Clinical Utility of FDG-PET for Head and Neck CA

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Topics

• Introduction
• PET for staging/workup.
• PET for prognostication.
• PET for RT Treatment Planning.
• PET for followup/re-staging.
• The Future.

PET for Staging/Workup

What is the Most Important Diagnostic, Staging, and Treatment Planning Tool in HNC?
Helping Hand . . .
Diagnostic Tools in Cancer

- RTOG Standard:
  - Clinical Exam
  - CT scan of the site(s) of interest
  - Examination under anesthesia/biopsy
  - CXR.
- MRI as alternative/complement to CT.
- Ultrasound – +/− guided FNA prn.
- PET (PET/CT).

PET Avidity of Various Cancers

- Head and Neck Squamous Cell CA.
- Lung Cancer.
- Gastrointestinal Adenocarcinomas.
- Lymphoma.
- Melanoma.
- Breast Cancer.
- Brain Tumors
- Prostate Cancer

Head and Neck Cancer is extremely FDG-avid

(Detection of Known Primary Head and Neck Cancer)

- Minn, 1988: 19/19
- Bailet, 1992: 16/16
- Jabour, 1993: 12/12
- Rege, 1994: 29/30
- Greven, 1994: 24/27
- Wong, 1995: 14/14
- Laubenbacher, 1995: 22/22

False Negative PET's for HNC are usually due to very small tumors

Staging of Head and Neck CA

<table>
<thead>
<tr>
<th>Stage</th>
<th>N0</th>
<th>N1</th>
<th>N2</th>
<th>N3</th>
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<tbody>
<tr>
<td>Tis/T0</td>
<td>Stage 0</td>
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<tr>
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<td>Stage I</td>
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<td>T2</td>
<td>Stage II</td>
<td>Stage IVA</td>
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<td>Stage IVB</td>
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<tr>
<td>T4</td>
<td></td>
<td>Stage IIIA</td>
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</table>

Distant Metastases (M1) = IVC (not shown)

Prognosis

Treatment Selection is heavily influenced by Stage
T-staging

MRI shows unequivocal T4a (deep/extrinsic tongue invasion) clinically suspected though tongue mobility was intact. In this application, MRI is probably superior to PET and/or CT.

Assessing Extent of Primary Cancer With help from PET

Unknown Primary (UP) – i.e. upstaging from T0/x to T1-2

Review Article by Schoder/Yeung
- 11 studies, 300 patients.
- Sensitivity 10-60%!

High variability may be due to:
- Definition of UP prior to PET.
- Differences in post-PET confirmation of the primary site.

More recent review of a series of pts negative by PE and MRI: 27%.
Lymph Node Staging

- Clinical N0 neck – PET Sensitivity for cN0/pN+ slightly outperforms CT/MRI.
- Nahmias, J OMFS 2007: 80%.
  - Ng, J Nucl Med 2005: 75%.
  - Hafidh, Eur Arch ORL 2006: 73%.
- Clinical N+ neck – Sensitivity rates are higher but not likely to change management.

Nodal Positivity Correlated with both Size and SUV

Murakami, JIRBOP 2007

PET Staging for Distant Metastases

Head and Neck CA data

- PET is standard for NSCLC – 15-20% upstaging from III to IV.
- PET scan detects distant metastases in head and neck CA as well:
  - Fleming, Laryngoscope, 2007: 15%
  - Kim, Ann Oncol 2007: 7%
  - Brouwer, Oral Oncol 2006: 6%

Importance of Accurate Metastatic Staging

- **M0**: Radical (but highly toxic) Rx:
  - Radical Surgery (+ adjuvant therapy).
  - Concurrent chemoradiotherapy +/- ND.
- **M1**: Palliative intent Rx:
  - Upfront chemotherapy – maybe followed by RT if patient does OK.
  - Palliative dose RT +/- “lite” chemo.
  - Supportive care/hospice.
Distant Metastases for HNC  
Jefferson Experience

- 182 pts with PET for newly dx’d HNC.
- PET “positive” for distant mets in 25 pts (13.5%).
  - 10 True Positives (40% PPV).
  - 12 False Positives
  - 3 Uncertain (no biopsy/confirmation)
- All pts with PET-detected distant mets had local-regionally advanced disease.

