^{18}F-FDG-PET/CT in Cancer Treatment: Indications and Results in 2008

David L. Schwartz, M.D.
Departments of Radiation Oncology and
Experimental Diagnostic Imaging
U.T. M.D. Anderson Cancer Center

FDG-PET/CT—The Current Numbers

- 1.1M+ scans at 1700+ sites in 2005
- >90% of all new purchased scanners are PET/CT
- 90-95% of PET imaging is for cancer
- Current costs/financial issues:
  - Baseline $200K for new PET facility (room renovation, hot lab, radiation safety equipment)
  - $1.5M for new PET scanner
  - $1.7-2.5M for new PET/CT scanner
  - Personnel
  - Tracer costs
  - Reimbursement issues (DRA)

Roles of PET/CT in Cancer Treatment

- Diagnosis
- Staging
- Predict tumor behavior
- Geographic tumor delineation
- Treatment response
- Surveillance
- Restaging

Current CMS-Approved Cancer Sites for PET/CT Staging & Restaging

- Breast
- Cervix
- Colorectal
- Esophagus
- Head and Neck
- Lymphoma
- Non-Small Cell Lung
- Melanoma
- Sarcoma
- Thyroid

http://www.cms.gov/coverage

CMS-Approved Cancer Sites/Indications for NOPR Enrollment

- Pancreas
- Ovarian
- Small Cell Lung
- Multiple Myeloma
- Unknown Primary
- Additional indications for CMS-approved sites
  - Lymphoma response assessment
  - NSCLC/H&N response assessment
  - Brain/Cervix restaging

http://www.cms.gov/coverage

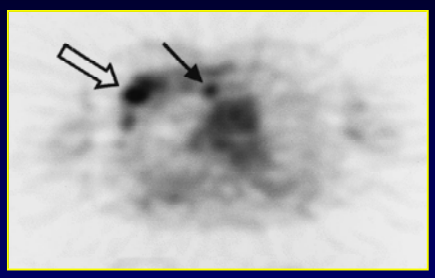
Overview

- Site-by-site summary of accepted or evolving indications for FDG-PET/CT (orange = not CMS-approved)
- Current head and neck cancer FDG-PET/CT practice, with case examples
- Future directions

Breast Cancer

- Staging of high risk disease
  - Nodal staging
- Characterization of bone lesions
- Staging recurrent disease
- Response to chemotherapy

Breast Cancer



Bellon J, et. al. *Am J Clin Oncol* 27(4):407-10 [2004]

Breast Cancer—Axillary Staging

Table 1. Tabulated Summary of Studies Assessing Axillary Staging

Study	Year	No. of Patients	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)
Veronesi et al[15]	2002	226	97	96	98	92
Gil-Pereda et al[16]*	2003	145	94.5	96.5	95.4	95.6
Chung et al[17]*	2006	51	80	100	—	—
Kumar et al[18]*	2005	60	44	95	—	—
Derossi et al[19]*	2004	200	84	98	82	79
Lovrics et al[20]	2004	69	40	97	96	74
Bauer et al[21]	2004	74	70	99	97	77
Wahl et al[22]	2004	500	61	80	62	96
Beringer et al[23]*	2003	23	20	100	—	—
van der Heoven et al[24]*	2002	70	26	97	63	95
Guller et al[25]	2002	31	43	94	86	67
Keleman et al[26]*	2002	15	30	93	56	69
Yang et al[27]	2001	18	50	100	—	—
Schrenkeisler et al[28]	2001	117	70	93	82	76
Greco et al[29]	2001	167	94	96	94	96
Yutani et al[30]	2000	38	50	100	100	100
Chippa et al[31]	1998	72	95	91	—	—
Hun et al[32]	1998	27	40	100	—	—
Smith et al[33]	1998	58	90	97	95	95
Chippa et al[34]	1997	82	94	95	—	—

*These studies included a comparison with sentinel lymph node biopsy.

Hodgson and Gulenchyn, *J Clin Oncol 26:712-20* [2008]

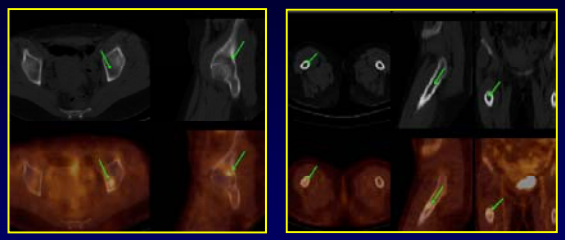
Breast Cancer—PET vs. SLNB

Measure	FDG-PET	SLNB
Sensitivity, %	37	96
Specificity, %	96	100
Positive predictive value, %	88	100
Negative predictive value, %	66	97
Overall accuracy, %	70	98

NOTE. Data adapted.[15]
Abbreviations: FDG-PET, fluorodeoxyglucose-positron emission tomography; SLNB, sentinel lymph node biopsy.

