Integrating Functional Imaging in Radiotherapy:

Head & Neck Squamous Cell Carcinoma

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NICSTAR 2018, 6th Mar 2018, Mumbai
Structural vs Functional Imaging

• **Structural imaging:**
  - defines anatomic extent accurately and reliably
  - relies on various structural characteristics of tumor/normal tissues
  - size, shape, density/intensity, enhancement, effacement
  - measures response generally by change in size

• **Functional imaging**
  - defines functional aspects of tumor/normal tissues
  - relies on in-vivo biological processes and phenomena
  - perfusion, hypoxia, metabolism, proliferation, angiogenesis
  - measures response by change in functional characteristics
Functional Imaging Modalities

- **Magnetic Resonance Imaging**
  - Magnetic Resonance Spectroscopy
  - Diffusion-weighted and Perfusion-weighted MRI
  - BOLD-MRI

- **Radionuclide Imaging**
  - Single Photon Emission Computed Tomography (SPECT)
  - Positron Emission Tomography (PET)

- **Optical imaging**
  - Raman Spectroscopy
  - Bio-luminescence Imaging
Evolution of clinical practice parallels developments in imaging
Technology has fuelled development in Radiation Oncology
Developments in imaging have consistently led to paradigm shifts in target volume delineation.
Potential Applications of Functional/Molecular Imaging: 

**PET/CT in Head & Neck Radiotherapy**

- Work-up-staging
- Prognostic evaluation
- GTV/CTV Selection/delineation
- Functional Image-guided IMRT
- Early response evaluation
- Final response evaluation
- Early detection of recurrence
Accuracy of FDG-PET/CT for staging

- T-stage
- N-stage
- M-stage
- Carcinoma of unknown primary (CUP)
- Clinical impact on therapeutic decision-making
- Restaging at suspected recurrence
Diagnostic accuracy of FDG-PET/CT at initial presentation

<table>
<thead>
<tr>
<th>Site</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>78–94</td>
<td>93–100</td>
</tr>
<tr>
<td><strong>H&amp;N</strong></td>
<td>93–100</td>
<td>90–100</td>
</tr>
<tr>
<td>Nodes</td>
<td>76–85</td>
<td>33–67</td>
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<tr>
<td>NSCLC</td>
<td>90</td>
<td>79–96</td>
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<tr>
<td>Nodes</td>
<td>83</td>
<td>89</td>
</tr>
<tr>
<td>Oesophagus</td>
<td>94</td>
<td>92</td>
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<tr>
<td>Nodes</td>
<td>24–82</td>
<td>81–99</td>
</tr>
<tr>
<td>Cervical</td>
<td>75</td>
<td>96</td>
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<tr>
<td>Nodes</td>
<td>38–91</td>
<td>83–100</td>
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<tr>
<td>Endometrial</td>
<td>89–97</td>
<td>50</td>
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<tr>
<td>Nodes</td>
<td>53–100</td>
<td>99</td>
</tr>
</tbody>
</table>

* a Amino acid PET.
* b N0 neck.
* c Lung nodules.
# Performance of FDG-PET/CT in CUP with neck nodes

## Table 8: Diagnostic performance of FDG-PET/CT in primary tumor detection

<table>
<thead>
<tr>
<th>Study and year</th>
<th>Primary tumor detection rate (%)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Value 95% CI</td>
<td>Value 95% CI</td>
</tr>
<tr>
<td>Fencl et al. [12], 2007</td>
<td>22</td>
<td>55 38–70</td>
<td>75 62–85</td>
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<tr>
<td>Nassenstein et al. [13], 2007</td>
<td>28</td>
<td>100 74–100</td>
<td>85 69–94</td>
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<tr>
<td>Fleming et al. [14], 2007</td>
<td>73</td>
<td>94 73–99</td>
<td>100 61–100</td>
</tr>
<tr>
<td>Bruna et al. [15], 2007</td>
<td>38</td>
<td>93 70–99</td>
<td>77 57–90</td>
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<tr>
<td>Wartski et al. [16], 2007</td>
<td>34</td>
<td>93 69–99</td>
<td>73 48–89</td>
</tr>
<tr>
<td>Ambrosini et al. [18], 2006</td>
<td>53</td>
<td>100 84–100</td>
<td>95 76–99</td>
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<tr>
<td>Fakhry et al. [20] 2006</td>
<td>32</td>
<td>70 40–89</td>
<td>75 47–91</td>
</tr>
<tr>
<td>Pelosi et al. [22], 2006</td>
<td>35</td>
<td>83 66–93</td>
<td>87 73–94</td>
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<tr>
<td>Nanni et al. [26], 2005</td>
<td>57</td>
<td>100 76–100</td>
<td>89 57–98</td>
</tr>
<tr>
<td>Freidenberg et al. [27], 2005</td>
<td>57</td>
<td>86 60–96</td>
<td>100 65–100</td>
</tr>
<tr>
<td>Gutzeit et al. [29], 2005</td>
<td>33</td>
<td>88 66–97</td>
<td>89 73–96</td>
</tr>
<tr>
<td>Pooled estimate</td>
<td>37</td>
<td>84 78–88</td>
<td>84 78–89</td>
</tr>
</tbody>
</table>

## Fig. 1: Locations of primary tumours detected by FDG-PET/CT

## Fig. 2: Locations of false-positive FDG-PET/CT findings

## Fig. 3: Locations of false-negative FDG-PET/CT findings

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Kwee et al, Eur Radiol 2009
FDG-PET in CUP with metastatic neck nodes:

TMC experience in a cohort of 112 patients

- Three subgroups: Gr I (only conventional imaging); Gr II (FDG-PET); Gr III (Both)
- Sensitivity & specificity of conventional imaging was 92% and 50% respectively
- Sensitivity & specificity of FDG-PET was 93% and 72% respectively
- FDG-PET detected additional sites of metastasis in 52% of patients
- Distant metastases was highly correlated with multiplicity of neck nodes
- In low neck nodes, FDG detected 12 primaries, 9 of which were infra-clavicular
- FDG-PET influenced overall change of management in 38% patients

FDG-PET is a valuable tool influencing management in CUP with neck nodes

Kannan et al, IJC 2011
Consistently proven medium/high clinical impact in nearly 1/3rd of patients
Significantly better accuracy than conventional work-up

Cacicedo et al, BJR 2016
Performance of FDG-PET in suspected recurrent head-neck cancer: Systematic review and meta-analysis in over 650 patients

Conclusions: $^{18}$F-FDG PET was useful in patients with suspected recurrence of head and neck cancer, showing a high sensitivity and intermediate-high specificity.

Pingarron et al, Acta Otorhinolaryngol 2008
TMC experience of FDG-PET at suspected recurrence

- 49 patients with suspected recurrence of head-neck cancer included
- Clinical examination at recurrence by oncologist blinded to FDG-PET findings
- Initial management plan based without any knowledge of FDG-PET
- Subsequent FDG-PET findings made available to the clinicians
- Any change in decision-making documented as “change in management”
- Overall 38% “change in management” based on FDG-PET information
- 16% patients had major change in therapeutic decision-making
- 22% patients avoided additional diagnostic procedures (endoscopy, biopsy, EUA)

FDG-PET has significant impact in suspected head-neck recurrence

*Pantavidya et al, J Surg Oncol 2009*
Integrated PET/CT scanners

Useful adaptations for Radiation Oncology
## Technological advances in PET/CT

### Utility in Radiotherapy Planning

<table>
<thead>
<tr>
<th>Technical and methodological advance</th>
<th>Objective</th>
<th>Consequence</th>
<th>Importance for PET/CT-guided RTP</th>
</tr>
</thead>
</table>
| New crystal materials                | LSO and LYSO replace BGO and GSO  
↑ light output  
↑ response/dead time | ↓ scan time  
↑ patient comfort | ↓ involuntary motion artifacts  
↑ diagnostic confidence |
| Fast detector electronics            | Timing resolution < 600 ps; measure coincidence time differences (time-of-flight [95]) | ↑ signal-to-noise ratio in PET images (more prominent for large patients) | ↑ diagnostic confidence |
| Smaller detector size                | From 6 × 6 mm² to 4 × 4 mm² face area; improved spatial resolution | ↓ partial volume effects  
↑ quantification | ↑ therapy response assessment  
↑ diagnostic confidence |
| Retrospective correction for point spread function (PSF) | Account for variable image resolution inside active field-of-view | Gain uniform image resolution (<detector element size)  
↑ image quality  
↑ volume sensitivity  
↓ scan time | ↑ therapy response assessment  
↑ diagnostic confidence  
↑ involuntary motion artifacts |
| Extended axial field-of-view         | Added additional layer of PET detectors in z-direction | | |
| Large bore diameter                  | Extending from 68 to 85 cm with corresponding increase in transverse FOV | Position patients in treatment-planning position; no truncation artifacts  
↓ motion artifacts  
↑ co-registration accuracy and attenuation correction | ↑ co-registration of planning PET/CT and treatment delivery  
↑ therapy planning |
| Gating                               | Respiratory and cardiac gating for CT and PET (synced) available | | |

*Sattler et al, Radiother Oncol 2010*
Typical methodology for GTV delineation on PET images

*Delineation method:*

- Visual assessment
- Fixed threshold (SUV2.5 or 3)
- Relative threshold (%SUVmax)
- Adapting threshold to the signal-to-background ratio (SBR)
- Iterative threshold or adaptive SBR
- Other models/paradigms:
  - Gradient crest (active contours, watersheds, etc.)
  - Clustering (with or without probabilistic/fuzzy models)
Threshold-based segmentation

Which threshold?

Upper landmark (none or some maximum estimate?)

Threshold

Lower landmark (zero or some baseline?)

Lee et al, MIRO 2010
Analysis of thresholding

Threshold (without wall)

Threshold (with wall, thickness = FWHM/5)

Average tumor size

40% on average

Lee et al, MIRO 2010
Gradient-based segmentation

- Image processing
  - Raw Image
  - Denoised Image
  - Deblurred Image

- Gradient-based segmentation
  - Gradient magnitude
  - Watersheds
  - Clusters
  - Contours

Geets et al, EJNM 2007
Lee et al, MIRO 2010
Comparison of various PET segmentation methods

SUV50%max threshold & SBR methods gave best results

Schinagl et al, IJROBP 2007
Variability in delineation of gross tumor volume (GTV) in head neck cancers using CT (yellow), MRI (blue), and FDG-PET (green)

Table 2: Comparison Between CT, MRI, and FDG-PET for the Delineation of the Primary Tumor Gross Tumor Volume (GTV) in Pharyngolaryngeal Squamous Cell Carcinoma

