

XVII. APPENDIX 4: Data Abstraction Tables of Included Diagnostic Efficacy Studies of FDG-PET in Cancer

Diagnostic Efficacy of FDG PET in Head and Neck Cancer

Study	Patients/Methods	Results/Comments
Lowe et al. (1997) (St. Louis Health Sciences Center, Missouri)	<p>Purpose To evaluate (?prospectively) chemotherapy response using PET in patients with advanced head and neck cancer</p> <p>Cases 28 consecutive patients with Stage III/IV head and neck cancer who were participating in a neoadjuvant organ-preservation protocol using taxol and carboplatin</p> <p>Methods</p> <ul style="list-style-type: none"> PET scans and tissue biopsy performed on all patients before and after (1-2 weeks) chemotherapy Tissue obtained after 2 courses if clinical response by clinical exam and CT was > 50% as determined by change in primary tumor size, and after 3 courses if response was > 50% Blinded visual consensus analysis of PET by two readers using a before and after comparison format on one page per patient using a 4-point scale ROIs measured and SURs calculated corrected for body weight while blinded to pathology results Post therapy biopsies obtained after PET blinded to PET data Patients classified as pathologic complete response (PCR) or residual disease (RD) based on biopsy results <p>Limitations of study design</p> <ul style="list-style-type: none"> Small sample size Short follow up time No comparison data presented 	<p>Detecting disease recurrence (with 95% CI) (21 positive cases, 6 negative cases) PET: Se=90% (77-100%); Sp=83% (53-100%); PPV=95%; NPV=71%; Accuracy=89%; LR+=5.43; LR-=0.11</p> <p>Authors' comments</p> <ul style="list-style-type: none"> PET may be used in situations when sampling bias is more likely eg, difficult access, questionable post-therapy biopsy results, or a normal, reepithelialized appearance of tumor site post-therapy PET scan should be obtained before biopsy to avoid possible confusing effects of post biopsy inflammation or wait 5-7 days after needle biopsy or 6 weeks after surgical resection Positive PET scan may be indicative of residual tumor and warrant repeat tissue sampling or resection Negative PET scan may also necessitate tissue confirmation to rule out false negative results

<p>Purposes To prospectively evaluate primary disease, early nodal metastases, and recurrent disease in patients head and neck cancer</p> <p>Cases 54 consecutive patients who presented to head and neck clinics at both hospitals for assessment of squamous cell carcinoma (31 with primary disease, 23 with suspected recurrence or residual disease)</p> <ul style="list-style-type: none"> • of which 16 had neck dissections (N0=8; N1=4; N2a=2; N2b=2) <p>Methods</p> <ul style="list-style-type: none"> • All patients examined under anesthesia and clinically staged before imaging • All suspicious areas of aerodigestive tract were biopsied • All patients had PET and anatomic imaging: CT (n=37); MRI (n=13); CT+MRI (n=4) • Clinical assessment, CT, MRI, PET evaluation, and histology each performed independently • Standard size and morphological criteria used to assess nodal disease on CT/MRI <p>Limitations of study design</p> <ul style="list-style-type: none"> • Small sample sizes in subgroup analyses • High suspicion of malignancy (referral bias) • Only biopsy-verified cases analyzed (work up bias) • Criteria for positive PET not defined (potential test review bias) • Blinding unclear (potential test review bias) • PET data analysis not fully described • Order of biopsy and imaging not described 	<p>Detecting known primary disease (31 positive cases, 0 negative cases) All 31 primary malignant tumors were detected by PET as hypermetabolic areas</p> <p>Detecting nodal metastases (12 positive cases, 4 negative cases)</p> <p>PET: Se=67% CT/MRI: Se=67% Clinical exam: Se=58%</p> <ul style="list-style-type: none"> • 7 of 12 patients with involved nodes had clinically obvious nodal metastases; all were identified by PET • PET identified 1 of 5 patients with occult nodal disease <p>Detecting local recurrence (10 patients with recurrences, 2 non recurrences) PET correctly identified presence or absence of disease in all 12 patients Se=100%</p> <p>Detecting nodal recurrence (8 positive patients, 5 negative patients)</p> <p>PET: Se=100%; Sp=100% CT/MRI: Se=75%; Sp=80% Clinical exam: Se=100%; Sp=60%</p> <p>Other findings</p> <ul style="list-style-type: none"> • Abnormal uptake unrelated to malignancy was caused by osteomyelitis of the mandible following dental extraction and surgery performed within 2 months of PET imaging. • Findings did not affect clinical management • Effects of post-biopsy inflammation on imaging unclear.

Study	Patients/Methods	Results/Comments
Myers et al. (1998) (SUNY, VA Medical Center, Buffalo, NY)	<p>Purpose To assess retrospectively the clinical effectiveness of PET in the evaluation of N0 staged neck patients with squamous cell cancer (SCC) of the upper aerodigestive tract</p> <p>Cases 14 patients with N0 disease (24 total neck dissections) on clinical exam.</p> <ul style="list-style-type: none"> • Stage I=1; Stage II=8; Stage III=2; Stage IV=3 <p>from a larger study of 116 consecutive patients diagnosed with head and neck cancer, of which:</p> <ul style="list-style-type: none"> • 72 had biopsy-proven SCC • 26 underwent neck dissections <p>Methods</p> <ul style="list-style-type: none"> • All patients had complete exam consisting of PET and panendoscopy • Nine patients had preoperative CT • All patients had modified radical neck dissections with removal of levels 1 to V • Pathologic specimens examined for number of nodes, presence of malignancy, and extracapsular spread. • PET scans correlated with pathologic results, site of primary tumor, and CT <p>Limitations of study design</p> <ul style="list-style-type: none"> • Small number of cases • Imaging tests influenced selection of patients for surgery and nodal sampling not described (work up bias) • Thresholds for characterizing disease on imaging not reported (potential test review bias) • Independent blind evaluation of tests and gold standard not reported (potential test review bias and diagnostic review bias) 	<p>Detecting nodal metastases (9 positive dissections, 15 negative dissections)</p> <p>PET: Se=78%; Sp=100%; PPV=100%; NPV=88%; accuracy=92% CT: Se=57%; Sp=90%; PPV=80%; NPV=75%; accuracy=76%</p> <p>*tend in increased accuracy of PET over CT ($P = 0.11$) PET + CT: Se=86%; Sp=100%; PPV=100%; NPV=91%; accuracy=95%</p> <p>Other findings</p> <ul style="list-style-type: none"> • PET accurately detected presence or absence of cervical metastases in all 8 patients with SCC of the oral cavity • In 5 patients with either carcinoma of the oropharynx or hyopharynx PET correctly identified cervical metastases in two of four patients with neck metastases

Diagnostic Accuracy Efficacy Studies of FDG PET in Breast Cancer

Study	Patients/Methods	Results/Comments
Ulech et al. (1996) (Univ. of Illinois College of Medicine and Downstate Clinical PET Center, Peoria, Illinois)	<p>Purpose To study PET for staging axillary lymph node metastases in breast cancer</p> <p>Cases 124 patients with newly diagnosed and histologically proven breast cancer who were studied with PET prior to therapy:</p> <ul style="list-style-type: none"> • Stage I=65; Stage IIa=30; Stage IIb=23; Stage IIIa=6 • Tumor size: < 1cm=16; >1cm=49; >2cm=30; >3cm=29 • Mixed types- 82% invasive ductal carcinoma • Hyperglycemic patients excluded • Axillary status: 10 patients with positive lymph nodes on clinical exam, 4 patients on mammography <p>Methods</p> <ul style="list-style-type: none"> • All patients had ER and PR assays, DNA flow cytometry, SPF, PET • DUR calculated for primary and axillary node uptake: DUR 1-3 for metastases and ≥ 3 for primary tumor • Qualitative PET read as positive if discrete focal uptake > background • Images read by experienced radiologists, final read by nuclear medicine physician from hard copy and video monitor blinded to lymph node status; reader aware of primary carcinoma • All patients had level II dissection, some had Level III • Average # dissected nodes=20 (range 7-39) for true positives; 16 (range 7-36) for false negatives; 20 (range 9-46) for false positives • Qualitative PET compared to pathology • 20 patients with false positive results followed for 1-2 years for recurrence • DUR correlated with tumor size, grade and histopathology, SPF, DNA ploidy, and hormone receptors <p>Other findings</p> <ul style="list-style-type: none"> • Weak correlation between DUR of metastatic axillary lymph nodes and tumor size and between SPF • No correlation between DUR and tumor grade or histopathology • Correlation between DUR and hormone receptors was undetermined <p>Authors' comments</p> <ul style="list-style-type: none"> • False positive findings may benefit from complementary use of lymphoscintigraphy • Confirmation is needed to determine if PET should be considered the initial test in axillary lymph nodes 	<p>Detecting axillary lymph node involvement (44 positive cases, 80 negative cases)</p> <ul style="list-style-type: none"> • PET: Se=100%; Sp=75%; PPV=69%; NPV=100% • Reasons for false positive results undetermined <p>Limitations of study design</p> <ul style="list-style-type: none"> • Source population unclear: ?consecutive series (potential referral bias) • Order of testing unclear • Influence of PET results on biopsy procedure unclear (potential diagnostic review bias but minimized by extensive nodal sampling)