Veronesi J, et. al. *Ann Oncol 18:473-78* [2007]

Breast Cancer—Bone Lesions

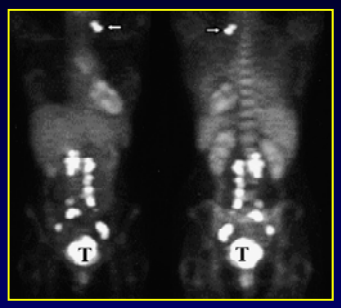


Groheux D, et. al. *IJROBP* 71(3):695-704 [2008]

Cervix Cancer

- Staging of high risk disease
  - Nodal staging
- Staging recurrent disease
- Radiation treatment planning

Cervix Cancer

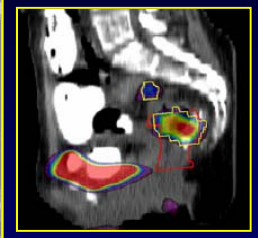


Grigsby P, et. al. *Clin Positron Imaging* 2:105-9 [1999]

Colorectal Cancer

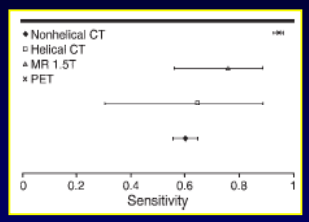
- Staging of rectal disease
  - Nodal staging
- Staging of non-liver metastases
  - Patient selection for liver surgery
- Staging recurrent disease
- Radiation treatment planning
- Response to chemotherapy

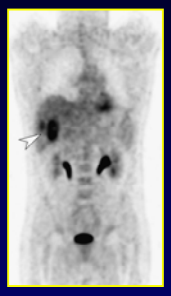
Rectal Cancer—Nodal Staging/XRT Planning



Anderson C, et. al. *IJROBP* 69:155-62 [2007]
Bassi M, et. al. *IJROBP* 70:1423-26 [2008]

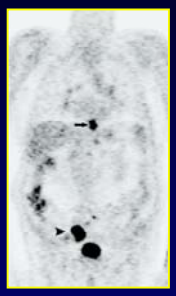
Colorectal Cancer—Extrahepatic Staging

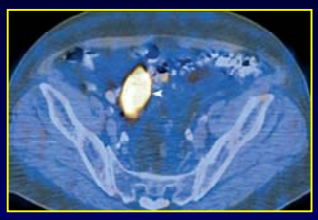




Bipat S, et. al. *Radiology* 237:123-31 [2005]
Herbertson R, et. al. Ann Oncol 18:1744-81 [2007]

Occult Colorectal Cancer





Bruzzi J, et. al. *Curr Probl Diagn Radiol* 36:21-9 [2007]

Esophageal Cancer

- Staging of distant disease
- Response to preoperative therapy
  - Needs to be done with endoscopic UTS
  - Timing remains key issue

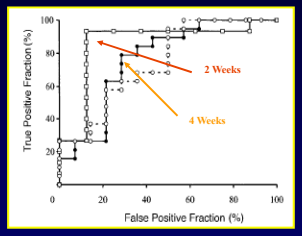
Esophageal Cancer

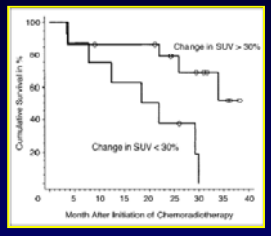
Upfront DM Staging

Preop Restaging

Bruzzi J, et. al. *Radiographics* 27:1635-52 [2008]

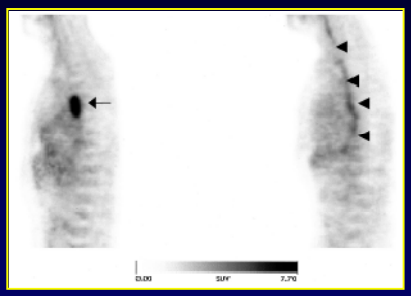
Esophageal Cancer—Early Response





Wieder H, et. al. *J Clin Oncol* 22:900-8 [2004]