<table>
<thead>
<tr>
<th>Author</th>
<th>n</th>
<th>Site</th>
<th>T-stage</th>
<th>GTV&lt;sub&gt;CT&lt;/sub&gt; (mL)</th>
<th>GTV&lt;sub&gt;MRI&lt;/sub&gt; (mL)</th>
<th>GTV&lt;sub&gt;PET&lt;/sub&gt; (mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daisne et al&lt;sup&gt;15&lt;/sup&gt;</td>
<td>10</td>
<td>Oro</td>
<td>T2-T4</td>
<td>32 (5.1-137.7)</td>
<td>27.9 (0-92.8)</td>
<td>20.3 (5.1-88.9)</td>
</tr>
<tr>
<td></td>
<td>19</td>
<td>Lar/Hyp</td>
<td>T2-T4</td>
<td>21.4 (1.9-55.6)</td>
<td>21.4 (1.4-58.4)</td>
<td>13.4 (1.2-34.2)</td>
</tr>
<tr>
<td>Delouya et al&lt;sup&gt;41&lt;/sup&gt;</td>
<td>25</td>
<td>Oro, Lar, NPC</td>
<td>T1-T4</td>
<td>24 (1-53)</td>
<td>n.a.</td>
<td>18 (1-48)</td>
</tr>
<tr>
<td>Chatterjee et al&lt;sup&gt;42&lt;/sup&gt;</td>
<td>20</td>
<td>Oro</td>
<td>T1-T4</td>
<td>36.6 (3.4-184)</td>
<td>n.a.</td>
<td>25.2 (1.6-166)</td>
</tr>
<tr>
<td>Caldas-Magalhaes et al&lt;sup&gt;43&lt;/sup&gt;</td>
<td>10</td>
<td>Lar, Hyp</td>
<td>T3-T4</td>
<td>14.9 ± 5.3&lt;sup&gt;#&lt;/sup&gt;</td>
<td>18.3 ± 10.5</td>
<td>9.8 ± 4.1</td>
</tr>
<tr>
<td>Ligtenberg et al&lt;sup&gt;45&lt;/sup&gt;</td>
<td>25</td>
<td>Lar</td>
<td>T3-T4</td>
<td>17.5 (5.9-88.7)</td>
<td>15.5 (4.9-66.3)</td>
<td>14.5 (6.1-82.7)</td>
</tr>
</tbody>
</table>
Figure 3. Bar diagram showing gross tumour volume of the primary site for every individual patient averaged across the three observers. Note the smaller volumes of primary tumour in most patients on PET (GTV_Pri_PET) compared with CECT (GTV_Pri_CECT). CECT, contrast-enhanced computed tomography; GTV, gross tumour volume; PET, positron emission tomography.

Figure 4. Significant reduction in interobserver variability and improved concordance between observers with the use of PET-CT compared with CECT alone for delineation of gross tumour volume at the primary site. CECT, contrast-enhanced computed tomography; PET-CT, positron emission tomography/computed tomography.

TMC experience of the impact of FDG-PET on GTV delineation and inter-observer variability
Comparison of various PET-segmentation techniques

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Summary of main pros/cons of the various categories of PET image segmentation techniques</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Category</strong></td>
<td><strong>Characteristics</strong></td>
</tr>
<tr>
<td>Thresholding techniques</td>
<td>Most frequently used due to their simple implementation and high efficiency</td>
</tr>
<tr>
<td>Variational approaches</td>
<td>Subpixel accuracy, boundary continuity and relatively efficient. They are mathematically well developed and allow for incorporation of priors such as shape</td>
</tr>
<tr>
<td>Learning methods</td>
<td>Utilize pattern recognition power. Two main types: supervised (classification) and unsupervised (clustering)</td>
</tr>
<tr>
<td>Stochastic models</td>
<td>Exploit statistical differences between tumour uptake and surrounding tissues. Most natural to deal with the noisy nature of PET</td>
</tr>
</tbody>
</table>

Zaidi et al, EJNMMI 2010
PET auto-segmentation methods

- **AAPM Task Group 211: Classification, Advantages and Limitations of the Numerical Lesion Segmentation Approaches for PET.**

- **Aim:** To study the advantages, limitations, and applicability of proposed PET automatic segmentation (AS) methods. The TG report published in 2016 lists 24 PET-AS methods.

- **Conclusion:** The more sophisticated the method, the better. But, there is no clear winner.
Uncertainties and recommended quality control measures for application of PET/CT for RT planning

Table 1. Overview of uncertainties and quality control measures for applications of PET/CT in radiation therapy treatment planning. Similar uncertainties exist for all other molecular imaging modalities, which require specific quality control measures.

