The Use of Dose Gradient Control Structures to Force Higher Doses into the GTV

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Anne Arundel Medical Center
Annapolis Maryland
Located on the Beautiful Chesapeake Bay
85 patients a day
3 Certified Radiation Oncologist
3 Certified Clinical Physicists
3 Certified Medical Dosimetrist
12 Certified Radiation Therapist
3 LINACS 2-2100EX’s (OBI) and 1-Novalis TX
Special Procedures: SRS/SRT Cranial, SBRT (Lung, Spine, Pancreas, H&N and Liver): HDR Cylinders+ MAMOSITE and LDR Prostate Seed Implants
Eclipse Treatment Planning (AAA+ Acuros+ Monte Carlo)
I-Plan Brain Lab Treatment Planning for SRT+MIMS VISTA
Mission Impossible

- Dosimetrist Scope of Practice is to achieve the impossible
- 83 yo H&N Patient
- Medical Comorbidities
- “Aggressive Palliation”
- Solitary Ipsi-Lateral Tumor
- 30Gy (6Gy x 5Fractions)
SLAM DUNK!

- Covered Dosimetric Plan Criteria
- Positive Vibes
- Reviewed with Physics
- SHOCK and AWE Moment
Evolution of Fractionation in Radiation Oncology

EXPOSURE TO DELIVERY
Roentgen’s X-Ray’s

- In 1895 Roentgen discovered X-Rays
- Radiation Oncology was born
First few decades of the 20th Century Radiation used to treat malignancies

- Breast and Uterine Cervix
- Brachytherapy Treatments
  - Radium discovered by Marie Curie
  - Method was EXPOSURE
- Tumors were rarely cured without significant normal tissue damage
Fractionation was first tested in 1911 (Claudius Regaud)

- This series established the basis of fractionation in external beam radiation today

Henri Coutard began utilizing fractionated treatments (20’s)

- Treatment schemes for H/N malignancies
- Desquamation and mucositis noted
- Customize patients treatments to limit Normal Tissue effects
Radiation Oncologist Magnus Strandqvist monitored his patients for dermatitis during skin XRT:

- Adjusted Doses continuously for patient Tx’s
- Defined duration and total dose for Tx’s

![Time-Dose Relationships](image)

**Fig. 1.** The Strandqvist dose-time or iso-effect curves graph showing radiation effects for treatments extending over different periods of time. The details are worked out on skin cancers of moderate size, treated with medium voltage (i.e. hvl of 2.0 mm Al to 1.0 mm Cu). For single-shot treatment the doses are: (A) necrosis 3000 R; (B) cancérocidal dose 2250 R; (C) moist desquamation 2000 R; (D) dry desquamation 1600 R; (E) erythema 1000 R. The single-shot dose of 2250 R is equivalent to 4200 R in 6 days (i.e. 6 increments of 700 R daily).

(From Strandqvist.)
Nominal Standard Dose Formula and The Linear Quadratic Model

* Ellis formulated NSD Model
* 1st equation for bio effect with dose
* Weakness only for acute responses in NT

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NSD = D N^{-0.24} T^{-0.11}
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D = dose
N = the number of fractions
T = treatment time in days

* LQ model (1980) used to quantitatively explain cell survival vs dose
* Different types of cells respond differently
* Estimates probability of late effects, early effects, and repair of radiation damage
* The LQ provides a bases for fraction schemes
Fractionation was formulated using the LQ model and the Radiobiological 5R’s.

Typical XRT scheduling consist of daily treatments:

- Standard delivery consists of small doses of 1.2-3Gy/Fx.
  - The small doses allow normal tissue repair.
  - Differential repair for tumors and normal tissues.
- LQ Model fails with Hypo fractionated schemes 9-20Gy/Fx.

Modern Fractionation
The risk of Normal Tissue complication has been examined.