Esophageal Cancer—Residual vs. Inflammation



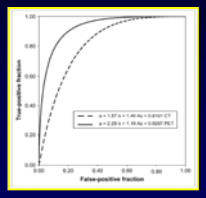
Wieder H, et. al. *J Clin Oncol* 22:900-8 [2004]

Non-Small Cell Lung Cancer

- Diagnose solitary pulmonary nodules
- Mediastinal and distant staging
  - Preoperative assessment (Ph III data)
- Staging recurrent disease
- Radiation treatment planning
  - One Ph II series
- Response to chemotherapy

Solitary Pulmonary Nodule

PET vs.CT



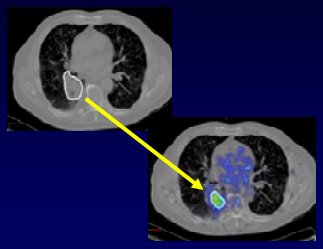
532 pts, 7.0-30.0 mm
Sensitivity: 92% (v. 96% CT)
Specificity: 82% (v. 41% CT)

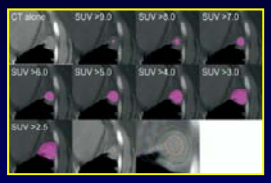
PET/CT

119 pts, 6.2-30.0 mm
Sensitivity: 96% (v. 81% CT)
Specificity: 93% (v. 88% CT)

Yi C, et. al. *J Nucl Med* 47:443-50 [2006]
Fletcher J, et. al., *J Nucl Med* 49:179-85 [2008]

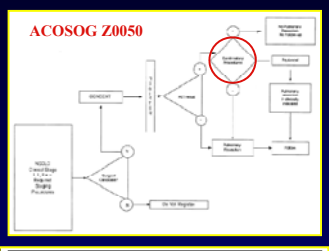
Non-Small Cell Lung Cancer—XRT Planning





Hong R, et. al. *IJROBP* 67:720-26 [2007]
Faria S, et. al. *IJROBP* 70:1035-38 [2008]

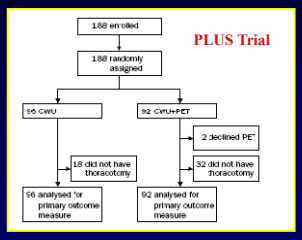
Non-Small Cell Lung Cancer—Ph III Data



Confirmed pathology	CT alone (%)	PET alone (%)	CT plus PET (%)	*P* value (PET vs CT)
N0	147/168 (88%)	128/168 (76%)	132/168 (89%)	>.5
N1	4/31 (13%)	13/31 (42%)	14/31 (45%)	.0177
N2/N3	13/57 (32%)	32/57 (56%)	30/57 (53%)	.004

Reed C, et. al. *J Thorac Cardiovasc Surg 126*::1943-51 [2003]

Non-Small Cell Lung Cancer—Ph III Data



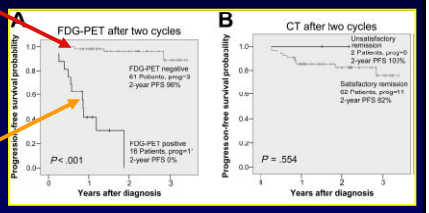
	CWU (n=96)	CWU+PET (n=92)
No thoracotomy	18 (19%)	32 (35%)
Confirmed N2/3	10	18
Confirmed distant metastases	1	7
Benign primary lesions	2	3
Other tumour	2	1
Intercurrent morbidity, refusal	2	3
Thoracotomy	78 (81%)	60 (65%)
Non-futile thoracotomy	39 (41%)	41 (44%)
Futile thoracotomy	39 (41%)	19 (21%)
Benign	2	2
Explorative thoracotomy	1	1
IIIA–N2	6	4
IIIB	6	2
Recurrence or death within 1 year	19	10

Van Tinteren H, et. al. *Lancet* 359:1388-92 [2002]

Lymphoma

- Characterize post-chemotherapy mass
- Response to chemotherapy
  - FDG-PET is formal part of IWG guidelines
- Staging recurrent disease

Lymphoma—Chemotherapy Response



Hutching M, et. al. *Blood* 107:52-9 [2006]

