PET/CT for radiotherapy planning in lung cancer

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Talk Outline - PET/CT for RTP

• Background / Impact of PET in NSCLC staging
• Radiotherapy planning (RTP) with PET/CT and PET based target volume delineation (TVD)
• Respiratory Motion and PET/CT
• PET in adaptive radiotherapy
• Non-FDG PET isotopes in RTP
• Non-PET based functional imaging
• PET for prediction of outcome and for follow-up after RT
• PET and SCLC
### Mediastinal LN Staging Performance of PET

<table>
<thead>
<tr>
<th>Study</th>
<th>CT mediastinal staging performance</th>
<th>PET mediastinal staging performance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sensitivity</td>
<td>Specificity</td>
</tr>
<tr>
<td>Meta-analysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dwamena et al (1999)</td>
<td>60 (58-62)*</td>
<td>77 (75-79)*</td>
</tr>
<tr>
<td>Toloza et al (2003)</td>
<td>57 (49-66)*</td>
<td>82 (77-86)*</td>
</tr>
<tr>
<td>Birim et al (2005)</td>
<td>59 (50-67)*</td>
<td>78 (70-84)*</td>
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</tbody>
</table>

Effect of PET for Patient Selection for Radical Therapy

Possible impact of PET based target volume delineation in NSCLC

- CT - standard imaging modality for TVD definition
- Despite technical improvements in RT delivery, increased use of systemic therapies and more accurate staging, survival remains poor
- Up to 50% local failure despite radical local therapy
- Failure to accurately define target may be a causative reason
- PET/CT is more accurate than CT alone in the staging of NSCLC
Inter-observer variation with CT based TVD

Reduction of Inter-observer variation with PET


p=0.02
Reduction of Inter-observer variation with PET/CT

Reduction of Inter-observer variation with PET/CT

<table>
<thead>
<tr>
<th>GTV Comparisons</th>
<th>n</th>
<th>Median CI\textsubscript{CT:CT} (IQ Range)</th>
<th>Median CI\textsubscript{PET/CT:PET/CT} (IQ Range)</th>
<th>2 Tailed Significance Wilcoxon Signed Ranks test</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Cases</td>
<td>28</td>
<td>0.57 (0.41-0.71)</td>
<td>0.64 (0.47-0.71)</td>
<td>p=0.032</td>
</tr>
<tr>
<td>Induction Chemotherapy</td>
<td>14</td>
<td>0.44 (0.32-0.56)</td>
<td>0.49 (0.32-0.69)</td>
<td>p=0.022</td>
</tr>
<tr>
<td>Radiotherapy alone</td>
<td>14</td>
<td>0.67 (0.59-0.74)</td>
<td>0.69 (0.63-0.74)</td>
<td>p=0.470</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Atelectasis</th>
<th>n</th>
<th>Median CI\textsubscript{CT:CT} (IQ Range)</th>
<th>Median CI\textsubscript{PET/CT:PET/CT} (IQ Range)</th>
<th>2 Tailed Significance Wilcoxon Signed Ranks test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of atelectasis</td>
<td>10</td>
<td>0.51 (0.33-0.57)</td>
<td>0.61 (0.39-0.69)</td>
<td>p=0.007</td>
</tr>
<tr>
<td>Absence of atelectasis</td>
<td>18</td>
<td>0.61 (0.49-0.74)</td>
<td>0.62 (0.52-0.74)</td>
<td>p=0.983</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage Grouping</th>
<th>n</th>
<th>Median CI\textsubscript{CT:CT} (IQ Range)</th>
<th>Median CI\textsubscript{PET/CT:PET/CT} (IQ Range)</th>
<th>2 Tailed Significance Wilcoxon Signed Ranks test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I and II</td>
<td>13</td>
<td>0.68 (0.57-0.78)</td>
<td>0.68 (0.63-0.74)</td>
<td>p=0.917</td>
</tr>
<tr>
<td>Stage III</td>
<td>15</td>
<td>0.41 (0.35-0.58)</td>
<td>0.52 (0.33-0.67)</td>
<td>p=0.084</td>
</tr>
</tbody>
</table>

PET/CT in RTP – Atelectasis

- Significant potential benefit by reducing RT volumes

- However:
  - False positive uptake in post-obstructive inflammation
  - Histological correlation of PET findings with pathology are lacking

PET/CT in RTP – Atelectasis

• Significant potential benefit by reducing RT volumes

• However:
  – False positive uptake in post-obstructive inflammation
  – Histological correlation of PET findings with pathology are lacking

PET acquisition for RTP - Options

1. **Staging PET/CT**
   - Visual correlation of images - use only as a visual aid to guide target volume delineation
   - Formal registration of staging PET/CT to RTP CT scan (beware of registration Issues)

