Longitudinal Monitoring of Functional Changes in Irradiated Head and Neck Tumors Using Optical Spectroscopy

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Session: Treatment Response and Monitoring II
Conflicts of Interest

Nothing to disclose
Measurements of changes in gross tumor volume does not consider functional changes within lesions

Treatment efficacy and outcomes have been shown to depend on tumor oxygen levels in HNC

Obtain non-invasive, longitudinal measurements of changes in tumor hypoxia during treatment

<table>
<thead>
<tr>
<th>Clinical Options</th>
<th>Cost</th>
<th>Portable</th>
<th>Contrast</th>
<th>Longitudinal Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>MR</td>
<td>High</td>
<td>No</td>
<td>Extrinsic</td>
<td>~weeks</td>
</tr>
<tr>
<td>CT</td>
<td>High</td>
<td>No</td>
<td>Extrinsic</td>
<td>~weeks-months</td>
</tr>
<tr>
<td>PET</td>
<td>High</td>
<td>No</td>
<td>Extrinsic</td>
<td>~weeks</td>
</tr>
<tr>
<td>Optical</td>
<td>Low</td>
<td>Yes</td>
<td>Intrinsic</td>
<td>~daily-hourly</td>
</tr>
</tbody>
</table>
Diffuse Optical Spectroscopy

\[
\mu_a(\text{HbO}_2) \leftrightarrow [\text{HbO}_2]; \quad \mu_a(\text{dHb}) \leftrightarrow [\text{dHb}]
\]

Total Hemoglobin, \([\text{THb}]= [\text{HbO}_2]+ [\text{dHb}]\)

Oxygen Saturation, \(\text{SO}_2 = 100 \times [\text{HbO}_2]/[\text{THb}]\)

Probed depth \(\sim 2-4\) mm
Diffuse Optical Spectroscopy

- Optical method has been validated to extract [THb] (1-60 µM) and the relationship between SO₂ and pO₂ (measured using a microelectrode) in optical phantoms (Bender et.al; IEEE Trans. BME; 56(4): p. 960-968; 2009)

- In 4T1 preclinical models we have observed concordance between:
  - pO₂ (microelectrode) and SO₂ (optical) during carbogen breathing
  - Hypoxic fraction (from IHC) and [dHb] (deoxy-Hb concentration) longitudinally

Vishwanath et.al; Neoplasia; 11(9): p. 889; 2009
Clinical Study: Protocol

- Patients at the Durham VA Medical Center with confirmed HNSCC lesions that were accessible directly via oral cavity were consented.
- CT based treatment was planned in customized immobilization devices with IV contrast.
- PTV1, was 44-50 Gy (2 Gy daily fractions); PTV2 including all known gross disease boosted to 70 Gy.
- Patients with Stage III and above received concurrent chemotherapy.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Week 1</th>
<th>Week 2</th>
<th>Week 3</th>
<th>Week 4</th>
<th>F/U</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optical</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>RT</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
</tbody>
</table>
## Clinical Study: Recruitment

<table>
<thead>
<tr>
<th>Patient</th>
<th>Treatment</th>
<th>HPV</th>
<th>Clinical outcome</th>
<th>Pathological outcome (@ Neck Node)</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1</td>
<td>Cetuximab + RT</td>
<td>-</td>
<td>Complete clinical response</td>
<td>Negative for SCC</td>
</tr>
<tr>
<td>P2</td>
<td>Cisplatin + RT</td>
<td>+</td>
<td>Complete clinical response</td>
<td>NA</td>
</tr>
<tr>
<td>P3</td>
<td>RT only</td>
<td>-</td>
<td>Complete clinical response</td>
<td>NA</td>
</tr>
<tr>
<td>P4</td>
<td>Cisplatin + RT</td>
<td>-</td>
<td>Complete clinical response</td>
<td>NA</td>
</tr>
<tr>
<td>P5</td>
<td>Cisplatin + RT</td>
<td>-</td>
<td>Persistent disease</td>
<td>Positive for SCC</td>
</tr>
<tr>
<td>P6</td>
<td>Cisplatin + RT</td>
<td>+</td>
<td>Complete clinical response</td>
<td>NA</td>
</tr>
<tr>
<td>P7</td>
<td>RT only</td>
<td>+</td>
<td>Progressive disease</td>
<td>NA</td>
</tr>
<tr>
<td>P8</td>
<td>RT only</td>
<td>+</td>
<td>Complete response at primary</td>
<td>NA</td>
</tr>
</tbody>
</table>
T:N Ratio for SO$_2$: Temporal Trends

- **Patient**
  - Tumor (lesion)
  - Normal site

- **Diffuse Reflectance**

- **Tumor %SO$_2$**
- **Normal %SO$_2$**

- **T/N %SO$_2$**
T:N Ratio for SO$_2$: Temporal Trends

**T:N Ratio for Clinical Responders**

- Mean across P1, P2, P3, P4, P6, P8

**T:N Ratio for Clinical Non-Responders**

- Mean across P5 and P7
Animal Studies (Single Fraction)

- Nude mice grown with FaDu tumors on right flank
- Treated (N = 23) animals received radiation
- Control (N = 11) received sham radiation
- Optical probe placed on tumor and reflectance measured

<table>
<thead>
<tr>
<th></th>
<th>D0</th>
<th>39 Gy X 1 (TCD 50)</th>
<th>Week1</th>
<th>Week2</th>
<th>Weeks 3-15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume</td>
<td>x</td>
<td></td>
<td>x</td>
<td>x</td>
<td>X (once/week)</td>
</tr>
<tr>
<td>Optical</td>
<td>x</td>
<td></td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
</tbody>
</table>

Vishwanath, K. et.al; Journal of Biomedical Optics 14(5). 2009
1X RT: Changes in Tumor SO$_2$

Vishwanath, K. et.al; Journal of Biomedical Optics 14(5). 2009
Fractionated (5X) Studies

- We have tested 5X daily-fractions:
  - N = 27 mice (20 Treated, 7 control) with 15.5 Gy/fraction
  - N = 27 mice (20 Treated, 7 control) with 13.5 Gy/fraction

- As before, optical measurements obtained over a period of 2 weeks

- For each dose, optical measurements were obtained just before the animals were irradiated (PRE) and immediately after completion (POST)
Statistically significant ($p < 0.05$) increases post-irradiation in tumor $SO_2$, on the order of minutes, were observed each day for each fraction.
Optical spectroscopy can detect changes in vascular tumor oxygenation

Irradiated tumors show increases in oxygen saturation

Longitudinal measurements of functional optical endpoints could prove useful to plan treatment

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People:
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Individual Changes in T:N of %SO$_2$