- Overall Total Dose
- Fraction Size (hyper/hypo fractionation)
- Tissue Type (diff tissues respond diff to rad)
- Portion of tissue irradiation (serial vs parallel)

**Serial Structures**
Small Fx Produces Toxicity
eg. Spinal Cord + Esophagus

**Parallel Structures**
Small Fx no Clinical Toxicity
Threshold to Volume Causes Damage
eg. Lung + Kidneys
Dose Constraints for NT

  - NT tolerance dose at 5% and 50% NTCP within 5 years survival
  - some of the data was “guess work”

- Quantec (2007) update to Emami.
  - standard fractionation
  - 16 Specific Sites
  - volume based end points and partial volume NT doses

- SBRT(AAPM 2013 Grimm) Used for Hypo fractionation Schemes.
  - multiple fractional schemes
  - absolute volume based data
  - BED based doses
Looking Under the Hood of the PTV

- PTV is normal tissue
- Different HU’s within target
- Normal structure within and at the edge of the PTV
- Margin size to accommodate movement
PTV Can be a Moving Target

Intrafractionation
Variation within Fx
Breathing
Organ filling

Interfractionation
Variation between Fx
Set-Up variations
Anatomical Changes

Implementation of IGRT/4-D CT/MIMS has been very effective!
Quest for Conformality

- Currently AAMC only has IMRT and 3-D Conformal methods for hypo fx treatments

- Conformal XRT Methods
  - Limits dose to NT
  - Reduction of NT doses allows for higher dose deliveries
  - Can lead to possible issues during planning process
Dosimetric Dilemma

- Constant tug of war during the Planning/Optimization Process
- Coverage is Key
- OAR Sparing is Paramount
  - Hot spots formation
  - Loss of coverage
  - Dose dumping
- Conformality is Power
- Homogeneity is hard with different HU’s in the target
IMRT & SBRT PROS

**IMRT**
- Conformal
- Dose escalation
- NT spare = better quality of life

**SBRT**
- Conformality+homogeneity
- Dose escalation
- Tumor control rate 60-90%
- Shorter treatment courses
- Minimized radiation-induced normal tissue damage
IMRT & SBRT CONS

**IMRT**
- Lacks homogeneity (hot + cold spots)
- Integral dose
- Rapid dose fall off dose at edge
- Dose dumping in and around PTV
- Marginal vol miss

**SBRT**
- Toxicities to OARs
- Not beneficial in a wide range of cancers
- Small volumes/no nodal chains
AAMC’s Planning Paradigm Shift

- Control placement of hotspots
  - Eliminate Calc Box control
- Drive the high doses into center of the target
- Apply the Radiobiological principles & knowledge of TCP
- Keep Conformality and strive for homogenous distribution
- Consider how increased doses effect small volumes of NT

![Graph showing Decrease in TCP with Size of Cold Spot]
Pushing Heat in GTV provides TCP
- Deliver high doses to necrotic tumor core
- Comfortable with heat falling in the GTV/CTV interface instead of the PTV/TV interface
  - TV is Normal Tissue
  - Increases dose to NT
  - Increases NT toxicity in cc’s to volumes
Modified Planning Approach

- Develop “Dose Gradient Controlling Structures (DGCS)”
- Manipulate DGCS to control hot doses in the NT
- Use DGCS to assist with maintaining Homogenous dose in PTV
What Are DGCS?

- GTV
- PTV Eval
- DGCS1
- DGCS2
- DGCS3

Is the DGCS in the PTV? NT/PTV interface? Periphery? Will the HU’s within the volume affect dose placement? What Normal Tissues will be affected?
The answers to the previous questions determine:

- Volume of DGCS structure
- The Dose constraint to the DGCS structure
- The optimization priority
- Vary according to site
85yo Male

Squamous Cell Carcinoma L Parotid/Neck

SBRT 5Gy x 5 Fractions

CBCT Daily

Previous SBRT to L Temporal Skin
L Parotid/Neck SBRT Tumor

* DGCS1-3 Are used to manage the low dose in the periphery
  * Only upper constraints were utilized
  * DGCS3-40%/DGCS2-50%/DGCS1-60%
L Parotid/Neck SBRT Tumor

