Clinical Utility of FDG-PET for Head and Neck CA

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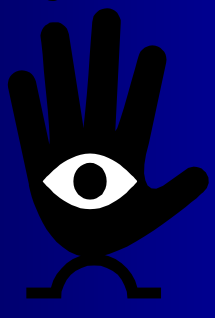
Topics

- 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

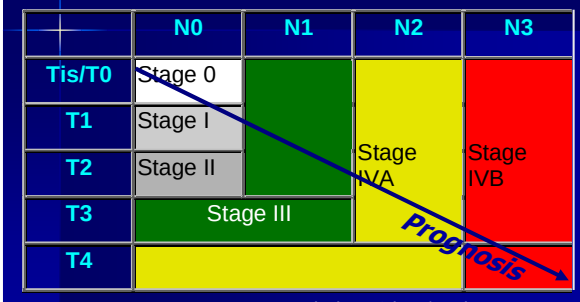
Head and Neck Cancer is extremely FDG-avid

(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

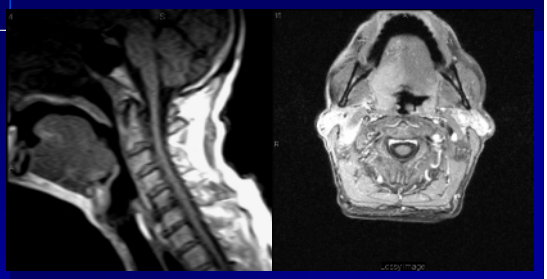
Staging of Head and Neck CA



Distant Metastases (M1) = IVC (not shown)

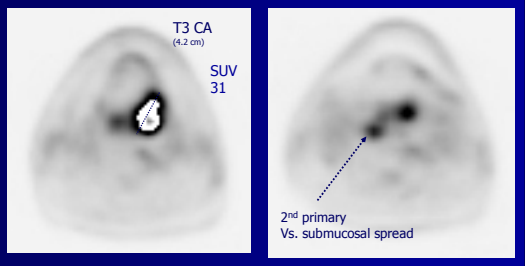
Treatment Selection is heavily influenced by Stage

T-staging

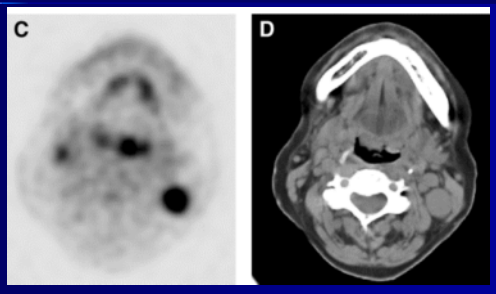


MRI shows unequivocal T4a (deep/extrinsic tongue invasion) clinically suspected though tongue mobility was intact.
In this application, MRI is probably superior to PET and/or CT

Assessing Extent of Primary Cancer With help from PET



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



Schoder/Yeung, Semin Nuc Med 2004

Unknown Primary (UP) Detection

- 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.

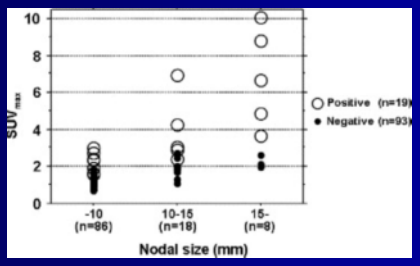
• More recent review of a series of pts negative by PE and MRI: 27%.

