Guidelines for Molecular Imaging and PET-CT in Cancer
Vol VIII

Part C

Editors

Dr. Venkatesh Rangarajan DRM, DNB.
Professor & Officer in Charge, Bio-Imaging Unit,
Tata Memorial Hospital

Dr. Nilendu C Purandare DMRD, DNB.
Assistant Professor, Bio-Imaging Unit,
Tata Memorial Hospital.

Dr. Anshu Rajnish Sharma DRM, DNB.
Associate Professor, Bio-Imaging Unit,
Tata Memorial Hospital.

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Guidelines for Molecular Imaging and PET-CT in Cancer

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Dedicated to
All our patients at
The Tata Memorial Hospital
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Preface

Imaging has played an important role in cancer diagnosis and management. Developments in integrated modalities incorporating morphological imaging and functional imaging in the form of Positron Emission Tomography (PET-CT) and Single Photon Emission Computerized Tomography (SPECT-CT) have contributed significantly and brought about a paradigm shift in cancer imaging. In the past few years these modalities, have been subjected to critical evaluation, both with regards to utility as well as cost-effectiveness. Health Technology assessment (HTA) initiatives by several countries have lead to an evidence based evaluation of FDG PET & PET-CT technology. Current practice of PET/CT integrates anatomical and functional imaging within a single modality and this has had a considerable impact on the’ decision-making process in oncology.

Tata Memorial Centre was the first in the country to introduce this hybrid imaging modality when a dedicated PET-CT scanner was installed in December 2004. The eighth volume of Evidence Based Management guidelines brought out by the Tata Memorial Centre addresses the issue of molecular imaging and its utility in cancer through an evidence based
perspective. It represents a continuation of the our long standing commitment to improve overall cancer care in India. Not only is the best available evidence presented in this volume, but areas where evidence is lacking are also highlighted. It is sincerely hoped that this volume would not only enable cancer specialists to optimize their reference and utility of these molecular imaging tools, but also stimulate researchers to improve the evidence-base in areas where it is lacking.

February, 2009
Mumbai, India

R. A. Badwe
Director, Tata Memorial Centre
Contributors

Dr. Anshu Rajnish Sharma, DRM, DNB
Dr. Aditya Daftary, MD
Dr. Nilendu C Purandare, DMRD, DNB
Dr. Pramesh C S, MS, FRCS,
Dr. Sneha Shah, DRM, DNB
Dr. Umesh Mahantshetty, MD
Dr. Venkatesh Rangarajan, DRM, DNB
Section — I

Approach to Evidence Collection for PET/CT
Approach to Evidence Collection for PET PET/CT

Positron Emission Tomography (PET) Computerized Tomography (CT) is an imaging modality. The following approaches were used for the evidence documentation for PET/CT.

1. HTA – Health Technical Assessment Approach. Here Fryback and Thornbury’s Hierarchy of Diagnostic Efficacy was used. This is summarized in the following table.

<table>
<thead>
<tr>
<th>Level</th>
<th>Title</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 1</td>
<td>Technical Efficacy</td>
<td>The ability to produce usable information</td>
</tr>
<tr>
<td>Level 2</td>
<td>Diagnostic Accuracy</td>
<td>Diagnostic Accuracy: Refers to the test’s ability to detect or exclude disease in patients compared with a criterion standard or reference test. Test characteristics are sensitivity, specificity, predictive values,</td>
</tr>
<tr>
<td>Level 3</td>
<td>Diagnostic Thinking</td>
<td>likelihood ratios and ROC curves</td>
</tr>
<tr>
<td>---------</td>
<td>---------------------</td>
<td>----------------------------------</td>
</tr>
<tr>
<td></td>
<td>Assessment of the effect of test information on diagnostic reasoning and disease categorization. It serves as a proxy for estimating the effect of a test on patient care</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Level 4</th>
<th>Therapeutic Impact</th>
<th>In what proportion of patients did the information change the intended management?</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Level 5</th>
<th>Patient Outcome</th>
<th>Knowledge about patient outcome efficacy.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>At this level expected harm, such as burden, pain, risk due to the test, can be weighed directly against its expected benefit, such as improving life expectancy, quality of life, disease related morbidity,</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Level 6</th>
<th>Cost-Effectiveness Analysis</th>
<th>whether the cost for use of a given test is acceptable for society. Is the price for the positive effect on patient outcome worthwhile?</th>
</tr>
</thead>
</table>

A diagnostic test does not necessarily have to demonstrate effectiveness at each level before it can be used in clinical practice, but the possible gain and remaining uncertainty on the test’s efficacy is clearly presented by this approach.
**Definitions of the appropriateness criteria for the utility of PET**

<table>
<thead>
<tr>
<th>Relevance of Test</th>
<th>Description</th>
</tr>
</thead>
</table>
| Appropriate       | Evidence of improved diagnostic performance (higher sensitivity and specificity) compared with other current techniques  
The information derived from the PET scan influences clinical practice  
The information from PET has a plausible impact on the patient’s outcome, either through adoption of effective practice or non adoption of ineffective or harmful practice |
| Probably Appropriate | evidence of improved diagnostic performance (higher sensitivity and specificity) compared with other current techniques, but lacking evidence for an impact on treatment and outcome |
| Potentially Appropriate | Insufficient evidence available for assessment, although there is a strong rationale for a benefit of PET. |
| Inappropriate     | Clinical situations for which improved accuracy of stage will not alter management, or for which the performance of PET is inferior to other current techniques. |
### Definitions of the Timing for PET scanning

- **Diagnosis**
  Characterization of mass lesion – indication whether a mass lesion is benign or malignant.

- **PET guided biopsy** – assistance in guiding biopsy to the most PET intense region of a tumor.

