PET/CT – Imaging in Radiooncology

Role of imaging in Radiotherapy (1)

- Target volume definition
- Target volume delineation
  - delineation of the primary, delineation of the lymph nodes
  - biologically relevant subvolumes
- Adaptive Image guided radiation
  - tumor motion
  - patients positioning and patient movement
  - organ motion (e.g. bladder, rectum) in patients with prostate cancer undergoing radiotherapy
  - Changes in biologically relevant subvolumes
PET/CT – Imaging in Radiooncology
Role of imaging in Radiotherapy (2)

Blumstein, Estro 2004
Schaefer, O.; Detection of recurrent rectal cancer with CT, MRI and PET/CT Eur Radiol. 2007 Aug;17(8):2044-54
not a talk about role of PET/CT as a
- staging tool
- method for early response assessment
- possibility to visualize early disease recurrence
Clinical data

- few patients
- various sites
- sub-optimal segmentation methods
- no validation with „a gold standard“ in prospective trials
PET/CT – Imaging in Radiooncology

Target definition (1)

Comparison between CT (MRI) and FDG-PET for nodal staging

<table>
<thead>
<tr>
<th>Site</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CT (%)</td>
<td>FDG-PET (%)</td>
</tr>
<tr>
<td>NSCL lung cancer</td>
<td>45</td>
<td>80–90</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>81</td>
<td>86–89</td>
</tr>
<tr>
<td>Head and neck cancer</td>
<td>36–86</td>
<td>50–96</td>
</tr>
</tbody>
</table>

Gregoire V. Is there any future in radiotherapy planning without the use of PET? Radiother & Oncol, 2004
Antoch G, Accuracy of whole-body dual-modality fluorine-18-2-fluoro-2-deoxy-D-glucose positron emission tomography and computed tomography (FDG-PET/CT) for tumor staging in solid tumors: comparison with CT and PET, JCO 2004
### Target definition (2) Esophagus

**Imaging methods**

<table>
<thead>
<tr>
<th>Imaging methods</th>
<th>lymph node regions (n)</th>
<th>pts. (n)</th>
<th>Influence of PET</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT/EUS (+) vs. FDG-PET (-)</td>
<td>9</td>
<td>8 (27%)</td>
<td>3 (10%) smaller</td>
</tr>
<tr>
<td>CT/EUS (-) vs. FDG-PET (+)</td>
<td>8</td>
<td>6 (20%)</td>
<td>3 (10%) larger</td>
</tr>
</tbody>
</table>

Vrieze et al. Radiother Oncol 2004
**PET/CT – Imaging in Radiooncology**

**Target definition (3) Head and Neck**

<table>
<thead>
<tr>
<th>Imaging methods</th>
<th>Vol ml</th>
<th>Mismatch x/CT</th>
<th>Mismatch x/MR</th>
<th>Mismatch x/PET</th>
<th>Mismatch x/Macro</th>
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<tbody>
<tr>
<td>n = 29 (larynx/hypophyrynx)</td>
<td>20.8</td>
<td>28%</td>
<td>48%</td>
<td>18%</td>
<td></td>
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<tr>
<td>CT</td>
<td>23.8</td>
<td>45%</td>
<td>67%</td>
<td>107%</td>
<td></td>
</tr>
<tr>
<td>MR</td>
<td>16.3</td>
<td>17%</td>
<td>15%</td>
<td>47%</td>
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<tr>
<td>FDG-PET</td>
<td>12.6</td>
<td>10%</td>
<td>9%</td>
<td>13%</td>
<td></td>
</tr>
<tr>
<td>Macro</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Daisne et al., Radiology 2004</td>
</tr>
<tr>
<td>Year</td>
<td>Journal</td>
<td>Patient/Tumor</td>
<td>Method</td>
<td></td>
<td></td>
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<td>------</td>
<td>---------</td>
<td>---------------</td>
<td>--------</td>
<td></td>
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<tr>
<td>2004</td>
<td>Macmanus, Int J Radiat Oncol Biol Phys 1; 60(3):1005-6</td>
<td>PET</td>
<td></td>
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<tr>
<td>2004</td>
<td>Yap, Cancer 10(4): 221-33</td>
<td>PET</td>
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<tr>
<td>2004</td>
<td>Delbeke, Cancer 10(4): 201-13</td>
<td>PET</td>
<td></td>
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<tr>
<td>2003</td>
<td>Schmucking, Recent Results Cancer Res 162;195-202</td>
<td>PET</td>
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<tr>
<td>2003</td>
<td>Ciernik, Int J Radiat Oncol Biol Phys 11; 57(3):853-63</td>
<td>PET/CT</td>
<td></td>
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<tr>
<td>2002</td>
<td>Perez, Rays 27(3): 157-73</td>
<td>PET</td>
<td></td>
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<td></td>
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<tr>
<td>2003</td>
<td>Antoch, Radiology 230(3):753-60</td>
<td>Leber(pig) PET/CT</td>
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<tr>
<td>2004</td>
<td>Levivier, J Nucl Med 45 (7): 1146-54</td>
<td>57 PET</td>
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<td>2003</td>
<td>Karger, Phys Med Biol 21; 48(2): 211-21</td>
<td>PET/SPECT</td>
<td></td>
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<td>2002</td>
<td>Eubank, Radiographics 22(1): 5-17</td>
<td>PET</td>
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</table>
## PET/CT – Imaging in Radiooncology

