Imaging markers for prediction and assessment of response in head-neck cancer

Uulke A. van der Heide

Dose Painting in Head & Neck Cancer

- additional dose to tumor regions resistant to treatment to achieve better local-regional control

Heukelom et al. BMC Cancer 2013;13:84

Phase II randomized trials on dose painting

- FDG-PET
  - University Hospital Ghent
  - ArtForce, multi-center
- Hypoxia PET tracers
  - F-MISO PET: Tübingen University
- Perfusion/permeability
  - DCE-MRI: University of Michigan
Phase II randomized trials on dose painting

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Evidence for dose painting based on FDG-PET

- Pre-clinical studies
- Patterns of failure
  - Recurrences overlap with pre-treatment FDG positive volume


Soto et al. Radiother Oncol 2008;89:13-8

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Soto et al. Radiother Oncol 2008;89:13-8
Combining dose painting based on FDG-PET with adaptive RT

Dose planning for a) fractions 1-10, b) fractions 11-20; c) fractions 21-30

Berwouts et al. Radiather Oncol 2013;107:310-316

<table>
<thead>
<tr>
<th></th>
<th>Standard</th>
<th>Dose redistribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTV-PET-Primary</td>
<td>70</td>
<td>77 mean dose (70-84)</td>
</tr>
<tr>
<td>PTV-Primary</td>
<td>70</td>
<td>67 mean dose (64-70)</td>
</tr>
<tr>
<td>PTV-Lymphnodes</td>
<td>70</td>
<td>70</td>
</tr>
<tr>
<td>PTV-elective</td>
<td>54.25</td>
<td>54.25</td>
</tr>
</tbody>
</table>

Artforce
Pt with T3N1 tonsillar fossa

Dose gradient from 64-84 Gy
PET hypoxia measurements

Accumulation of tracers in hypoxic regions
- FMISO, FAZA, HK4, .. (nitroimidazoles)
- Cu-ATSM, ..


Baseline dyn. FMISO PET is prognostic for loco-regional control

LRC rates
- F-MISO PET +: 32%
- Non-hyp: 100%
- p = 0.048

Time after RT [months]

Baseline dyn. FMISO PET is prognostic for loco-regional control

Hypoxia dose painting (HDP) in HNC: A randomized phase II trial in Tübingen

- Feasibility and toxicity of PET-based HDP
- Prospective validation of a hypoxia TCP model

- Planning CT + FDG PET/CT
- Dynamic FMISO PET/CT in treatment position
- Second dyn. FMISO PET/CT after approx. 2 weeks of RT

- Randomization of hypoxic patients in 2 arms:
  - Arm 1: Standard IMRT - 70 Gy in 35 fx
  - Arm 2: HDP - homogeneous dose escalation of 10% in hypoxic tumor areas defined on dynamic FMISO PET/CT data

Courtesy Daniela Thorwarth
Dynamic FMISO PET: Different Shapes of voxel-based Time Activity Curves


Dynamic Contrast-Enhanced (DCE) MRI/CT


K trans
Hypoxia with MR

<table>
<thead>
<tr>
<th>Method</th>
<th>Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCE</td>
<td>1/100 sec</td>
</tr>
<tr>
<td>R2*</td>
<td>mmol/L</td>
</tr>
<tr>
<td>Relaxometry</td>
<td>pO2</td>
</tr>
<tr>
<td>MRS</td>
<td>T2-relaxation</td>
</tr>
</tbody>
</table>


Correlate DCE-MRI with hypoxia gene expression in cervix cancer

Halle et al. 2012; Cancer Res. 72:5258–5295

Evidence for dose painting based on DCE-MRI

- Several (small) studies suggest that a high value of $\text{K}_{\text{trans}}$ is associated with good response;

Patients with higher pretreatment $\text{K}_{\text{trans}}$ values (solid line) demonstrate significantly prolonged disease-free survival compared with patients with lower $\text{K}_{\text{trans}}$ values (dashed line, $P = .029$).

Increase in BV predicts good response in head-neck cancer

- DCE-MRI pre-treatment and after 2 weeks of CRT
- Local control (top): increase in blood volume
- Local failure (bottom): little change in blood volume


UMCC 2013-062: Schema

Workflow

CT sim
MRI sim (DCE)
Tx Plan preRT

1st Fx
10th Fx
16th Fx w adaptive plan
35th Fx

DCE MRI End of RT

DCE data analysis
Persisted hypoperfusion subvolume
New boosting Tx plan
IMRT QA

Supported by NIH RO1 CA184153
U01 CA183848

PI: Eisbruch
Image PI: Cao
Supported by NIH
RO1 CA184153
U01 CA183848

Randomize (n=80)

ARM A: Chemo+IMRT with boost to persist hypoperfusion [Boost arm]

ARM B: Standard Chemo+IMRT (control arm)

Screening
Baseline DCE MRI
Begin Chemo-IMRT
Repeat DCE MRI after 2 wks (after IMRT fraction 9 and before fraction 12)

Stratify:
A. Hypoperfused BV > or < 10 cc

Hypoperfused tumor sub-volume > 1 cc present?