Study	Patients/Methods	Results/Comments
<p>Purpose to prospectively evaluate FDG-PET as a screening test for axillary lymph node metastases in breast cancer</p> <p>Cases 50 patients with 52 axillary dissections (2 patients with bilateral disease) who met the following inclusion criteria:</p> <ul style="list-style-type: none"> • Age ≥ 30 years • Operable breast cancer • At least level 2 axillary lymph node dissection to be performed within 3 months of PET • Minimum of 10 lymph nodes dissected • Ability to fast for at least 4 hours <p>Exclusion criteria were:</p> <ul style="list-style-type: none"> • History of ipsilateral axillary lymph node dissection • Preoperative systemic therapy • Primary tumor < 5mm • Uninterpretable PET scan (2) <p>Final primary tumor staging: T0=1; T1=31; T2=17; T3=3</p> <p>Methods</p> <ul style="list-style-type: none"> • Transmission and emission PET scans obtained on two scanners (Scanditronix SP3000 and CTI ECAT EXACT) • PET scans reviewed by two independent readers blinded to all information other than axilla side • PET scans graded on a 5-point Likert scale for presence of increased FDG uptake and scan quality: discrepancies resolved by consensus; scores ≥ 3 are positive • Histopathology obtained: all lymph nodes dissected (average #/patient=17) • Operating characteristics of both scanners compared <p>Limitations of Study Design</p> <ul style="list-style-type: none"> • Patient source unclear; 2 consecutive series (potential referral bias) • Association between test result and gold standard determination unclear (potential diagnostic review bias minimized by extensive nodal sampling) • No follow-up data presented • Authors used higher dose of FDG and longer scanning times than in other studies 		

Study	Patients/Methods	Results/Comments
Crippa et al. (1998) (National Cancer Institute, Milan, Italy)	<p>Purpose to evaluate prospectively noninvasive staging of axillary nodes using PET for metastases</p> <p>Cases 68 consecutive patients with palpable breast nodules (unilateral disease=64; bilateral=4) who were scheduled for breast surgery w/ or w/o ALND based on clinical and instrumental (mammography and/or ultrasonography) results</p> <ul style="list-style-type: none"> • 61 with ALND with 72 total axilla sampled: N0=36; N1a=21; N1b=13; N2=2 • 11 with no ALND were classified as negative • total # breast nodules=81 (73 malignancies, 8 benign): T1=45; T2=30; T3=2; T4=4 - 63% of malignancies were infiltrating ductal carcinomas - benign conditions were proliferative dysplasia without atypia or focal inflammation - average size = 20mm (4mm-67mm) <p>Methods</p> <ul style="list-style-type: none"> • PET emission and transmission scans performed 1 to 7 days before surgery • PET visual interpretation blinded to histopathology: localized uptake > surrounding tissue classified as positive • Mean SUVs of breast carcinoma were calculated • ROC analysis performed using SUVs between two groups to assess SUV as a prognostic indicator • Average # dissected nodes/axilla=21 (range 12-38) • No treatment decisions made on the basis of PET <p>Limitations of study design</p> <ul style="list-style-type: none"> • High index of suspicion of malignancy (referral bias, minimized by using consecutive series) • Blinding of readers to other clinical information not reported (potential test review bias) • Diagnostic review bias minimized by extensive nodal sampling • PET used in test sequence, incremental value not assessed 	<p>Detecting axillary node involvement</p> <p>No disease (10 positive axilla, 26 negative axilla) PET: Se=70%; Sp=92%; accuracy=86%</p> <p>N1a disease (8 positive axilla, 13 negative axilla) PET: Se=87.5%; Sp=100%; accuracy=95%</p> <p>N1b-2 (9 positive axilla, 6 negative axilla) PET: Se=100%; Sp=67%; accuracy=87%</p> <p>overall (27 positive axilla, 45 negative axilla) PET: Se=85%; Sp=91%; accuracy=89%; PPV=85%; NPV=91%</p> <ul style="list-style-type: none"> • false positives due to vascular uptake and undetermined causes • false negatives due to microscopic and unexplained macroscopic involvement, mean size=6mm (5-8mm) <p>Other findings</p> <ul style="list-style-type: none"> • Median SUV in carcinomas with axillary metastases (4.6) was higher than that in carcinomas without axillary metastases (2.9) but there was a significant overlap between the two groups (interquartile ranges= 2.7-7.2 and 1.9-4.5, respectively) • ROC analysis showed best cutoff value of SUV (2.9) was associated with a Se=74% and Sp=58%. • Any change in reading of ROC curve was not useful in patient management referred for ALND • Authors propose using PET in patients with very low probability of axillary metastases (Ia), in whom axillary surgery may be avoided, to monitor relapses • SUV value of primary not a prognostic indicator of axillary spread

Study	Patients/Methods	Results/Comments
<p>Palmedo et al. (1997) (University of Bonn, Germany)</p> <p>Purpose to compare prospectively the diagnostic accuracy of FDG PET vs. scintimammography (SMM) (planar and single-photon emission tomography) using ^{99m}Tc MIBI</p> <p>Cases 20 patients with 22 suspicious primary lesions detected by PE or mammography scheduled for excisional biopsy <ul style="list-style-type: none"> • 14 patients with 15 malignant primary lesions (including 2 local recurrences); mean size 29mm (range 8-53mm); 3 patients with tumors \leq 8mm • 5 patients with 30 axillary node metastases (all diameters \geq 12mm) </p> <p>Methods <ul style="list-style-type: none"> • SMM followed by PET scans of breasts and axillary regions were performed > 24 hrs apart in all patients during the week prior to surgery • ROIs analyzed. MIBI TNR on planar images and SUV FDG uptake calculated • Mammograms used for scintigraphic localization • Focal uptake classified as normal or abnormal • Independent, blinded interpretation of SMM and PET by two nuclear medicine physicians • PET and SMM results each compared with histopathology </p> <p>Limitations of study design <ul style="list-style-type: none"> • Small size • High index of suspicion for malignancy (potential referral bias) • Extent of blinding to other clinical information not clear (potential test review bias) • Association between test result and gold standard determination unclear (potential diagnostic review bias) • Incremental value of test used in work up not assessed </p> <p>Detecting unknown primary (13 malignant tumors, 7 benign tumors)</p> <p>PET: Se=92%; Sp=86% SMM: Se=92%; Sp=86% <ul style="list-style-type: none"> • calculations excluded 2 recurrences • false positives due to fibroadenoma • false negatives due to local recurrences with diameters < 9mm </p> <p>Axillary node involvement (5 positive patients, 7 negative patients)</p> <p>PET correctly detected axillary involvement in all 12 patients <ul style="list-style-type: none"> • (30 positive nodes) • PET detected 9 of 30 nodes • SMM detected 8 of 30 nodes </p> <p>Quantitative analysis</p> <p>PET: mean SUV=2.57 (0.3-6.2 with median SUV=1.6) SMM: mean TNR=1.97 (1.42-3.1 with median TNR=1.8)</p> <p>Authors' comments <ul style="list-style-type: none"> • Menstrual cycle may alter MIBI uptake in normal tissue • Diffuse FDG uptake in normal tissue declines with age • Thresholds and variations in SUV calculations can impact test characteristics • Both tests could detect axillary node involvement but not extent of disease • Larger cohort needed to confirm results </p>		