### Clinical data (2002-2004)

<table>
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<tr>
<th>NSCLC</th>
<th>Jahr</th>
<th>Journal</th>
<th>Pat.</th>
<th>Methode</th>
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<tr>
<td>Bradley</td>
<td>2004</td>
<td>Int J Radiat Oncol Biol Phys 8; 22(16):3248-54</td>
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<td>Bradley</td>
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<td>Int J Radiat Oncol Biol Phys 5; 59(1):78-86</td>
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<td>Mah</td>
<td>2002</td>
<td>Int J Radiat Oncol Biol Phys 2; 52(2):339-50</td>
<td>30</td>
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<td>Erdi</td>
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<td>Radiother Oncol 62(1):51-60</td>
<td>11</td>
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<td>HNO</td>
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<td>Int J Radiat Oncol Biol Phys 15; 59(4):1001-10</td>
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<td>Scarfone</td>
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<td>Int J Radiat Oncol Biol Phys 4; 58(5):1506-12</td>
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<td>Cervix</td>
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<td>Int J Radiat Oncol Biol Phys 3; 58(4):1289-97</td>
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<td>Pankreas</td>
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<td>J Gastroenterol 39(1): 50-5</td>
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<td>Int J Radiat Oncol Biol Phys 180(1):15-20</td>
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<td>Semin Nucl Med 34 (3): 209-23</td>
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<td>Hocht</td>
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<td>Strahlenther Onkol 180(1):15-20</td>
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<td>Sarkome</td>
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<td>Clin Nucl Med 28(10): 815-20</td>
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<td>Johnson</td>
<td>2003</td>
<td>Orthopäde 31(9):921-9</td>
<td>79</td>
<td>PET</td>
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</table>
# PET/CT – Imaging in Radiooncology

**Literature research (2005 - 08/2008)**

PET/CT in Oncology \( n = 927 \)

## PET/CT and radiotherapy/ integration for treatment planning

<table>
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<th>2006</th>
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<th>2008</th>
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<td>General aspects/technical note</td>
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<td>8</td>
<td>17</td>
<td>11</td>
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<td>Lung cancer/Pleura mesothelioma</td>
<td>10</td>
<td>8</td>
<td>6</td>
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<td>Head and Neck</td>
<td>3</td>
<td>10</td>
<td>7</td>
<td>9</td>
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<td>brain tumours</td>
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<td>1</td>
<td>1</td>
<td>2</td>
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<td>thyroid cancer</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2</td>
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<td>breast cancer</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>2</td>
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<tr>
<td>Lymphoma</td>
<td>2</td>
<td>0</td>
<td>4</td>
<td>1</td>
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<tr>
<td>Esophagus cancer</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td>0</td>
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<td>Liver cancer/metastases</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Rectal cancer</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Cervix carcinoma</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>2</td>
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<tr>
<td>Prostate cancer</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Anal cancer</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>27</strong></td>
<td><strong>37</strong></td>
<td><strong>41</strong></td>
<td><strong>42</strong></td>
</tr>
</tbody>
</table>

\[ 147/927 = 16\% \]
Ich sehe die Venusfliegenfalle, eine Schnecke, einen Hund, einen Baum am Nagel, einen breiten, offenen Mund; zwei Vieren, zwei Fledermäuse, vier fünfzackige Sterne, eine große, grüne Raupe, das Fahrrad lenk' ich gerne.
Ich sehe die Venusfliegenfalle, eine Schnecke, einen Hund,
einen Baum am Nagel, einen breiten, offenen Mund;
zwei Vieren, zwei Fledermäuse, vier fünfzackige Sterne,
eine große, grüne Raupe, das Fahrrad lenk’ ich gerne.
Ich sehe die Venusfliegenfalle, eine Schnecke, einen Hund, einen Baum am Nagel, einen breiten, offenen Mund; zwei Vieren, zwei Fledermäuse, vier fünfschikfige Sterne, eine große, grüne Raupe, das Fahrrad lenk' ich gerne.
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PET/CT – Imaging in Radiooncology