Fogh, 2008

Pet Staging of DM

- Patient with bulky hypopharyngeal CA
- Pulmonary lesion (not visible on CXR) identified on PET/CT.
- Proven in followup to be metastatic disease.

PET Staging for DM

Pt with Neuroendocrine CA of Paranasal Sinuses. PET showed both extensive regional nodal disease and liver metastases (Bx proven).

False Positive Body PET

Pt with TH2 laryngopharynx CA was presumed to have M1 disease by PET-CT. Mediastinoscopy and multiple biopsies showed sarcoid.
False Positive Body PET

Intense FDG uptake at site of PEC Flap inflammation/necrosis

Causes of ‘False Positives’

- Physiologic Uptake/Hyper-uptake
  - e.g. muscle spasm.
- Infection.
  - e.g. focal/subclinical aspiration pneumonitis.
- Inflammatory condition.
  - e.g. Sarcoidosis.
- Secondary/Tertiary Primary Tumor.
  - e.g. metastatic colorectal CA to liver.

Quantitative PET findings (SUV) as a Biomarker of Outcome

Staging of Head and Neck CA

<table>
<thead>
<tr>
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<th>N0</th>
<th>N1</th>
<th>N2</th>
<th>N3</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Stage 0</td>
<td>Stage I</td>
<td>Stage IVA</td>
<td>Stage IVB</td>
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<tr>
<td>T1</td>
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<td>T3</td>
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<tr>
<td>T4</td>
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</tbody>
</table>

Distant Metastases (N2) = IVB (not shown)
**Molecular Prognostic Biomarkers**

- EGFR
- p53 (mutations)
- Ki-67
- HPV
- p16
- BCL-2
- Cyclin D1
- Survivin
- HIF-1 alpha
- CA (Carbonic Anhydrase) IX
- Osteopontin
- Epo Receptor
- GLUT-1

Etc. – Over 2,000 articles in Medline

**SUV**

- SUV = Tissue activity (mCi/mL) 
  Injected FDG dose (mCi)/body weight (kg)

- Threshold SUV of 2.5-3.5 has been proposed for distinguishing CA from “benign” SPN.
- Average SUV of HNC/NSCLC approx. = 8.
- Average SUV of breast CA approx. = 3-4.
- Average SUV of post-XRT changes ~ 2-3

**Factors (other than Tumor Biology) that can affect SUV**

- **Clinical**
  - Patient body composition (fat/muscle).
  - Serum glucose concentration/Diabetes.
  - Time from injection to imaging.
  - Success of IV placement

- **Technical**
  - Organ/Tumor motion
  - Partial Volume Averaging
  - DeF'n of SUV: SUV\text{mean} vs. SUV\text{max} vs. SUV\text{peak}

**SUV vs. SUV\text{peak}**

SUVpeak: First, the SUV\text{max} must be found. Next a 1 cm circular ROI is drawn centered around the point of SUV\text{max}. Then, the software is queried to determine the mean SUV within that precisely defined ROI.
Pre-treatment PET in NSCLC: Correlation between Local and Central SUV's

Can SUV serve as a “Cheap” Biomarker?

- Intensity of PET-FDG uptake is associated with biological phenotypes:
  - Proliferation (Ki-67).
  - Growth Factors (EGFR).
  - Metabolism (GLUT-1).

- Disadvantages of Tissue Biomarkers
  - Expensive.
  - Paraffin-embedded (loses some data)
  - Samples only one portion of the tumor.