Study	Patients/METHODS	Results/Comments
Bender et al. (1997) (University of Bonn, Germany)	<p>Purpose To assess the feasibility of PET in staging recurrent breast carcinoma</p> <p>Cases 75 patients with suspected recurrent or with metastatic disease in undecided or equivocal cases</p> <ul style="list-style-type: none"> • primary tumor histology: well-differentiated ductal carcinoma (n=46); infiltrating lobular carcinoma (n=10) • all patients had PET; 63 patients had PET and CT/MRI of which: <ul style="list-style-type: none"> - 14 pts with confirmed local recurrence; 17 pts w/ confirmed lymph node mets • no recurrence (N=15); local recurrence (N=20); lymph node involvement (N=28); distant metastases (N=22) <p>Methods</p> <ul style="list-style-type: none"> • All patients had routine work-up consisting of physical exam, axillary lymph node US, optional thorax/abdomen CT and/or MRI, bone scintigraphy and serum tumor markers • All had histologic confirmation (surgery or biopsy) - except 4 by follow-up • PET evaluated qualitatively using a 4-point scale (intense, moderate, low, none) • Two readers of PET not blinded to available data • PET compared independently to each of the standard imaging modalities • All patients followed for at least 6 months (1-2 visits) <p>Limitations of study design</p> <ul style="list-style-type: none"> • Small study size in subgroup analyses • High index of suspicion for malignancy (potential referral bias) • Patient inclusion based in part on results of CT/MRI (work up bias but minimized by all patients receiving definitive disease verification) • Interpretation of PET results not blinded to other clinical and imaging data; positivity criteria not defined (test review bias) • Association between test result and gold standard determination unclear (potential diagnostic review bias) 	<p>Direct visual comparison (63 patients available for direct comparison)</p> <p>Local recurrence (15 positive lesions, 48 negative lesions)</p> <p>PET: Se=73%; Sp=96%; PPV=85%; NPV=92%; Acc=90% CT/MRI: Se=91%; Sp=98%; PPV=91%; NPV=98%; Acc=97%</p> <p>Lymph nodes (22 positive lesions, 41 negative lesions)</p> <p>PET: Se=9%; Sp=93%; PPV=88%; NPV=97%; Acc=94% CT/MRI: Se=74%; Sp=95%; PPV=89%; NPV=87%; Acc=88% (discrepancies in total numbers of PET lesions vs. total number of CT/MRI lesions)</p> <p>Bone (13 positive lesions, 50 negative lesions)</p> <p>PET: Se=100%; Sp=96%; PPV=87%; NPV=100%; Acc=97% CT/MRI: Se=46%; Sp=98%; PPV=88%; NPV=86%; Acc=87%</p> <p>Lung (6 positive sites, 57 negative sites; in 5 patients)</p> <p>PET had 2 false positive* and 1 false negative results CT/MRI had 2 false positive and 1 false negative results Reasons for CT/MRI false positives not reported</p> <p>Liver (2 positive sites, 73 negative sites; in 2 patients)</p> <p>PET had one false positive* result and no false negative results CT/MRI had 1 false positive and 1 false negative result *due to artifact wrongly interpreted during the learning phase of the facility</p> <p>Authors' comments</p> <ul style="list-style-type: none"> • PET and CT/MRI had similar results re lung and liver metastases • CT/MRI identified more local recurrences correctly • PET identified 1/3 more patients with lymph node metastases, suggesting the use of PET early in restaging of breast cancer. • Semiquantitative analysis and tumor appearance info may decrease number of false positive results • Results suggest the importance of PET as a complement to morphologic tests in the staging of recurrence • PET may also play a role in whole body staging of high risk patients • Further studies are needed to assess the clinical impact of PET in the management of recurrent breast cancer and its consequence on overall survival

Study	Patients/Methods	Results/Comments
Moon et al. (1998) (UCLA, Los Angeles, California and University of Ulsan, Seoul, Korea)	<p>Purpose To retrospectively evaluate the diagnostic accuracy of PET in patients with suspected recurrent or metastatic breast cancer</p> <p>Cases 57 female patients with 83 reference sites (29 with disease, 28 no recurrence or metastases) <ul style="list-style-type: none"> • who underwent primary surgery with or without adjuvant chemo- or radiation therapy and • who were referred to the UCLA PET center from October 1990 to October 1995 (mean time interval between diagnosis and PET scan=4 yrs. range 1 mo. To 17 yr 9 mo) • who had a clinical suspicion of disease recurrence not resolved by conventional imaging • patients who underwent chemo- or radiation therapy within 3 mo before PET • lesions that were biopsied • lesions diagnosed with known disease </p> <p>Methods</p> <ul style="list-style-type: none"> • All patients underwent history and PE, multiple labs and imaging tests • Diagnostic confirmation based on biopsy, lesion morphology for tumor on 2 or more imaging studies, and for at least 6 months clinical and radiographic follow up • PET abnormalities that resolved without treatment were considered to be false-positive results • ECAT 931 and ECAT 961 were used • Independent visual inspection of PET by 3 readers informed clinical suspicion of metastases, but blinded to gold standard; discrepancies resolved by 4th reader aware of a discrepancy but not of specifics • PET images scored from 1 (definitely negative) to 5 (definitely positive) • Lesion site defined as any abnormality suggesting the possibility of breast recurrence or metastases either clinically or on imaging, therefore, analysis was biased toward positive lesions • Analysis by patient and by lesion 	<p>Overall diagnostic accuracy (29 positive cases, 28 negative cases)</p> <p>Scores ≥ 4 defined as positive PET: Se=93%; Sp=61%; PPV=82%; NPV=92%</p> <p>Scores ≥ 3 defined as positive PET: Se=93%; Sp=79%; PPV=82%; NPV=92%</p> <p>Overall diagnostic accuracy (41 positive lesions, 39 negative lesions)</p> <p>Scores ≥ 4 defined as positive PET: Se=85%; Sp=79%; PPV=81%; NPV=84%</p> <p>Scores ≥ 3 defined as positive PET: Se=90%; Sp=54%; PPV=67%; NPV=84%</p> <p>ROC analysis Az=0.91 for patient detection; Az=0.88 for lesion detection</p> <p>Interobserver variability</p> <ul style="list-style-type: none"> • In 48% of patients, scores of all 3 observers were the same • In 38% of patients, a score from one reader deviated one score grade from the other 2 readers • In 14% of patients, a score from 1 reader deviated more than 1 score grade from the other readers <p>Other findings</p> <ul style="list-style-type: none"> • Bone metastases had a larger proportion of false-negative lesions than other malignant sites when scores of 4 or 5 were regarded as positive; Bone Se=69% (11 of 16) vs. Non-bone Se=96% (24 of 25) ($p<0.05$) • False negative lesions (scored ≥ 4) included 5 bone metastases and one small breast site, of which 3 bone and one breast lesion showed mild uptake (scored 2-3), one lesion was confirmed positive on follow up PET scan • When scores of ≥ 3 were regarded as positive, lymph node sites had more false positives than other sites; Lymph Sp=13% vs. Other Sp=79% ($p<0.05$); with scores ≥ 4, Lymph Sp=60% vs. Other Sp=92% ($p<0.001$) • PPV=62% for lesions with a score of 4 and PPV=90% for lesions with a score of 5 • False positive lesions (scored ≥ 3) were attributed to muscle uptake, inflammation, and physiological and artifactual FDG uptake, and unknown causes • Characteristics of 5 patients with fasting blood glucose levels > 110 mg/dl: 4 diabetics, 2 received insulin, 3 were true negative, one true positive. <p>Authors' comments</p> <ul style="list-style-type: none"> • More strict attention to patient preparation, recognition of artifactual uptakes, and information on clinical history (re inflammatory disease) will improve specificity of PET • Limitations of study: study biased toward positive lesions and more difficult cases, not all regions were prospectively examined with other conventional imaging studies • Attenuation correction would provide a more accurate representation of tracer distribution • A prospective study is needed to further assess the role of PET in post-surgical breast cancer management <p>Limitations of study design</p> <ul style="list-style-type: none"> • Only more difficult cases included and suspicious sites assessed (referral bias) • Not all regions were prospectively examined with other conventional imaging tests • Partial blinding (potential test review bias) • Blinding of gold standard diagnosis (confirmation) to PET results unclear (potential diagnostic review bias)