Schoder/Yeung, Semin Nuc Med 2004
Menda/Graham, Semin Nuc Med 2005

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, IJRBOP 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

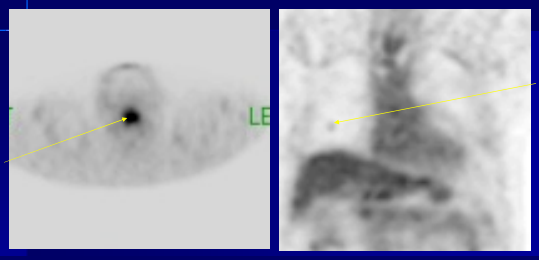
- M0: Radical (but highly toxic) Rx:
  - Radical Surgery (+ adjuvant therapy).
  - Concurrent chemoradiotherapy +/- ND.
- M1: Palliative intent Rx:
  - Upfront chemotherapy– maybe followed by RT if patient does OK.
  - Palliative dose RT +/- "lite" chemo.
  - Supportive care/hospice.

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.

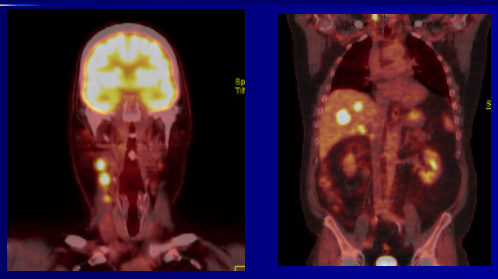
Fogh, 2008

Pet Staging of DM



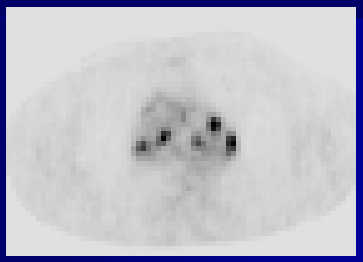
•Patient with bulky hypopharyngeal CA
•Pulmonary lesion (not visible on CXR) identified on PET/CT.
•Proven in followup to be metastatic disease.

PET Staging for DM



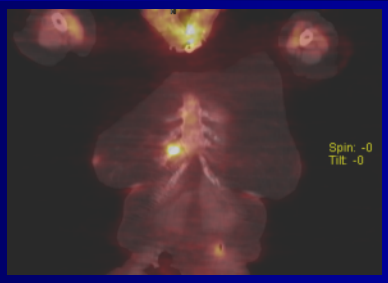
Pt with Neuroendocrine CA of Paranasal Sinuses. PET showed both extensive regional nodal disease and liver metastases (Bx proven).

False Positive Body PET



Pt with T4N2 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

	N0	N1	N2	N3
Tis/T0	Stage 0			
T1	Stage I			
T2	Stage II		Stage IVA	Stage IVB
T3	Stage III			
T4				

Prognosis

Distant Metastases (M1) = IVC (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

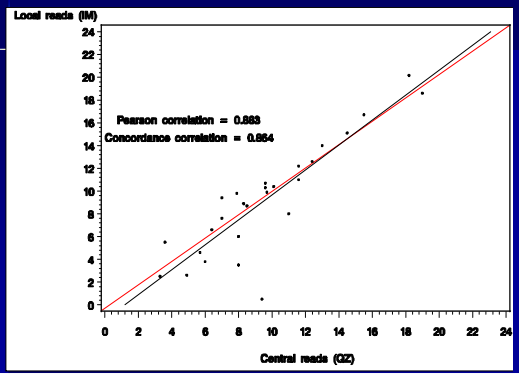
- Clinical
  - Patient body composition (fat/muscle).
  - Serum glucose concentration/Diabetes.
  - Time from injection to imaging.
  - Success of IV placement
- Technical
  - Organ/Tumor motion
  - Partial Volume Averaging
  - Def'n of SUV: SUV_{mean} vs. SUV_{max} vs. SUV_{peak}

SUV vs. SUV_{peak}

SUVpeak: First, the SUV_{max} must be found. Next a 1 cm circular ROI is drawn centered around the point of SUV_{max}. Then, the software is queried to determine the mean SUV within that precisely defined ROI.