Future begins in the past
PET/CT – Imaging in Radiooncology
Future begins in the past

Warburg – effect (1920,1957)

Robert A. Gatenby Robert J. Gillies
Why do cancers have high aerobic glycolysis?
Nature Reviews Cancer 4, 891-899 (November 2004)

Christofk, H. R. et al.
Pyruvate kinase M2 is a phosphotyrosinebinding protein.
Nature 13 Mar 2008

Christofk, H. R. et al.
Pyruvate kinase M2 is a phosphotyrosinebinding protein.
Nature 13 Mar 2008
Dedicated PET/CT-Scanner

110 cm
60 cm

CT  PET

Necrotic Area
Hypoxic Area
Normoxic Area
Blood Vessels

Cell Death
Genetic Instability
Changes in oncogenes and anti-oncogenes
Sustained HIF Expression
VEGF
GLUT-1
Fuc-T VII
ST301
UDP-Gal T

More malignant cancer cells with increased sialyl LeX/a
Hypoxia-resistant Tumor angiogenesis
Infiltrative growth
High metastatic activity

GlycoWard
Radiation therapy (RT) of an osseous metastasis in men suffered from prostate cancer
Before RT and five month after RT (30 Gy)
Recurrent glioblastoma multiforme. $^{11}$C-methionine positron emission tomography shows tumor infiltration in areas (arrows) located outside of the contrast enhancement on computed tomography and T1-magnetic resonance imaging.


Ulrich, Clin Cancer res, 2008 ($^{18}$F-FLT)
Size of FDG-based GTV is influenced by the contouring method

N= 25, primary NSCLC, FDG based GTVs

Contouring methods:
- Visually
- Threshold = SUV 2.5
- 40% of maximum accumulation
- Contrast dependent algorithm

Significant differences correlating with:
- SUV max
- Size of lesion
- Inhomogeneity of accumulation

Results of the use of different methods for contouring the GTV in a large inhomogeneous tumor.

Red (black arrow): isocontour comprising 40% of the maximum accumulation of the lesion. Green (white arrow): isocontour derived from source/background algorithm

Nestle U et al. Radiotherapy & Oncology 2006
## Table 1

<table>
<thead>
<tr>
<th>Author</th>
<th>Study Type</th>
<th>Patients</th>
<th>PET/CT Image Fusion</th>
<th>Method of GTV Contouring (PET)</th>
<th>Change of GTV, PTV using PET</th>
<th>Increase of GTV, PTV using PET</th>
<th>Decrease of GTV, PTV using PET</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hebert et al. [46]</td>
<td>Prospective</td>
<td>20</td>
<td>Comparison X-ray, CT, PET</td>
<td>Visual evaluation of FDG-PET</td>
<td>GTV7/20 P (33%)</td>
<td>GTV 3/20 P (15%)</td>
<td>GTV 4/20 P (20%)</td>
<td>PET may be useful for delineation of lung cancer. PET detects positive lymph nodes, not useful in tumor delineation</td>
</tr>
<tr>
<td>Kircher et al. [54]</td>
<td>Prospective</td>
<td>15</td>
<td>Graphical coregistration of coronal PET with AP simulator image</td>
<td>Visual evaluation of FDG-PET</td>
<td>GTV: 7/15 P (47%)</td>
<td>GTV: 4/15 P (27%)</td>
<td>PET &amp; PTV: 4/15 P (27%)</td>
<td></td>
</tr>
<tr>
<td>Munley et al. [63]</td>
<td>Retrospective</td>
<td>35</td>
<td>CT/PE co-registered manually using transmission PET PET portal compared to CT portal</td>
<td>Visual evaluation of FDG-PET</td>
<td>PTV:12/35 P (34%)</td>
<td>PTV: 12/35 P (34%)</td>
<td>PET target smaller than CT not evaluated</td>
<td></td>
</tr>
<tr>
<td>Mesile et al. [69]</td>
<td>Retrospective</td>
<td>34</td>
<td>PET portal compared to CTPortal</td>
<td>Visual evaluation of FDG-PET</td>
<td>change of field size in 12P (53%) Median: 19, 3% (cm2)</td>
<td>Increase of field size 9 P (28%)</td>
<td>Decrease of field size 3 P (9%)</td>
<td>Change of field size in patients with dys or atelectasis</td>
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<tr>
<td>Vosyssel et al. [92]</td>
<td>Retrospective</td>
<td>73</td>
<td>(N=) CT-Manuke map compared with CT-PET-Manuke map and pathology</td>
<td>Visual evaluation of FDG-PET</td>
<td>GTV: 45/73 P (62%)</td>
<td>GTV: 16/73 P (22%)</td>
<td>GTV: 29/73 P (40%)</td>
<td>PET data vs. pathology: 36 P (49%) - pathology 2 P (3%) inappropriate 3P insufficient</td>
</tr>
<tr>
<td>MacManus et al. [81]</td>
<td>Prospective</td>
<td>153</td>
<td>PET results used for treatment planning, no image fusion</td>
<td>Visual evaluation of FDG-PET</td>
<td>GTV: 22/102 P (21%)</td>
<td>GTV: 22/102 P (21%)</td>
<td>Exclusion of atelectasis and lymph nodes</td>
<td>Post-PET stage not pre-PET stage was significant associated with survival</td>
</tr>
<tr>
<td>Kaliff et al. [33]</td>
<td>Prospective</td>
<td>34</td>
<td>No Image fusion</td>
<td>Visual evaluation</td>
<td>22/34 altered treatment delivery</td>
<td>n.e.</td>
<td>n.e.</td>
<td>Part of a study on impact of FDG-PET on various endpoints (n=105) 4/12 lymph nodes 1/12 atelectasis and distant meta (a) Addition of PET does lower physician variation in PTV delineation</td>
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<td>Gisela et al. [40]</td>
<td>Prospective</td>
<td>12</td>
<td>CT/PET Image fusion</td>
<td>Visual evaluation of FDG-PET</td>
<td>GTV: PTV 5/12 P (42%)</td>
<td>n.e.</td>
<td>n.e.</td>
<td></td>
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<td>Mah et al. [62]</td>
<td>Prospective</td>
<td>30</td>
<td>Image coregistration CT-PET with external fiducial markers</td>
<td>50% intensity level of max. FDG uptake</td>
<td>GTV: 5/23 P (22%)</td>
<td>PTV: 30/78% of cases (varied between the 3 physicians)</td>
<td>PTV: 24/70% of cases (varied between the 3 physicians)</td>
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### PET/CT – Imaging in Radiooncology

