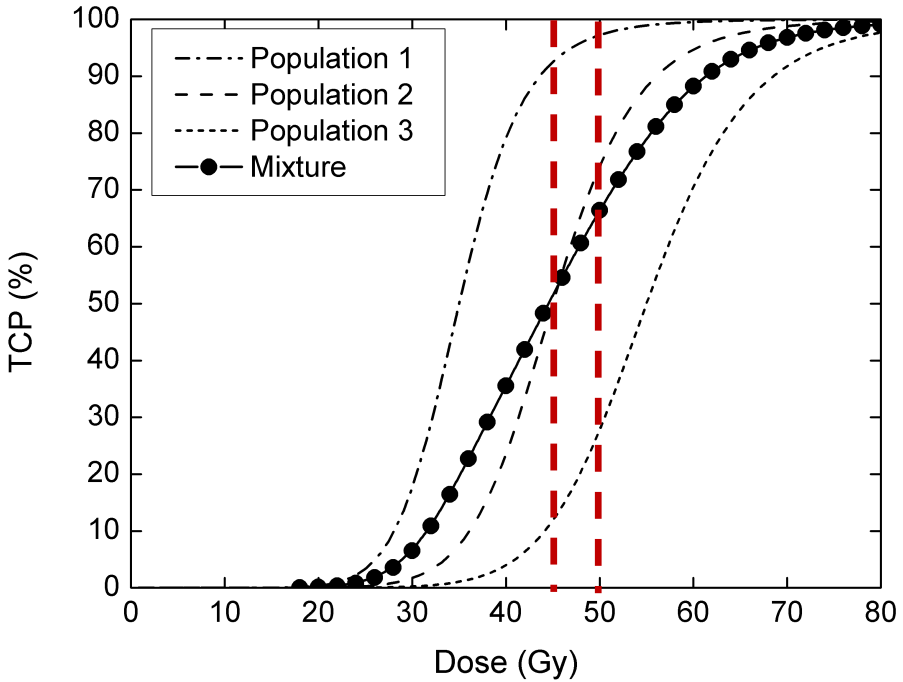




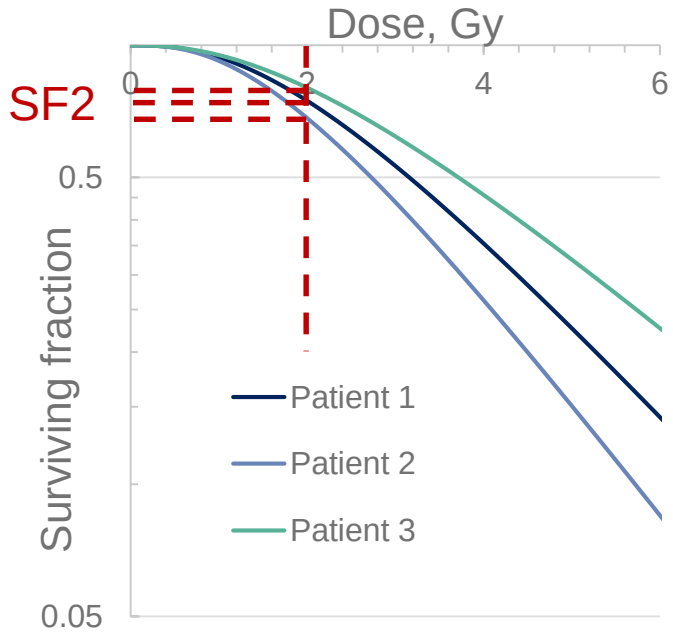
Benefit from dose escalation is different for different populations