SUV peak = 15

Pre-treatment PET in NSCLC: Correlation between Local and Central SUV's



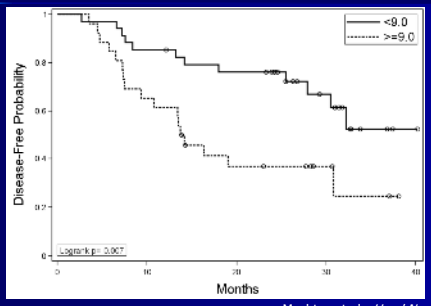
Can SUV serve as a "Cheap" Biomarker?

- Intensity of PET-FDG upatke is associated with biological phenotypes:
  - Proliferation (Ki-67).
  - Growth Factors (EGFR).
  - Metabolism (GLUT-1).
- Disadavantages of Tissue Biomarkers
  - Expensive.
  - Paraffin-embedded (loses some data)
  - Samples only one portion of the tumor.

SUV as a Prognostic Biomarker in HNC

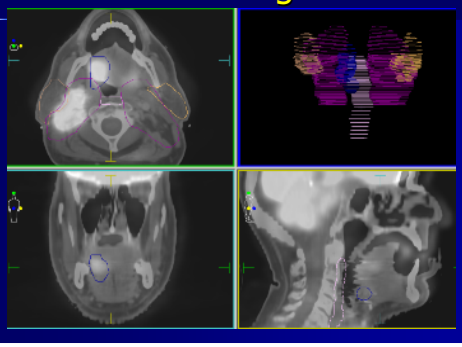
Series	N	Results
Roh (2007)	79	SUV > 8 → worse DFS (p=0.007)
Kubicek (2007)	93	SUV not predictive
Schwartz (2004)	54	SUV > 9.0 → worse DFS (p=0.03)
Allal (2004)	120	SUV > 4.75 → worse DFS (p=0.005)
Kitagawa (2003)	20	SUV > 7.0 → less likely CR
Halfpenny (2002)	58	SUV > 10.0 → worse survival (p=0.003).
Brun (2002)	47	SUV > 9.0 → worse LRC (p=0.002).
Greven (2001)	45	SUV not predictive.
Minn (1997)	37	SUV > 9.0 → worse DFS.

Pre-treatment SUV & Outcome: Jefferson Experience



Machtay et al., *Head Neck* in press

PET for RT Treatment Planning

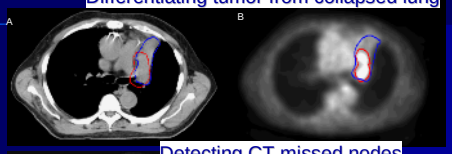


PET-based RT Planning: Head and Neck vs. Lung CA

	Lung	HNC
FDG Avidity	High	High
Risk of + regional nodes	High	High
Risk of + Distant Mets	High	Low-Mod
Risk of 'marginal miss' (if RT is limited to GTV)	Low-Mod	High
Artifacts – ↑ FDG in adjacent Normal Tissue	Low	Moderate
Artifacts – Organ Motion	High	Moderate

FDG-PET in Lung Cancer Target Delineation

Differentiating tumor from collapsed lung

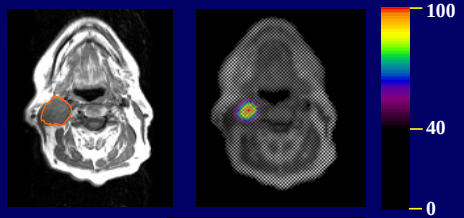


Detecting CT missed nodes

Courtesy of Spring Kong (UMich)