**FDG-PET/CT in lung cancer**

<table>
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<tr>
<th>Study</th>
<th>Study Type</th>
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<th>Description</th>
<th>PTV</th>
<th>GTV</th>
<th>PET/CT Improvement</th>
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<tr>
<td>Erdt et al. [34]</td>
<td>Prospective</td>
<td>11</td>
<td>Image fusion: manual method using transmission PET data compared with automated image registration based on mutual information integrated PET/CT</td>
<td>PTV: 11/11 P (100%)</td>
<td>GTV: 6/6 P (100%)</td>
<td>PET/CT improves GTV and PTV definition</td>
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<td>Ciernik et al. [23]</td>
<td>Prospective</td>
<td>6</td>
<td>Patient immobilization PET/CT fusion</td>
<td>PTV: 14/24 P (58%)</td>
<td>GTV 5/6 (17%)</td>
<td>PET/CT improves GTV delineation</td>
</tr>
<tr>
<td>Bradley et al. [13]</td>
<td>Prospective</td>
<td>26</td>
<td>PET/CT visual fusion technique</td>
<td>GTV and PTV: 12/21 P (57%)</td>
<td>GTV 4/6 (67%)</td>
<td>PET/CT improves GTV delineation</td>
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<tr>
<td>Van Der Weij et al. [89]</td>
<td>Prospective</td>
<td>21</td>
<td>PET/CT visual fusion technique</td>
<td>GTV and PTV: 12/21 P (57%)</td>
<td>PET/CT improves GTV delineation</td>
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<tr>
<td>Brienza et al. [7]</td>
<td>Retrospective</td>
<td>28</td>
<td>PET/CT</td>
<td>GTV/CTV: 11/25 (56%) 6/11</td>
<td>PET/CT</td>
<td>PET/CT improves GTV delineation</td>
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<td>Ashamalla et al. [7]</td>
<td>Prospective</td>
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<td>PET/CT integrated PET/CT</td>
<td>GTV/CTV: 11/25 (56%) 6/11</td>
<td>PET/CT</td>
<td>PET/CT improves GTV delineation</td>
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<tr>
<td>Cieni et al. [14]</td>
<td>Prospective</td>
<td>10</td>
<td>PET/CT halo phenomenon image fusion using fiducial markers</td>
<td>PTV: 43/101 (43%)</td>
<td>GTV: 24/101 (24%)</td>
<td>PET/CT improves GTV delineation</td>
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<tr>
<td>Deniard-Alexandre et al. [89]</td>
<td>Retrospective</td>
<td>28</td>
<td>PET/CT total CT</td>
<td>GTV: 5/19 (26%)</td>
<td>GTV: 4/19 (21%)</td>
<td>PET/CT improves GTV delineation</td>
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<td>Stenström et al. [81]</td>
<td>Prospective</td>
<td>22</td>
<td>PET/CT standardized windowing identification of affected anatomical structures by FDG</td>
<td>Significant reduction of mean GTV</td>
<td>Significant reduction of inter observer variation with PET simulator TCP sign. higher MTCP sign. lower</td>
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<td>De Ruyscher et al. [26]</td>
<td>Prospective</td>
<td>21</td>
<td>PET-CT simulator vs. CT simulator</td>
<td>14/21 (66%)</td>
<td>2/21 (10%)</td>
<td>PET/CT improves GTV delineation</td>
</tr>
</tbody>
</table>