SUV as a Prognostic Biomarker in HNC

<table>
<thead>
<tr>
<th>Series</th>
<th>N</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roh (2007)</td>
<td>76</td>
<td>SUV &gt; 8 → worse DFS (p=0.007)</td>
</tr>
<tr>
<td>Kucharczyk (2007)</td>
<td>43</td>
<td>SUV not predictive</td>
</tr>
<tr>
<td>Solbiati (2004)</td>
<td>56</td>
<td>SUV &gt; 9.0 → worse DFS (p=0.03)</td>
</tr>
<tr>
<td>Allal (2004)</td>
<td>120</td>
<td>SUV &gt; 4.75 → worse DFS (p=0.005)</td>
</tr>
<tr>
<td>Katagawa (2001)</td>
<td>20</td>
<td>SUV &gt; 7.0 → less likely CR</td>
</tr>
<tr>
<td>Halfpenny (2002)</td>
<td>55</td>
<td>SUV &gt; 10.0 → worse survival (p=0.003)</td>
</tr>
<tr>
<td>Bonn (2002)</td>
<td>47</td>
<td>SUV &gt; 9.0 → worse LRC (p=0.002)</td>
</tr>
<tr>
<td>Greven (2001)</td>
<td>45</td>
<td>SUV not predictive</td>
</tr>
<tr>
<td>Mina (1997)</td>
<td>77</td>
<td>SUV &gt; 9.0 → worse DFS</td>
</tr>
</tbody>
</table>

Pre-treatment SUV & Outcome: Jefferson Experience

Machtay et al., Head Neck in press
**PET for RT Treatment Planning**

**PET-based RT Planning: Head and Neck vs. Lung CA**

<table>
<thead>
<tr>
<th>Artifacts – FDG in adjacent Normal Tissue</th>
<th>Lung</th>
<th>HNC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-Mod</td>
<td>Moderate</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>Low-Mod</td>
<td></td>
</tr>
</tbody>
</table>

**Moderate** vs. **High** Artifacts – Organ Motion

**Moderate** vs. **Low** Risk of **marginal miss** (if RT is limited to GTV)

**High** vs. **Low** Risk of + Distant Mets and + regional nodes

**FDG Avidity**

<table>
<thead>
<tr>
<th>Lung</th>
<th>HNC</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>High</td>
</tr>
</tbody>
</table>

**FDG-PET in Lung Cancer Target Delineation**

Detecting CT missed nodes

Differentiating tumor from collapsed lung

**PET Fusion with CT/MRI**

Registered images (H&N):

- MRI
- FDG-PET + MRI

Courtesy of Spring Kong (UMich)
PET improves visualization of Oral Cavity CA (less dental artifact)

PET evaluation of non-palpable nodal regions

Clinically Obvious Disease (GTV70)

Clinically Negative But PET+ GTV66

PET Evaluation Post-op/Pre-RT

Gross residual disease in the retropharyngeal space and this received boost irradiation to 70 Gy (with concurrent chemo).

Planning RT after Induction Chemo

In 2008 there is renewed interest in induction TPF chemo – Often gives dramatic tumor response. GTV/CTV volumes should be based on pre-chemo PET/CT
CT/MRI vs. PET for GTV: A Larynx Cancer Study

Daisne et al., Radiology 2004

P < 0.01

PET for RT planning

- Nishioka (IJROBP 2002): 21 cases
  - 19/21 had no change with PET
- Ciernik (IJROBP 2003): 12 HNC cases
  - GTV by >25% (2 pts); GTV by >25% (2 pts)
- Koshy (Head&Neck 2005): 40 cases
  - GTV\textsubscript{PET} was lower than GTV\textsubscript{CT} in all but 7 pts.
- Wang (IJRBOP 2006): 16 cases
  - GTV\textsubscript{PET} was lower than GTV\textsubscript{CT} in 9 pts

PET for RT planning

- Heron (IJRBOP 2005): 21 cases
  - PET identified GTV in all cases
    - (CT failed to identify GTV at all in 3).
  - In 8 cases, additional area(s) of disease were found by PET.
  - Mean GTV\textsubscript{PET} (43 cc) was significantly lower than Mean GTV\textsubscript{CT} (65 cc) --- p=0.002.
  - The ratio of GTV\textsubscript{PET} vs. GTV\textsubscript{CT} ranged from 0.3 to 23.