Yes
No

Standard Chemo+IMRT [Observational Cohort]

Workflow

1st Fx
10th Fx
16th Fx w adaptive plan
35th Fx

DCE MRI End of RT

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Yes
No

Standard Chemo+IMRT [Observational Cohort]
**Diffusion-weighted MRI (DWI)**

- Measures the freedom of water protons to move
- Reflects
  - micro-anatomy
  - Response to treatment

**Diffusion-weighted MRI as early imaging marker for response to treatment**

Head-neck cancer

- >25% increase in ADC after 2 weeks of chemoradiation is associated with good loco-regional control

Vandecaveye et al. 2010; Eur. Radiol. 20:1703-14

**Diffusion-weighted MRI in head-neck**

- Possibly use DWI to identify the most resistant part of a tumor for boosting

Galbán et al. Transl Oncol 2009;18:184-90
Many plausible imaging techniques for dose painting

- FDG-PET
- Hypoxia:
  - F-MISO and other PET tracers
  - DCE-MRI
- Response:
  - DWI

FDG-PET and diffusion-weighted MRI

- 19 radiotherapy HN patients
  - Oral cavity, oropharynx, nasopharynx, hypopharynx
- Planning CT, PET and MRI exam
  - Within 2 weeks
- GTV delineated by radiation oncologist according to local clinical guidelines
  - GTV volume: 3 ml - 120 ml

Do these techniques identify the same Biological Target Volume?
Imaging protocol: $^{18}$FDG-PET

- Philips Gemini TF scanner
  - In RT mask
- CT
  - Attenuation correction
  - Registration to planning CT
- $^{18}$FDG-PET scan
  - 3 minutes per bed position
  - $2 \times 2 \times 2$ mm$^3$ voxels
  - Standardized uptake value (SUV$_{max}$) calculated

Imaging protocol: DWI

- Philips Achieva 3T scanner
  - Without RT mask
  - 16 element neurovascular coil
- T1-weighted scan
  - Registration to planning CT
- DWI scan
  - EPI imaging with SENSE factor of 2
  - $2.1 \times 2.6 \times 4$ mm$^3$ voxels
  - b-values: 0 and 1000
  - Apparent diffusion coefficient (ADC) calculated on scanner

Results: Tumor heterogeneity

Houweling et al. Radiother Oncol. 2013;106:250-4
**Results: Dice similarity coefficient**

\[
DSC = \frac{2(A \cap B)}{A + B}
\]

<table>
<thead>
<tr>
<th>Volume (ml)</th>
<th>Dice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>Range</td>
</tr>
<tr>
<td>SUV, 40% SUV_max</td>
<td>6.4</td>
</tr>
<tr>
<td>ADC &lt; 10^{-7} m/s²</td>
<td>8.7</td>
</tr>
<tr>
<td>ADC, 10^{-7} m/s²</td>
<td>15.5</td>
</tr>
<tr>
<td>ADC, 1.5 x 10^{-7} m/s²</td>
<td>23.6</td>
</tr>
</tbody>
</table>

Houweling et al. Radiother Oncol. 2013;106:250-4

**Results: Spearman correlation**

- Consistent information
  - High SUV correlates with low ADC

Houweling et al. Radiother Oncol. 2013;106:250-4
• Consistent information
  — High SUV correlates with low ADC
• Conflicting information
  — High SUV correlates with high ADC
• Complementary information
  — Weak correlation

Results: Spearman correlation

<table>
<thead>
<tr>
<th>Patient number</th>
<th>SUV</th>
<th>ADC</th>
</tr>
</thead>
<tbody>
<tr>
<td>18</td>
<td>76.0</td>
<td>705-797</td>
</tr>
<tr>
<td>17</td>
<td>75.0</td>
<td>695-735</td>
</tr>
<tr>
<td>16</td>
<td>74.0</td>
<td>695-747</td>
</tr>
<tr>
<td>15</td>
<td>73.0</td>
<td>695-843</td>
</tr>
</tbody>
</table>

Results: Dose distribution

Houweling et al. Radiother Oncol. 2013;106:250-4

Coverage of BTV based on FDG-PET or DWI

<table>
<thead>
<tr>
<th>Table 3: Dose coverage of the different SUV- and ADC-criteria.</th>
</tr>
</thead>
<tbody>
<tr>
<td>SUV (max)</td>
</tr>
<tr>
<td>Dose (Gy)</td>
</tr>
<tr>
<td>------------</td>
</tr>
<tr>
<td>Median:</td>
</tr>
<tr>
<td>Average:</td>
</tr>
<tr>
<td>Range:</td>
</tr>
</tbody>
</table>

*Significantly different from the SUV (min) criterion with p < 0.05.
FDG-PET and DCE-MRI

- Which tumor regions are resistant to treatment?

