Relating acute esophageal toxicity to radiotherapy dose using \(^{18}\)F-FDG-PET in concurrent chemo-radiotherapy for locally advanced non-small cell lung cancer

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**Objective**

- To model the relation between esophageal RT dose and post-RT \(^{18}\)F-FDG-PET uptake
- To correlate post-RT FDG uptake to acute esophagitis grade
- To utilize the local dose-effect model to improve AET probability modeling

**Conclusions**

- Esophageal FDG uptake up to 4 weeks post-RT is associated with acute esophagitis grade
- Only dose above 55 Gy is associated with increased FDG uptake
- Improved acute esophagitis ≥ grade 2 LKB model with narrow confidence interval based on the dose-effect model

**Patients & Methods**

- Locally advanced non-small cell lung cancer patients
- Treatment
  - 24 x 2.75 Gy IMRT
  - Daily lowdose Cisplatin
- Data
  - Esophageal wall planned dose (Gy) was sampled
  - Esophageal wall PET standard uptake value (SUV) (<3 months after treatment) was sampled
  - Acute esophagitis grade was scored prospectively
- Modeling
  - Relation between dose (Gy) and post-RT PET (SUV) using corresponding points
  - Dose surface histogram correlated to AE grade
  - PET surface histogram correlated to AE grade
  - Lyman-Kutcher-Burman (LKB) NTCP model on the data (comparing different dose-volume and EUD parameters)
  - Improved LKB model using the local dose-effect relation for the EUD parameter

**Results**

- 82 patients included (Table 1)
- PET SUV is only increased up to 4 weeks after treatment (Fig. 1)
- An increase in PET SUV is only associated with dose levels > 55 Gy (Fig. 1)
- Local dose-effect was fitted with
  \[ \text{SUV}_D = 1.85 \left(\frac{D}{72}\right)^{0.130} \]
- PET and SUV are both correlated to AE grade (Fig. 2)
- Improved LKB model to predict acute esophagitis using n=0.117 with 3 DOF
  \[ \text{EUD} = 50.4 \text{ Gy} (37.5-55.4) \]
- Large reduction of the 95% CI of the LKB model achieved
- Derived model outperformed proposed dose-volume parameters such as \(V_{35}, V_{50}, V_{70}\) and \(D_{mean}\) (Table 3)

**Figure 1**: Relation between the planned RT dose on the esophagus wall and the PET SUV measured after RT. Top: data stratified in four groups based on weeks between the last RT fraction and acquisition of the PET scan. A dose response is only visible within 4 weeks after RT. Bottom: mean data for all PET scans acquired within 4 weeks after RT, the error bars denote the 95% confidence interval, the solid line is the fit of the data.

**Figure 2**: Esophageal dose surface histogram based on the treatment plan (top) and corresponding PET surface histogram (bottom) for patients with the PET scan within 28 days after RT. Data is divided into groups with grade 0-1 AE (n=9, white), grade 2 AE (n=22, grey) and grade 3 AE (n=16, black).

**Figure 3**: The predicted probability of developing grade ≥2AE using the Lyman-Kutcher-Burman model. Left: LKB model based on the clinical data and the RT dose. Right: NTCP model when applying n=0.130 from the dose-effect relation resulting in (Fig. 3)

**Table 1**: Clinical and pathological characteristics in groups of acute esophagitis (AE) grade

<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>Median (range)</th>
<th>Gender</th>
<th>T-stage</th>
<th>N-stage</th>
<th>TNM stage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>60 (47-79)</td>
<td>Male</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>62 (50-78)</td>
<td>Female</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>63 (37-77)</td>
<td></td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**Table 2**: Dose-volume parameters and their corresponding deviance when used in a Lyman-Kutcher-Burman model for predicting acute esophagitis grade ≥2

<table>
<thead>
<tr>
<th>Grade 0-1 AE (1SD)</th>
<th>Grade 2-3 AE (1SD)</th>
<th>p-value (2-sided t-test)</th>
<th>Deviance</th>
</tr>
</thead>
<tbody>
<tr>
<td>36.8 (17.0)</td>
<td>47.5 (15.4)</td>
<td>0.006</td>
<td>93.07</td>
</tr>
<tr>
<td>28.4 (15.4)</td>
<td>40.8 (15.3)</td>
<td>0.001</td>
<td>89.66</td>
</tr>
<tr>
<td>25.3 (14.7)</td>
<td>37.6 (15.4)</td>
<td>0.001</td>
<td>89.50</td>
</tr>
<tr>
<td>21.6 (14.2)</td>
<td>33.6 (15.5)</td>
<td>0.001</td>
<td>89.92</td>
</tr>
<tr>
<td>27.3 (9.2)</td>
<td>33.6 (9.7)</td>
<td>0.007</td>
<td>93.00</td>
</tr>
<tr>
<td>52.6 (11.5)</td>
<td>59.1 (4.7)</td>
<td>&lt;0.001</td>
<td>88.52</td>
</tr>
<tr>
<td>53.5 (11.4)</td>
<td>59.9 (4.5)</td>
<td>&lt;0.001</td>
<td>88.51</td>
</tr>
<tr>
<td>69.5 (10.0)</td>
<td>73.6 (2.3)</td>
<td>0.004</td>
<td>91.20</td>
</tr>
</tbody>
</table>

**Table 3**: Dose-volume parameters and their corresponding deviance when used in a Lyman-Kutcher-Burman model for predicting acute esophagitis grade ≥2