Lymphoma—IWG Response Criteria

Response	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
CR	Disappearance of all evidence of disease	(a) FDG-avid or PET positive prior to therapy; masses of any size permitted if PET negative (b) Variably FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative
PR	Regression of measurable disease and no new sites	≥ 50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes (a) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site (b) Variably FDG-avid or PET negative; regression on CT	≥ 50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Involvement if positive prior to therapy; cell type should be specified
SD	Failure to attain CR/PR or PD	(a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET (b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT		
Relapsed disease or PD	Any new lesion or increase by ≥ 50% of previously involved sites from nadir	Appearance of a new lesion(s) > 1.5 cm in any axis, ≥ 50% increase in SPD of more than one node, or ≥ 50% increase in longest diameter of a previously identified node > 1 cm in short axis Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy	> 50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

Cheson B, et. al. *J Clin Oncol* 25:579-86 [2007]

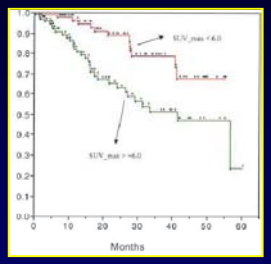
Melanoma

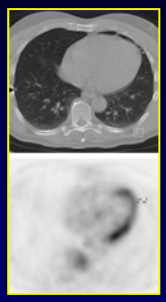
- Staging of nodes and distant disease
- Staging recurrent disease

Sarcoma

- Staging of distant disease
  - Complements MRI and bone scanning
  - Inferior to spiral CT for lung assessment
- Clarification of CT/MRI findings
  - Fixation devices, post-operative scarring
- Staging recurrent disease
- Tumor grading/prognosis
- Response to chemotherapy

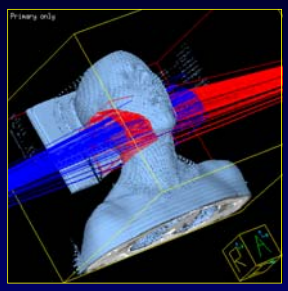
Sarcoma—Promise and Pitfalls

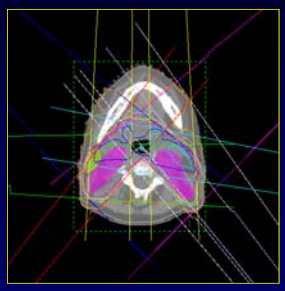




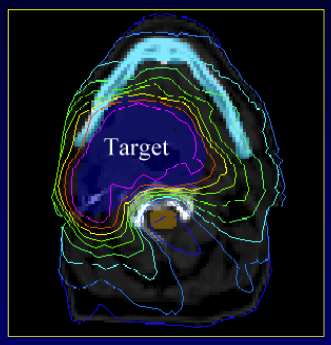
Eary J, et. al. *Eur J Nucl Med* 29:1149-54 [2002]
Iagaru A, et. al. *Nucl Med Comm* 27:795-802 [2006]

Head and Neck Cancer

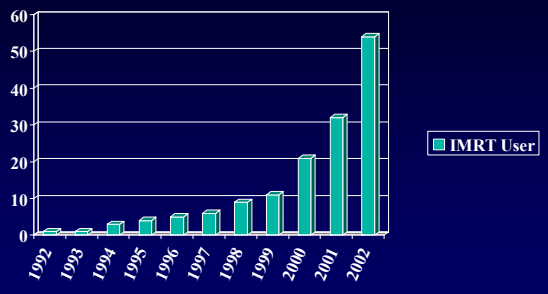




"Dose Sculpting" to Avoid Normal Tissues



Cumulative IMRT Adoption



Mell L, et. al. *Cancer* 98:204-211 [2003]

Locoregional Control of Oropharyngeal Carcinoma

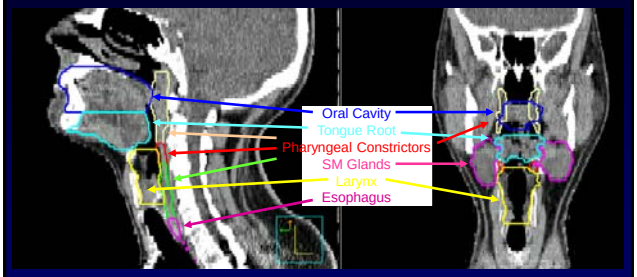
Conventional		IMRT
70-90%	T1-2	92%
30-70%	T3-4	87-94%