Diagnostic Accuracy Efficacy of FDG PET in Lung Cancer

Study	Patients/Methods	Results/Comments
Bury et al. (1997) (CHU Liège, Belgium)	<p>Purpose to prospectively compare the accuracy of FDG-PET and conventional imaging (CI) for staging NSCLC</p> <p>Cases 141 consecutive patients between 9/94-10/96 with newly diagnosed NSCLC based on spum cytology, needle biopsy, or flexible bronchoscopy. <ul style="list-style-type: none"> exclusion criteria included poor physiological status (n=21) and inappropriate follow up (n=1) of which 109 were enrolled in the study: 77 men, 32 women; mean age=64 (44-83) squamous cell=50; adenosquamous cell=8; adenocarcinoma=46; undifferentiated large cell=5 stage I=32; stage II=8; stage IIIA=22; stage IIIB=8; stage IV=39; N1=20; N2=10; N3=4; T4=4 benign conditions = nonspecific inflammation, pneumonia, multinodular goiter, localized FDG uptake in hepatic-splenic angle of colon 66 cases with suspected mediastinal involvement on CT or PET had biopsy confirmation </p> <p>Methods <ul style="list-style-type: none"> all patients had CI before PET; CI = chest and abdominal CT scanning and bone scintigraphy suspicious lesions on bone scintigraphy confirmed by bone radiography contrast CT positive criteria > 10mm on short axis PET data analyzed by visual interpretation; positive results=moderate (about twice the activity in contralateral or reference region) and intense (markedly higher than reference activity) FDG uptake PET and CI interpreted separately by 2 nuclear medicine readers and 2 radiology readers blinded to N and M histology but not blinded to histology of primary tumor confirmation of suspected mediastinal involvement or distant metastases on CI or PET done within 21 days of imaging N staging confirmed by extensive nodal sampling M staging confirmed by biopsy (2) or clinical and/or radiologic follow-up (88); absence of demonstrated metastases 6 months after negative imaging considered negative for metastases statistical analysis by patient </p> <p>Limitations of study design <ul style="list-style-type: none"> choice of N stage cohort influenced by imaging tests; only biopsy verified cases included in N cohort (work up bias minimized by all patients having both tests) readers not blinded to primary tumor histology (partial test review bias) strong association between test results and determination of gold standard (diagnostic review bias minimized by extensive nodal sampling in N staging) incomplete reporting of methods for evaluating changes in treatment strategy </p>	<p>Defining known primary disease (109 cases) <ul style="list-style-type: none"> all primary tumors showed increased focal FDG uptake; intense in 101 cases, moderate in 8 cases no correlation between histopathology and FDG uptake </p> <p>Mediastinal involvement (34 positive cases, 32 negative cases) PET: Se=89% (95% CI: 72-96%); Sp=87% (95% CI: 71-97%); PPV=89%; (95% CI:72-96%); NPV=87% (95% CI: 71-98%); accuracy=83% CT: Se=79%; Sp=71%; PPV=75%; NPV=76%; accuracy=75% (no 95% CI reported) <ul style="list-style-type: none"> disagreement between PET and CT in 29 cases (44%); correct changes by PET=22 cases (33%); correct changes by CT=7 (11%) disagreement between PET and CT in 29 cases (44%); correct changes by PET=22 cases (33%) </p> <p>Distant metastases (39 positive cases, 70 negative cases) PET: Se=100% (95% CI: 91-100%); Sp=94% (95% CI: 86-98%); PPV=90% (95% CI: 78-97%); NPV=100% (95% CI: 95-100%); accuracy=98% (95% CI: 90-98%) CI: Se=82%; Sp=89%; PPV=80%; NPV=89%; accuracy=86% (95% CI not reported) <ul style="list-style-type: none"> moderate FDG uptake in 7 of 8 cases were < 2 cm. PET false positives caused by nonspecific inflammation in axillary lymph node, pneumonia sequelae, benign multinodular goiter, anatomical misidentification PET had no false positive FDG uptake in adrenal glands PET correctly changed M stage, as determined by CI, in 15 cases (14%) </p> <p>Changes in therapeutic strategy PET modified therapy in 27 patients (20%) (10 to curative surgery, 8 to a more curative approach with chemo- and/or radiation therapy, 9 to more palliative approach) <ul style="list-style-type: none"> no patient follow up data reported </p> <p>Other findings authors found PET more useful than CI in evaluating adrenal masses <ul style="list-style-type: none"> false positive PET in axillary site probably caused by extravasation of antecubital vein during FDG injection lack of anatomical markers limited precise localization of some PET findings CI + PET could increase the accuracy of detection prospective comparison needed to compare PET with bone scanning </p>

Study	Patients/Methods	Results/Comments
<p>Erasmus et al. (1997) (Duke Univ. Medical Center, Durham, NC)</p> <p>Purpose To assess PET in differentiating benign from metastatic adrenal masses in patients with bronchogenic carcinoma</p> <p>Cases 27 consecutive cases with 33 total lesions (23 malignant, 10 benign) presenting to thoracic surgery, oncology, or pulmonary between January 1993 and January 1996 with bronchogenic carcinoma and an adrenal mass detected by CT</p> <p>Characteristics:</p> <ul style="list-style-type: none"> • 19 men, 8 women; mean age 57 yrs (range 39-76) • 24 with NSCLC, 3 small cell; bilateral masses in 6 patients • mean diameter of adrenal masses=3 cm (range 1-9cm) <p>Methods</p> <ul style="list-style-type: none"> • FDG PET performed after CT • Independent interpretation of adrenal activity by 3 readers blinded to clinical and pathologic findings and other imaging test • Positive activity= activity > background; negative activity= activity ≤ background • ROI and SUR determined blinded to biopsy results • Confirmation of adrenal masses by: <ul style="list-style-type: none"> - percutaneous needle biopsy (n=1) within a mean of 5 days before PET (n=9) and after (n=2), - growth characteristics on follow up (mean=4 months) CT (n=16), and - CT Hounsfield unit measurement < 10H diagnostic of a benign lesion (n=6) <p>Limitations of study design</p> <ul style="list-style-type: none"> • High probability of malignancy and benign conditions not depicted (potential referral bias) • Association between PET results and choice of confirmation method unclear (potential diagnostic review bias) • Incremental value of PET in test sequence not determined 	<p>Defining adrenal disease (23 malignant lesions, 10 benign lesions)</p> <p>PET visual analysis: Se=100%; Sp=80% SUR analysis: malignant lesions mean-6.28 ± 2.5 vs. benign lesions mean=1.77 ± 0.89 (p < 0.0001)</p> <p>Other findings</p> <ul style="list-style-type: none"> • Characteristics of malignant masses: <ul style="list-style-type: none"> - mean diameter = 4 cm - n=6 new on follow up CT (mean time=4 months), n=10 growth changes on CT; n=7 by biopsy - changes in adrenal masses on CT consistent with changes in thorax • Characteristics of benign masses: <ul style="list-style-type: none"> - n=4 by biopsy; n=5 with features < 10 H on CT; n=1 with benign features on CT 	