- **PET intense region of a tumor.**

- **Detection of occult primary-**

- **raised tumor markers** – determine the presence of cancer

- **metastasis** – determine the primary site when metastases have been detected

<table>
<thead>
<tr>
<th>Staging</th>
<th>to determine the extent of disease prior to initiation of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Restaging</td>
<td>following initial therapy or when recurrence has been confirmed</td>
</tr>
<tr>
<td>Suspected Recurrence</td>
<td>determine the presence of cancer following clinical suspicion of recurrence</td>
</tr>
<tr>
<td>Followup</td>
<td>surveillance in the absence of clinical evidence of recurrence</td>
</tr>
<tr>
<td>RT Planning</td>
<td>To aid the placement of radiation fields</td>
</tr>
</tbody>
</table>
Level of Evidence based on the type of study: Oxford Centre for Evidence-based Medicine Levels of Evidence (May 2001) (DIAGNOSIS)

<table>
<thead>
<tr>
<th>Level</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Systematic review of prospective studies / prospective study</td>
</tr>
<tr>
<td>2</td>
<td>Retrospective study, databases, poor follow up</td>
</tr>
<tr>
<td>3</td>
<td>Systematic review of homogenous case control studies</td>
</tr>
<tr>
<td>4</td>
<td>Case control study, poor, non independent reference standard</td>
</tr>
<tr>
<td>5</td>
<td>Opinion</td>
</tr>
</tbody>
</table>
Section — II

Haematolymphoid Malignancies
**Lymphoma**

**Introduction**
Hodgkin’s lymphoma & Non Hodgkin’s lymphoma are most commonly occurring hematological malignancies. However they also have the reputation of being potentially curable disease. Hence accurate staging, risk stratification, treatment planning could make this mission possible.

**Conventional staging/imaging:**
Hematological, biochemical profile, bone marrow studies, CSF analysis are performed. X-ray chest, USG provides useful information. But multiregional CECT is performed on most patients. MRI is preferred in CNS lymphoma.

Ga67 Citrate Planar Nuclear scans which were popular before have been replaced by FDG PET where available.

**Summary of Evidence for FDG PET :**

**Initial diagnosis**
Due to the necessity of a histological diagnosis, the role of PET in the initial diagnosis of lymphoma is very limited.
Staging and recurrence diagnosis

FDG uptake seems related to the histological grade of lymphoma with higher uptake in the more aggressive forms (high grade lymphoma according to the European American Lymphoma classification from the International Lymphoma Study Group). However, PET could give very good results in low grade Follicular NHL. The role of PET in the initial staging of the disease implies a non-invasive evaluation of lymph node involvement and locating the preferred biopsy sites with more accuracy than CT. In that indication, the sensitivity of PET is 99.2% and the specificity is 100%, compared with CT sensitivity of 83.2% and specificity of 99.8% 84. PET done in the staging process could represent a good reference investigation allowing comparison with a PET done in the follow up process

For other localizations of the disease, PET has a global sensitivity of 77% to 100%, specificity of 72% to 100% and an accuracy of 83% to 100%, compared with 50% to 95%, 51% to 95% and 63% respectively for gallium scintigraphy and 20% to 100%, 33% to 100% and 73% for CT. The positive predictive value of PET varies between 62% to 100%, and the negative predictive value from 50% to 100%.

For bone marrow involvement, PET showed a sensitivity of 79%, a specificity of 76%, a positive predictive value of 62% and a negative predictive value of 90% and bone marrow biopsy showed a sensitivity of 58% and specificity of 100%. The role of PET for detection of lesions in bones or bone marrow is controversial.

For evaluation of spleen involvement, PET has a sensitivity of 92%, specificity of 100% and an accuracy of 97%. For the evaluation of extra lymphatic localizations, several studies have shown that PET is responsible for a change in patient management in 14% to 23% of cases (change in staging or
change in treatment). Therefore, PET could be indicated in addition to classical imaging techniques in the initial staging of Hodgkin’s disease, aggressive NHL and low grade Follicular NHL if a staging change could affect the therapy. The recurrence diagnosis is not different from initial staging.

For Pediatric lymphomas the PET sensitivity and specificity was 100% and 93% versus 94% sensitivity and 72.4% specificity for Conventional Imaging.

**Residual mass evaluation, prognosis and treatment response:**
For the evaluation of a residual mass the sensitivity and specificity of PET spans from 43% to 100% and from 69% to 100%, compared with CT sensitivity of 71% to 100% and specificity of 17% to 65%. The positive predictive value of PET spans from 44% to 100% and the negative predictive value from 67% to 100%, compared with CT PPV and NPV of 19% to 60% and 50% to 100%, respectively. In case of a positive PET the global survival of patients is 20% to 18% after 1 year and 0% to 4% after 2 years with 100% recurrence, but in case of a negative PET, the survival is 87% to 100% after 1 year and 79% to 85% after 2 years with 17% recurrence. Therefore, PET should be indicated for the diagnosis of residual disease (Hodgkin’s disease and aggressive or follicular Non Hodgkin’s lymphoma) in case of intense FDG uptake during initial staging and for early evaluation of therapeutic response. Clearly in that case, it is assumed that a PET examination would have to be done during the initial staging work up to all patients with Hodgkin’s disease and aggressive or follicular non Hodgkin’s lymphoma. Furthermore, the NHS Scotish Executive Health Department recommends on the basis of the HTBS HTA report, the use of PET in case of Diffuse Large B Cell Non Hodgkin’s lymphoma, after 6 weeks treatment for patients with extensive disease to
assess response to treatment and at the completion of chemotherapy to assess the need for consolidation radiotherapy. However, the external Experts Group found that PET is not indicated to decide whether to irradiate or not because it is unable to detect a small amount of residual disease (External Experts Group). Mostly, PET is indicated for Hodgkin’s disease patients after initial therapy in order to select those for whom no further treatment is needed or additional consolidation is needed.

The intensity of FDG uptake (standardized uptake value - SUV) before treatment could serve as a prognostic indicator. The interest of disposing a good prediction technique rests on the possibility for the clinician to intensify the treatment and to plan a bone marrow transplant. Several studies have shown the good prognostic value of PET for recurrence before and after bone marrow transplant. Other studies have shown that the FDG uptake estimated with SUV has dropped down after chemotherapy. The best results to estimate the prognosis seem to be obtained after one course of chemotherapy (sensitivity of 82%, positive predictive value of 90%), or at mid term of the treatment and not after completion of treatment (sensitivity of 45%, positive predictive value of 83%)

In a Phase II study of risk-adapted therapy of newly diagnosed, aggressive non-Hodgkin lymphoma based on midtreatment FDG-PET scanning; Those with negative PET on semiquantitative visual interpretation completed standard therapy. Those with positive PET received platinum-based salvage chemotherapy, high-dose therapy, and autologous stem cell transplantation (ASCT). Midtreatment PET was positive in 33 (56%); 28 received ASCT with an actuarial 2-year EFS of 75% (95% confidence interval, 60%-93%). On intention-to-treat analysis, 2-year EFS was 67% (53%-86%) in all PET-positive patients and 89% (77%-100%) in PET-negative patients. No association was found between the International
Prognostic Index category and the mid treatment PET result. The favorable outcome achieved here in historically poor-risk patients warrants further, more definitive investigation of treatment modification based on early PET scanning.