*Note: n.e.: not evaluated.*
Atelectasis in PET/CT

Significant potential benefit by FDG - PET: Reduction radiation volumes

but:

False positive uptake in postobstructive inflammation is possible

Histological correlation of PET - findings with pathology are lacking

Van der Welt et al, Int J Radiat Oncol Biol Phys, 2005
De Ruysscher et al, Radiother Oncol, 2005
PET/CT – Imaging in Radiooncology

Theoretical radiation dose escalation with PET/CT planning (2)
Computed tomography image with the contours made by all 11 radiation oncologists. **blue labeled as disagreement region** (i.e., <9 of 11 radiation oncologists agreed).

All patients had some form of atelectasis.

Color wash represents overlay of matched 2-[18F]fluoro-2-deoxy-D-glucose positron emission tomography.
PET/CT – Imaging in Radiooncology

Further reduction of the interobserver variability with automatic contouring (2)

Table 5. For all anatomic regions, theoretical PTV margin for upper and lower lobe tumor with motion amplitude (peak–peak) of 0.2 cm and 1.2 cm, respectively, and delineation based on CT only (first phase) and matched CT–FDG-PET (second phase)

<table>
<thead>
<tr>
<th>Anatomic region</th>
<th>Upper lobe tumor</th>
<th>Lower lobe tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>First phase</td>
<td>Second phase</td>
</tr>
<tr>
<td>Tumor–lung</td>
<td>1.4</td>
<td>0.8</td>
</tr>
<tr>
<td>Tumor–mediastinum</td>
<td>1.8</td>
<td>1.1</td>
</tr>
<tr>
<td>Tumor–chest wall</td>
<td>1.0</td>
<td>0.9</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>3.6</td>
<td>2.0</td>
</tr>
<tr>
<td>Tumor–atelectasis</td>
<td>4.7</td>
<td>1.2</td>
</tr>
<tr>
<td>All</td>
<td>2.5</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Further reduction of the interobserver variability with automatic contouring (3)

Example of (a) manual and (b) auto-contour-based delineation of a primary tumor (Gross Tumor Volume 1, and lymph node volume, Volume 2) delineated by the five observers. Arrows indicate changes in interobserver variation in delineation between the two methods.
PET/CT – Imaging in Radiooncology
FDG-PET based RT planning in NSCLC


**N = 44, NSCLC I - III**

10/44 mediastinal downstaging by PET

Dose escalation to 64.8 Gy/1.8 Gy b.i.d.

GTV= tumor + FDG-PET positive LN - stations

After median follow-up of 16 months 1 isolated out field recurrence at LN pre-treatment cN0 in CT and PET

<table>
<thead>
<tr>
<th>Patterns of recurrence</th>
<th>No. of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>26 (59)</td>
</tr>
<tr>
<td>In-field</td>
<td>10 (23)</td>
</tr>
<tr>
<td>Exclusively in-field</td>
<td>5</td>
</tr>
<tr>
<td>In-field and distant</td>
<td>5</td>
</tr>
<tr>
<td>Isolated nodal</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Nodal (outside of CTV) along with local or distant failure</td>
<td></td>
</tr>
<tr>
<td>Distant only</td>
<td>7 (16)</td>
</tr>
<tr>
<td>Brain only</td>
<td>1</td>
</tr>
</tbody>
</table>

Abbreviation: CTV = clinical target volume.
PET/CT – Imaging in Radiooncology

Risk of marginal miss after FDG based RT planning with visual aids

26 local recurrences after FDG-based RT planning in advanced NSCLC after doses > 60 Gy
12/18 recurrences located at margin of GTV or PTV


<table>
<thead>
<tr>
<th>Dose</th>
<th>Within GTV/PTV</th>
<th>Within GTV/PTV and outward</th>
<th>Marginal miss (within PTV and outward)</th>
<th>Geographic miss (outside but within 1 cm of PTV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$D_{95} &lt; 60$ Gy</td>
<td>6</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>$D_{95} &lt; 60$ Gy</td>
<td>6</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>$D_{95} \geq 60$ Gy</td>
<td>6</td>
<td>11</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>$D_{95} \geq 60$ Gy</td>
<td>6</td>
<td>11</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>
Interfractional anatomic variation in patients treated with respiration-gated radiotherapy