Salivary Recovery After IMRT

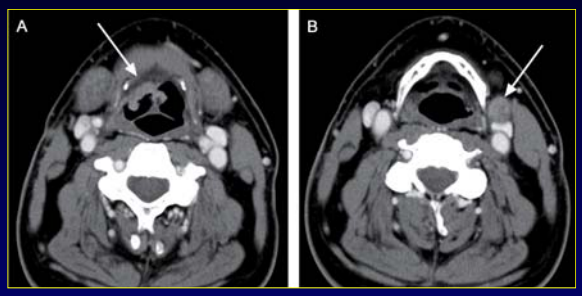
Group	N 6 M	Mean 6 M	N 12 M	Mean 12 M	Wilcoxon Rank Sum
3D XRT	12	0.33	11	0.43	P = 0.43
IMRT	38	0.49	20	0.82	P = 0.002

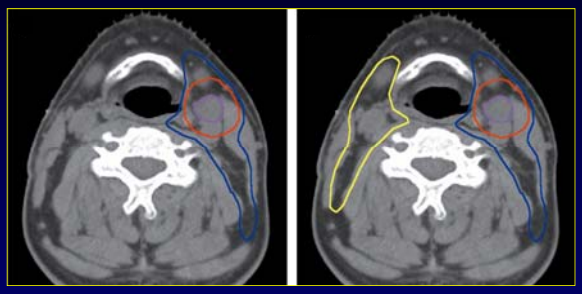
Chao K, et. al. *IJROBP* 49(4):907 [2001]

"Dysphagia Structures"



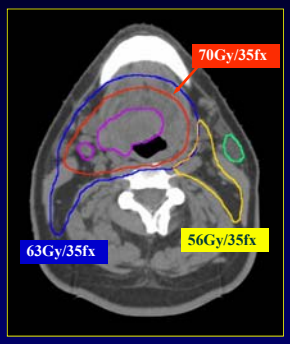
H&N CT for Target Delineation



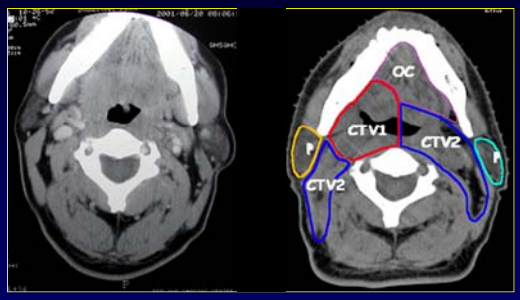


Chao K, et. al. (eds.) *Practical Essentials of IMRT, 2nd Edition* [2005]

IMRT Dose Prescriptions

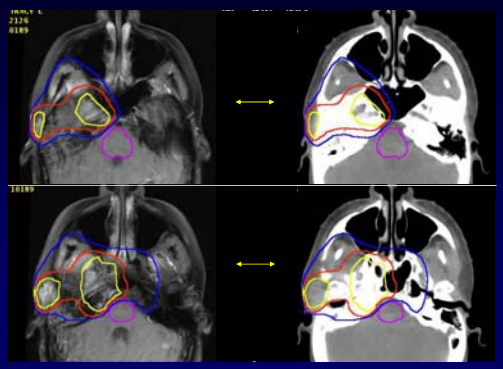


CT Target Delineation



Chao K, et. al. (eds.) *Practical Essentials of IMRT, 2nd Edition* [2005]

MR Fusion for Target Delineation



How Could PET/CT Help XRT?

- Tumor localization
  - Enlarge/reduce/confirm primary tumor target
  - Enlarge/reduce/confirm neck coverage
- Treatment selection
  - Locoregional and whole body staging
  - Biological characterization
- Response assessment
  - Need for neck dissection

H&N FDG-PET Staging—Early Data

- 90-100% primary lesions visualized
- Neck Staging
  - Sensitivity: 74-91%
  - Specificity: 88-98%
  - Negative Predictive Value: 88-99%
- cN0 neck staging accuracy?

