Serial 4DCT/4DPET imaging to predict and monitor response for locally-advanced non-small cell lung cancer chemo-radiotherapy

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Why is Lung Cancer of Interest to Physicists?

• Target subject to physiological motions
  – Breathing ("regular" motion)
  – Coughing, discomfort (regular motion)
• Difficult to deliver high, tumoricidal doses without increasing normal tissue complications
• Many patients have co-morbidities (other lung & heart disease)
• Low survival rates – deserves attention.

"5D" CBCT (Sonke, NKI)
Monitoring Tumor Response with CBCT

- CBCT image quality is insufficient
  - Only 50% of primary tumours can be contoured
  - Nodal disease cannot be seen on CBCT

- Tumor volume increases in 1/6 pts!!!

- 14/31 had a shift in centre-of-mass coordinates (p < 0.05)
Findings from serial rcCBCT

- CBCT can tell us that variations occur, but not precisely.
- Need higher quality images to monitor tumor response and perhaps intervene.
- Repeat 4DCT? PET imaging? MR???

PET Imaging for Lung Cancer

![PET Imaging](image)

Investigation

- Monitor tumor response using 4DCT, 4DPET
  - Identify responders from non-responders
  - Identify radio-resistant parts of the tumor with PET
  - Justify and evaluate replanning and boosting to transform non-responders to responders

This research is funded by the Canadian Cancer Society (grant #020348)
**4D PET/CT**

- Monitoring Response to Treatment

- **Feature Definition**
  - \( \text{V3SUV}_{\text{tumor}} \): Volume containing voxels with SUV ≥ 3 within the primary tumor
  - \( \text{V3SUV}_{\text{nodes}} \): Volume containing voxels with SUV ≥ 3 within the nodal volume
  - \( \text{V3SUV}_{\text{tumor + nodes}} \): Volume containing voxels with SUV ≥ 3 within all diseased areas
  - \( \text{SUV}_{\text{peak}, \text{tumor}} \): 95th percentile of the SUV distribution within the primary tumor
  - \( \text{SUV}_{\text{peak}, \text{nodes}} \): 95th percentile of the SUV distribution within the nodal volume
  - \( \text{SUV}_{50\% , \text{tumor}} \): Volume with a SUV ≥ 0.5 x \( \text{SUV}_{\text{max}, \text{tumor}} \)
  - \( \text{SUV}_{50\% , \text{nodes}} \): Volume with a SUV ≥ 0.5 x \( \text{SUV}_{\text{max}, \text{nodes}} \)
  - \( \text{GTV}_{\text{tumor}} \): Volume of the primary tumor as contoured on 4DCT
  - \( \text{GTV}_{\text{nodes}} \): Volume of the affected lymph nodes as contoured on 4DCT

**FDG-PET/CT Image Analysis**

- Identified features from the literature
- Extract 4DCT and 4DPET features for each time point
  - 4DCT contours by experienced radiation oncologist
  - 4DPET volumes obtained from automatic contouring and analysis of Intensity Volume Histograms
- Calculate rate of change of these features with time.
Materials and Methods: Image Analysis

- Build time trend for each patient.
- Dichotomize according to outcome 2 years post-RT.
- Assess for statistical significance using Mann-Whitney, and log-rank tests.
- Identify optimal cut-offs using recursive partitioning method.
- Perform Kaplan-Meier survival statistics.

[Graph showing time trend for each patient]

[Graph showing dichotomized data]

[Graph showing statistical significance analysis]

[Graph showing optimal cut-offs]

[Graph showing Kaplan-Meier survival statistics]
Focus on dichotomized trends with $p < 0.005$

- Image features correlate better with PFS, LRFS, and LRRFS
- Some nodal features correlate with DRFS

<table>
<thead>
<tr>
<th>Week 0</th>
<th>Week 2</th>
<th>Week 4</th>
<th>Week 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feature</td>
<td>OS</td>
<td>PFS</td>
<td>LRFS</td>
</tr>
<tr>
<td>V3SUV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>tumor</td>
<td>-</td>
<td>0.006</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>nodes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>V3SUV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>tumor + nodes</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SUVpeak, tumor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SUVpeak, nodes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GTVtumor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GTVnodes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SUV50%, tumor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SUV50%, nodes</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Optimal cut-offs with $p < 0.005$

- Combined (tumor + nodes) $^{18}$F-FDG PET volumes < 94 cm$^3$ are more likely to achieve local control ($p < 0.005$)
- CT volumes do not correlate as strongly (0.05 < $p$ < 0.01)

Kaplan-Meier statistics

- Analysis performed for all features and time points
- Favorable features indicate outcomes advantage
  - 37% higher chance of local relapse-free survival at 1 year, and 28% higher chance at 2 years

Typical trends with prognostic value

- Large vs. small initial volumes
- Large vs. small rate of change late in treatment

PET imaging and Lung Cancer RT

- The available evidence demonstrates substantial benefits for the use PET-CT for radiotherapy dose planning in NSCLC.
- Improvements target volume delineation
- Patient selection
- Change in treatment intent from radical to palliative in a significant proportion of patients.