FDG-PET
- Loco-regional failure in high SUV areas
- Jansen et al. 2012

DCE-MRI
- Low $K_{\text{trans}}$ related to poor treatment outcome
- Bisdas et al. 2010

Aim: voxel-based comparison

Patient Inclusion

- 28 patients with head & neck cancer receiving radiotherapy
- FDG-PET/CT and DCE-MRI exam within one week
- All exams in radiotherapy mask

FDG-PET scan parameters
- Gemini TF Philips
- $190-240$ MBq FDG
- Voxel size = $2*2*2$ mm$^3$(recon)
- 3 bed positions (FH 36 cm)
- Total scan time = 9 min

DCE-MRI scan parameters
- 1.5 T (Achieva Philips)
- $TR/TE/\alpha = 4.0/1.16/15$
- FOV = $250*200*115$
- Voxel size = $3*3*4$ mm$^3$(acq)
- 1.4*1.4*4 (recon)
- 29 slices
- Dyn scan time = 2.5 s
- Total scan time = 3 min
- 15 mL dotarem 3 ml/s

FDG-PET scan parameters
- Gemini TF Philips
- $190-240$ MBq FDG
- Voxel size = $2*2*2$ mm$^3$(recon)
- 3 bed positions (FH 36 cm)
- Total scan time = 9 min

Tracer kinetics modeling – Tofts Model

- Extended Tofts model:
  \[ C_{\text{org}}(t) = v_p \cdot C_o(t) + K_{\text{trans}} \cdot C_d(t) \otimes R(t) \]
  with $R(t) = e^{(-K_{\text{trans}}/v_p) \cdot t}$

Fractional volume of Extravascular Extracellular Space ($V_d$)

\[ V_d = \frac{K_{\text{trans}}}{v_p} \]

\[ K_{\text{trans}} \]

\[ v_p \]

\[ C_o(t) \]

\[ C_d(t) \]

\[ R(t) \]

\[ e^{(-K_{\text{trans}}/v_p) \cdot t} \]

\[ C_{\text{org}}(t) \]

\[ v_p \cdot C_o(t) \]

\[ K_{\text{trans}} \cdot C_d(t) \otimes R(t) \]
Comparison SUV and DCE maps

Correlation SUV and DCE parameters

<table>
<thead>
<tr>
<th></th>
<th>$\rho$ voxel-level</th>
<th>$\rho$ patient-level</th>
</tr>
</thead>
<tbody>
<tr>
<td>SUV vs. $K^{trans}$</td>
<td>0.25* (-0.35 – 0.55)</td>
<td>0.15</td>
</tr>
<tr>
<td>SUV vs. $k_p$</td>
<td>0.36* (-0.33 – 0.64)</td>
<td>0.18</td>
</tr>
<tr>
<td>SUV vs. $v_e$</td>
<td>-0.11 (-0.56 – 0.33)</td>
<td>0.11</td>
</tr>
<tr>
<td>SUV vs. $v_p$</td>
<td>0.11 (-0.29 – 0.34)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

* $p < 0.01$

Correlation coefficients between SUV and tracer-kinetics parameters from DCE-MRI

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Observations

- Different imaging modalities are prognostic for response to (chemo-)radiotherapy
- Their predictive value is currently tested in dose painting trials of head and neck cancer
- Limited correlation between these imaging modalities reflects a high degree of tumor heterogeneity
- Correlations between FDG SUV and $K_{trans}$ and $k_{ep}$ were significant and higher at voxel-level
  - High FDG-PET uptake and low perfusion/permeability seem to identify different parts of the tumor

Dose escalation to BTV

- Probability of local control increases with dose escalation
- Normal tissue complication probability also increases with dose escalation
Dose escalation to BTV

Standard treatment

Dose painting

• Probability of local control increases with dose escalation
• Normal tissue complication probability also increases with dose escalation

Dose redistribution between BTV and PTV

Standard treatment

Dose painting

• If integral dose to the PTV is the same between both arms, the TCP should not change, unless the imaging modality is predictive

Strategy for dose painting trials

• Dose redistribution is more likely to test the benefit of dose painting than simple dose escalation
• Choose one imaging modality as the basis for dose painting
• Include as many other modalities as feasible in the pre-treatment imaging protocol
  – Analyze outcome using all imaging modalities
  – Use this to generate hypotheses for the next generation of clinical trials
Conclusions

- Ongoing trials of dose painting in head-neck cancer use different imaging techniques to identify a biological target volume.
- Limited correlation between these imaging modalities.
- It is impractical to test all functional imaging modalities in clinical trials.
- Dose redistribution is more likely to test the benefit of dose painting than simple dose escalation.
- By adding multiple imaging modalities to a dose painting trial, we can possibly derive dose-effect relationships for more modalities within a single trial.

Acknowledgments