<table>
<thead>
<tr>
<th>Category</th>
<th>Procedure</th>
<th>Uncertainties</th>
<th>Quality Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scanning protocol</td>
<td>Patient preparation</td>
<td>• Metabolism levels (FDG) • Blood glucose levels (FDG)</td>
<td>• Limit physical activity • Blood glucose measurement with exclusion criteria; fasting • Fasting protocol</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Bowel size/positioning</td>
<td></td>
</tr>
<tr>
<td>Radiotracer injection</td>
<td></td>
<td>• Residual activity in syringe • Decay correction errors</td>
<td>• Measure/correct for residual activity • Scanner-clock synchronization</td>
</tr>
<tr>
<td></td>
<td>Patient positioning</td>
<td>• Spatial offset between PET and treatment planning CT • Quantitative uncertainties from attenuating objects</td>
<td>• Ensure consistent patient positioning using identical positioning devices • Avoid placing objects outside the image FOV</td>
</tr>
<tr>
<td>Acquisition</td>
<td>Scanning</td>
<td>• Patient motion • Attenuation correction uncertainties from iodine contrast • Equipment failure or electronic drift • Longer uptake period increases SUV</td>
<td>• Implement motion management strategies • Acquire separate low-dose CT or apply corrections • Frequent detector and equipment calibrations • Strict protocol for uptake period</td>
</tr>
<tr>
<td>Reconstructio</td>
<td>Reconstruction</td>
<td>• Selection of optimal image reconstruction method/parameters • Randoms, scatter, attenuation, detector sensitivity, and partial volume effect</td>
<td>• Benchmark algorithms using phantoms (task-specific) • Apply appropriate calibrations and corrections</td>
</tr>
<tr>
<td>Segmentation</td>
<td></td>
<td>• Differentiation of normal tissue and tumor uptake • Segmentation uncertainties</td>
<td>• Knowledge of radiotracer’s normal biodistribution • Develop segmentation protocol; benchmark algorithms with phantoms • Include margins</td>
</tr>
<tr>
<td>Analysis</td>
<td>Quantification</td>
<td>• Quantitative accuracy • Selecting relevant quantitative measures</td>
<td>• Calibrate PET scanner to dose calibrator • Compare semi-quantitative metrics with kinetic analysis-derived parameters; consult literature • Quantitative harmonization of scanners</td>
</tr>
<tr>
<td>Treatment planning</td>
<td>Target definition</td>
<td>• Quantitative differences between scanners/institutions</td>
<td>• Benchmark algorithms using physical or digital phantoms; crop images • Use the same motion management method as was used during imaging</td>
</tr>
</tbody>
</table>

Jeraj et al, JNM 2015
What about post-RT response assessment & restaging?

<table>
<thead>
<tr>
<th>Study</th>
<th>Number</th>
<th>CT sensitivity (%)</th>
<th>CT specificity (%)</th>
<th>MRI sensitivity (%)</th>
<th>MRI specificity (%)</th>
<th>CT/MRI sensitivity (%)</th>
<th>CT/MRI specificity (%)</th>
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<tbody>
<tr>
<td>Bongers et al. 20</td>
<td>33</td>
<td>50</td>
<td>33</td>
<td></td>
<td></td>
<td>71</td>
<td>33</td>
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<td>Farber et al. 23</td>
<td>28</td>
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<td></td>
<td></td>
<td></td>
<td>55.6</td>
<td>50</td>
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<td>Gandhi et al. 26</td>
<td>19</td>
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<td></td>
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<td>33</td>
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<tr>
<td>Greven et al. 24</td>
<td>23</td>
<td>58</td>
<td>100</td>
<td></td>
<td></td>
<td>75</td>
<td>29.6</td>
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<tr>
<td>Hanasono et al. 12</td>
<td>CT-4,</td>
<td>50</td>
<td>100</td>
<td>72</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>MRI-13</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hermans et al. 60</td>
<td>66</td>
<td>83</td>
<td>95</td>
<td></td>
<td></td>
<td>75</td>
<td>29.6</td>
</tr>
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<td>Kitagawa et al. 17</td>
<td>21</td>
<td>75</td>
<td>59</td>
<td>100</td>
<td>41</td>
<td></td>
<td></td>
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<tr>
<td>Kubota et al. 15</td>
<td>43</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>53</td>
<td>79</td>
</tr>
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<td>Lell et al. 59</td>
<td>39</td>
<td>86</td>
<td>80</td>
<td></td>
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<tr>
<td>Li et al. 22</td>
<td>38</td>
<td></td>
<td></td>
<td></td>
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<td>79</td>
</tr>
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<td>Lowe et al. 8</td>
<td>30</td>
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<td></td>
<td></td>
<td></td>
<td>38</td>
<td>85</td>
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<tr>
<td>Rege et al. 21</td>
<td>17</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>70</td>
<td>42.9</td>
</tr>
</tbody>
</table>

Diagnostic performance of CT/MRI for response assessment: Suboptimal

*Isles et al: Clin Otolaryngol, 2008*
# Neck recurrence rates after definitive RT/CRT