Even in follicular lymphoma PET scan has the potential to impact staging and thereby treatment.

PET is not indicated in the initial diagnosis.

- For initial staging and recurrence diagnosis (lymph nodes involvement and extra lymphatic localization), there is evidence for diagnostic accuracy including the determination of sensitivity and specificity but without mentioning a post-test probability or diagnostic threshold. There are some studies treating changes in patient management but with high heterogeneity (level 2).

- For residual mass evaluation, there is clinical evidence up to the diagnostic thinking level because PET allows directing the medical decision on the follow up strategy (level 3). There is evidence from one modeling study for cost-effectiveness of PET for re-staging Hodgkin’s disease.

- For prognosis, there is evidence of diagnostic accuracy including the determination of sensitivity and specificity (level 2).

- For evaluation of treatment response, there is evidence of diagnostic accuracy including the determination of sensitivity and specificity (level 2).
Timing of the Hierarchy of Relevance of Level of PET/CT Diagnostic Test Efficacy

<table>
<thead>
<tr>
<th>Timing of the PET/CT</th>
<th>Hierarchy of Diagnostic Efficacy</th>
<th>Relevance of Test</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis</td>
<td>Level 1</td>
<td>Potentially appropriate (site of biopsy)</td>
<td>Level 1</td>
</tr>
<tr>
<td>Staging</td>
<td>Level 3</td>
<td>appropriate</td>
<td>Level 1</td>
</tr>
<tr>
<td>Response evaluation</td>
<td>Level 4</td>
<td>appropriate</td>
<td>Level 1</td>
</tr>
<tr>
<td>Restaging</td>
<td>Level 3</td>
<td>Appropriate</td>
<td>Level 2</td>
</tr>
<tr>
<td>Suspected recurrence</td>
<td>Level 3</td>
<td>Appropriate</td>
<td>Level 2</td>
</tr>
<tr>
<td>Follow up</td>
<td>Level 2</td>
<td>Possibly appropriate</td>
<td>Level 3</td>
</tr>
<tr>
<td>RT planning</td>
<td>Level 2</td>
<td>Potentially useful</td>
<td>Level 2</td>
</tr>
</tbody>
</table>

Selected Abstracts:


OBJECTIVE: To evaluate the diagnostic value of bone marrow (BM) involvement detected by F-18-flurodeoxyglucose-positron emission tomography/computed tomography ((18)F-FDG PET/CT) in patients with newly diagnosed diffuse large B-cell lymphoma (DLBCL). METHODS: The study population comprised 81 consecutive patients with newly diagnosed DLBCL. All patients had both (18)F-FDG PET/CT and standard BM biopsy at iliac crest. In 9 patients, additional direct BM biopsy at FDG-avid bone lesion was performed. RESULTS: Among all 81 cases, 23 were diagnosed as BM involvement by PET/CT. Of the 23 positive cases 17 were confirmed by biopsy. However, only 11 cases were diagnosed by merely bilateral iliac crest biopsy. In patients in
early stage of disease (18)F-FDG PET/CT had the same results as bilateral iliac crest biopsy. CONCLUSION: (18)F-FDG PET/CT is superior to standard BM biopsy in detecting BM involvement in newly diagnosed DLBCL patients. In patients with FDG-avid bone lesions, direct PET/CT-guided bone biopsy seems to be more accurate than standard BM biopsy. PMID: 19176040


In newly diagnosed aggressive non-Hodgkin lymphoma (NHL), a positive midtreatment fluorine-18 fluorodeoxyglucose positron emission tomography (PET) scan often carries a poor prognosis, with reported 2-year event-free survival (EFS) rates of 0% to 30% after standard therapy. To determine the outcome of early treatment intensification for midtreatment PET-positive disease, a phase II trial of risk-adapted therapy was conducted. Fifty-nine newly diagnosed patients, 98% with B cell lymphoma, had PET/CT performed after 2 or 3 cycles of first-line chemotherapy. Those with negative PET on semiquantitative visual interpretation completed standard therapy. Those with positive PET received platinum-based salvage chemotherapy, high-dose therapy, and autologous stem cell transplantation (ASCT). Midtreatment PET was positive in 33 (56%); 28 received ASCT with an actuarial 2-year EFS of 75% (95% confidence interval, 60%-93%). On intention-to-treat analysis, 2-year EFS was 67% (53%-86%) in all PET-positive patients and 89% (77%-100%) in PET-negative patients. No association was found between the International Prognostic Index category and the midtreatment PET result. The favorable outcome
achieved here in historically poor-risk patients warrants further, more definitive investigation of treatment modification based on early PET scanning.

PMID: 19167684

**The role of FDG-PET imaging and involved field radiotherapy in relapsed or refractory diffuse large B-cell lymphoma.** Hoppe BS, Moskowitz CH, Zhang Z et al. Bone Marrow Transplant. 2009 Jan 12.

We examined the role of flourodeoxyglucose-positron emission tomography (FDG-PET) and the addition of involved field radiotherapy (IFRT) as potential modifiers of salvage therapy. From January 2000 to June 2007, 83 patients with chemosensitive relapsed or primary refractory diffuse large B-cell lymphoma (DLBCL) underwent FDG-PET scans following second-line chemotherapy before high-dose therapy with autologous stem cell rescue (HDT/ASCR). We evaluated the prognostic value of having a negative FDG-PET scan before HDT/ASCR and whether IFRT improved the outcomes. Median follow-up was 45 months, and the 3-year PFS, disease-specific survival (DSS) and OS were 72, 80 and 78%, respectively. Multivariate analysis revealed that a positive FDG-PET scan had worse PFS (hazard ratio=(HR) 3.4; P=0.014), DSS (HR=7.7; P=0.001) and OS (HR=5.4; P=0.001), and that patients not receiving IFRT had worse PFS (HR=2.7; P=0.03) and DSS (HR=2.8, P=0.059). Patients who received IFRT had better local control with fewer relapses within prior involved sites compared with those that did not receive IFRT (P=0.006). These outcomes confirm the important prognostic value of FDG-PET scans before undergoing HDT/ASCR. It also suggests that the role of IFRT should be evaluated further. Bone Marrow Transplantation advance online publication, 12 January 2009; doi:10.1038/bmt.2008.408.