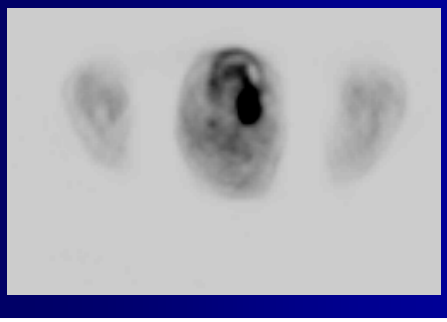
PET Fusion with CT/MRI

- **Registered images (H&N):**

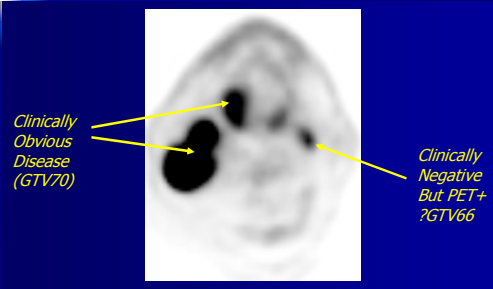


MRI **FDG-PET + MRI**

PET improves visualization of Oral Cavity CA (less dental artifact)

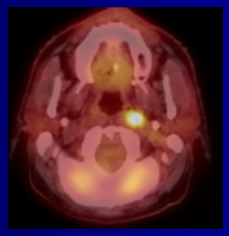


PET evaluation of non-palpable nodal regions



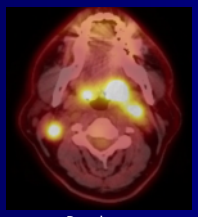
PET Evaluation Post-op/Pre-RT

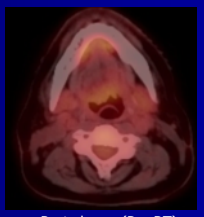
Gross residual disease in the retropharyngeal space and this received boost irradiation to 70 Gy (with concurrent chemo).



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


Pre-chemo


Post-chemo (Pre-RT)

CT/MRI vs. PET for GTV: A Larynx Cancer Study

Patient No.	Tumor Site	T Stage	GTV (cm^3) CT	MR Imaging	FDG PET	Surgical Specimen
1	PS	T4	47.7	36.3	19.3	NA
2	GL	T3	18.0	9.9	6.0	NA
3	GL	T3	41.1	30.2	9.2	NA
4	RC	T3	7.1	10.6	7.3	NA
5	PS	T2	4.1	9.1	2.3	NA
6	SGL	T2	3.7	1.4	1.2	NA
7	SubGL	T3	5.8	7.0	3.2	NA
8	PS	T3	17.3	17.6	12.6	NA
9	PS	T4	13.1	30.7	11.4	NA
10	PS	T4	55.6	53.4	34.2	NA
11	SubGL	T2	1.9	2.4	3.4	2.2
12	GL	T4	6.2	9.8	8.5	5.1
13	LAR	T4	41.0	58.4	30.2	30.9
14	LAR	T4	11.1	6.6	8.0	4.1
15	LAR	T4	14.6	22.0	10.2	5.6
16	LAR	T4	18.4	22.0	11.4	8.6
17	LAR	T4	28.1	32.3	26.6	17.3
18	LAR	T4	25.0	23.5	20.0	15.4
19	LAR	T4	40.4	37.3	28.7	24.3
Mean						
All patients (n = 19)	---	---	21.4	21.4	13.4*	NA
Patients with specimen available (n = 9)	---	---	20.8	23.8	16.3	12.6*

P< 0.01

Daisne et al., Radiology 2004

PET for RT planning

- Nishioka (IJROBP 2002): 21 cases
  - 19/21 had no change with PET
- Ciernik (IJRBOP 2003): 12 HNC cases
  - ↓GTV by >25% (2 pts); ↑GTV by >25% (2 pts)
- Koshy (Head&Neck 2005): 40 cases
  - GTV_{PET} was lower than GTV_{CT} in all but 7 pts.
- Wang (IJRBOP 2006): 16 cases
  - GTV_{PET} was lower than GTV_{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_{PET} (43 cc) was significantly lower than Mean GTV_{CT} (65 cc) --- p=0.002.
  - The ratio of GTV_{PET} vs. GTV_{CT} ranged from 0.3 to 23.