Challenges in PET RT Planning

- Obtaining up-to-date PET’s (insurance blockage).
- False Positives and False Negatives.
- Fusion/Deformable Registration.
- ‘Edge’ Effect –
  - Use absolute SUV?
  - Relative SUV (730% of max)?
  - Threshold algorithms?
  - Clinical judgment?
PET Summary, 2008
Head and Neck CA

- Role is still being defined.
  - Exciting areas of clinical research.
- PET is highly sensitive for SCCHN.
  - Useful tool for staging, RT treatment planning, and followup/restaging.
  - A Negative PET in followup is good news!
- PET may allow some pts to avoid additional intervention(s).
- Specificity/False Positives are a concern
  - Confirm a positive PET with biopsy.

Current Clinical use of PET in Head and Neck CA at TJUH

PET scan at 8-12 weeks after radiation

Pre-Tx PET/CT -- Staging & RT Tx Planning

Sequence

Suspected Distant Met?

Definitive XRT

Biopsy

DEFINITIVE XRT

Repeat PET 3 - 4 mo.

Repeat PET 6 - 12 mo.

NED

PET's per year

Acknowledgements and Thanks

- Greg Kubicek, M.D.
- Shannon Fogh, M.D.
- Rani Anne, M.D.
- Ying Xiao, Ph.D.
- Anthony Doemer, M.S.
- Colin Champ, B.S.
- Jorosali Lavarino, B.A.
- Denise Moore

- William Keane, M.D.
- Marc Rosen, M.D.
- Rita Axelrod, M.D.
- Charles Intenzo, M.D.
- Karen Tripoli

Support by Grant from Commonwealth of Pennsylvania (Tobacco Settlement Grant)
FDG-PET for Followup, Restaging and Prognosis

Pre-treatment: Stage IVA tonsil CA

Post-treatment (2 yrs): NED
In-field Local Failure (T4 BOT CA)

Obvious case of Local-regional failure – PET/CT probably not too additive

Regional Failure after Trimodality Therapy – Neck Fibrosis vs. Regional Recurrence

PET Re-staging and Detection of Recurrence “Marginal Miss” Regional Failure

PET in Long-term followup: R/O Recurrence

Selection of Peer Review Reports

<table>
<thead>
<tr>
<th>Study</th>
<th># Ps</th>
<th># Positive</th>
<th>Sensitivity</th>
<th>Other Data</th>
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</thead>
<tbody>
<tr>
<td>Scaun (2007)</td>
<td>30</td>
<td>9</td>
<td>100%</td>
<td>1 FP</td>
</tr>
<tr>
<td>Wong (2002)</td>
<td>143</td>
<td>66</td>
<td>96%</td>
<td>72% specificity</td>
</tr>
<tr>
<td>Lapela (2000)</td>
<td>56</td>
<td>34</td>
<td>61%</td>
<td>84% specificity</td>
</tr>
<tr>
<td>Farber (1999)</td>
<td>20</td>
<td>13</td>
<td>65%</td>
<td>55%</td>
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<tr>
<td>Flexibon (1998)</td>
<td>15</td>
<td>22</td>
<td>97%</td>
<td>1 FN, 8 FP</td>
</tr>
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</table>
Review of 188 pts with post-XRT PET.
- Mixture of sites/stage and therapy (most Stage III/IV primary RT-chemo).
- Qualitative Analysis of PET (Pos vs. Neg).
- Assessment of Primary Tumor Bed.
- Assessment of Cervical Nodal Bed.
- Assessment of Larynx.