Ellen Yorke,1 Kenneth E. Rosenzweig,2 Raquel Wagman,2 and Gikas S. Mageras1

Department of Medical Physics1, Department of Radiation Oncology,2 Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York City, New York 10021 U.S.A.
Intrafractional average marker displacement ± SD and interfractional variation of on target verification for all fractions for patient 1 with a lung and patient 3 with a liver tumor.
Illustration of tumor motion during treatment (a) without respiratory gating, and (b) with gating technology.
Juhler-Nottrup et al., Acta Oncol, 2008

Interfractional changes in tumour volume and position during entire radiotherapy courses for lung cancer with respiratory gating and image guidance
N= 10; 60 Gy/ED 2.0 Gy

Lung tumours reduction: 19%
mediastinal tumours/Lnn: 34 %
Mobility vector: 0.51 cm (+/- 0.21) for matching bony landmarks
0.85 cm (+/- 0.54) for matching skin tattoos
0.55 cm (+/- 0.19) for matching bony landmarks
0.72 cm (+/- 0.43) for matching skin tattoos

interfractional overlap (lung tumor): 80%-87% for using bony landmarks
70%-76% for using skin tattoos

overlap (mediastinal tumors): 60%-65% for using bony landmarks
41%-47% for using skin tattoos
PET/CT – Imaging in Radiooncology

Why 4D-imaging?

- Radiation treatment planning for lung is mostly based on CT and PET images.
- Different acquisition times for CT (fast) and PET (slow) improved tumor volume delineation.
- 4D-Imaging improved SUV determination.
- 4D-Imaging improved (automatic tumor) contouring.
- 3D CT is used for attenuation correction of PET (in PET/CT-scanners). This can lead to geographical errors and false positive lesions.

De Ruysscher, Radiology, 2003; 226:906-910
Respiration correlated PET:

Why is 4D CT attenuation correction needed for 4D PET?

- Up to 196% overestimation SUV without respiratory correlation

Influence of margins on volume

Innovation in image-guided radiotherapy
Dirk Verellen, Mark De Ridder, Nadine Linthout, Koen Tournel, Guy Soete & Guy Storme
Nature Reviews Cancer 7, 949-960 (December 2007)
PET/CT – Imaging in Radiooncology
Respiration correlated PET – 4D autodelineation

- Autodelineation across all PET phases
- Ability to adapt contouring threshold per phase
- Ability to detect necrotic or hypoxic areas using 4D PET
- Overall, 4D PET SUV contour will be more realistic due to better SUV estimation
PET/CT – Imaging in Radiooncology
Active breathing control

Do we need any margins? (INT)
**Figure 2.** Example of “4D Gated CT” images in a patient with a peripheral lung tumor demonstrating axial (top left), sagittal (top right), coronal (bottom left) views of tumor location at full expiration (blue outline) and inspiration (yellow outline) as well as at 50% inspiration (red outline). Note that the tumor moves with breathing in all three dimensions in a non-uniform manner.
Image guided respiratory gated hypofractionated Stereotactic Body Radiation Therapy (H-SBRT) for liver and lung tumors: Initial experience

Authors: R. E. Wurm a; F. Gum a; S. Erbel a; L. Schlenger a; D. Scheffler a; D. Agaoglu a; R. Schild a; B. Gebauer b; P. Rogalla c; M. Plotkin b; K. Ocran d; V. Budach a

Hypoxia imaging in lung cancer reported e.g. with $^{18}$F-MISO and $^{60}$Cu-ATSM.

Possible prognostic value (high hypoxia = bad prognosis).

Value for treatment planning unclear.
PET/CT – Imaging in Radiooncology

Imaging of proliferation (FLT)

- FLT-uptake correlates with proliferation
- Evaluation as diagnostic tracer for lung cancer
- FLT-uptake lower compared to FDG-uptake
- Unspecific uptake possible
- Diagnostic use unclear, no clear advantage over FDG
- No studies on integration in RT planning
PET/CT – Imaging in Radiooncology

Imaging of proliferation (FLT)

NSCLC, niedrige Proliferationsrate

proliferation 25%

proliferation 56%

NSCLC, hohe Proliferationsrate

FLT-SUV 2,1

 FLT-SUV 4,8

Buck et al., Cancer Res 2002
PET imaging with 89 Zr-Cetuximab for identification of radioresistant areas within the tumor

(Epidermal growth factor receptor status in Imaging and for treatment)

