Deconvolving Dose Response to Maximize Therapeutic Ratio

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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

Characterized by $D_{50}$ (dose corresponding to 50% incidence or control) and $\gamma_{50}$ (normalized slope) $\gamma_{50} = D_{50} \frac{\partial P(D)}{\partial D}$.

$D_{50}$ and $\gamma_{50}$ depend on site and stage. For most cancers, $\gamma_{50}$ is between 1 and 3, i.e., 1 to 3% increase in local control per 1% increase in dose around $D_{50}$.
# TCP: LOGISTIC EQUATION

<table>
<thead>
<tr>
<th>Tumor site</th>
<th>Comment</th>
<th>Source</th>
<th>$TCD_{50}$, Gy</th>
<th>$\gamma_{50}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasopharynx</td>
<td>T1-4</td>
<td>Bedwinek et al. 1980</td>
<td>61.59</td>
<td>3.38</td>
</tr>
<tr>
<td>Melanoma</td>
<td></td>
<td>Overgaard et al. 1986</td>
<td>49.84</td>
<td>0.99</td>
</tr>
<tr>
<td>Tonsil</td>
<td>N1-3</td>
<td>Perez et al. 1982</td>
<td>54.02</td>
<td>1.03</td>
</tr>
</tbody>
</table>

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
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

Relationship between tumor control and normal tissue toxicity

Hall & Giaccia, 2006

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

Proportion of patients with bNED

prostate bNED
intermediate risk pts

$\gamma_{50} = 1.94$

$D_{50} = 65.7$ Gy

Late rectal bleeding $\geq$ grade 2

LKB–QUANTEC

LKB–best fit

Liu et al. 2010
TUMOUR CONTROL PROBABILITY: POPULATION-BASED vs STRATIFIED

Can we filter out each population?

Yorke et al. 2018  Can we filter out each population?
TUMOUR CONTROL PROBABILITY: POPULATION-BASED vs STRATIFIED

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

SF2
Surviving fraction
Dose, Gy

Patient 1
Patient 2
Patient 3

TCP (%)
Dose (Gy)

Population 1
Population 2
Population 3
Mixture

Yorke et al. 2018
TUMOUR CONTROL PROBABILITY: POPULATION-BASED vs STRATIFIED

- Oropharyngeal cancer
- Radiosensitivity established in vitro
- Clinical $\gamma_{50} = 1.6$
- Following stratification $\gamma_{50}$ 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
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