Study	Patients/Methods	Results/Comments
<p>Guhlmam et al. (1997) (University of Ulm, Germany)</p> <p>Purpose to evaluate retrospectively the accuracy of FDG PET in thoracic lymph node staging in patients with NSCLC</p> <p>Cases 46 consecutive patients (32 cases, 14 benign processes) who underwent thoracotomy for lung tumors from 1994 to 8/95: <ul style="list-style-type: none"> • 41 men, 5 women; mean age=56.7 yrs (24-78) • squamous cell (n=19); adenocarcinoma (n=7); large cell (n=6) • T1=3; T2=12; T3=10; T4=7; N0=12; N1=5; N2=11; N3=4. • benign conditions: pneumonia (n=4); tuberculosis (n=3); one each of florid abscess, aspergiloma, hamartoma, aneurysm of subclavian artery, lung fibrosis, inflammatory pseudotumor of which 32 malignant cases underwent further mediastinal evaluation</p> <p>Methods <ul style="list-style-type: none"> • all patients underwent contrast CT of chest prior to PET 3 weeks before surgery • positive node on CT defined as > 10mm in short axis diameter • blind, independent interpretation of CT by two experienced radiologists to clinical and PET findings • blind, independent visual interpretation of PET by 2 experienced nuclear medicine physicians • histopathology and TN classification confirmed surgically on patients with primary lung cancer • surgeon conducted thorough dissection of mediastinal nodes, data on extent not reported • PET and CT results mapped and compared to histologic findings • statistical analysis reported by patient </p> <p>Limitations of study design <ul style="list-style-type: none"> • retrospective study of surgical series—high probability of malignancy (potential referral bias) • small sample size (limits subgroup analyses) • only biopsy verified cases analyzed (work-up bias) • association between test results and biopsy confirmation unclear (potential diagnostic review bias, minimized by extensive nodal sampling) </p>	<p>Defining unknown primary tumor (32 malignant cases, 14 benign cases) PET: Se=94%; Sp=86%; accuracy=91% CT: data not reported</p> <ul style="list-style-type: none"> • PET false positives caused by an aspergiloma with active inflammation and a florid abscess • PET false negatives caused by a 1 cm intrapulmonary adenocarcinoma metastasis and bronchioalveolar carcinoma <p>Mediastinal/Hilar involvement (with 95% CI) (20 positive cases, 12 negative cases) PET: Se=80% (56%-94%); Sp=100% (73%-100%); accuracy=87% (71%-96%)</p> <ul style="list-style-type: none"> • PET accuracy (# patients): N0=12/12; N1=3/5; N2=9/11; N3=4/4 • CT: Se=50% (27%-73%); Sp=75% (43%-95%); accuracy=59% (41%-76%) ($p<.02$ for overall accuracy) • CT accuracy (# patients): N0=9/12; N1=2/5; N2=6/11; N3=2/4 • CT false positive nodes caused by nonspecific inflammation including sarcoidosis, inflammatory pseudotumor, and pneumonia • PET false positive hilar nodes caused by nonspecific inflammation • PET differentiated N1/N2 disease from N3 disease in 4 patients, but only 2 of 4 with CT <p>Other findings <ul style="list-style-type: none"> • curative resection would have been avoided in 2 patients with N3 disease on PET but not with CT • tumor involvement of peribronchial hilar nodes and mediastinal nodes adjacent to the bronchus may be enhanced with anatomic/ metabolic imaging • PET + CT may decrease the need for invasive diagnostic procedures such as mediastinoscopy </p>	

Study	Patients/Methods	Results/Comments
Hagberg et al. (1997) (VA Palo Alto Health Care System and Stanford University School of Medicine)	<p>Purpose</p> <ul style="list-style-type: none"> to evaluate retrospectively PET in characterizing pulmonary nodules and staging bronchogenic carcinoma to compare CT with PET for diagnosing N2 disease <p>Cases</p> <p>49 consecutive patients presenting between 9/94 and 3/96 (31 malignant cases, 18 benign cases) with 54 pulmonary nodules (44 positive nodules, 10 negative nodules):</p> <ul style="list-style-type: none"> 45 men, 4 women; mean age=63 (37-85) squamous=15 nodules; adenocarcinoma=16; large cell=3; adenosquamous=3; bronchoalveolar=2; atypical carcinoid=1; small cell=1; renal cell=2; malignant melanoma=1 benign conditions: granuloma=4; hamartoma=3; necrotic tissue=2; fungal ball=1 exclusion criteria: indefinite PET scan (2) and inadequate histopathologic information of mediastinum (11) 18 of 31 malignant cases had complete PET, CT, and histopathology information and were included in analysis of mediastinal nodes (N2 only) <p>Methods</p> <ul style="list-style-type: none"> CT performed and interpreted prior to PET CT interpreted by one investigator; positive mediastinal lymph nodes > 1 cm in short axis diameter initial PET scans visually interpreted by one investigator not blinded to CXR or CT findings blinded mediastinal PET images reread by two investigators PET FDG uptake classified as positive, negative or indeterminate—no difference between initial read and reread, but methods for comparison not described all pulmonary nodules confirmed by histo- or cytopathology; extent of nodal sampling not reported data analyzed by node <p>Limitations of study design</p> <ul style="list-style-type: none"> small number of subjects retrospective design—patient source and filters unclear (potential referral bias) influence of imaging tests on selection of surgical candidates unclear; N stage cohort restricted to biopsy verified cases (work up bias) association of test results and determination of gold standard unclear (potential diagnostic review bias) interpretation of primary tumor not blinded (test review bias) 	<p>Defining unknown primary tumor (44 positive nodes, 10 negative nodes)</p> <p>PET: Se=93%; Sp=70% CT: no data reported</p> <ul style="list-style-type: none"> all false positives caused by granulomas 3 false negatives caused by poor quality PET scans (hyperglycemia at the time of scan, no attenuation correction, r outdated scanner); one false negative due to renal cell carcinoma unexplained <p>Medastinal Involvement—N2 disease only (9 positive nodes, 9 negative nodes)</p> <p>PET: Se=67%; Sp= 100% CT: Se=56%; Sp=100%</p> <ul style="list-style-type: none"> small numbers, selection and verification bias may contribute to lack of significance between PET and CT <p>Other findings/Comments</p> <ul style="list-style-type: none"> quantitative analysis may allow more accurate differentiation of disease balanced discussion of the influence of study size, selection bias and verification biases on results further study needed to clarify role of PET in staging cost-effectiveness studies needed prior to advocating the routine use of PET in management of NSCLC

Study	Patients/Methods	Results/Comments
<p>Steinert et al. (1997) (University Hospital, Zurich, Switzerland)</p> <p>Purpose to compare prospectively (?) the accuracy of FDG PET with CT in staging NSCLC</p> <p>Cases 62 surgical candidates with suspected or proven NSCLC who had PET between 2/94 and 3/96 and who had no prior neoadjuvant therapy or diabetes</p> <ul style="list-style-type: none"> • exclusion criteria: inadequate CT=2; distant metastases=8; inadequate nodal sampling=5 • therefore, 47 patients with suspected or confirmed NSCLC of mixed types remained in the study • squamous=24; adenocarcinoma=17; large cell=6 • 29 (62%) with nodal metastases; N0=N1=34; N2=7; N3=6 <p>Methods</p> <ul style="list-style-type: none"> • CT, emission and transmission PET obtained on all patients • blind, independent interpretation of PET and CT scans before surgical staging • CT positive criteria=nodes > 10mm in short axis diameter, except upper paraatracheal stations > 7mm or infracarinal station > 1mm • presence and site of mediastinal and tracheobronchial nodes recorded according to ATS lymph node station mapping system; extent of lymph node metastases classified according to AJC lung cancer staging system • all patients underwent extended surgical lymph node staging regardless of PET or CT findings or nodal size • PET and CT available to surgeon during surgery • patients undergoing left thoracotomy had limited sampling of mediastinal lymph nodes; care was taken to resect all preoperatively staged positive lymph nodes • PET and CT correlated with histopathologic results <p>Limitations of study design</p> <ul style="list-style-type: none"> • Real-time prospective design unclear • Patient source unclear and high probability of malignancy in surgical series (potential referral bias) • Only biopsy verified cases analyzed (work up bias) • Strong correlation between imaging results and biopsy confirmation (diagnostic review bias) minimized by nodal sampling 	<p>Detecting mediastinal lymph node metastases (28 positive nodes, 84 negative nodes)</p> <p>PET: Se=89%; Sp=99%; PPV=96%; NPV=9%; accuracy=9%</p> <p>CT: Se=57%*, Sp=94%; PPV=78%; NPV=87%; accuracy=85% * (P=.0066)</p> <p>(n=47 patients)</p> <ul style="list-style-type: none"> • PET: 45/47 (96%) correctly staged vs. CT: 37/47 (79%) (P=.0134) <p>Other findings</p> <ul style="list-style-type: none"> • no statistically significant difference between staging with conventional CT and with spiral CT • correlation of nodal station on imaging with surgical results matched except for one case 	