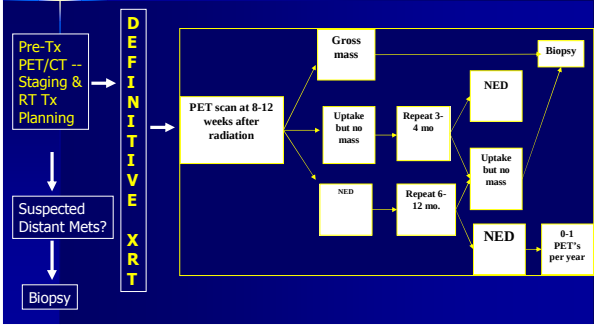
Challenges in PET RT Planning

- Obtaining up-to-date PET's (insurance blockage).
- False Positives and False Negatives.
- Fusion/Deformable Registration.
- 'Edge' Effect –
  - Use absolute SUV?
  - Relative SUV (?30% 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



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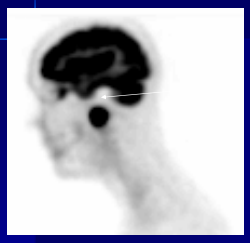
FDG-PET for Followup, Restaging and Prognosis

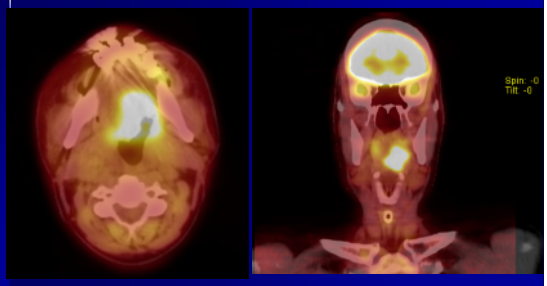
PET Restaging/Followup



Pre-treatment: Stage IVA tonsil CA

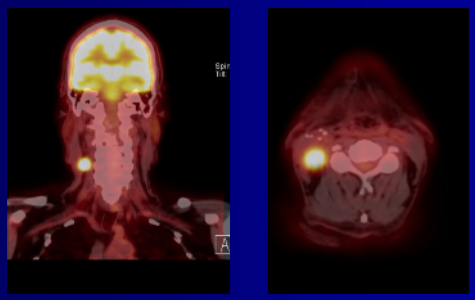
Post-treatment (2 yrs): NED

In-field Local Failure (T4 BOT CA)

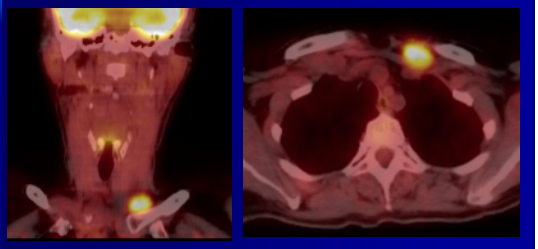


Obvious case of Local-regional failure – PET/CT probably not too additive

Regional Failiure 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

Study	# Pts	# Positive PETs	Sensitivity	Other Data
Salaun (2007)	30	9	100%	1 FP
Wong (2002)	143	66	96%	72% specificity
Lapela (2000)	56	34 ("Lesions")	95%	84% specificity
Farber (1999)	28	13	86%	2 FN
Fischbein (1998)	35	22	97%	1 FN, 8 FP

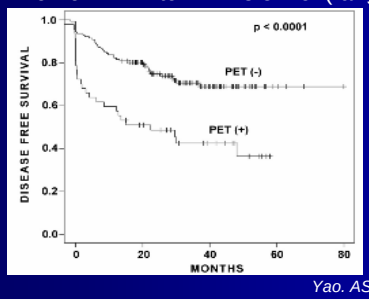
University of Iowa: Early Post-XRT PET

- 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.