PMID: 19139730
The majority of transformed lymphomas have high standardized uptake values (SUVs) on positron emission tomography (PET) scanning similar to diffuse large B-cell lymphoma (DLBCL). Noy A, Schöder H, Gönen M, et al. Ann Oncol. 2009 Jan 12.

BACKGROUND: We previously correlated non-Hodgkin’s lymphoma (NHL) histology with (18)fluoro-2-deoxyglucose-positron emission tomography (FDG-PET) intensity: a standardized uptake value (SUV) >10 predicted aggressive lymphoma with >80% certainty and an SUV >13, with >90% certainty. PATIENTS AND METHODS: To evaluate SUV in transformed lymphoma, we identified all FDG-PET scans for NHL at Memorial Sloan-Kettering Cancer 1999-2007 with (i) biopsy-proven transformation, (ii) no therapy 60 days before PET scan and (iii) FDG-PET scans no more than 60 days before or 90 days after transformation. RESULTS: In 5 of 40 patients, the biopsy site was excised before PET; in two, only marrow was biopsied. In the remaining 33 patients, the SUV of the biopsy site ranged from 3 to 38, mean 14, median 12. Eighteen of 33 biopsies (55%) had an SUV >10 and 16 (48%) >13. The highest SUV in a transformed lymphoma PET scan (SUV(study-max)) ranged from 3.2 to 40, mean 15, median 12. Twenty-five of 40 patients (63%) presented with an SUV(study-max) >10 and 20 (50%) >13. CONCLUSIONS: Like de novo aggressive lymphomas, the majority of transformations have a high SUV(study-max) for a given pretreatment staging study, although many do not have very high values. Transformation should be suspected in indolent lymphoma with high SUVs on FDG-PET. Biopsies should be directed to the site of greatest FDG avidity.

PMID: 19139176

This study reports on our experience with (18)F-fluorodeoxyglucose (FDG) positron emission tomography (PET) in pediatric patients affected by Hodgkin’s disease (HD) and non-Hodgkin’s lymphoma (NHL). We studied 20 pediatric subjects (12 males, 8 females; mean age, 10 years; range, 6 months to 14 years) with malignant lymphoma (9 HD, 11 NHL) for a 4-year period of time. Overall, 45 PET scans were performed: 7 at disease presentation and 38 for evaluation of response to therapy or follow-up study. All PET results were compared with conventional imaging (CI), mainly computed tomography (CT) and/or magnetic resonance imaging (MRI), and supported by clinical follow-up and/or histologic data. In 18 of 20 patients, PET findings correctly identified the status of disease. Two (2) subjects (respectively, 1 HD and 1 NHL, both at follow-up) resulted falsely positive: 1 due to prominent thymic uptake, and the other due to nonspecific inflammation. Of 45 scans, PET findings were consistent with clinical follow-up and other CI data in 43 cases (16 true-positive and 27 true-negative results) and resulted falsely positive in the remaining 2 scans. On a lesion-by-lesion basis (overall, 153 lesions: 84 nodal and 69 extranodal), we found a concordance between CI and PET findings in 25 nodal (29.8%) and in 22 extranodal sites (32%). PET was more accurate than CI, as it identified active disease in 1 patient negative at CI and excluded relapse in 6 patients with inconclusive CI and in 2 patients with a falsely positive CI. Overall, PET sensitivity and specificity was 100% and 93% versus 94% sensitivity and 72.4% specificity for CI. This comparative study shows FDG PET to be more accurate
than CI in evaluating children with lymphoma. Our data also confirms that 18 F-FDG PET may show false-positive findings.

PMID: 19111053


**PURPOSE OF REVIEW:** Risk-adapted treatment strategies are currently under investigation in the management of patients with lymphoma. This review presents the latest evidence for the use of early interim [(18)F]-fluorodeoxyglucose-positron emission tomography for risk-adapted treatment in Hodgkin’s lymphoma. **RECENT FINDINGS:** In recent years, PET after two cycles of ABVD (adriamycin, bleomycin, vincristin, and dexamethasone) was shown to be the only independent prognostic factor for the prediction of relapse in Hodgkin’s lymphoma and to have at least the same prognostic accuracy as end-of-treatment PET. A high prognostic value of PET was reported even earlier, before the second cycle of chemotherapy. The earlier PET becomes negative, the more chemosensitive the disease, which may offer opportunities toward the limitation of the therapy. However, more false-positive lesions occur at earlier time points, and preliminary results indicate that accuracy of PET results differs after BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) and immunotherapy. **SUMMARY:** [(18)F]-Fluorodeoxyglucose-positron emission tomography after two cycles of ABVD is now recognized as the single most important factor in defining disease-specific outcome and is highly promising for investigation of response-adapted treatment strategies. It is now recognized that the optimal time point of PET for response evaluation is crucial and dependent on the administered treatment. Standardization
of PET-response is essential and should be adapted to time-dependent and therapy-dependent changes.

PMID: 19106652


PURPOSE: To assess, in patients with diffuse large B-cell lymphoma (DLBCL), whether the low sensitivity of (18)F-fluorodeoxyglucose positron emission tomography (FDG-PET) for bone marrow assessment may be explained by histological characteristics of the cellular infiltrate. METHODS: From a prospective cohort of 110 patients with newly diagnosed aggressive lymphoma, 21 patients with DLBCL had bone marrow involvement. Pretherapeutic FDG-PET images were interpreted visually and semiquantitatively, then correlated with the type of cellular infiltrate and known prognostic factors. RESULTS: Of these 21 patients, 7 (33%) had lymphoid infiltrates with a prominent component of large transformed lymphoid cells (concordant bone marrow involvement, CBMI) and 14 (67%) had lymphoid infiltrates composed of small cells (discordant bone marrow involvement, DBMI). Only 10 patients (48%) had abnormal bone marrow FDG uptake, 6 of the 7 with CBMI and 4 of the 14 with DBMI. Therefore, FDG-PET positivity in the bone marrow was significantly associated with CBMI, while FDG-PET negativity was associated with DBMI (Fisher’s exact test, p=0.024). There were no significant differences in gender, age and overall survival between patients with CBMI and DBMI, while the international prognostic index was significantly higher in patients with CBMI. CONCLUSION: Our study suggests that in patients with DLBCL with bone marrow involvement bone marrow FDG uptake depends on
two types of infiltrate, comprising small (DBMI) or large (CBMI) cells. This may explain the apparent low sensitivity of FDG-PET previously reported for detecting bone marrow involvement.