Laubenbacher C, et. al. *J Nucl Med* 36:1747 [1995]
Braams J, et. al. *J Nucl Med* 36:211 [1995]

H&N FDG-PET Staging—Meta-Analysis

- 32 series, 1236 cases with neck dissection path
  - All series pre-2005 studied PET alone
- Validated FDG-PET for neck staging
  - Sensitivity: 79% [CI = 72-85%]
  - Specificity: 86% [CI = 83-89%]
  - Outperformed CT head-to-head
- Not effective for staging cN0 patients

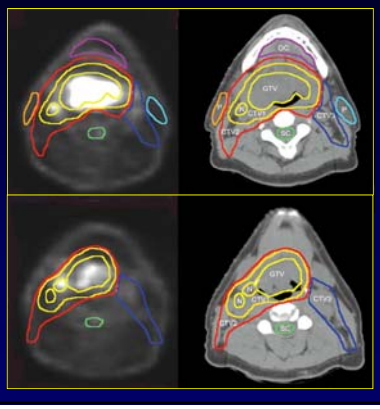
Kyzas P, et. al. *J Natl Cancer Inst* 100:712-20 [2008]

H&N FDG-PET Whole Body Staging

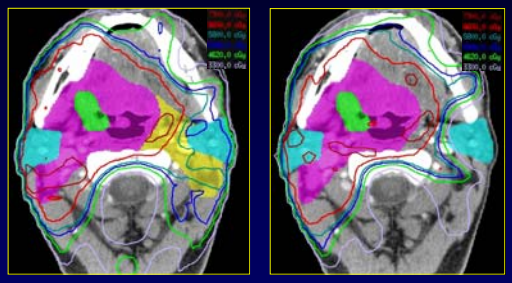
- 33 scans in 35 consecutive pts
- 7 pts (21%) FDG+ distant disease
  - 4 pts with lung/liver/bone mets
  - 3 pts with secondary cancers
- FDG-PET provided higher yield staging
  - CT missed 2/3 mediastinal mets
  - CT missed distant disease in 2/7 patients

Schwartz D, et. al. *Arch Otolaryngol Head Neck Surg*, 129:1173 [2003]

PET/CT GTV Delineation



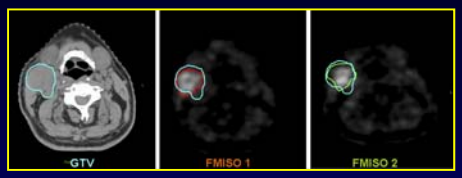
IMRT Guided by PET/CT Staging

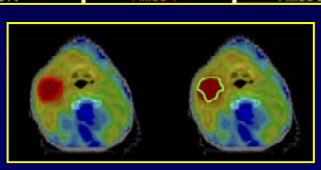


Based on CT only | Based on PET/CT

Schwartz D, et. al. *Head Neck* 27:478-87 [2005]

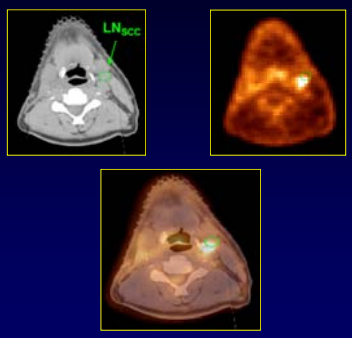
FMISO-PET/CT—Dose Painting by Numbers





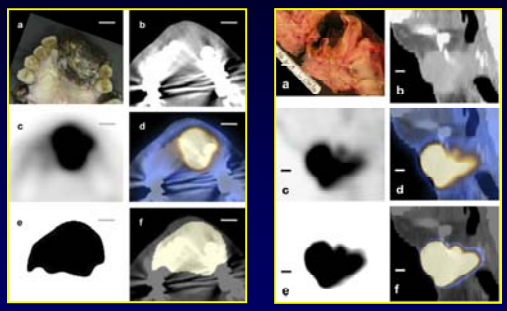
Lin Z, et. al. *IJROBP* 70:1219-28 [2008]

PET/CT Challenges—GTV Registration



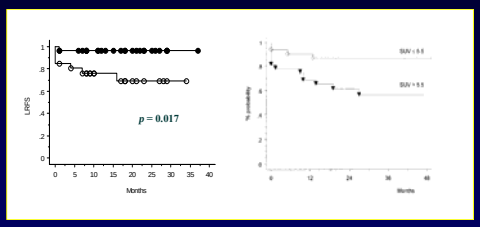
Frank S, et. al. *Nat Clin Pract Oncol* 2:526-33 [2005]

PET/CT Challenges—GTV Thresholding



Burri RJ, et. al. *IJROBP* 71:682-88 [2008]