DGCS3
40% Dose Constraint

DGCS2
50% Dose Constraint

DGCS1
60% Dose Constraint
L Parotid/Neck DGCS Isodose Lines

Dose Coverage @ 100% 105% “Hot Spots”
L Parotid/Neck NO DGCS Isodose Lines

Dose Coverage @ 100% 105% “Hot Spots”
L Parotid/Neck SBRT Tumor

- Blue Line=Mandible (Max Point=25.8Gy 103% Hot Spot)
- Green Line=PTV Eval (Max Point=26.4Gy 105% Hot Spot)
- Red Line=GTV (Max point=26.9Gy 107% Hot Spot)
L Parotid/Neck SBRT Tumor

- ▲ Triangles=No DGCS  □ Squares=DGCS
- Blue Line=Mandible (Larger HS with No DGCS 26Gy)
- Green Line=PTV Eval (Hot Spot is within structure for No DGCS)
- Red Line=GTV (Cooler than PTV Eval for No DGCS)
Esophageal Cancer

- 74yo Male
- Adenocarcinoma of the Distal Esophagus
- PET/CT Scan during Sim
- Total Dose 54Gy
  - (1.8Gy x 28 Fractions)
- CBCT Daily
Esophageal Cancer

- DGCS 1-3 Initiated to maintain low dose in the periphery
- Bone PTV Coverage + to manage hotspots from high HU’s
Esophagus DGCS vs NO DGCS

- NO DGCS does not have adequate dose to maintain TCP
- Different HU’s causes Hot and Cold Spots
- DGCS warmer in the core of tumor
Esophagus DGCS vs NO DGCS

DVH

* Triangles=DGCS  Squares=No DGCS
* GTV Dose is higher for DGCS vs PTV Eval for No DGCS
* Hot Spot Located in Heart for No DGCS (Presence of Tail)
UCLA SBRT Protocol for Prostate

- 68yo Male
- Low-Risk Prostate Cancer
- PSA 7.1
- Gleason Score 3+3=6
- MRI obtained to define Prostate
- CBCT Daily
- Total Dose 36.25 Gy
  - (7.25 x 5 Fractions)
MRI Fusion Highly Diffused Region of the Prostate

- Maintain uniform dose across entire PTV
- Force all “Hot Spots” into the diffused region of MRI
DGCS for SBRT Prostate

- DGCS utilized all areas to maintain coverage and dose homogeneity.
- Bladd+Rec DGCS to force out 105%
Isodose Lines and Coverage for SBRT Prostate

Dose 103% and up are within the Diffused Region

Great TCP!!
With the changes in fractionation schemes in SBRT, how do we consider if the treatment is adequate or if the normal tissues are not going to be damaged

- e.g. of early = skin, bone marrow, testes
- e.g. of late = bladder, cord, kidney

\[
BED = nd(1 + \frac{d}{\alpha / \beta})
\]

- n = number of fractions
- d = fractional dose
- Alpha/Beta = properties of the tissue we are considering.
  (10 = Early responding
   3 = Late responding)
The Use of BED calculation with SBRT Prostate

<table>
<thead>
<tr>
<th># Fx’s</th>
<th>D (dose/fx)</th>
<th>D (total Dose)</th>
<th>EQD₂</th>
<th>EQD₂ ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>6Gy</td>
<td>36Gy</td>
<td>82.5Gy</td>
<td>1.09</td>
</tr>
<tr>
<td>5% hot spot</td>
<td>37.8Gy</td>
<td>90.2Gy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>44</td>
<td>1.8Gy</td>
<td>79.2Gy</td>
<td>74.1Gy</td>
<td>1.08</td>
</tr>
<tr>
<td>5% hot spot</td>
<td>83.2Gy</td>
<td>80.3Gy</td>
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<td></td>
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</tbody>
</table>

