Dose painting for Medical Oncologists

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Disclosures

- Dr. Jordi Giralt has no disclosures
Radiotherapy Techniques

- **3D-RT**
  Homogeneous dose in the whole treatment volume

- **IMRT**
  Sculpting the dose to the target shape, allows normal tissue protection

- **Dose painting (IMRT Dose intensification)**
  The prescription of a nonuniform radiation dose distribution to the target volume based on functional / molecular images
3D-RT
## Patterns of relapse

<table>
<thead>
<tr>
<th>Author</th>
<th>Regimen</th>
<th>Year</th>
<th>TD (Gy)</th>
<th>LocoReg</th>
<th>Distant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rischin</td>
<td>RT-cisplatin</td>
<td>2010</td>
<td>70</td>
<td>26%</td>
<td>8%</td>
</tr>
<tr>
<td>Bourhis</td>
<td>RT-carbo/5FU</td>
<td>2012</td>
<td>70</td>
<td>42%</td>
<td>25%</td>
</tr>
<tr>
<td>Bonner</td>
<td>RT- cetuximab</td>
<td>2006</td>
<td>70-77</td>
<td>50%</td>
<td>17%</td>
</tr>
<tr>
<td>Vermorken</td>
<td>TPF → RT</td>
<td>2007</td>
<td>70</td>
<td>57%</td>
<td>13%</td>
</tr>
<tr>
<td>Posner</td>
<td>TPF → RT-carbo</td>
<td>2007</td>
<td>70-74</td>
<td>30%</td>
<td>5%</td>
</tr>
</tbody>
</table>
IMRT

Administration of the radiation dose fields using NON uniform (≡ Modulation) fluence (≡ intensity)
Dose distribution
IMRT reduces toxicity

- Xerostomia in nasopharyngeal carcinoma
  - Recovery stimulated saliva flow 6% (3DRT) vs. 50% (IMRT)
  - Better quality of life (QLQ-H&N35 questionnaire)
    
- Xerostomia in pharyngeal squamous-cell carcinoma
  - Salivary flow rates reduction of 90% (3DRT) vs. 40% (IMRT)
  - Grade ≥ 2 xerostomia 74% (3DRT) vs. 38% (IMRT)

- Dysphagia in pharyngeal squamous-cell carcinoma
  - Pharyngeal constrictor muscles, glottis, esophagus
  - Worsening liquid swallowing was correlated with dose
IMRT Dose intensification
Dose painting

- Definitions / examples
- Biological tumor volume
- Adaptive RT
- Clinical results
General principles

- Local recurrences arise from cells that are resistant at the standard radiation dose
- Functional imaging will allow spatiotemporal mapping of these regions of relative radioresistance
- Advances in radiation therapy facilitate the delivery of a graded dose within the GTV
General principles

• Define subvolumes with higher risk of relapse
  "biological target volume" (BTV) → PET

• Define an inhomogeneous distribution of dose gradients → Complex IMRT

• Consider impact of volume variation during treatment and its effect on dose → Adaptive RT
Plan Aims

- Maximize probability of local tumour control
- Minimize probability of toxicity due to normal tissue damage
- Physical constraints on dose delivery
Dose painting methods

- Dose painting by volume
- Dose painting by numbers
Dose painting by volume

- Define discrete biologically different tumour regions
- Radioresistant region within a tumour
- Prescribe different doses to these volumes
- Threshold to determine extent of “Biological Target Volume”
  - SUV (PET)
  - Choline/Citrate Ratio (MRSI)
Dose painting by numbers