*Upstaging of disease is a concern because of the time lapse between diagnostic imaging and commencement of radiotherapy.*

Disease Progression

- Median time between diagnostic and treatment planning PET imaging: 21 days (average: 24.6 days)
- Overall, 25% of patients were upstaged; 7% in T, 14% in N, and 11% in M.
- New nodal stations were found in 32% of patients

- Biopsy proven metastatic deposit in Spleen
  - July 20th
  - August 31st
Predictive model for overall staging
PM + Peter Mac + UPENN data (N=99)

Looking to pool data from NKI.

Pooled PM, Peter Mac, and UPENN data

<table>
<thead>
<tr>
<th>Time lapsed between staging PET and 1st RT treatment (days)</th>
<th>Probability of upstage in T (%)</th>
<th>Probability of upstage in N (%)</th>
<th>Probability of upstage in M (%)</th>
<th>Probability of overall upstage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>0%</td>
<td>3%</td>
<td>0%</td>
<td>2%</td>
</tr>
<tr>
<td>20</td>
<td>2%</td>
<td>6%</td>
<td>5%</td>
<td>7%</td>
</tr>
<tr>
<td>30</td>
<td>4%</td>
<td>11%</td>
<td>8%</td>
<td>7%</td>
</tr>
<tr>
<td>40</td>
<td>4%</td>
<td>18%</td>
<td>8%</td>
<td>21%</td>
</tr>
<tr>
<td>60</td>
<td>7%</td>
<td>27%</td>
<td>8%</td>
<td>47%</td>
</tr>
<tr>
<td>80</td>
<td>7%</td>
<td>47%</td>
<td>8%</td>
<td>56%</td>
</tr>
</tbody>
</table>

Wait time distribution 2012-2017 (Cancer Care Ontario, NSCLC)

Should anticipate an overall upstage rate of ~22%, and ~8% upstage in M.
Adaptive Planning

• Groundwork for adaptive RT
  – Is it clinically feasible using current tools?
  – What is the best time to adapt?

• Examine two approaches:
  1. Recalculate plan on serial images
  2. Adapt therapy
     • Design a concurrent boost on “radioresistant” subvolume

Recalculating the clinical plan

Fractional Dose to Targets
**Fractional dose changes to OARs**

![Graph showing fractional dose changes to OARs over time]

**Estimated Impact on Total Dose**

<table>
<thead>
<tr>
<th>Dose metric</th>
<th>Average change to total dose (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>D99% GTV, tumor</td>
<td>0.7 ± 0.3</td>
</tr>
<tr>
<td>D99% GTV, nodes</td>
<td>0.6 ± 0.3</td>
</tr>
<tr>
<td>D99% PTV, tumor</td>
<td>-0.5 ± 1.0</td>
</tr>
<tr>
<td>D99% PTV, nodes</td>
<td>-1.2 ± 0.7</td>
</tr>
<tr>
<td>Max dose to canal</td>
<td>1.2 ± 0.7</td>
</tr>
<tr>
<td>Lung V20</td>
<td>0.7 ± 0.4</td>
</tr>
<tr>
<td>Mean lung dose</td>
<td>2.6 ± 1.3</td>
</tr>
<tr>
<td>Heart V60</td>
<td>11.2 ± 5.1</td>
</tr>
<tr>
<td>Esophagus V35</td>
<td>4.7 ± 3.0</td>
</tr>
</tbody>
</table>

**Metabolically-Adaptive Approach**

- Boost dose to volumes of high metabolic activity (i.e., SUV\textsubscript{50%}), where recurrence is likely
- Plan with a concurrent boost to SUV\textsubscript{50%} with dose as high as possible
- Don’t exceed accepted toxicity thresholds (RTOG 0617)
- Simulate adaption with boost at week 0, 2 or 4
Clinical Plan
66 Gy

Boost Plan
Week 0

Tumor Boost:
9000 cGy

Nodal Boost:
7455 cGy

Max dose:
11686 cGy

Yap et al., Clinical Oncology 28 (12): e199-e205, 2016

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