PMID: 19096842 [PubMed - as supplied by publisher]


We retrospectively evaluated (18)F-FDG PET/CT for monitoring the response of non-Hodgkin’s lymphoma to radioimmunotherapy. METHODS: A total of 33 clinical patients received (131)I-tositumomab (n = 23) or (90)Y-ibritumomab tiuxetan (n = 10) and underwent (18)F-FDG PET/CT scans before radioimmunotherapy and at 12 wk after radioimmunotherapy. A third scan was performed on 13 patients at 24 wk after radioimmunotherapy, 12 of whom did not receive interval therapy. Tumor metabolic activity was assessed before and after radioimmunotherapy visually and quantitatively by lean maximum standardized uptake value (SUV(lean) max). Response was assessed by the International Workshop Criteria (IWC) and Revised IWC, which includes (18)F-FDG PET (IWC-PET). RESULTS: Mean SUV(lean) max decreased from baseline in 244 target lesions 12 wk after radioimmunotherapy (from 6.51 +/- 4.05 to 3.94 +/- 4.41; P < 0.01), regardless of response at 12 wk after radioimmunotherapy (P </= 0.02). After radioimmunotherapy, SUV(lean) max was lower for responders than for nonresponders (P </= 0.01). Median percentage change in SUV(lean) max of target lesions per patient was -51% (-95% to 97%). No significant difference in decline in SUV(lean) max between patients who received (131)I-tositumomab and those who received (90)Y-ibritumomab tiuxetan was demonstrated (-31% +/- 51% vs. -47% +/- 46%; P = 0.38).
Patients with greater than a 52% decline in SUV(lean) max tended toward longer survival ($P = 0.09$) than those with lesser declines. The 12-wk overall response rate to radioimmunotherapy based on IWC was 42% (14/33); complete response rate was 15% (5/33). Eleven of 12 patients with progression at 12 wk had new disease sites, and in 4 patients, new disease sites were the only sites of progression. Of 108 lesions evaluated at 12 and 24 wk after radioimmunotherapy, 49 resolved at 12 wk and remained resolved at 24 wk, 17 gradually declined in SUV over 24 wk, and 37 initially decreased at 12 wk but increased at 24 wk. PET showed disease progression at 24 wk in 10 of 13 patients; 7 patients had new lesions and 1 was reclassified from partial response to complete response. CONCLUSION: In non-Hodgkin’s lymphoma, (18)F-FDG uptake in tumors typically drops significantly after radioimmunotherapy. A continued decline in tumor SUV(lean) max between 12 and 24 wk without additional therapy can occur, suggesting a need for delayed-response assessment. In patients who progress after radioimmunotherapy, new sites of disease commonly develop, rather than recurrence or progression at previous disease sites. Large declines in (18)F-FDG uptake tend to be seen in those with the longest progression-free survival.

PMID: 19091903


Assessing the response to treatment as soon after treatment initiation is one of the key reasons for imaging lymphoma patients. The optimal time after initiating treatment for assessing response to treatment has yet to be determined. Therefore, we were prompted to review our experience with serial (18)F-FDG PET/CT in patients undergoing treatment
for Hodgkin’s disease (HD) and non Hodgkin’s lymphoma (NHL). This is a retrospective study (Feb 2003 - Oct 2004) of 20 patients, 11 men and 9 women, with age range of 7-75 years with diagnosis of HD (10) and NHL (10), who had PET/CT at our institution prior, during and at the completion of therapy. Restaging PET/CT was done after 2 cycles of chemotherapy in 10 patients (group A) and after 4 cycles of chemotherapy in 10 pts (group B). A total of 60 scans were reviewed. The DeltaSUV from baseline to first PET/CT was on average 67.6% in group A and 75.1% in group B. This had no statistical significance (P value: 0.31). The DeltaSUV from baseline to post-therapy PET/CT was on average 72.9% in group A and 79.8% in group B. This difference also had no statistical significance (P value: 0.24). The correlation coefficient was 0.98 in group A and 0.80 in group B. Results of PET/CT after 2 cycles of chemotherapy did not statistically differ from the results of PET/CT after 4 cycles of chemotherapy. These results need to be confirmed in larger, prospective, randomized trials.

PMID: 19081857


BACKGROUND: Revised response criteria for aggressive lymphomas have been proposed (Cheson, J Clin Oncol, 2007) stressing the role of (18)fluorodeoxyglucose-positron emission tomography (PET) in posttreatment evaluation. The value of PET after four cycles compared with the International Workshop Criteria (IWC) remains to be established.

PATIENTS AND METHODS: In all, 103 patients with
untreated diffuse large B-cell lymphoma were prospectively enrolled to evaluate the prognostic impact of PET after two and four cycles. RESULTS: Median age was 53 years (19-79), 68% male. The International Prognostic Index was low = 22%, low-intermediate = 19%, intermediate-high = 33% and high risk = 26%. Treatment consisted of cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) (30%) or dose-intensified CHOP (70%), with rituximab (49%) or without (51%). Ninety-nine patients were evaluated by PET and IWC at four cycles: 77 (78%) had a negative PET, while 22 (22%) remained positive. The 5-year event-free survival (EFS) was 36% for patients with a positive PET versus 80% with a negative examination, whatever the response [complete response (CR) versus partial response (PR)] according to IWC (P < 0.0001). Positive PET patients had a 5-year EFS of 58% if in CR/CR unconfirmed by IWC and 0% if not (P < 0.0001). The same observations could be made in patients treated with and without rituximab. CONCLUSION: The integration of PET in treatment evaluation offers a powerful tool to predict outcome.