<table>
<thead>
<tr>
<th>Study centre</th>
<th>Tumour sites</th>
<th>Treatment</th>
<th>Number of patients with complete response after therapy</th>
<th>Isolated neck recurrence with observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Armstrong et al (2006)</td>
<td>USA</td>
<td>Larynx, hypopharynx, oropharynx</td>
<td>CRT</td>
<td>17</td>
</tr>
<tr>
<td>Peters et al (1996)</td>
<td>USA</td>
<td>Oropharynx</td>
<td>RT</td>
<td>62</td>
</tr>
<tr>
<td>Johnson et al (1998)</td>
<td>USA</td>
<td>Head and neck</td>
<td>RT</td>
<td>58</td>
</tr>
<tr>
<td>Garden et al (1999)</td>
<td>USA</td>
<td>Head and neck</td>
<td>CRT</td>
<td>27</td>
</tr>
<tr>
<td>Robbins et al (1999)</td>
<td>USA</td>
<td>Head and neck</td>
<td>CRT</td>
<td>17</td>
</tr>
<tr>
<td>Ahmed et al (2000)</td>
<td>USA</td>
<td>Head and neck</td>
<td>CRT</td>
<td>4</td>
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<tr>
<td>Corry et al (2000)</td>
<td>Australia</td>
<td>Head and neck</td>
<td>CRT</td>
<td>21</td>
</tr>
<tr>
<td>Chan et al (2001)</td>
<td>USA</td>
<td>Supraglottis</td>
<td>RT or ART</td>
<td>74</td>
</tr>
<tr>
<td>Clayman et al (2001)</td>
<td>USA</td>
<td>Oropharynx</td>
<td>CRT</td>
<td>29</td>
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<tr>
<td>Grabenbauer et al (2003)</td>
<td>Germany</td>
<td>Head and neck</td>
<td>CRT</td>
<td>41</td>
</tr>
<tr>
<td>Pletcher et al (2003)</td>
<td>USA</td>
<td>Base of tongue</td>
<td>RT</td>
<td>25</td>
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<tr>
<td>Argiris et al (2004)</td>
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<td>Head and neck</td>
<td>CRT</td>
<td>30</td>
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<td>Vongtama et al (2004)</td>
<td>USA</td>
<td>Head and neck</td>
<td>CRT</td>
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<td>Yao et al (2005)</td>
<td>USA</td>
<td>Head and neck</td>
<td>CRT</td>
<td>42</td>
</tr>
<tr>
<td>Forest et al (2006)</td>
<td>Canada</td>
<td>Head and neck</td>
<td>CRT</td>
<td>123</td>
</tr>
<tr>
<td>Goguen et al (2006)</td>
<td>USA</td>
<td>Head and neck</td>
<td>CRT</td>
<td>13</td>
</tr>
<tr>
<td>Liao et al (2006)</td>
<td>USA</td>
<td>Head and neck</td>
<td>CRT</td>
<td>161</td>
</tr>
<tr>
<td>Thariat et al (2006)</td>
<td>USA</td>
<td>Head and neck</td>
<td>CRT</td>
<td>NR</td>
</tr>
<tr>
<td>Corry et al (2008)</td>
<td>Australia</td>
<td>Head and neck</td>
<td>CRT</td>
<td>60</td>
</tr>
<tr>
<td>Nayak et al (2007)</td>
<td>USA</td>
<td>Head and neck</td>
<td>CRT</td>
<td>33</td>
</tr>
<tr>
<td>Lau et al (2008)</td>
<td>Canada</td>
<td>Head and neck</td>
<td>CRT</td>
<td>54</td>
</tr>
<tr>
<td>Lopez et al (2008)</td>
<td>Spain</td>
<td>Head and neck</td>
<td>CRT</td>
<td>28</td>
</tr>
<tr>
<td>Rengan et al (2008)</td>
<td>USA</td>
<td>Head and neck</td>
<td>CRT</td>
<td>65</td>
</tr>
<tr>
<td>Vedrine et al (2008)</td>
<td>France</td>
<td>Head and neck</td>
<td>CRT</td>
<td>63</td>
</tr>
</tbody>
</table>

RT—radiotherapy. ART—accelerated radiotherapy. CRT—chemoradiotherapy. NR—not reported.

Table 1: Studies of neck recurrence in patients under observation after radiotherapy
# Post-treatment assessment with FDG-PET

## Soft criterion

<table>
<thead>
<tr>
<th>Resi/Recc Disease</th>
<th>Vs</th>
<th>Post-Rx changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intense</td>
<td></td>
<td>Mild-moderate intensity</td>
</tr>
<tr>
<td>Focal</td>
<td></td>
<td>Diffuse</td>
</tr>
<tr>
<td>Asymmetric</td>
<td></td>
<td>Symmetrical</td>
</tr>
<tr>
<td>SUV &gt; 3</td>
<td></td>
<td>SUV &lt; 3</td>
</tr>
</tbody>
</table>

*Above criteria indicate probability and not certainty*
TMC experience of diagnostic accuracy of response FDG-PET/CT

- **Sensitivity**
  - Primary: 50%
  - Neck: 62.50%
  - Overall: 53.80%

- **Specificity**
  - Primary: 91.80%
  - Neck: 98%
  - Overall: 88.60%

- **PPV**
  - Primary: 50%
  - Neck: 83.30%
  - Overall: 58.30%

- **NPV**
  - Primary: 91.80%
  - Neck: 94.10%
  - Overall: 86.70%

- **Accuracy**
  - Primary: 86%
  - Neck: 93%
  - Overall: 80.70%
PET imaging in head and neck

Diagnostic performance of response assessment FDG-PET/CT in patients with head and neck squamous cell carcinoma treated with high-precision definitive (chemo)radiation

Tejpal Gupta a,*, Sandeep Jain a, Jai Prakash Agarwal a, Venkatesh Rangarajan b, Nilendu Purandare b, Sarbani Ghosh-Laskar a, Ketayun A Dinshaw a

- Potential to detect residue/recurrence when conventionally undetectable
- Low to moderate sensitivity, but high specificity: better than CT/MRI
- Suboptimal PPV for primary site: Should be correlated with biopsy
- Moderately high PPV for neck nodes: Mandates salvage neck dissection
- Exceptionally high NPV for primary site & neck: Guides decision-making
- FDG negativity - potentially a significant prognostic & predictive factor
How did we compare to previously published data?