Primary H&N Tumor SUV & Outcomes



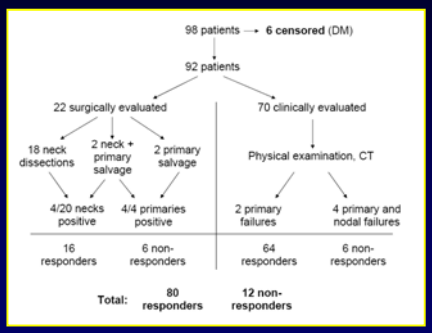
Allal A, et. al. *J Clin Oncol* 25:1398 [2002]
Schwartz D, et. al. *Arch Otolaryngol Head Neck Surg* 130:1361 [2004]

FDG-PET Response Assessment

- U Iowa (85 pts/retrospective)
  - 98-100% NPV at primary and neck if FDG-PET negative after IMRT
  - Limited primary tumor specificity
- Stanford (103 pts/retrospective)
  - 96-97% NPV overall
  - Scanning >1 month post XRT improved sensitivity and NPV
- What is the optimal timing for post XRT PET imaging?

Yao M, et. al. *IJROBP* 60(5):1410 [2004]
Ryan W, et. al. *Laryngoscope* 115:645 [2005]

MDACC H&N PET/CT Trial— Prospective Response Assessment

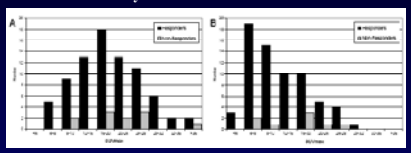


Moeller B, et. al. *Submitted*

MDACC H&N PET/CT Trial— Pre-XRT vs. Post-XRT SUV

Pre-treatment

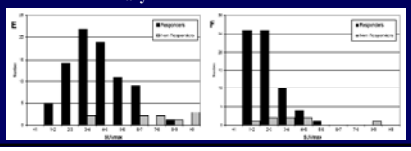
Primary Nodes



P = n.s.

Post-treatment

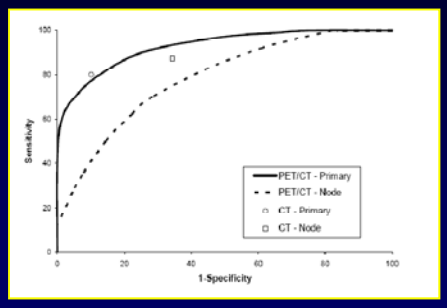
Primary Nodes



$P < 0.001$

Moeller, et. al.

MDACC H&N PET/CT Trial— Restaging Accuracy



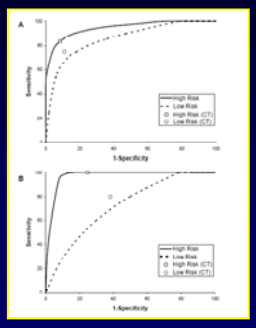
Moeller B, et. al. *Submitted*

MDACC H&N PET/CT Trial— "Risk-Stratified" PET-CT Assessment

High Risk	Low Risk
HPV-negative	HPV-positive
- OR -	**- OR -**
Non-OP primary	OP primary
- OR -	**- AND -**
Tobacco user	Tobacco non-user

Moeller B, et. al. *Submitted*

MDACC H&N PET/CT Trial— "Risk-Stratified" PET-CT Assessment



Moeller B, et. al. *Submitted*
Schwartz D, Macapinlac H, Weber R *J Natl Cancer Inst* 100:688-9 [2008]

SUV Standardization Issues

- PET instrumentation/reconstruction parameter standards
- ROI delineation standards
- Partial volume/attenuation correction standards
- Time of SUV determination relative to injection
- Body mass/plasma glucose SUV corrections
- Patient/disease stage selection issues
- PET/CT central review/QA process?

Thie J, *J Nucl Med* 45(9):1431 [2004]
Weber W, *J Nucl Med* 46:983-95 [2005]

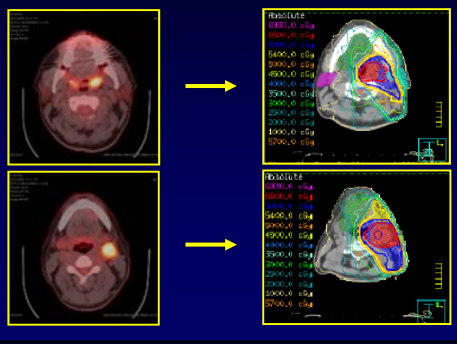
PET/CT—Settling Into a Mature Niche

- Refinement of PET/CT Tumor Localization
  - What will be our gold standard?
- Refinement of PET/CT's Diagnostic Role
  - Interactions with other tests
  - Interactions with other clinical risk factors
  - Individualize targeted therapy?
- Does PET/CT truly improve treatment results?