$^{64}$Cu-DOTA-Cetuximab, a PET-Imaging Agent for Epidermal Growth-Factor Receptor-Positive Tumors Receptor-Binding,

Biodistribution, and Metabolism Studies of $^{64}$Cu-DOTA-Cetuximab, a PET-Imaging Agent for Epidermal Growth-Factor Receptor-Positive Tumors

In addition to FDG other PET radiopharmaceuticals are available that image specific biological tumour characteristics involved in radiation resistance, such as hypoxia, proliferative activity and tyrosine kinase receptor expression.
PET/CT – Imaging in Radiooncology

Head and neck (2)

- $^{18}$F-FAZA
- $^{18}$F-Miso
- $^{18}$F-FDG
- $^{18}$F-Annexin ?
- $^{11}$C-Methionin no

Heron et al., IJROBP, 2004
Koshy, Head and Neck, 2005
Schwartz et al., IJROBP, 2005
Paulino, IJROBP, 2005
Wang, IJROBP, 2006
Geets, 2006
Deantonio, Radiation Oncology, 2008
Rischkin, JCO 2008
PET/CT and treatment with IMRT (n = 45) improved cure rates compared to patients without PET/CT and IMRT.

Overall survival with PET/CT and IMRT  
97% and 91% at 1 and 2 years  
vs. 74% and 54% (p=0.002)

The event-free survival rate of the patients on the PET/CT group was  
90% and 80% at 1 and 2 years  
compared to 72% and 56% in the control group (p=0.005)

\(^{18}\text{F-FDG-PET/CT Staging followed by Intensity-modulated Radiotherapy (IMRT) improves treatment outcome of locally advanced pharyngeal Carcinoma: a matched-pair comparison}

Rothschild S et al., Radiation Oncology 2007, 2:22
PET/CT – Imaging in Radiooncology

**11C-Cholin PET/CT in prostate cancer**

- F-18 Fluorodeoxyglukose
- C-11 Acetate
- C-11 Choline
- F-18 Fluormethylcholine
- Ga-68 Bombesin

**Imaging Prostate Cancer with 11C-Choline PET/CT**

Sven N. Reske¹, Norbert M. Blumstein¹, Bernd Neumaier¹, Hans-Werner Gottfried², Frank Finsterbusch¹, Darius Kocot¹, Peter Möller¹, Gerhard Glatting¹, and Sven Perner³

*J Nucl Med 2006; 47:1249–1254*

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>26</td>
</tr>
<tr>
<td>SUV</td>
<td>&gt; 2.6</td>
</tr>
<tr>
<td>Sens</td>
<td>82%</td>
</tr>
<tr>
<td>Spez</td>
<td>86%</td>
</tr>
<tr>
<td>PPV</td>
<td>84%</td>
</tr>
<tr>
<td>NPV</td>
<td>84%</td>
</tr>
<tr>
<td>ACC</td>
<td>84%</td>
</tr>
</tbody>
</table>
PET/CT – Imaging in Radiooncology

$^{11}$C-Cholin PET/CT in prostate cancer (2)

![Graph showing sensitivity vs. 1 - specificity for visual classification and SUV$_{\text{max}}$.](image)
**Figure 2**

- **SUV\textsubscript{max}**
  - Controls
  - PET/CT\textsubscript{neg}
  - PET/CT\textsubscript{pos}
  - LR\textsubscript{pos}

**Figure 4**

- **PSA**
  - PET/CT\textsubscript{neg}
  - PET/CT\textsubscript{pos}
PET/CT – Imaging in Radiooncology

Local relapse and detection rate by PSA-level

Reske SN, Blumstein NM et al.

[(11)C]choline PET/CT imaging in occult local relapse of prostate cancer after radical prostatectomy.
PET/CT – Imaging in Radiooncology

Local recurrence after RPX
Abb. 1: Zustand nach Brachytherapie der Prostata mit J-125 Seeds eines low risk-Patienten

Abb. 2: Zustand nach Brachytherapie der Prostata mit J-125 Seeds (Lokalrezidiv)

D 90: 159.2 Gy
PET/CT – Imaging in Radiooncology

$^{11}$C-Choline in prostate cancer (5)
PET/CT – Imaging in Radiooncology

\(^{11}\text{C}-\text{Choline in prostate cancer (6)}\)


[\(^{11}\text{C}\)Choline PET/CT for targeted salvage lymph node dissection in patients with biochemical recurrence after primary curative therapy for prostate cancer. Preliminary results of a prospective study.
Urol Int. 2008;81(2):191-7

De Neve, Estro 2008 (Ghent)

Dose-volume characteristics and acute toxicity of hypofractionated intensity-modulated arc therapy (IMAT) and androgen deprivation (AD) as primary therapy for lymph node metastasized prostate cancer
PET/CT – Imaging in Radiooncology