PMID: 19074215


PURPOSE: Radioimmunotherapy has been approved for relapsed follicular lymphoma (FL), including rituximab-refractory FL. This study was designed to determine the CR rate with short-course chemoimmunotherapy with cyclophosphamide, doxorubicin, vincristine, prednisone, and rituximab (CHOP-R) followed by 90-Y ibritumomab tiuxetan (RIT) with extended rituximab as first-line treatment.
EXPERIMENTAL DESIGN: Between March 2004 and February 2007, 60 patients with stage II to IV symptomatic or bulky FL from a single institution supported by a large community network entered this phase II trial. Patients received CHOP-R for three treatment cycles before RIT followed by four additional weekly treatments with rituximab. Response was determined using fusion [(18) F] fluorodeoxyglucose-positron emission tomography (PET)-computed tomography (CT) imaging. RESULTS: Of the 60 patients entering this trial, 55 patients completed all protocol therapy. The median follow up was 19.7 months (range, 0.26-35.9 months). For intent-to-treat analysis, the complete response (CR) rate after CHOP-R, as assessed by CT and PET imaging, was 40% and 46%, respectively. After RIT, the CR rate improved, as assessed by CT and PET imaging, to 82% and 89%, respectively. Ten patients have progressed, including eight from best response of CR. Seven of 18 patients who were PET positive after CHOP-R progressed compared with 3 of 37 patients who were PET negative (P=0.010). CONCLUSIONS: In patients with previously untreated, symptomatic or bulky FL, short-course chemoimmunotherapy and consolidation RIT and extended rituximab resulted in a high CR rate. Failure to achieve an early PET CR after CHOP-R indicated high risk of relapse.

PMID: 18981007


PURPOSE: In non-Hodgkin lymphomas (NHLs), the bone marrow (BM) involvement is a sign of extensive disease and the iliac crest BM biopsy (BMB) is the established method for the detection of BM infiltration. However, iliac crest BMB is associated with a high rate of false negative results. We
assess the ability of 18-F-fluorodeoxyglucose positron emission tomography (F-FDG PET) scan to ascertain the presence of BM involvement in NHL. METHODS: After reviewing charts of histologically proven NHLs, 97 patients were eligible for our study. All patients were examined by whole-body F-FDG PET scan for initial staging, and all had unilateral posterior iliac crest BMB. BM involvement was established after the result of unilateral posterior iliac crest BMB and image-guided BMB after positive F-FDG PET scan in selected patients. RESULTS: Our data demonstrate an overall sensitivity of 79% for the F-FDG PET scan detecting BM involvement in all patients and specificity of 91%. Further analysis revealed no significant difference in the ability of the F-FDG PET scan to detect BM involvement between the indolent-NHL and the aggressive/highly aggressive-NHL groups (sensitivity P = 0.23, specificity P = 0.64). CONCLUSION: F-FDG PET scan shows potential to detect BM involvement in NHL. In particular, image-guided repeat BMB should be considered in patients with negative initial iliac crest BMB, whose F-FDG PET scan demonstrates BM involvement in a different site.

PMID: 18838874


BACKGROUND: Limited data exist about the role of second-line chemotherapy response assessed by positron emission tomography (PET) as a prognostic factor in patients with aggressive non-Hodgkin Lymphoma (NHL) who undergo autologous stem cell transplantation (ASCT). The objective of this analysis was to investigate the main determinants of prognosis in patients with aggressive B-cell NHL who undergo
ASCT, focusing on the impact of pretransplantation PET, secondary age-adjusted International Prognostic Index (sAA-IPI) score, histology, and previous response to first-line chemotherapy. METHODS: Seventy-five patients with diffuse, large B-cell lymphoma or grade 3 follicular lymphoma who were treated at the author’s institution with second-line chemotherapy (combined ifosfamide, etoposide, and epirubicin [IEV]) followed by ASCT between September 2002 and September 2006 were included. All patients were evaluated by PET after 1 to 3 courses of IEV chemotherapy before ASCT, and all patients received a conditioning regimen of combined carmustine, etoposide, cytosine arabinoside, and melphalan. The prognostic impact of pretransplantation PET, sAA-IPI score, histology, and previous response to first-line chemotherapy was evaluated by univariate and multivariate analyses. RESULTS: Seventy-two of 75 patients underwent ASCT. In a univariate analysis for progression-free survival (PFS) and overall survival (OS), a significant association was observed with pretransplantation PET (PFS, P< .00001; OS, P< .01) and previous first-line response (PFS, P= .02; OS, P= .04). In the multivariate framework, pretransplantation PET was identified as the only independent prognostic factor (PFS, P< .001; OS, P= .01). CONCLUSIONS: The current data indicated that pretransplantation PET is the main prognostic predictor in patients with aggressive B-cell NHL who are scheduled for ASCT.

PMID: 18833583


Mantle cell lymphoma (MCL) is a rare but aggressive non-Hodgkin lymphoma subtype with a poor prognosis; most patients relapse despite initial response to therapy. Response was traditionally evaluated by computed tomography (CT),
but the introduction of [(18)F]Fluorine-Deoxyglucose Positron Emission Tomography (PET) changed response assessment in aggressive lymphoma. However, the value of PET-evaluation in MCL has not been studied yet. Therefore, PET- and CT-findings were investigated in 37 patients with MCL (239 scans) and categorised following standardised response criteria for CT-evaluation (IWC-criteria), PET-evaluation (EORTC-criteria) and combined PET/CT-evaluation (IWC + PET-criteria). FDG-PET showed a high sensitivity for the detection of deposits of MCL and a higher FDG-uptake was shown in patients with the more aggressive blastoid-variant of MCL versus common MCL. However, routine use of PET for end-of-treatment response assessment in MCL cannot be recommended because CT- and PET-based designation systems had equivalent prognostic value. PET-based end-of-treatment response assessment only provided additional information over CT-based response assessment in a subpopulation of patients with highly FDG-avid MCL. PET allowed early detection of preclinical relapse during post-therapy surveillance, but the therapeutic consequences of such information are currently unclear.

PMID: 18798104


This study aims to describe 18F-fluorodeoxyglucose (18F-FDG) positron emission tomography/computed tomography (PET/CT) findings in patients with AIDS-related Burkitt lymphoma, at various times of treatment, and to define its utility for a better patient management. We retrospectively studied 13 consecutive HIV-positive patients with Burkitt lymphoma who underwent one or more PET/CT. In 5 of
5 patients imaged before treatment, PET/CT confirmed all involved sites detected at conventional work-up and demonstrated additional sites in 4 of 5 patients. Lymph node involvement, which is known to be uncommon in endemic or sporadic Burkitt lymphoma, was present in 54% of patients. Additionally, in 3 patients, Burkitt lymphoma was predominantly located in parotid lymph nodes, which is also an unusual finding. A negative scan was encountered in 3 of 10 patients imaged during treatment and in 1 of 4 patients imaged after treatment completion and was always associated with lasting complete remission. Presence of residual area of uptake was related to both favorable and unfavorable outcome whether performed during treatment (5/7 and 2/7, respectively) or after (1/3 and 2/3, respectively). Areas of increased uptake could be observed in lung (4 cases) or esophagus (3 cases), and were clinically related to pneumonia or esophagitis. We recommend PET/CT for accurate initial staging of patients with AIDS-related Burkitt lymphoma. PET/CT is also useful to monitor treatment response, as regression of initial disease can be early observed. Furthermore, PET/CT appears to have prognostic value, as a negative scan was always associated with a favorable outcome.