Study	Patients/Methods	Results/Comments
Vansteenkiste et al (1997) (UHG, Leuven, Belgium)	<p>Purpose to compare prospectively?? CT, PET, and PET + CT in staging mediastinal lymph nodes in patients with NSCLC</p> <p>Cases Unknown # of patients with suspected or biopsy proven NSCLC who were potentially operable after standard staging for distant metastases</p> <ul style="list-style-type: none"> • exclusion criteria: diabetes; treatment with oral corticosteroids; ischemic cardiomyopathy; mediastinal invasion of primary tumor; obvious bulky metastases • records of 50 patients treated between 9/95 and 4/96 were analyzed <ul style="list-style-type: none"> - squamous=32; adenocarcinoma=10; large cell=8 - T1=3; T2=32; T3=15; N0=35; N2=15 <p>Methods</p> <ul style="list-style-type: none"> • interpretation of contrast CT by two interpreters blinded to bronchoscopic or pathologic findings; positive node ≥ 15 mm long axis diameter • SUV PET images interpreted blinded to clinical CT, and pathologic data by two independent readers; five point semiquantitative scale used 1-5; positive node= 4 or 5 • CT + PET visually interpreted by two readers blinded to pathologic data • surgical staging done by mediastinoscopy and intraoperative staging in case of resection • CT, PET, and surgical staging carried out within one month • MLN map used for imaging and surgical staging • data analyzed by patient <p>Limitations of study design</p> <ul style="list-style-type: none"> • Small sample size • Limited patient data: high probability of malignancy (potential referral bias) • prospective design unclear • only biopsy verified cases analyzed (work up bias) • association between test results and determination of gold standard unclear (diagnostic review bias) • extent of nodal sampling not reported • blinding to clinical data on visual interpretation not reported (potential test review bias) • methods for assessing changes in treatment not reported 	<p>Detecting mediastinal involvement (15 positive cases, 35 negative cases)</p> <p>PET: Se=67%; Sp=97%; accuracy=88%; PPV=91%; NPV=87%</p> <p>CT: Se=67%; Sp=63%; accuracy=64%; PPV=43%; NPV=81%</p> <p>PET + CT: Se=93%; Sp=97%; accuracy=96%; PPV=33%; NPV=97%</p> <ul style="list-style-type: none"> • of 18 discordant results, CT was correct in 1/18, and PET was correct in 17/18 ($p=0.004$) <p>Authors' comments</p> <ul style="list-style-type: none"> • mediastinoscopy could be omitted in patients with normal CT and PET or in patients with abnormal CT but normal PET • all patients with abnormal mediastinal PET should still proceed to invasive mediastinal staging, to be sure that no patient with N0 or N1 disease is denied the chance of cure by direct surgical resection • in this study the need for invasive mediastinal staging could be reduced to 13 or 50 patients, resulting in important savings in operation time • if accuracy of mediastinal PET will be confirmed in future data, it is likely that PET will substantially change current clinical practice of staging of NSCLC

Study	Patients/Methods	Results/Comments
Sasaki et al. (1996) (Kyushu University, Fukuoka, Japan)	<p>Purpose to compare prospectively FDG PET with CT in the detection of mediastinal lymph node metastases</p> <p>Cases 29 newly diagnosed patients with NSCLC of mixed types who had undergone surgery and who had pathologic confirmation of disease • adenocarcinoma= 18; squamous= 9; • NO-N1= 17; N2= 11; N3= 1 • 132 out of 261 mediastinal lymph nodes were surgically resected and histopathology confirmed of - 71 regions had CT, PET, and histopathologic information and were included in the study</p> <p>Methods • mediastinal lymph nodes classified into nine regions based on mapping proposed by the Japan Lung Cancer Society • FDG uptake measured by TMR of the primary tumor • visual interpretation of PET images performed by 3 nuclear medicine readers • PET positive criteria were FDG uptake in nodes> that in other mediastinal structures contrast CT interpreted by 2 radiologists • CT positive nodes >10 mm on short axis diameter • gold standard biopsy obtained surgically • data analyzed by nodal region</p>	<p>Detection of known primary (29 lesions) PET FDG uptake: 9.1±4.6 (TMR±SD) CT: 43.3±18.5 mm (mean ± SD)</p> <p>Mediastinal lymph node metastases (17 positive regions, 54 negative regions) PET: Se=76%; Sp=98%*; Accuracy=93%**; PPV=93%; NPV=93% CT: Se=65%; Sp=87%*; Accuracy=82%**; PPV=61%; NPV=89% * ** - ($P<0.05$)</p> <ul style="list-style-type: none"> • All PET false negatives < 7mm in short axis diameter due to partial volume effect • smallest true positive on PET was 7mm in short axis diameter • CT false positives caused by non-specific inflammatory changes and an enlarged tracheobronchial lymph node of unreported cause • PET false positive caused by an enlarged tracheobronchial lymph node of unreported cause <p>Authors' Comments</p> <ul style="list-style-type: none"> • voluntary and involuntary movement can contribute to underestimation of FDG uptake • mediastinal evaluation may have been limited by PET field of view • use of quantitative analysis using PET is limited in lymph node evaluation due its complexity, the influence of the partial volume effect, and limited visual identification of lymph nodes • authors suggest PET as a complementary diagnostic method with CT; improvements in technical and quantitative methods should improve the diagnostic ability of PET <p>Limitations of study design</p> <ul style="list-style-type: none"> • not real-time prospective design (referral bias) • regions included in analysis represent an unknown number of patients • only biopsy verified cases analyzed (work up bias) • blinding of readers not reported (test review bias) • association between test results and determination of gold standard unclear, and extent of nodal sampling not described (potential diagnostic review bias)

Diagnostic Accuracy and Diagnostic Thinking Efficacy Studies of FDG PET in Solitary Pulmonary Nodules

Study	Patients/Methods	Results/Comments
Dewan et al (1997) (Creighton University and VAMC Omaha, NE)	<p>Purpose to compare the probability of cancer (pCA) in a SPN using standard criteria with Bayesian Analysis and PET (retrospective analysis)</p> <p>Cases 52 consecutive patients (37 malignant cases, 15 benign cases) who met the following selection criteria: underwent PET imaging between April 1990 and February 1994 noncalcified, noncavitory SPN based on CXR and CT classified as indeterminate age > 30 years nodule size ≤ 3 cm group included 3 patients with extrathoracic malignancy and one patient with stable nodule for > 2 yrs Reported patient characteristics: • 43 men, 9 women; mean age=63.6 yrs \pm 11.3yrs; 79% current smokers of which 52% smoked ≥ 20 cigs/day Edge characteristics (%malignant cases vs. %benign cases): Sharp, smooth=14% vs. 20%; Lobulated=30% vs. 40%; Slightly irregular w/ few spiculations=38% vs. 33%; Grossly irregular and spiculated=19% vs. 7%</p> <p>Methods</p> <ul style="list-style-type: none"> • PET performed within 2-4 weeks after CT; CT densitometry not performed • histologic diagnosis obtained by thoracotomy, mediastinoscopy, bronchoscopy, or needle lung biopsy • qualitative PET scans read by one reader blinded to histology, clinical and radiologic data available to the reader varied, but size and location was known in all patients • benign PET = no focal FDG uptake; malignant PET = focal FDG accumulation greater than surrounding tissue but more than mild nodule edge on CT interpreted independently by 2 pulmonologists using 4 type classification system • blinded to clinical diagnosis; discrepant interpretations reached by consensus • odds-likelihood of malignancy estimated using Bayes' Theorem • standard criteria for probability of cancer (pCA) based on patient's age, smoking history, history of prior malignancy, nodule size and edge, and presence of calcification • pCA of standard criteria compared to standard criteria + PET and PET alone <p>Limitations of Study Design</p> <ul style="list-style-type: none"> • retrospective design • all patients has invasive biopsy determination, implying a high index of suspicion for malignancy (referral bias) • source of patient cohort influenced by test results (work up bias) • association between test results and determination of gold standard unclear (potential diagnostic review bias) • blinding of clinical and radiologic information varied (test review bias) • PET and other tests not independent, a requirement of Bayes' Theorem • pre-PET probability of cancer in patients unknown 	<p>Diagnostic Accuracy (37 malignancies, 15 benign)</p> <p>Overall PET+CT: Se=95%; Sp=87%; accuracy=92%</p> <p>nodules ≤ 1.5 cm PET+CT: Se=83%; Sp=100% nodules > 1.5 cm PET+CT: Se=100%. Sp=67%</p> <ul style="list-style-type: none"> • 2 false positives due to histoplasma granuloma with active inflammation • 2 false negatives were 1 cm scar adenocarcinoma and adenocarcinoma <p>Diagnostic Thinking Efficacy</p> <p>Bayes' Theorem</p> <ul style="list-style-type: none"> • LR for malignant SPN with abnormal PET=7.11 (95% CI, 6.36 to 7.96) • LR for malignant SPN with normal PET=0.06 (95% CI, 0.05 to 0.07) <p>ROC curve analysis</p> <p>PET alone was the best predictor of malignancy at different levels of pCA, the standard criteria the worst, and standard criteria + PET was intermediate</p>