H&N Case Examples

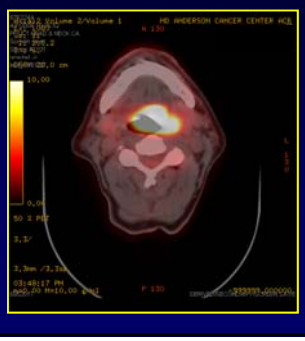
"Useful" FDG-PET/CT GTV

- Stage III Tonsil CA



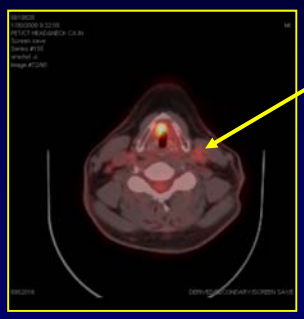
"Equivocal" FDG-PET/CT GTV

- Stage III Base of Tongue CA



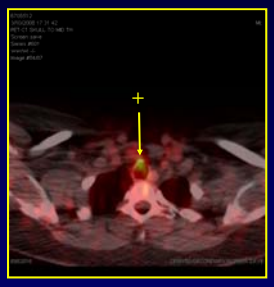
“Equivocal” FDG-PET/CT N Staging

- Stage II High Grade True Vocal Cord CA



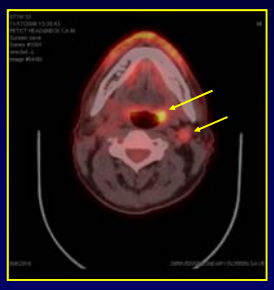
Mixed False +/True + Staging

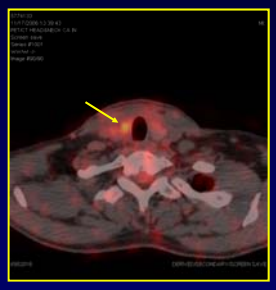
- Stage III Tonsil CA and…



Incidental Thyroid Screening

- Stage IVa Tonsil CA and…



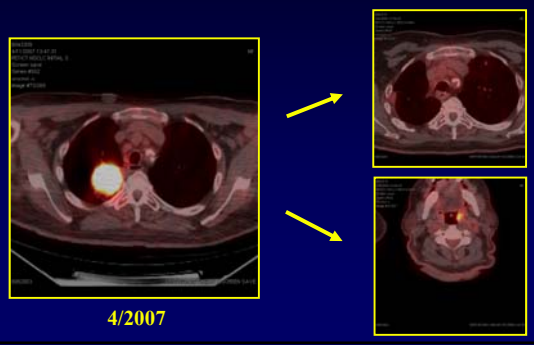


Incidental Parotid/Lung Screening

- Stage III Larynx CA and…

Incidental H&N Primary

- Follow-up for resected Stage II lung adeno CA



4/2007

Future Directions

RTOG 0522

- Phase III trial comparing chemoXRT +/- C225 EGFR blockade
- First treatment Phase III with PET/CT outcomes (NCI/CMS/FDA)
  - Post-treatment neck response staging accuracy
  - Pre/post chemoXRT primary tumor and nodal SUV_{max} & outcomes
  - Post hoc PET/CT image processing analysis

http:/www.rtog.org/members/protocols/0522/0522.pdf

National Oncologic PET Registry

- Prospective collection of clinical/imaging data for candidate indications, in exchange for CMS reimbursement
- Opened in 2006
- Pilot publication
  - 22,975 cases from 1,178 centers
  - PET/CT altered management in 36.5% of cases

Hillner B, et. al. *J Clin Oncol* [2008]

Novel Non-FDG Tracers

- Amino Acids
  - *O*-(2-18F-fluoroethyl)-L-tyrosine (FET)
  - L-3-18F-fluoro-α-methyltyrosine (FMT)
  - 3,4-dihydroxy-6-18F-fluoro-L-phenylalanine (FDOPA)
- Lipids
  - 18F-fluorocholine (FCH)
  - 18F-fluoroacetate
- 18F-16α-17β-fluoroestradiol (FES)
- 3'-deoxy-3'-18F-fluorothymidine (FLT)
- 18F-fluoromisonodazole (FMISO)

Vallabhajosula S, *Sem Nucl Med* 37:400-19 [2007]

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MDACC H&N SPORE
VA MERIT