- Hot spots should be placed in the center of your target not on the periphery to protect normal structures from hot dose.
- Prostate tumors may respond better if hot spot is placed in disease site instead of spread throughout the gland [In prostate with \( \alpha/\beta = 1.1 \text{Gy} \) hot spots of 5% dose have roughly 10% more biological effect regardless of dose fractionation.
- Location of heat is Paramount.
What About Arc Therapy???
L Parotid/Neck Arc Treatment

100% Dose Coverage

105% Hot Spots
Esophagus Arc Treatment

100% Dose Coverage

105% Hot Spots
Arc Treatment DVH Analysis

* VMAT was successful utilizing DGCS.
* Hotter doses were placed within the GTV.
* Some high dose spillage was witnessed.
* Small hot spots were dumped in the mandible and heart.
* Overall dose more uniform than IMRT.
### Results

<table>
<thead>
<tr>
<th>Patient</th>
<th>DGCS/Non-DGCS</th>
<th>GTV $D_{max}$</th>
<th>PTV Eval $D_{max}$</th>
<th>OAR $D_{max}$</th>
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<tbody>
<tr>
<td>H&amp;N</td>
<td>Non-DGCS</td>
<td>107.2</td>
<td>107.2</td>
<td>104.4</td>
</tr>
<tr>
<td>(Mandible)</td>
<td>DGCS</td>
<td>107.8</td>
<td>105.9</td>
<td>103.0</td>
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<tr>
<td>Esophagus</td>
<td>Non-DGCS</td>
<td>104.5</td>
<td>105.9</td>
<td>105.7</td>
</tr>
<tr>
<td>(Heart)</td>
<td>DGCS</td>
<td>108.3</td>
<td>107.4</td>
<td>104.5</td>
</tr>
<tr>
<td>Prostate</td>
<td>Non-DGCS</td>
<td>108.9</td>
<td>108.9</td>
<td>105.6</td>
</tr>
</tbody>
</table>
| (Bladder)| DGCS          | 105.7         | 104.5               | 102.9         

- Comparison of doses for presented cases
- DGCS and non-DGCS normalized to same PTV coverage
- DGCS plan the maximum point dose in the GTV
  - Drop in dose across the chart
- Non-DGCS maximum point dose is in the PTV Eval
  - Increase across the chart
Results

- H&N and Esophagus: overall global max is higher in the DGCS plans
- Prostate case overall global max is lower in the DGCS plans
- The more DGCS used causes increase in overall dose
- DGCS: all OAR’s had a lower dose max point

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Discussion

* There are a variety of ways in which structures are used to manipulate dose within the optimization process
* As we move into the era of Hypofractionation I challenge us to think more Radiobiologically
* Manually force hot spots can deliver the hottest doses into the core of the GTV
* Split your PTV into portions of the most concern
* The affect of small hotspots is not known
  * Need more biological information to understand
  * Different normal tissue responses to hotspots may have a significant affect on the overall treatment outcome
Conclusion

- DGCS has been found to be effective in forcing hotspots into the GTV, while maintain PTV coverage
- Don’t be a slave to the algorithm. Break the PTV into sections to control dose distribution
- Understand that different tissues respond to dose differently and the dose response could have a different biological effect.
- Utilizing the BED calculation we are able to witness the equivalent dose that is truly distributed to Normal Tissues.
- Be mindful of the direction in which our field is going with accelerated doses, and consider where hotspots are placed. ULTIMATELY, BE CLINICIANS!!
Thank You!!

- Anne Arundel Medical Center Dosimetry Staff
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- Dr. Brian Hasson, PhD.,
  - Chief of Clinical Physics
- Charles Geraghty, M.S.
  - Clinical Physicist

Roswell Park’s own Dr. Luqman Dad
References

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PEOPLE, GET A HALF-LIFE!

MARIE CURIE TEACHING SCIENCE FOR SLACKERS.