Study	Patients/Methods	Results/Comments
Lowe et al (1998) (multi-site study from 9 U.S. sites)	<p>Purpose To prospectively evaluate the diagnostic accuracy of FDG-PET imaging in evaluating SPNs</p> <p>Cases 89 of 105 consecutive patients who met the following inclusion criteria: <ul style="list-style-type: none"> • Imaging performed between October 1993 and August 1994 • SPNs 0.7cm-4.0cm in size visualized on CT • Considered indeterminate for malignancy by CXR and CT and clinical data • Definitive pathologic confirmation by TTNA (n=29) or surgery (n=60) • Excluded patients. 8 no definitive pathology; 4 definitely benign SPN on CXR/CT; 2 w/o CT Reported patient characteristics: <ul style="list-style-type: none"> • 61 men, 28 women; mean age= 63 ± 9 yrs </p> <p>Methods</p> <ul style="list-style-type: none"> • Imaging performed prior to treatment of SPN • AP and lateral CXR and CT of at least chest and adrenals obtained; thin-section transaxial images and IV contrast used in some studies • Independent qualitative interpretation of CXR and CT by readers at 2 participating sites other than where the studies were performed, blinded to clinical, PET, and gold standard results • Semiquantitative analysis (SUV) performed: SUV > 2.5 = malignant • Independent visual analysis of PET by 2 readers (of 3 available readers) blinded to clinical, CXR/CT, and gold standard results in each case; focal uptake > mediastinal blood pool structures= malignant • PET compared to histology; Se, Sp, accuracy, and LRs calculated • K value assessed for interobserver variability <p>Limitations of study design</p> <ul style="list-style-type: none"> • small sample size in subgroup analyses • ? real-time prospective data collection or retrospective data collection from surgical series • conditional independence among tests unclear • high prevalence of malignancy in study population (referral bias) • inclusion criterion of biopsy verification biased toward patients with high probability of malignancy (work-up bias) • blinding of surgeons to PET results not always conducted for ethical reasons (diagnostic review bias) • pre-PET probability of cancer in patients unknown 	<p>Defining SPN (60 malignant cases, 29 benign cases) reported with 95% CI</p> <p>Overall (£ 4cm) SUV: Se=92% (82-100%); Sp=90% (79-100%); Acc=91%; LR+=9.0; LR=0.09 Visual: Se=98% (95-100%); Sp=69% (57-81%); Acc=89%; LR+=3.0; LR=0.02</p> <ul style="list-style-type: none"> • Malignant mean SUV \pm 1 SD = 6.9 ± 3.9 vs. benign = 1.7 ± 1.0 ($P < 0.001$) <p>£ 1.5cm (15 positives, 19 negatives) SUV: Se=80% (60-100%); Sp=55% (85-100%); Acc=88%; LR+=15.0; LR=0.2 Visual: Se=100% (100-100%); Sp=74% (55-93%); Acc=95%; LR+=4.0; LR=0.0</p> <p>>1.5cm (45 positives, 10 negatives) SUV: Se=96% (90-100%); Sp=80% (55-100%); Acc=93%; LR+=5.0; LR=0.06 Visual: Se=98% (94-100%); Sp=60% (46-74%); Acc=91%; LR+=2.0; LR=0.04</p> <p>£ 3.0cm (51 positives, 26 negatives) SUV: Se=90% (82-98%); Sp=92% (85-99%); Acc=91%; LR+=12.0; LR=0.1 Visual: Se=98% (94-100%); Sp=69% (56-82%); Acc=88%; LR+=3.0; LR=0.03</p> <p>Other findings</p> <ul style="list-style-type: none"> • K=0.95; 2/89 discrepant cases caused by granuloma and acute inflammation • benign conditions: granuloma (7), coccidiomycosis (4), benign cellular debris (4), nonspecific inflammation (3), necrotizing granuloma (3), fibrosis (1), hemangioma (1), aspergillosis (1), metaplasia (1) • malignancies: NSCLC (50), melanoma (5), Hodgkin's lymphoma (1), small-cell (1), malignant neural tumor (1), malignant carcinoid (1), colon cancer (1) • SUV false negatives (5): 2.0cm bronchioalveolar cancer, 1.5cm squamous cell cancer, 1.0cm melanoma nodule, 2.5cm squamous cell cancer in a patient with blood glucose=341; all false negatives in R upper lobe • Visual false negatives, (1): 2.0cm bronchioalveolar cancer • SUV and visual false positives (3): granuloma, necrotizing granuloma, necrotizing granuloma with histoplasmosis; 2 in R upper lobe, 1 in upper lobe • Serum glucose values on 61 patients, mean \pm SD=99 ± 56 mg/dl; 27 diabetics had elevated glucose levels with 1 false positive and 2 false negative results • In 4 cases CXR did not identify the SPN <p>Authors' comments</p> <ul style="list-style-type: none"> • Results from visual analysis might be more helpful than quantitative analysis for small nodules, (≤ 1.5cm) and in cases in which elevated glucose levels are unavoidable to reduce the number of false negative cases • Given the multisite nature of the study and multiple radiologists used to interpret the films across sites, study population is representative of the proportion of indeterminate SPNs from the sites included

Diagnostic Accuracy and Therapeutic Efficacy Studies of FDG PET in Colorectal Cancer

Study	Patients/Methods	Results/Comments
<p>Delbeke et al. (1997) (Vanderbilt University Medical Center, Nashville, Tennessee)</p> <p>Purposes</p> <ul style="list-style-type: none"> Prospective assessment: To assess the accuracy of FDG PET vs. CT vs. CT arterial portography (CTAP) in detecting liver metastases To assess the accuracy of FDG PET vs. CT in detecting extrahepatic metastases To evaluate the impact on management of patients with recurrent colorectal carcinoma (retrospective) <p>Cases</p> <p>52 consecutive patients presented on 61 occasions for evaluation of suspected recurrent carcinoma based elevated CEA levels or abnormal findings on CT (includes 9 repeat patients)</p> <ul style="list-style-type: none"> 45 had liver metastases, including 16 with concomitant extrahepatic disease, 10 had extrahepatic disease only Total liver lesions: 104 malignant, 23 benign (0.3 cm-6 cm in size) Total extrahepatic lesions: 34 malignant, 5 benign Benign conditions: Normal liver (7), Post surgical site (8), Local fibrosis (2), Resolving abscess (1), hepatic cyst (1), hematoma (1) 31 men, 21 women; Mean age 63 ± 11 yrs <p>Methods</p> <ul style="list-style-type: none"> 40 patients underwent abdominal CT, CT portography=40, or both=29 PET, CT, and CT portography (both with contrast) performed within 2 months of each other Patients with abnormal PET scans in extra-abdominal areas had additional CT scan of that region PET visually interpreted, and analyzed semiquantitatively using SUR corrected for body weight. by two nuclear medicine physicians; SUR calculations excluded lesions < 1 cm in diameter CT and CT portography interpreted independently by two experienced radiologists All readers blinded to other imaging results Disease confirmed with clinical or radiologic follow up (n=17) or histopathology obtained surgically (n=44), except for two lesions that were examined after percutaneous fine needle aspiration Surgical exam and intraoperative ultrasound used to confirm nonresected liver lesions Changes in patient management retrospectively reviewed with the surgeons <p>Limitations of Study Design</p> <ul style="list-style-type: none"> High prevalence of malignancy and unclear patient source (potential referral bias) Strong association between imaging results and choice of patient cohort; CT of extrahepatic areas dependent on PET results (work up bias, minimized by follow up of all patients) Criteria for positive test and cut-off for semiquantitative analysis not reported (potential bias) Blinding to other clinical information not reported (potential test review bias) Association between imaging test results and gold standard determination unclear (potential diagnostic review bias) Details of methods for evaluating therapeutic efficacy not reported 	<p>Detecting recurrences overall** (55 patients with recurrences, 6 with scar)</p> <p>PET: Se=98%; Sp=83% CT: insufficient data to calculate results CTAP: insufficient data to calculate results</p> <p>Detecting liver lesions** (104 malignant lesions, 23 benign lesions)</p> <p>PET: Se=91%; Sp=96%; accuracy=92% CT: Se=81%; Sp=60%; accuracy=78% CTAP: Se=97%; Sp=5%; accuracy=80% Excluding lesions < 1 cm (18 malignant, 5 benign) PET: Se=99%; accuracy=98% CT: Se=87%; accuracy=93% CTAP: Se=97%; accuracy=80%</p> <p>Other findings</p> <ul style="list-style-type: none"> If only histologically proven lesions were included, test characteristics remained within 1% of above values, but no data available to replicate calculations Accurate differentiation of postsurgical changes from malignant recurrence: PET = 12/14 sites; CT = 7/11 sites; CTAP = 5/11 sites <p>Detecting extrahepatic lesions** (34 malignant lesions, 5 benign lesions)</p> <p>PET: Se=100% CT: Se=74%</p> <p>Quantitative analysis of hepatic lesions**</p> <ul style="list-style-type: none"> SUR malignant = 8.1 ± 4.1 vs. SUR benign = 2.0 ± 1.0 ($p < 0.0001$) For extrahepatic lesions the SUR was less helpful than CT in differentiating bowel uptake from metastases <p>Therapeutic efficacy**</p> <ul style="list-style-type: none"> PET helped to plan surgery by identifying site of recurrence in 10% of patients (n=6) PET helped to avoid unnecessary surgery in 18% of patients (n=11) Impact of false positive and false negative PET scans on patient management was not reported 	<p>*Note: PET utility was evaluated complementary to diagnostic tests done earlier in the work up.</p>