- Directly link image signal to prescription dose on a voxel-by-voxel basis
- Each voxel receives a different dose based on the intensity of a given image parameter
- The dose is prescribed at the voxel level
- The dose plan optimizer arrives at the best physically deliverable dose distribution
Procedure
Procedure
<table>
<thead>
<tr>
<th>Homogeneously delivered</th>
<th>Dose painting by volume</th>
<th>Dose painting by numbers</th>
</tr>
</thead>
<tbody>
<tr>
<td>70 70 70 70 70 70</td>
<td>70 70 70 70 70 70</td>
<td>70 75 75 80 80 70</td>
</tr>
<tr>
<td>70 70 70 70 70 70</td>
<td>70 70 70 70 70 70</td>
<td>70 75 80 75 75 70</td>
</tr>
<tr>
<td>70 70 70 70 70 70</td>
<td>70 70 80 80 80 70</td>
<td>70 75 86 80 75 80</td>
</tr>
<tr>
<td>70 70 70 70 70 70</td>
<td>70 70 80 80 80 80</td>
<td>70 70 80 86 86 80</td>
</tr>
<tr>
<td>70 70 70 70 70 70</td>
<td>70 70 80 80 80 80</td>
<td>70 70 80 86 80 80</td>
</tr>
</tbody>
</table>
Dose painting by volume
Dose painting by volume
Dose painting by volume

- 68 Gy
- 70 Gy
- 73 Gy
- 76 Gy
- 79 Gy
IMRT Dose intensification

Dose painting

- Definitions / examples
- Biological tumor volume
- Adaptive RT
- Clinical results
Biological Target Volume

Biologic targets

• Tumor burden
  – FDG uptake is a good surrogate for tumor cell burden
  – In a imaging study FDG-PET leads to better estimate of true tumor volume

• Proliferation
  – [18F] fluorothymidine-PET correlates with Ki-67 index
  – Signal changes in FLT PET may precede tumor response

• Hypoxia
  – FMISO-PET imaging is associated with a high risk of LRF
  – Interval for the administration and spatiotemporal stability
Pretreatment PET and failure

- Correlation between pretreatment PET-BTV with anatomical sites of loco-regional failure
- Retrospective study of 61 patients treated definitively with either 3-D CRT or IMRT who had a pre-therapy PET/CT
- A recurrence volume ($V_r$) was identified and was mapped to the pretreatment planning CT and pretreatment PET scan
- LRF 9/61; 100% (9/9) of failures were inside the GTV
- Only 1/9 (11%) had $V_r$ outside pretreatment PET-BTV, while 8/9 patients had $V_r$ within the PET-BTV

*Soto DE. R&O 89:13-18; 2008*
Pretreatment PET and failure

Soto DE. R&O 89:13-18; 2008
Pretreatment PET and failure
Adaptive RT

• Involves changes to the radiotherapy plan during treatment on the basis of patients specific changes
  ✓ Patients weight
  ✓ Tumor volume
  ✓ Position

• Tumor assessed by repeated CT shrink by 1-2% daily

• Progressive increase in dose
Study design

TARGETS: GTV, CTV, PTV1 & PTV2
OAR: Parotids, Spinal cord, Oral cavity & Mandible

CLINICAL WEEKLY ASSESSMENT:
- Weight control
- Acute toxicity control

## Weight loss

<table>
<thead>
<tr>
<th>CT-1</th>
<th>CT-2</th>
<th>CT-3</th>
<th>Variation (CT-1/CT2)</th>
<th>Variation (CT1/CT3)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>69.1</td>
<td>66.4</td>
<td>63.3</td>
<td>- 3.91 %</td>
<td>- 7.89 %</td>
<td>1.46% / 20.54%</td>
</tr>
</tbody>
</table>

**Mean weight (kg):**

<table>
<thead>
<tr>
<th>Weight (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>110</td>
</tr>
<tr>
<td>100</td>
</tr>
<tr>
<td>90</td>
</tr>
<tr>
<td>80</td>
</tr>
<tr>
<td>70</td>
</tr>
<tr>
<td>60</td>
</tr>
<tr>
<td>50</td>
</tr>
<tr>
<td>40</td>
</tr>
<tr>
<td>30</td>
</tr>
</tbody>
</table>

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CT-1 | CT-2 | CT-3
---|---|---