University of Iowa: Early Post-XRT PET

Lung CA Data:
PET after XRT +/- Chemo
- On multivariate analysis, PET response was a more significant predictor (p=0.006) than KPS (p=.09) and wt loss (p=.14).

On average time from XRT to PET: 3.5 mo. (range 1-10)

University of Iowa: Early Post-XRT PET

- Primary Tumor Bed Evaluation:
  - Positive Predictive Value (PPV): 21%
  - Negative Predictive Value (NPV): 99%
- Cervical Lymph Node Evaluation:
  - Positive Predictive Value (PPV): 71%
  - Negative Predictive Value (NPV): 99%
Restaging PET Scan
Approx. 3 mo. Post-XRT

- Complete Metabolic Response (CMR) statistically significant predictor for survival

What causes False Positive PET after Treatment?

- Same things that cause False Positive pre-treatment PET! (see earlier slides):
  - e.g. Sarcoidosis.
- Post-treatment Inflammation:
  - e.g. Radiation Laryngitis.
  - Particularly if/when PET is performed < 8 wks after completion of RT
    - (Andrade et al., IJR OBP 2006)

University of Iowa:
Significance of Post-XRT PET
Non-tumor related Larynx Uptake

PET imaging of Post-XRT toxicity

Severe post-RT inflammation is associated with FDG-PET uptake.
This might provide an objective means of assessing extent of RT injury and/or improvement after intervention (e.g. Hyperbaric oxygen).
Post-RT PET for Management of the Neck

- Conventional Teaching: N2-3 neck requires post-RT neck dissection.
- Is this true in the era of modern chemo-RT?
- Post-RT neck dissection is difficult and increases toxicity and cost.

### Post-RT PET for Management of the Neck

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>NPV</th>
<th>PPV</th>
<th>% neg scans</th>
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<tbody>
<tr>
<td>Ware (2004)</td>
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<td>83</td>
<td>95</td>
<td>52</td>
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<tr>
<td>Kupota</td>
<td>43</td>
<td>91</td>
<td>78</td>
<td>50</td>
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<tr>
<td>Nayak (2007)</td>
<td>43</td>
<td>97</td>
<td>70</td>
<td>76</td>
</tr>
<tr>
<td>Yao (2007)</td>
<td>53</td>
<td>100</td>
<td>43</td>
<td>90</td>
</tr>
</tbody>
</table>

RTOG 0522: Phase III Trial – with PET sub-study

1. Chemo-RT
2. Chemo-RT + Cetuximab.
Relevance of Topic

- PET scans are not in most organizations’ guidelines for head and neck cancer.
- However, PET is commonly used and approved by many insurance companies for HNC.
- PET is noninvasive, no sig. risk to pts.
- However, PET is expensive and often results in additional tests/interventions.
  - Toxicity.
  - Delay in definitive therapy.

PET Scans in Staging/Diagnosis

- T-stage/size of primary tumor.
  - Identification of ‘unknown’ primary.
- N-stage/cervical lymph node metastases.
- R/O distant metastases.
- R/O 2nd primary CA.

Change in management!
Principles of RT Treatment Planning for HNC

- **DO NOT MISS THE TUMOR!**
  - GTV = ROI(s) known to harbor tumor
    - Positive by PE, Panendoscopy, Imaging.
    - Requires 66-76 Gy.
  - CTV60 = ROI(s) likely heavily microscopically infested.
    - E.g. Jugulodigastric nodal region
    - Requires ~60 Gy
  - CTV50 = ROI(s) that may harbor microscopic tumor
    - E.g. supraventricular nodal region
    - Requires ~50 Gy

CT+ vs. PET-CT for Gross Tumor Volume (GTV) in HNC

Evaluation of the Contralateral Hemineck

Integrating PET into RT Planning: The Future

- RT Dose escalation > 72 Gy.
- PET during RT to identify slowly responding area(s) for boost.
- RT planning with new tracers, especially hypoxia-PET markers.
FDG and F-Miso PET Scanning

RT Dose Escalation Based on PET F-Miso

Selected areas treated from 84 – 105 Gy.