Impact of PET/CT to radiotherapy planning
considerations
<table>
<thead>
<tr>
<th>Authors</th>
<th>Median Follow-Up (Months)</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive Predictive Value</th>
<th>Negative Predictive Value</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>de Wit et al (33)</td>
<td>26</td>
<td>100% (10/10)</td>
<td>78% (18/23)</td>
<td>67% (10/15)</td>
<td>100% (18/18)</td>
<td>85% (28/33)</td>
</tr>
<tr>
<td>Dittmann et al (34)</td>
<td>6</td>
<td>87% (7/8)</td>
<td>94% (17/18)</td>
<td>87% (7/8)</td>
<td>94% (17/18)</td>
<td>92% (24/26)</td>
</tr>
<tr>
<td>Spaepen et al (35)</td>
<td>32</td>
<td>50% (5/10)</td>
<td>100% (50/50)</td>
<td>100% (5/5)</td>
<td>91% (50/55)</td>
<td>92% (55/60)</td>
</tr>
<tr>
<td>Weihrauch et al (36)</td>
<td>28</td>
<td>67% (6/9)</td>
<td>80% (16/20)</td>
<td>60% (6/10)</td>
<td>84% (16/19)</td>
<td>76% (22/29)</td>
</tr>
<tr>
<td>Guay et al (37)</td>
<td>16</td>
<td>79% (11/14)</td>
<td>97% (33/34)</td>
<td>92% (11/12)</td>
<td>92% (33/36)</td>
<td>92% (44/48)</td>
</tr>
<tr>
<td>Friedberg et al (38)</td>
<td>24</td>
<td>80% (4/5)</td>
<td>85% (23/27)</td>
<td>50% (4/8)</td>
<td>96% (23/24%)</td>
<td>84% (87/32)</td>
</tr>
<tr>
<td>Panizo et al (39)</td>
<td>28</td>
<td>100% (9/9)</td>
<td>85% (17/20)</td>
<td>75% (9/12)</td>
<td>100% (17/17)</td>
<td>90% (26/29)</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>80% (52/65)</td>
<td>91% (174/192)</td>
<td>74% (52/70)</td>
<td>93% (174/187)</td>
<td>88% (226/257)</td>
</tr>
</tbody>
</table>


Occult nodal
Residual mass

Follow up after 4 weeks:
Rapid progress

FDG PET/CT of a residual occult viable NHL 8 weeks after completion of chemotherapy. Rapid progression at 4 week follow-up.
PET/CT – Imaging in Radiooncology

Breast cancer
PET/CT – Imaging in Radiooncology

Rectal cancer
PET/CT – Imaging in Radiooncology
Pancreatic cancer
PET/CT – Imaging in Radiooncology

Cervical cancer

Adapting optimized therapy

Cozzi, L. et al.

A treatment planning study comparing volumetric arc modulation with RapidArc and fixed field IMRT for cervix uteri radiotherapy

Radiation and Oncology, 2008 (in press)
Response to Therapy

Hypothesis: A measure of metabolism such as FDG PET should be a sensitive way to detect response to therapy.
The technological basis of in-beam PET is a double head positron camera integrated into the therapy unit.

The horizontal carbon ion beam leaves the beam pipe visible through a 20´20 cm² window in the centre of the picture. To provide sufficient space for patient positioning, the PET scanner can be moved on rails parallel to the beam between the measuring position displayed and the parking position upbeam.

Clinical application of in-beam PET at the carbon ion therapy facility at GSI Darmstadt.

As an example, the irradiation of a chondrosarcoma of the skull base with a lateral portal coming from the left side of the patient, i.e. right side in the picture, (maximal dose: 0.63 Gy) is displayed.

As indicated by the dose distribution superimposed onto the computed tomogram (left), the carbon ions must not penetrate the brain stem as an organ at risk. The comparison of the predicted (middle) with the measured (right) b+-activity distributions shows that this was fulfilled during the treatment. The isodose and isoactivity lines are decoded in rainbow colours and denote 5, 15 … 95 % of the maxima.
Monte Carlo calculated (left) and measured (right) activity distribution after proton irradiation of a clivus chordoma patient at Massachusetts General Hospital, Boston. Images by courtesy of K. Parodi and T. Bortfeld.

PET/CT – Imaging in Radiooncology

Last image (nearly)

- PET tracer (s)
- PET images and reconstruction
- PET/CT vs. gated PET/CT
- PET and real tumor extension?
- PET imaging: when?
- Image fusion? Which images?
PET/CT – Imaging in Radiooncology

Many options – known limitations – solutions are possible

Target is moving