PMID: 18793085


PURPOSE: Positron emission tomography with the thymidine analogue 3′-deoxy-3′-[18F]fluorothymidine (FLT) has been reported to closely reflect lymphoma proliferation in vivo. In this preclinical study, we have investigated if FLT can also be utilized for imaging therapy-induced alterations of the nucleoside metabolism and if FLT is a surrogate marker for
early response to cytotoxic treatment. MATERIALS AND METHODS: Immunodeficient mice bearing high-grade lymphoma xenotransplants were treated with the cytotoxic agent doxorubicin (day 0). In the time course of day +1 to +9, antiproliferative effects were assessed non-invasively with FLT-PET and correlated to changes of the proliferation fraction and induction of apoptosis, as assessed by immunohistochemistry. RESULTS: Tumor growth in untreated animals was significantly higher than in treated animals. In FLT-PET scans, these observations correlated with a significant decrease of tumor-to-background ratio in the therapy group already at day 1. Likewise, median tumor-to-muscle ratio of FLT uptake already declined at day 1. The proliferation fraction assessed by Ki-67 immunohistochemistry decreased after chemotherapy, while activated caspase 3 increased, suggesting both cell cycle arrest and induction of apoptosis as underlying mechanisms of the observed PET-signal alterations. CONCLUSION: In a lymphoma xenotransplant model, we show that positron emission tomography using the proliferation marker FLT is suitable to detect early response to cytotoxic treatment. A significant decrease of FLT uptake but not tumor growth was detectable already 24 h after therapy and correlated with reduced proliferation and induction of apoptosis. Thus, FLT-PET has a potential for imaging early response to treatment in malignant lymphoma.

PMID: 18704591
Introduction

Multiple myeloma accounts for approximately 10% of hematologic malignancies. Almost all patients are thought to evolve from an asymptomatic premalignant stage termed monoclonal gammopathy of undetermined significance (MGUS). Progression of MGUS to myeloma is characterized by the development of bone lesions. Lytic bone lesions in myeloma are caused by an imbalance between the activity of osteoclasts and osteoblasts. The most common presenting symptoms of myeloma are fatigue and bone pain. Osteolytic bone lesions and/or compression fractures that can be detected on routine radiographs, magnetic resonance imaging (MRI), or computed tomographic (CT) scans are the hallmark of the disease and cause significant morbidity.

Current Staging/Imaging:

A complete blood count, urinalysis, and serum creatinine, calcium, microglobulin, albumin, C-reactive protein, and lactate dehydrogenase levels are needed for diagnosis, prognosis, and staging. In addition, patients require tests to identify and quantitate monoclonal proteins, bone disease, and bone marrow involvement. Specialized tests are also
performed on the bone marrow for risk stratification. Plain radiographic examination of all bones, including long bones (skeletal survey), is the preferred method of detecting lytic bone lesions in myeloma. Conventional x-rays show skeletal abnormalities in almost 80% of patients with myeloma; often, these lesions have a characteristic punched-out appearance. Osteoporosis and/or fractures are also detected by conventional radiography. Occasionally, osteosclerotic lesions can occur. CT and MRI scans are more sensitive than conventional radiography in detecting bone disease. Among asymptomatic multiple myeloma patients with normal x-rays, up to 50% have tumor-related abnormalities on MRI of the lower spine. CT and/or MRI studies are indicated when symptomatic areas show no abnormality on routine radiographs. Their routine use in assessing extent of bone disease in addition to skeletal radiographs is unclear. 99mTc MIBI, 18 F FDG PET scans are also used to evaluate the disease activity.

Summary of Evidence:
FDG uptake in the marrow has a high specificity of disease activity. CT provides skeletal details of osteoblastic, osteoclastic activity. FDG PET/CT is therefore likely to have a high accuracy in the assessment of disease status and viability. There are several case reports and small case series highlighting the uniqueness of FDG PET/CT in monitoring disease activity. Fluro Thymidine and Methioine are the other radiopharmaceuticals assessed as pilot studies with even better performance. A prospective study of 28 patients showed PET to be superior to skeletal survey, but MRI performs better in spinal infiltration detection. When compared side by side with MIBI, FDG detects more number of lesions. MIBI has a specific role in discriminating osteonecrosis from viable myeloma disease, which FDG PET is unable to do. In a retrospective study of 66 patients Whole-body (18)F-FDG PET provides important prognostic information, which is clinically
useful and complementary to conventional methods of evaluating plasma cell disorders. (18)F-FDG PET is a unique tool for evaluation of nonsecretory myeloma. Residual or recurrent disease after therapy, especially extramedullary disease, is a poor prognostic factor. FDG-PET has value for staging and RT planning in plasmacytoma and potentially could have a role in response-assessment after RT. Slow resolution of FDG uptake posttreatment does not necessarily imply an adverse prognosis

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<th>Timing of the PET/CT</th>
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**Selected Abstracts:**


PURPOSE: To evaluate the impact of (18)F-fluorodeoxyglucose positron emission tomography (FDG-PET) on management of patients with apparently isolated
plasmacytoma. METHODS AND MATERIALS: Twenty-one patients with apparently solitary plasmacytoma who underwent FDG-PET for staging or restaging were identified from a central PET database. They were either candidates for or had received definitive radiation therapy (RT). RESULTS: Seventeen patients had initial staging scans for bone (n = 11) or soft tissue (n = 6) plasmacytomas, and 11 had PET scans after RT. Only 1 of 14 known untreated sites of plasmacytoma was not identified on staging PET (lesion sensitivity = 93%). Three plasmacytomas were excised before PET. Staging PET influenced management in 6 of 17 patients (35%) by showing multiple myeloma (n = 1), discouraging RT after complete resection (n = 1), excluding plasmacytoma at a second site (n = 1), by increasing RT fields (n = 2), or by suggesting sarcoidosis (n = 1). Fifteen of 17 patients with initial staging PET scans received definitive RT. Restaging PET scans after RT showed complete metabolic response in 8 of 11 cases and progressive disease in 2. Two patients with either no response or partial metabolic response had late responses. Staging sestamibi and PET scans were concordant in five of six occasions (one sestamibi scan was false negative). CONCLUSIONS: FDG-PET has value for staging and RT planning in plasmacytoma and potentially could have a role in response-assessment after RT. Slow resolution of FDG uptake posttreatment does not necessarily imply an adverse prognosis.