Where’s the Tumor?

TJU PET/CT planning Flow
- Pt undergoes immobilization mask in rad onc dept.
- Pt undergoes CT (with IV contrast) for RT planning.
- Pt is brought (with mask) to PET center.
- Pt undergoes PET/CT with immobilization mask in place.
- PET/CT is fused with RT planning CT.
**TJU IMRT Prescription**

- **Targets**
  - GTV: 70 Gy
  - CTV66, CTV63, CTV60, CTV58, etc.

- **Organs at Risk (OAR’s)**
  - Spinal Cord, Brainstem.
  - Parotid Glands.
  - Mandible, Oral Cavity, Lips
  - Pharyngolaryngeal Complex (OARpharynx)

---

**University of Iowa: Early Post-XRT PET**

**Primary Tumor Bed**

<table>
<thead>
<tr>
<th>PET</th>
<th>Pathology/Clinical</th>
<th>Negative</th>
<th>Positive</th>
<th>Total</th>
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<tr>
<td></td>
<td></td>
<td>129</td>
<td>2</td>
<td>131</td>
</tr>
<tr>
<td></td>
<td></td>
<td>45</td>
<td>12</td>
<td>57</td>
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<tr>
<td>Total</td>
<td></td>
<td>174</td>
<td>14</td>
<td>188</td>
</tr>
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</table>

- **Specificity:** 74%
- **Sensitivity:** 86%

**Cervical Lymph Nodes**

<table>
<thead>
<tr>
<th>PET</th>
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<th>Negative</th>
<th>Positive</th>
<th>Total</th>
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<td></td>
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<td>169</td>
<td>2</td>
<td>171</td>
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<tr>
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<td></td>
<td>5</td>
<td>12</td>
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<tr>
<td>Total</td>
<td></td>
<td>174</td>
<td>14</td>
<td>188</td>
</tr>
</tbody>
</table>

- **Specificity:** 97%
- **Sensitivity:** 86%
RTOG 90-03 (RT alone)
EGFR expression and prognosis

Ang, Cancer Res 2002

One Patient –
4 different PET results!

T-stage: TP: Uptake within a known Larynx CA.
N-stage: TN: No uptake within cervical lymphatics.
M-stage: FP: Uptake in SI joint (probably OJD).
2nd primary: FN: No uptake within synchronous breast CA

Severe Post-RT Chondritis

Non-palpable Nodal Regions

Multiple biopsies showed inflammation, evolving post-RT necrosis

Clinically Indeterminate
But PET- GTV50

Pt #3
PET + Lt
Path + Lt, NA Rt
**SUV_{max} vs. SUV_{peak}**

SUV_{max}: A large ROI is drawn around the target lesion & the software is queried to determine the highest SUV in any pixel value in that ROI.

SUV_{max} = 17

---

**Inter-observer Variability in GTV contouring (CT+ vs. PET-CT)**

(6 Head/Neck Radiation Oncologists; 2 Neuroradiologists)

Both tests showed considerable inter-observer variability.

Interobserver Reliability Coefficient: 0.85

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**Post-treatment PET – Correlation between Local and Central SUV’s**

Pearson coefficient = 0.988

Concordance coefficient = 0.968

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**Post-RT PET for Management of the Neck**

43 Pts with N2-2 Nodal Disease Prior to XRT

10 Positive PET’s post-RT

23 Negative PET’s post-RT

7 TP (PPV 70%) 3 FP

32 TN (PPV 97%) 1 FN

Nayak et al., Laryngoscope 2007.
Is PET useful for T-staging?

• Usually not: MRI >> PET
  • T-stage depends upon size and extension (at times subtle) to adjacent organs – e.g.:
    • Lateral Pharyngeal Wall
    • Genioglossus Muscles
    • Mandibular Bone
    • Paravertebral Musculature
    • Carotid Artery