2. **Dedicated RTP PET/CT**
   - Combine with whole body diagnostic/staging scan
   - Dedicated planning only scan after staging PET/CT (limited to thorax only)
Lung board on PET/CT scanner

Requirements

- Flat bed couch insert
- Laser lights alignment system
- QA of image registration
- Appropriate staff
  i. Nuclear medicine technical officer
  ii. Therapy radiographer
  iii. Medical Physics staff

- Arms positioned above the head, T-bar grip and arm supports.
- Small bore - restricts the positioning of the arms

PET Target Volume Delineation Techniques

• **Manual / Visual interpretation** (Grey scale display, $W = SUV_{\text{MAX}}$ $L = 50\%$ of $SUV_{\text{MAX}}$)

• **Threshold Techniques**
  - $SUV = 2.5$
  - $35\%$ of $SUV_{\text{MAX}}$
  - $41\%$ of $SUV_{\text{MAX}}$

• **Source to Background Ratio Techniques**
  - Schaefer auto contour
  - Boellaard auto contour $= (0.42 \times (SUV_{\text{MAX}} + \text{BG}))$
Visual Based PET TVD
PET Target Volume Delineation Techniques

• **Manual / Visual interpretation** (Grey scale display, \(W=\text{SUV}_{\text{MAX}}\) \(L=50\%\) of \(\text{SUV}_{\text{MAX}}\))

• **Threshold Techniques;**
  – SUV of 2.5
  – 35\% of \(\text{SUV}_{\text{MAX}}\)
  – 41\% of \(\text{SUV}_{\text{MAX}}\)
Fixed Threshold based contouring

PET Target Volume Delineation Techniques

• **Manual / Visual interpretation** (Grey scale display
  - \( W = \text{SUV}_{\text{MAX}} \) \( L = 50\% \) of \( \text{SUV}_{\text{MAX}} \))

• **Threshold Techniques**;
  - SUV of 2.5
  - 35% of \( \text{SUV}_{\text{MAX}} \)
  - 41% of \( \text{SUV}_{\text{MAX}} \)

• **Source to Background Ratio Techniques**
  - Fixed ratio auto contour e.g. Threshold=(0.42*(\( \text{SUV}_{\text{MAX}} + \text{BG} \)))
  - Gradient based techniques (e.g. watershed segmentation)

Variation in background SUV – issues for auto-contouring

Limitations of SUV as an absolute value

\[
\text{SUV} = \frac{\text{Tissue Concentration}}{\text{Injected activity}} (\text{normalised by body weight})
\]

**Biological factors**
- patient weight / body composition
- blood glucose level
- post-injection uptake time
- respiratory motion
- lesion size
- patient movement artefacts

**Technical factors**
- variability of the scanner image-reconstruction parameters,
- FDG calibration and/or timing mismatch error
- Use of contrast material for PET/CT
- Residual activity in the administration system or syringe
- Intra- and inter-observer variability

Weiss GL, J Thorac Oncol 2012;7(12):1744-1746
Use PET to identify the tumour location
Use CT to define the edge of the target volume
The effect of respiration on PET/CT
Effect of respiration in PET/CT

- **Blurs the PET images**
  - Reduces image quality
  - Reduces calculated FDG uptake; attenuation correction calculations
  - Reduces contrast in the images
  - Affects size of determined lesion

- **Causes mis-alignment with CT**
  - Position
  - Size/shape

- **However may capture all of the tumour trajectory**
  - Hence may complement respiration correlated CT (4DCT) for dealing with tumour motion
Can PET define the ITV?

CT:

PET:

Comparison of ITVs on 4DCT and PET/CT

3DPET vs 4D PET vs 4DCT

Principle of Retrospective Gating
Phase based PET attenuation correction

CT in each Phase

PET in each Phase

Phase by Phase attenuated PET
Attenuation Correction

Detection of Small Lesions with 4D PET/CT

Lesion detected at hilar area in 4D PET; Not visible (blurred) using 3D PET.

# 3D vs 4D PET/CT

<table>
<thead>
<tr>
<th></th>
<th>3D PET/CT</th>
<th>4D PET/CT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Disadvantages</strong></td>
<td>- Respiratory Averaging</td>
<td>- Technically difficult</td>
</tr>
<tr>
<td></td>
<td>- Possibly inaccurate SUV</td>
<td>- Noisy patterns</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Prolonged Acquisition times</td>
</tr>
<tr>
<td><strong>Advantages</strong></td>
<td>- No Noise</td>
<td>- Accurate tumour volume definition</td>
</tr>
<tr>
<td></td>
<td>- Relatively Fast Acquisition</td>
<td>- Detection of Small Lesions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Better quantification of SUV (SUV(_\text{MAX}))</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Dose Painting / Better characterisation of heterogeneity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>within tumour</td>
</tr>
</tbody>
</table>
PET in adaptive radiotherapy

• Pre-treatment PET activity, as measured by SUV\textsubscript{MAX}, is highly predictive of outcome (Downey et al, 2004) (MacManus et al, 2005) (Kong et al, 2007).