A systematic review and meta-analysis of the role of positron emission tomography in the follow-up of head and neck squamous cell carcinoma following radiotherapy or chemoradiotherapy

Analysis included 658 patients from 27 studies

Isles et al, Clinical Otolaryngology, 2008
Diagnostic performance of post-treatment FDG PET or FDG PET/CT imaging in head and neck cancer: a systematic review and meta-analysis

Tejpal Gupta • Zubin Master • Sadhana Kannan • Jai Prakash Agarwal • Sarbani Ghosh-Laskar • Venkatesh Rangarajan • Vedang Murthy • Ashwini Budrukkar

Conclusion The overall diagnostic performance of post-treatment FDG PET(CT) for response assessment and surveillance imaging of HNSCC is good, but its PPV is somewhat suboptimal. Its NPV remains exceptionally high and a negative post-treatment scan is highly suggestive of absence of viable disease that can guide therapeutic decision-making. Timing of post-treatment imaging has a significant, though moderate impact on diagnostic accuracy.
Accuracy of FDG-PET(CT) for the primary site
(24 studies including 1122 patients)

Weighted mean (95%CI) pooled estimate

SENSITIVITY = 0.80 (0.74 – 0.85)

Specificity (95% CI)

SPECIFICITY = 0.87 (0.85 – 0.90)
Accuracy of FDG-PET(CT) for the neck nodes
(30 studies including 1525 patients)

Weighted mean (95% CI) pooled estimate

SENSITIVITY = 0.73 (0.67 – 0.78)

Weighted mean (95% CI) pooled estimate

SPECIFICITY = 0.88 (0.86 – 0.89)
PET-CT Surveillance versus Neck Dissection in Advanced Head and Neck Cancer

Hisham Mehanna, Ph.D., Wai-Lup Wong, F.R.C.R.,
Christopher C. McConkey, Ph.D., Joy K. Rahman, M.Sc.,
Max Robinson, Ph.D., Andrew G.J. Hartley, F.R.C.R., Christopher Nutting, Ph.D.,
Ned Powell, Ph.D., Hoda Al-Booz, F.R.C.R., Martin Robinson, F.R.C.R.,
Elizabeth Junor, F.R.C.R., Mohammed Rizwanullah, F.R.C.R.,
Sandra V. von Zeidler, Ph.D., Hulya Wieschmann, F.R.C.R., Claire Hulme, Ph.D.,
Alison F. Smith, M.Sc., Peter Hall, Ph.D., Janet Dunn, Ph.D.,
for the PET-NECK Trial Management Group*
Overall 54 neck dissections done in surveillance arm.

69% CR rates on PET/CT.

Overall 221 neck dissections done in PND arm.
Overall Survival: Primary Endpoint

A PET-CT Surveillance vs. Planned Neck Dissection, All Patients

- **PET-CT surveillance, 60 deaths**
- **Planned surgery, 62 deaths**

**Hazard ratio for death, 0.92 (0.65–1.32)**

- **P=0.004 for noninferiority**
- **P=0.66 for superiority**

**No. at Risk**

<table>
<thead>
<tr>
<th></th>
<th>Planned surgery</th>
<th>PET-CT surveillance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Months since Randomization</td>
<td>0</td>
<td>282</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>243</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>204</td>
</tr>
<tr>
<td></td>
<td>36</td>
<td>118</td>
</tr>
<tr>
<td></td>
<td>48</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>8</td>
</tr>
</tbody>
</table>
What is the most optimal time to do post-Rx FDG-PET/CT

• Need to strike a delicate balance between

  Increased false positivity (early PET) versus

  Unnecessary delay in decision-making (late PET)

• Optimal timing not defined; varies according to treatment modality

  Chemotherapy (for example after ICT): At least 2 wks after last cycle

  Chemo-radiotherapy: At least 8 wks, preferably 12 wks after end of CRT

  Surgical resection: At least 4-6 weeks from surgery
Quo Vadis?

- Beyond initial & post-treatment staging: Prognostic Biomarker
- Beyond metabolism: Assessing Tumor Microenvironment
- Beyond target volume delineation: Dose Painting
- Beyond IMRT/IGRT: Adaptive Radiotherapy (ART)
Standardized uptake value is of prognostic value for outcome in head and neck squamous cell carcinoma

Review: Primary tumor standardized uptake value is of prognostic value for outcome in head and neck squamous cell cancer
Comparison: 01 SUV > Threshold versus SUV < Threshold
Outcome: 01 LC

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>SUV &gt; Threshold n/N</th>
<th>SUV &lt; Threshold n/N</th>
<th>RR (fixed) 95% CI</th>
<th>Weight %</th>
<th>RR (fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brun E 2002</td>
<td>12/21</td>
<td>22/23</td>
<td></td>
<td>13.88</td>
<td>0.60 [0.41, 0.87]</td>
</tr>
<tr>
<td>Allal AS 2004</td>
<td>36/57</td>
<td>55/62</td>
<td></td>
<td>34.82</td>
<td>0.71 [0.57, 0.88]</td>
</tr>
<tr>
<td>Kim SY 2007</td>
<td>16/25</td>
<td>26/27</td>
<td></td>
<td>16.52</td>
<td>0.66 [0.49, 0.90]</td>
</tr>
<tr>
<td>Roh JL 2007</td>
<td>23/31</td>
<td>39/48</td>
<td></td>
<td>20.22</td>
<td>0.91 [0.71, 1.17]</td>
</tr>
<tr>
<td>Torizuka T 2009</td>
<td>16/29</td>
<td>19/21</td>
<td></td>
<td>14.56</td>
<td>0.61 [0.43, 0.87]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>163</td>
<td>181</td>
<td></td>
<td>100.00</td>
<td>0.71 [0.63, 0.81]</td>
</tr>
</tbody>
</table>