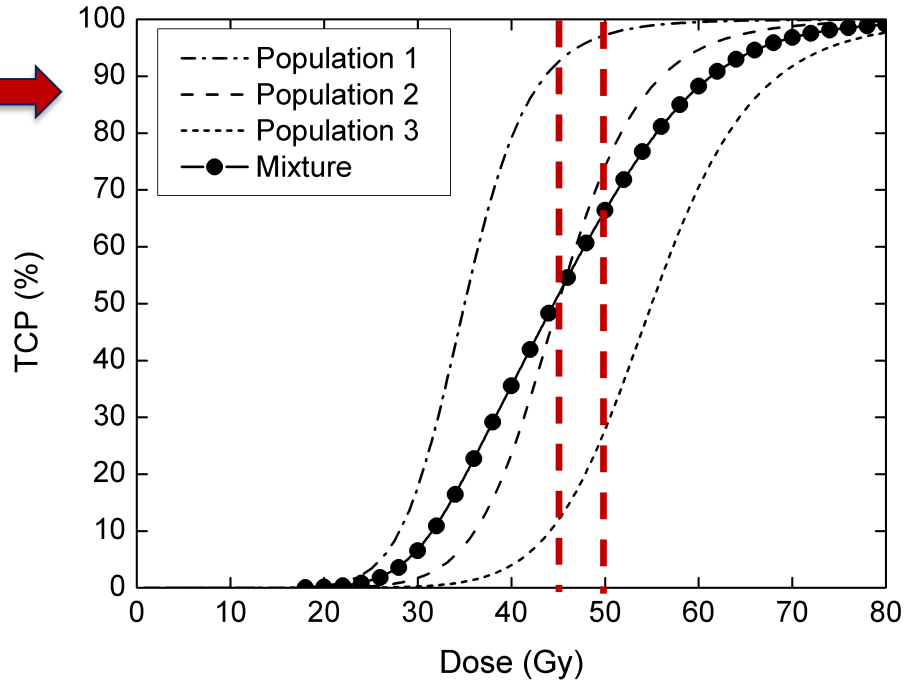
Stratification can be based on tumor features: hypoxia, FDG-PET SUV or

Patient-specific response to radiation (radiosensitivity)

Yorke et al. 2018

TUMOUR CONTROL PROBABILITY: POPULATION-BASED vs STRATIFIED





Yorke et al. 2018

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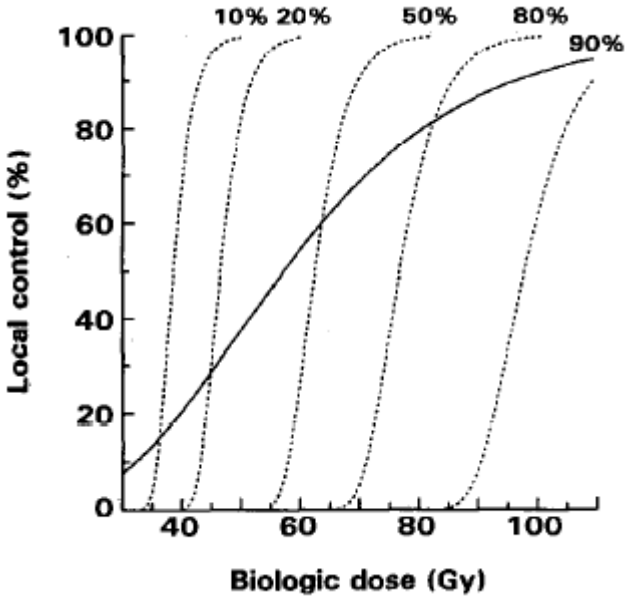

- Oropharyngeal cancer
- Radiosensitivity established in vitro
- Clinical γ_{50}=1.6
- Following stratification γ_{50} as high as 7.3

- Dose de-escalation is not an inviting option

Bentzen 1994

Factors in play

- Hypoxia: PET (FMISO, FAZA), DCE-MRI
- Tumor burden: tumor volume, FDG-PET
- Proliferation/repopulation: FLT-PET
- Intrinsic radiosensitivity: mostly retro or preclinical

Conclusion

- Accounting for patient-specific characteristics will allow us to stratify patients and maximize therapeutic ratio
- To stratify patients we need:
  - Tumor/normal tissue properties
  - Intrinsic radiosensitivity data
    - Fast
    - Definitive

Acknowledgement

Ellen Yorke

Andrew Jackson

Joseph Deasy

Randall Ten Haken

Issam El Naqa

Jimm Grimm

David Carlson

Lawrence Marks

Michael Milano