- Weight loss chart showing trends over time.
# Mean dose variation

<table>
<thead>
<tr>
<th></th>
<th>CT-1</th>
<th>CT-2</th>
<th>CT-3</th>
<th>Variation CT-1/CT-3</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean V100% GTV</td>
<td>72.1</td>
<td>79.3</td>
<td>83.5</td>
<td>11.44 %</td>
<td>-10.6 % / +41.46 %</td>
</tr>
<tr>
<td>Mean V95% GTV</td>
<td>99.1</td>
<td>99.0</td>
<td>99.2</td>
<td>0.08 %</td>
<td>-5.4 % / +3.8 %</td>
</tr>
<tr>
<td>Mean V100% PTV50</td>
<td>50.1</td>
<td>55.8</td>
<td>57.7</td>
<td>7.57 %</td>
<td>-3.4 % / +29.6 %</td>
</tr>
<tr>
<td>Mean V95% PTV50</td>
<td>82.3</td>
<td>82.4</td>
<td>84.6</td>
<td>2.3 %</td>
<td>-8.5 % / +3.8 %</td>
</tr>
<tr>
<td>Mean D parotid</td>
<td>39.32</td>
<td>43.58</td>
<td>45.01</td>
<td>16.11 %</td>
<td>(-1.8 % / +63 %)</td>
</tr>
<tr>
<td>Mean V26 parotid (%)</td>
<td>78.75%</td>
<td>80.06</td>
<td>85</td>
<td>9.18 %</td>
<td>(-7.8% / +35.6%)</td>
</tr>
<tr>
<td>D max spinal cord</td>
<td>42.6</td>
<td>44.13</td>
<td>44.21</td>
<td>3.9 %</td>
<td>(-4.8 % / +14.57%)</td>
</tr>
<tr>
<td>Mean D oral cavity (Gy)</td>
<td>46.46</td>
<td>47.26</td>
<td>47.26</td>
<td>1.47 %</td>
<td>(-8.6% / +9.07%)</td>
</tr>
</tbody>
</table>

Beltran et al J of Applied Clin Med Phy in press
Adaptive biological image-guided IMRT

- To assess the impact of anatomical/functional imaging modalities acquired prior to and during RT on the target delineation
- 10 patients treated with RT_QT (70 Gy + carbo/FU) in 7 weeks
- CT, T2-MRI, fat suppressed T2-MRI, and static and dynamic FDG-PET were acquired, basal and after doses of 14, 25, 35 and 45 Gy
- GTVs significantly decreased for all imaging modalities (p<0.001)
- PET-based GTVs significantly smaller compared to anatomical imaging modalities
- Adaptive PET IMRT has a significant impact on the delineation of target volumes

Geets X. R&O 85:105-115; 2007
Dose escalation

- Simultaneous treatment of PTV's with several levels of dose fractionation
- Median dose of 80.9 – 85.9Gy to the high-dose clinical target volume ($\text{GTV}_{\text{high\_dose}}$)
- 21 patients (7pt. 81 Gy / 14 pt. 86 Gy)
- No Grade 4 acute toxicity

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Dose level I</th>
<th>Dose level II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysphagia</td>
<td>5 (71%)</td>
<td>5 (36%)</td>
</tr>
<tr>
<td>Mucositis</td>
<td>3 (43%)</td>
<td>5 (36%)</td>
</tr>
<tr>
<td>Pain due to radiotherapy</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>1 (14%)</td>
<td>3 (21%)</td>
</tr>
<tr>
<td>Weight loss</td>
<td>1 (14%)</td>
<td>—</td>
</tr>
</tbody>
</table>
Dose escalation

- 18F-FMISO was administered intravenously for PET imaging.
- 10 HNC patients achieved 84 Gy to the GTVh and 70 Gy to the GTV, without exceeding the normal tissue tolerance.
Adaptive and innovative Radiation Treatment FOR improving Cancer treatment outcome (ARTFORCE)

Stage III-IV SCC H&N N= 360
Oral cavity, Oropharynx, Hypopharynx

CT scan in RT position is performed week 2 with replanning in week 3 in adaptive radiotherapy fashion.
Summary

• Technological development enables more precise RT

• Dose painting is a new strategy for optimal dose intensification

• Biological target volume means high-risk for relapse

• Controlled trials have shown dose painting it is feasible

• Clinical trials are required to validate this strategy