• Can PET be used to define areas of active disease during or at the end of radiotherapy treatment?

• van Baardwijk et al (2007) – 4 FDG PETs acquired on 23 patients receiving accelerated radical radiotherapy before, during and on completion of radiotherapy
  - Patients with a metabolic response to radiotherapy (as adjudged by PET), there was no significant increase in SUV\textsubscript{MAX} during treatment.
  - Non-responders 48% increase in SUV\textsubscript{MAX} during the first week of radiotherapy (p=0.02) and a 15% decrease in SUV during the second week of treatment (p=0.04).
PET to define areas for radiotherapy boost?

PET in lung cancer RT

The PET-boost randomised phase II dose-escalation trial in non-small cell lung cancer

Wouter van Elmpt\textsuperscript{a,}\textsuperscript{*}, Dirk De Ruyscher\textsuperscript{a}, Anke van der Salm\textsuperscript{a}, Annemarie Lakeman\textsuperscript{b}, Judith van der Stoep\textsuperscript{a}, Daisy Emans\textsuperscript{a}, Eugène Damen\textsuperscript{b}, Michel Ollers\textsuperscript{a}, Jan-Jakob Sonke\textsuperscript{b}, José Belderbos\textsuperscript{b}

\textsuperscript{a} Department of Radiation Oncology, Maastricht University Medical Centre, Maastricht; \textsuperscript{b} Department of Radiation Oncology, The Netherlands Cancer Institute, Amsterdam, The Netherlands

Dose = 66 Gy

Dose = 72 Gy
Adaptive RT: Prognostic Information from FLT PET during ChemoRT


FLT PET at baseline

FLT PET after 18 Gy – Pt now has SVCO

FLT PET after change to BD fractionation
CT and PET changes after SABR

PET uptake after SABR

PET/CT Staging performance in SCLC - Discordance

<table>
<thead>
<tr>
<th>% PET Correct</th>
<th>% Conventional Correct</th>
<th>% Indeterminate</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>67</td>
<td>7</td>
<td>26</td>
<td>Azad et al</td>
</tr>
<tr>
<td>33</td>
<td>0</td>
<td>66</td>
<td>Chin et al</td>
</tr>
<tr>
<td>94</td>
<td>0</td>
<td>6</td>
<td>Niho et al</td>
</tr>
<tr>
<td>79</td>
<td>14</td>
<td>7</td>
<td>Blum et al</td>
</tr>
<tr>
<td>60</td>
<td>20</td>
<td>20</td>
<td>Kut et al</td>
</tr>
<tr>
<td>65</td>
<td>18</td>
<td>18</td>
<td>Schumacher et al</td>
</tr>
<tr>
<td>72</td>
<td>15</td>
<td>12</td>
<td>Brink et al</td>
</tr>
</tbody>
</table>

- 9 % of SCLC patients would be upstaged to E.D. by PET
- Suggests that 2752 AUD per life-year gained by avoiding futile therapy

Ruben JD and Ball DL. J Thorac Oncol 2012;7:1015-1020
## Outcomes from PET/CT RTP in SCLC

<table>
<thead>
<tr>
<th>Recurrence</th>
<th>Patients with recurrence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td>30 (100)</td>
</tr>
<tr>
<td><strong>Locoregional Failure</strong></td>
<td></td>
</tr>
<tr>
<td>- in-field</td>
<td>3 (10)</td>
</tr>
<tr>
<td>- out-of-field</td>
<td>2 (7)</td>
</tr>
<tr>
<td>- in-field and out-of-field</td>
<td>2 (7)</td>
</tr>
<tr>
<td><strong>Distant Failure</strong></td>
<td>23 (77)</td>
</tr>
<tr>
<td>- distant metastases alone</td>
<td>18 (60)</td>
</tr>
<tr>
<td>- in-field and distant metastases</td>
<td>2 (7)</td>
</tr>
<tr>
<td>- out-of-field and distant metastases</td>
<td>2 (7)</td>
</tr>
<tr>
<td>- in-field, out-of-field and distant metastases</td>
<td>1 (3)</td>
</tr>
</tbody>
</table>

Outcomes from PET/CT RTP in SCLC

Conclusions

- PET is critical for baseline staging and patient selection for radical therapy.
- Functional imaging – essential for RTP in both NSCLC and SCLC.
- PET should be used to guide and inform TVD in NSCLC and SCLC.
- PET useful to identify relapse in patients treated with RT/SABR.
- PET may be useful as predictor of response and for adaptive radiotherapy.
- On-going research is required in the era of 4D PET/CT and novel PET tracers.