Yao. ASTRO 2007

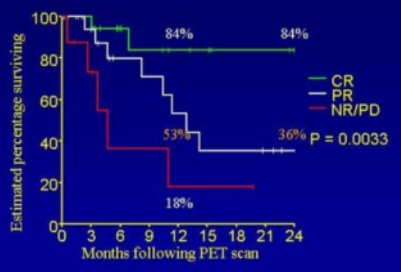
University of Iowa: Early Post-XRT PET

Ave. Time from XRT to PET: 3.5 mo. (range 1-10)



Yao. ASTRO 2007

Lung CA Data: PET after XRT +/- Chemo



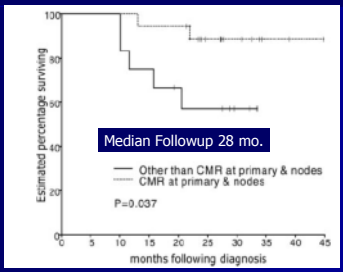
On multivariate analysis, PET response was a more significant predictor (p=0.006) than KPS (p=.09) and wt loss (p=.14).

University of Iowa: Early Post-XRT PET for Head/Neck CA

- 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%

Yao. ASTRO 2007

Restaging PET Scan Approx. 3 mo. Post-XRT



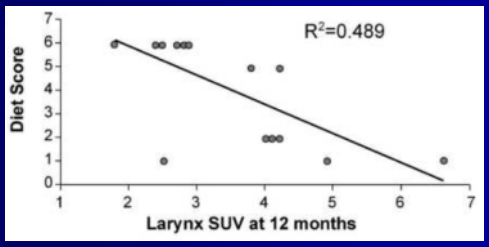
- Complete Metabolic Response (CMR) statistically significant predictor for survival

Connell, et al.

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., IJROBP 2006)

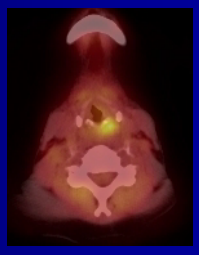
University of Iowa: Significance of Post-XRT PET Non-tumor related Larynx Uptake



Dornfeld. IJROBP 2008

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).



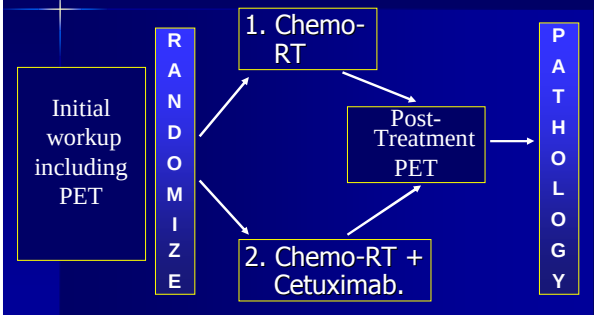
Post-RT PET for Management of the Neck

- 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 ncreases toxicity and cost.

Post-RT PET for Management of the Neck

Study	N	NPV	PPV	*% neg scans*
Ware (2004)	46	83	95	*52*
Kupota	43	91	78	*50*
Nayak (2007)	43	97	70	*76*
Yao (2007)	53	100	43	*90*

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



P.I.: Kian Ang

Leftover/Backup

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.

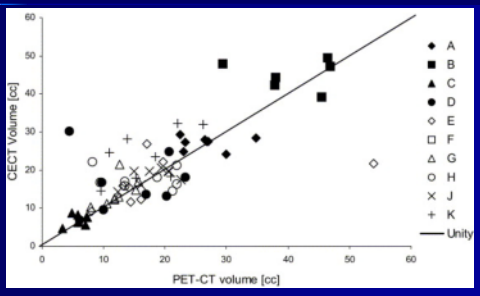
Change in management!

Principles of RT Treatment Planning for HNC

- DO NOT MISS THE TUMOR!