Study	Patients/Methods	Results/Comments
Ogundiji et al. (1997) (Washington Univ. School of Medicine, St. Louis, Missouri)	<p>Purpose Retrospective assessment: • To evaluate PET versus CT for staging recurrent and metastatic colorectal cancers • To assess the impact of PET on clinical management of patients with colorectal cancer</p> <p>Cases 58 patients had PET between 1/91 and 1/95 for evaluation of suspected recurrent (n=47) or advanced primary (n=11) disease: <ul style="list-style-type: none"> based on high clinical suspicion and equivocal or positive CT findings (n=39) or clinical suspicion alone, including raised CEA levels with normal CT (n=19) 33 men, 25 women; mean age 60 yrs. (23-81 yrs) benign conditions not reported in reproducible detail </p> <p>Methods <ul style="list-style-type: none"> All patients underwent colonoscopy and contrast CT of chest, abdomen and pelvis within 4 wks prior to PET CT interpreted for extent of local pelvic recurrence and presence of metastases Qualitative PET interpreted by two readers with access to CT results Malignancy=FDG uptake moderately or markedly intense; benign=no or mild uptake, or if abnormality identified on other imaging for which no corresponding abnormality was present on PET Gold standard= surgery, histology, or both (n=40); clinical and radiologic follow up (n=16): autopsy reports(n=2), and treatment outcomes All patients followed for at least 12 months after PET or until death Impact of PET on patient management was assessed: positive impact=alteration in clinical decisions with PET results </p>	<p>Defining local pelvic recurrence (21 disease, 26 no disease) PET+CT: Se=90%; Sp=100%; PPV=100%; NPV=93%; Acc=96% CT: Se=57%; Sp=81%; PPV=71%; NPV=70%; Acc=70% *(P = 0.008)</p> <ul style="list-style-type: none"> PET correctly identified presence of disease in all patients with true positive CT findings PET was useful in differentiating postoperative fibrosis from recurrence in 6 patients with positive CT scans PET confirmed disease in 4 patients with equivocal CT findings 2 false negatives on both PET and CT were diffuse mesorectal and anastomotic histologies proven by transrectal US-guided biopsies. <p>Defining hepatic metastases (23 disease, 35 no disease) PET+CT: Se=96%; Sp=100%; PPV=100%; NPV=97%; Acc=98% CT: Se=74%; Sp=86%; PPV=77%; NPV=83%; Acc=81% *(P = 0.02)</p> <ul style="list-style-type: none"> PET identified all 5 patients with solitary metastases, CT identified 2 patients with solitary mets PET identified 17/18 patients and CT identified 10/18 patients with multiple lesions One false negative on both CT and PET found to be multiple superficial hepatic lesions up to 3 cm in diameter <p>Defining extrahepatic metastases (20 disease, 38 no disease) PET identified extra-hepatic metastases in 21 sites in 20 patients, of which 9 lesions were missed on CT or CXR</p> <p>Therapeutic efficacy PET influenced clinical management in 47% (10/21) patients with local recurrent disease, 43% (10/23) with hepatic metastases, and 38% (8/20) with extrahepatic metastases</p> <p>Limitations of study design</p> <ul style="list-style-type: none"> ? Consecutive series Retrospective analysis High prevalence of malignancy (potential referral bias) Strong association between test results and choice of patient cohort (work-up bias, minimized by follow up of all subjects for at least 12 months after pet or until death) Criteria for positive result on imaging not reported Blinding not reported: CT results available to pet readers (test review bias) Incremental value of pet not assessed Association between test results and gold standard determination unclear (potential diagnostic review bias) Methods for assessing therapeutic efficacy not reported

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Flanagan et al. (1998) (Washington Univ. School of Medicine, St. Louis, Missouri)	<p>Purpose To retrospectively assess PET in patients with unexplained rising carcinoembryonic antigen (CEA) levels after treatment of colorectal cancer</p> <p>Cases 22 of 128 patients with a history of colorectal carcinoma who underwent PET from 6/93 to 6/96, were enrolled and were potential candidates for exploratory laparotomy:</p> <ul style="list-style-type: none"> • all had plasma CEA level > 5.0 ng/ml (mean 25 ng/ml), normal imaging studies, endoscopy, and physical exam on routine follow-up • all patients had normal CEA levels after resection of their primary tumors • 17 men, 5 women; ages 17-84 • Primary site: colon (9), rectum (10), rectosigmoid (2), appendix (1) • Stage B (10), Stages C (5), C1 (2), C2 (3); Stage D (2) <p>Methods</p> <ul style="list-style-type: none"> • Patients with history of rectal or rectosigmoid carcinoma had contrast CT of chest, abdomen, and pelvis • Patients with history of colon cancer had contrast CT of abdomen and pelvis • CT scans performed ≤ 4 weeks before PET • CT interpreted in "routine clinical fashion" • PET interpreted qualitatively in "routine clinical fashion", including correlating with CT, and by consensus of at least two readers • PET used in treatment management at the discretion of the referring surgeon • PET correlated with histology, long term radiologic and clinical follow-up ≥ 6 months • PET true positive= confirmation by biopsy or obvious disease site on follow up imaging directed by PET and within 6 months of PET • PET true negative= confirmation by biopsy or no abnormality verified by other imaging or clinical follow-up within 6 months of PET <p>Limitations of study design</p> <ul style="list-style-type: none"> • Retrospective analysis • High probability of malignancy (potential referral bias) • Methods for image interpretation unclear and readers not blinded to CT (test review bias) • Blinding of PET results and reference standard not reported; strong correlation between test results and gold standard determination (diagnostic review bias) • Methods for systematic assessment of therapeutic efficacy not reported 	<p>Detecting recurrent disease (15 recurrence, 7 no recurrence)</p> <p>PET: Se=100%; Sp=71%; PPV=89%; NPV=100%</p> <ul style="list-style-type: none"> • 2 false positives due to asymmetric activity in bowel and bladder diverticulum, and increased uptake in dome of liver in a patient in whom a poor quality PET scan was produced due to large patient size <p>Therapeutic efficacy</p> <ul style="list-style-type: none"> • Guided by the PET results, curative surgery was attempted in only 4 or 15 patients with disease • Neither false positives on PET resulted in mismanagement; both patients had equivocal findings, and referring physicians opted for additional radiologic and follow up studies • All 5 patients with negative PET scans were alive and disease free 9-24 months after PET; 2 patients had negative biopsy of anastomotic site, other 3 patients had no disease progression on follow up <p>*Note: overlapping patient populations with previous study</p>