Total events: 103 (SUV > Threshold), 161 (SUV < Threshold)
Test for heterogeneity: Chi² = 5.59, df = 4 (P = 0.23), I² = 28.4%
Test for overall effect: Z = 5.24 (P < 0.00001)

Pre-Rx SUV on FDG-PET/CT predicts outcomes

Zhang et al, Acta Otolaryngol 2011
Prognostic impact of pre-treatment MTV and TLG on outcomes

**FIGURE 5.** Forest plots of HR for death with TLG.
TMC experience of pre-Rx quantitative FDG-PET parameters as prognostic biomarkers

Gawande et al (being submitted)
Assessing tumor microenvironment

*Novel PET tracers: New kids on the block*

- Hypoxia: $^{18}$F-EF3
- $^{18}$F-MISO
- $^{60}$Cu-ATSM
- $^{18}$F-FAZA

- Metabolism: $^{18}$F-FDG
- $^{11}$C-Met

- Proliferation: $^{76}$Br-BFU
- $^{18}$F-FLT
Hypoxia in tumors: major cause of radioresistance

"... tumor oxygenation (...) is the most powerful predictor of overall and disease free survival..." (Höckel et al., 1996)

Stypinski 1998 (adapted)  *tissue $pO_2 < 10$ mm Hg
Exploratory prospective trial of hypoxia-specific PET imaging during radiochemotherapy in patients with locally advanced head-and-neck cancer

Daniel Zips b,1, Klaus Zöphel b,1, Nasreddin Abolmaali b, Rosalind Perrin a,*, Andrij Abramyuk b, Robert Haase a, Steffen Appold b, Jörg Steinbach c, Jörg Kotzerke b,2, Michael Baumann b,c,2

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline (0 Gy)</th>
<th>Week 1 (8–10 Gy)</th>
<th>Week 2 (18–20 Gy)</th>
<th>Week 5 (51–57 Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HV_{1.4} (cm³)</td>
<td>31.5 (0.4–155.1)</td>
<td>28.2 (0–143.1)</td>
<td>21.8 (0–115.6)</td>
<td>2.0 (0–48.4)</td>
</tr>
<tr>
<td>HV_{1.6} (cm³)</td>
<td>13.2 (0–101.0)</td>
<td>11.6 (0–99.2)</td>
<td>6.0 (0–69.5)</td>
<td>0.3 (0–10.2)</td>
</tr>
<tr>
<td>HV_{1.8} (cm³)</td>
<td>5.8 (0–70.8)</td>
<td>3.1 (0–63.1)</td>
<td>0.4 (0–38.3)</td>
<td>0 (0–5.69)</td>
</tr>
<tr>
<td>HV_{2.0} (cm³)</td>
<td>2.0 (0–59.8)</td>
<td>1.0 (0–34.1)</td>
<td>0.1 (0–28.2)</td>
<td>0 (0–1.1)</td>
</tr>
<tr>
<td>TBR_{max}</td>
<td>2.2 (1.4–4.0)</td>
<td>2.2 (2.0–3.9)</td>
<td>1.9 (1.7–3.4)</td>
<td>1.7 (1.5–2.2)</td>
</tr>
<tr>
<td>SUV_{max}</td>
<td>2.6 (1.9–4.3)</td>
<td>2.5 (1.7–4.3)</td>
<td>2.2 (1.0–3.8)</td>
<td>1.7 (0.3–2.4)</td>
</tr>
</tbody>
</table>

**Biological imaging before, during, and after Simultaneous Modulated Accelerated Radiation Therapy in Head and Neck Squamous Cell Carcinoma (Bio-SMART)**
Pre-treatment 18F-F-MISO-PET/CT images were acquired in 20 patients with HNSCC at 1-hour, 3-hours and 5-hours sequentially to assess the optimal timing of F-MISO acquisition and spatio-temporal variation, if any.

<table>
<thead>
<tr>
<th>Time of F-MISO imaging</th>
<th>Mean Background SUV</th>
<th>Mean Hypoxic Tumor Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-hour</td>
<td>1.54</td>
<td>1.72</td>
</tr>
<tr>
<td>3-hours</td>
<td>1.30</td>
<td>6.52</td>
</tr>
<tr>
<td>5-hours</td>
<td>1.18</td>
<td>7.24</td>
</tr>
</tbody>
</table>

- Delayed F-MISO (3-5 hours) imaging provides better resolution
- Hypoxic volumes changed significantly over time indicating it to be a complex and dynamic phenomenon with spatio-temporal variability
- Correlation of imaging biomarkers with tissue biomarkers (ongoing)
Area of increased radioresistance

Anatomical Imaging:

+ 

Functional Imaging:

Image registration

FDG-PET:
- Proliferation
- Hypoxia
- Tumor burden

FMISO-PET:
- Hypoxia

Diffusion-weighted MRI:
- Proliferation
- Hypoxia
- Tumor burden

Computed Tomography

Magnetic Resonance Imaging (T1 of T2)

GTV

BTV

Dirix et al, BJMO 2008
Beyond target volume delineation & selection

Dose-painting: Prescription of ‘non-uniform’ dose distribution to a target volume based on functional or molecular imaging validated to indicate the risk of local relapse

Bentzen et al., Radiother Oncol 2005
Gregoire & Bentzen, Semin Radiat Oncol 2011
Why Dose-Painting

Flat dose

Mean Tumor Dose = 2 Gy

Survival is non-flat
(higher in resistant areas)

Non-flat dose

More similar survival
across entire tumor

Gregoire et al, CCO 2011
Challenges in dose-painting

• Optimization engines in most contemporary commercially available TPS are generally tailored to provide dose distributions that can be described by few dose-volume parameters with delineation of volume structures as the only spatial guide

• The challenge of the dose painting approach is that the desired dose distributions are described by the heterogeneous spatial distribution of dose, which cannot easily be described by dose-volume parameters

• Uncertainties & unknowns of the imaging modality being used

• Unknown factors related to translation of the image to a prescription function for dose-painting
Strategies for dose-painting

1. Selective sub-volume boosting or dose-painting by contours

Selection of a ‘target within the target’ defined by image segmentation on the basis of the quantitative information in the image or morphologically, and this is related to image-based target volume selection and delineation.