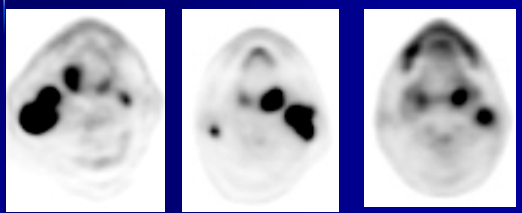
- GTV = ROI(s) known to harbor tumor
  - Positive by PE, Panendo, Imaging.
  - Requires 66-76 Gy.
- CTV60 = ROI(s) likely heavily microscopically infested.
  - E.g. Jugulodigastric nodal region
  - Requires ~60 Gy
- CTV50 = ROI(s) that may harbor microscopic tumor
  - E.g. supraclavicular nodal region
  - Requires ~50 Gy

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



Breen et al. (PMH), IJRBOP 2007

Evaluation of the Contralateral Hemineck

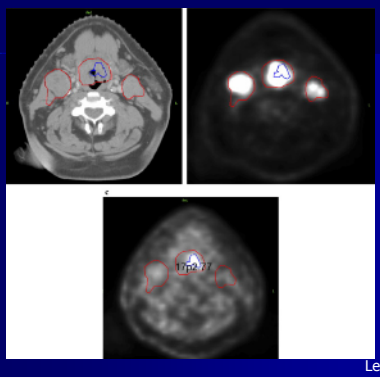


Pt #1	Pt #2	Pt #3
PET + bilaterally: Path + bilaterally	PET + bilaterally: Path + Lt but – Rt.	PET + Lt Path + Lt, NA Rt

Integrating PET into RT Planning: The Future

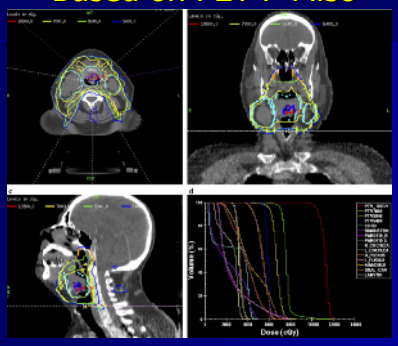
- RT Dose escalation > 72 Gy.
- PET during RT to identify slowly responding area(s) for boost.
- RT planning with new tracers, especially hypoxia-PET markers.

FDG and F-Miso PET Scanning



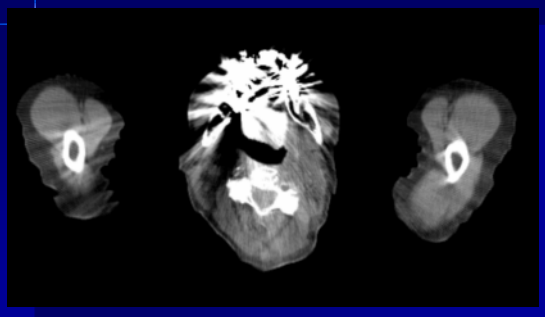
Lee, IJROBP 2008

RT Dose Escalation Based on PET F-Miso



Selected areas treated from 84 – 105 Gy. Lee, IJROBP 2008

Where's the Tumor?



TJU PET/CT planning Flow

- Pt undergoes immoblization 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 immoblization 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

	Pathology/Clinical		
PET	Negative	Positive	**Total**
Negative	129	2	131
Positive	45	12	57
Total	174	14	188

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

Yao. ASTRO 2007

University of Iowa: Early Post-XRT PET

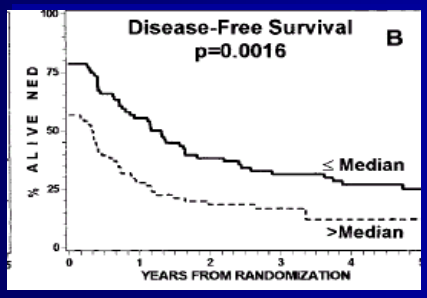
Cervical Lymph Nodes

	Pathology/Clinical		
PET	Negative	Positive	**Total**
Negative	169	2	171
Positive	5	12	17
Total	174	14	188

- *Specificity: 97%*
- *Sensitivity: 86%*

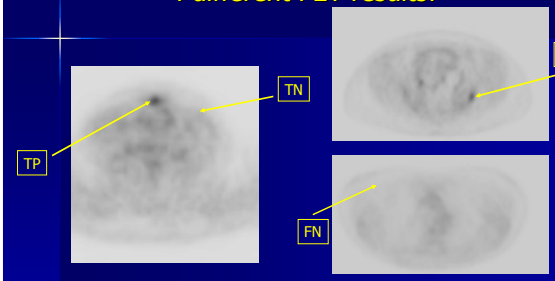
Yao. ASTRO 2007

RTOG 90-03 (RT alone)
EGFR expression and prognosis



Ang, Cancer Res 2002

One Patient –
4 different PET results!

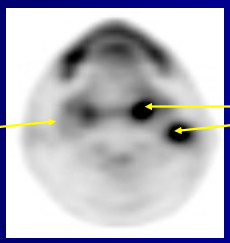


T-stage: TP: Uptake within a known Larynx CA.
N-stage: TN: No uptake within cervical lymphatics.
M-stage: FP: Uptake in Si joint (probably DJD).
2nd primary: FN: No uptake within synchronous breast CA

Severe Post-RT Chondritis

Multiple biopsies showed inflammation, evolving post-RT necrosis

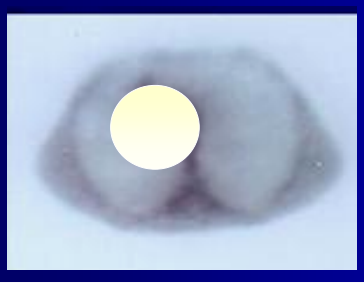
Non-palpable Nodal Regions



Pt #3
PET + Lt
Path + Lt, NA Rt

SUV_{max} vs. SUV_{peak}

SUVmax: 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.

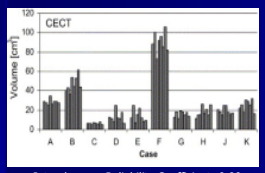


SUV max = 17

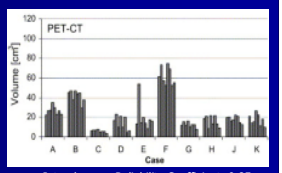
Inter-observer Variability in GTV contouring (CT+ vs. PET-CT)

(6 Head/Neck Radiation Oncologists; 2 Neuroradiologists)

Both tests showed considerable inter-observer variability.



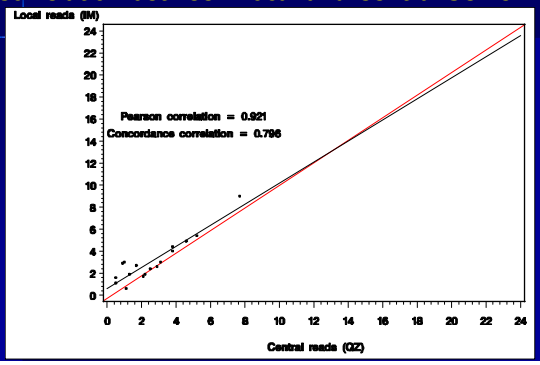
Interobserver Reliability Coefficient: 0.90



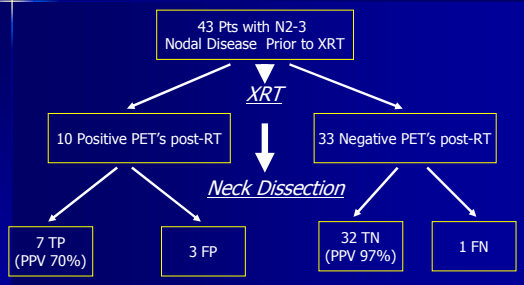
Interobserver Reliability Coefficient: 0.85

Breen et al. (PMH), IJRBOP 2005

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



Post-RT PET for Management of the Neck



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 Musculuature
    - Carotid Artery