2. Dose-painting by numbers

Dose painting by numbers is a voxel-level prescription of dose based on a mathematical transformation of the image intensity of individual pixels.
Schematic workflow for dose-painting with TPS

1. PET/CT
2. Prescription Function
3. Voxel-based Rx
4. Dose Discretization
5. Rx Dose Levels
6. PTV Substructures
7. PTV Substructure Rx
8. Clinical Tx Plan
Adaptive dose-painting by numbers

Duprez et al, IJROBP 2012
Ongoing randomized controlled trials in HNSCC using FDG-PET/CT for radiotherapy dose-painting

Table 3 Summary of the ongoing phase-III trials in radiotherapy “dose painting” for Head and Neck squamous cell carcinoma.

<table>
<thead>
<tr>
<th>Acronym/investigator (NCT #)</th>
<th>Tumor location</th>
<th>HPV status</th>
<th>Tumor stage</th>
<th>Molecular imaging</th>
<th>Phase</th>
<th>Study design</th>
<th>Completion date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xuzhou Medical College, China NPC (NCT# 02089204)</td>
<td>Not relevant</td>
<td>III-IVa</td>
<td>FDG-PET</td>
<td>III</td>
<td>Standard arm IMRT + ccddp + docetaxel</td>
<td>Experimental arm (1) IMRT + ccddp + docetaxel + boost dose on FDG (2) IMRT + ccddp + docetaxel + boost dose on FMISO</td>
<td>Q1 2018</td>
</tr>
<tr>
<td>De Neve (NCT# 01341535) Oro, Hyp, Cav, Lar</td>
<td>HPV-</td>
<td>III-IV</td>
<td>FDG-PET</td>
<td>rand. II</td>
<td>69/12/56 Gy in 6.5w + weekly ccddp</td>
<td>84/40 Gy in 6w + weekly ccddp</td>
<td>December 2015?</td>
</tr>
<tr>
<td>Eisbruch (NCT# 02031250) Oro, Hyp, Lar, Cav, NPC</td>
<td>HPV–HPV+ high risk</td>
<td>III-IV</td>
<td>DCE-MRI</td>
<td>rand. II</td>
<td>70 Gy in 7w + ccddp/carbo</td>
<td>80 Gy in 7w+ ccddp/carbo</td>
<td>December 2020</td>
</tr>
<tr>
<td>INTELOPE (NCT# 0275722) Oro, Hyp, Lar</td>
<td>n.a.</td>
<td>III-IV</td>
<td>FDG-PET</td>
<td>rand. II</td>
<td>66/54 Gy in 6w + concomitant ccddp</td>
<td>73.5/63/54 Gy in 6 weeks + ccddp</td>
<td>December 2020</td>
</tr>
<tr>
<td>Zips (NCT# 02352792) Oro, Hyp, Cav, Lar</td>
<td>n.a.</td>
<td>III-IV</td>
<td>FMISO-PET</td>
<td>Rand. II</td>
<td>70 Gy in 7w + 5Fu + mitomycin C or ccddp</td>
<td>77 Gy in 7w + 5Fu + mitomycin C</td>
<td>December 2022</td>
</tr>
<tr>
<td>ESCALOX (NCT # 01212354) Oro, Hyp, Cav</td>
<td>n.a.</td>
<td>III</td>
<td>FMISO-PET</td>
<td>III</td>
<td>70/56 Gy in 7w (SIB-IMRT) + concomitant ccddp</td>
<td>80.5/70/56 Gy in 7w (SIB-IMRT) + January 2025 concomitant ccddp</td>
<td></td>
</tr>
</tbody>
</table>

DCE, dynamic contrast-enhanced; Oro, oropharynx; Hyp, hypopharynx; Cav, oral cavity; Lar, larynx; NPC, nasopharynx; CH, chemotherapy; n.a., non available; rand., randomized.

Gregoire et al, Sem Rad Onc 2018
FIGURE 2 | Complexity of implementing functional imaging into the management of head and neck cancer. Each building block represents a challenge to be overcome in order to validate promising data and perform successful multi-center trials. Data acquisition (blue) needs to be standardized before the influence of biological factors (red) can be interpreted. Data transfer and widely available multi-modality viewing platforms (green) need to be developed with rigorous QA and robust data (orange) before ultimately, multi-center trials can be undertaken.
**Figure 1 | Overview of the imaging biomarker roadmap.** Imaging biomarkers must cross translational gap 1 to become robust medical research tools, and translational gap 2 to be integrated into routine patient care. This goal is achieved through three parallel tracks of technical (assay) validation, biological and clinical validation, and cost effectiveness.
From care to the “average” ...

Multidisciplinary Tumor board
... to personalized care
MISSION

SERVICE

EDUCATION

RESEARCH