PMID: 19038505

Istituto di Biostrutture e Bioimmagini-CNR, Napoli, Italy. fontir@tin.it
New imaging techniques have been introduced to assess the extent and severity of disease in multiple myeloma (MM) patients. The aim of our study was to compare newer imaging modalities—such as (18)F-FDG PET/CT, (99m)Tc-methoxyisobutylisonitrile ((99m)Tc-MIBI) scintigraphy, and MRI—to assess their relative contribution in the evaluation of MM patients at diagnosis. METHODS: Thirty-three newly diagnosed patients with MM were prospectively studied. Diagnosis and staging were made according to standard criteria. All patients underwent whole-body (18)F-FDG PET/CT, whole-body (99m)Tc-MIBI, and MRI of the spine and pelvis within 10 d, and imaging findings were compared. RESULTS: (18)F-FDG PET/CT was positive in 32 patients (16 focal uptake, 3 diffuse uptake, 13 focal and diffuse uptake), (99m)Tc-MIBI was positive in 30 patients (6 focal, 11 diffuse, 13 focal and diffuse uptake), and MRI of the spine and pelvis was positive in 27 patients (6 focal, 13 diffuse, 8 focal and diffuse uptake). (18)F-FDG PET/CT showed a total of 196 focal lesions (178 in bones and 18 in soft tissues), of which 121 were in districts other than the spine and pelvis, whereas (99m)Tc-MIBI visualized 63 focal lesions (60 in bones and 3 in soft tissues), of which 53 were in districts other than the spine and pelvis. In the spinal and pelvic regions, (18)F-FDG PET/CT detected 75 focal lesions (35 in spine and 40 in pelvis), (99m)Tc-MIBI visualized 10 focal lesions (1 in spine and 9 in pelvis), and MRI detected 51 focal lesions (40 in spine and 11 in pelvis). CONCLUSION: In whole-body analysis, (18)F-FDG PET/CT performed better than (99m)Tc-MIBI in the detection of focal lesions, whereas (99m)Tc-MIBI was superior in the visualization of diffuse disease. In the spine and pelvis, MRI was comparable to (18)F-FDG PET/CT and (99m)Tc-MIBI in the detection of focal and diffuse disease, respectively. Because myelomatous lesions may often occur out of spinal and pelvic regions, MRI should be reserved to the evaluation
of bone marrow involvement of these districts, whereas (18)F-FDG PET/CT can significantly contribute to an accurate whole-body evaluation of MM patients. Finally, whole-body (99m)Tc-MIBI, despite its limited capacity in detecting focal lesions, may be an alternative option when a PET facility is not available.

PMID: 18199607

**11C-choline vs. 18F-FDG PET/CT in assessing bone involvement in patients with multiple myeloma.** Nanni C, Zamagni E, Cavo M et al. World J Surg Oncol. 2007 Jun 20;5:68.

**BACKGROUND:** Multiple Myeloma (MM) is a B cell neoplasm causing lytic or osteopenic bone abnormalities. Whole body skeletal survey (WBSS), Magnetic resonance (MR) and 18F-FDG PET/CT are imaging techniques routinely used for the evaluation of bone involvement in MM patients. **AIM:** As MM bone lesions may present low 18F-FDG uptake; the aim of this study was to assess the possible added value and limitations of 11C-Choline to that of 18F-FDG PET/CT in patients affected with MM. **METHODS:** Ten patients affected with MM underwent a standard 11C-Choline PET/CT and an 18F-FDG PET/CT within one week. The results of the two scans were compared in terms of number, sites and SUVmax of lesions. **RESULTS:** Four patients (40%) had a negative concordant 11C-Choline and 18F-FDG PET/CT scans. Two patients (20%) had a positive 11C-Choline and 18F-FDG PET/CT scans that identified the same number and sites of bone lesions. The remaining four patients (40%) had a positive 11C-Choline and 18F-FDG PET/CT scans, but the two exams identified different number of lesions. Choline showed a mean SUVmax of 5 while FDG showed a mean SUVmax of 3.8 (P = 0.042). Overall, 11C-Choline PET/CT scans detected 37 bone lesions and 18F-FDG PET/CT scans detected 22 bone lesions.
lesions but the difference was not significant (P = 0.8). CONCLUSION: According to these preliminary data, 11C-Choline PET/CT appears to be more sensitive than 18F-FDG PET/CT for the detection of bony myelomatous lesions. If these data are confirmed in larger series of patients, 11C-Choline may be considered a more appropriate functional imaging in association with MRI for MM bone staging.

PMID: 17584499 [PubMed]


BACKGROUND AND OBJECTIVES: Bone lesions in multiple myeloma (MM) have been traditionally detected by whole body X-ray (WBXR) survey although magnetic resonance imaging (MRI) has become the gold standard for detecting MM involvement of the spine and pelvis. The aim of this study was to compare a new technique, positron emission tomography (PET) with 18F fluorodeoxyglucose (FDG) integrated with computed tomography (18F-FDG PET-CT), with MRI and WBXR for baseline assessment of bone disease in MM. DESIGN AND METHODS: We prospectively compared 18F-FDG PET-CT, MRI of the spine-pelvis and WBXR in a series of 46 patients with newly diagnosed MM. In 23 patients who received up front autologous transplantation, we also compared post-treatment PET-CT scans with MR images of the spine and pelvis. RESULTS: Overall, PET-CT was superior to planar radiographs in 46% of patients, including 19% with negative WBXR. In 30% of patients, PET-CT scans of the spine and pelvis failed to show abnormal findings in areas in which MRI revealed an abnormal
pattern of bone marrow involvement, more frequently of diffuse type. In contrast, in 35% of patients PET-CT enabled the detection of myelomatous lesions in areas which were out of the field of view of MRI. By combining MRI of the spine-pelvis and 18F-FDG PET-CT, the ability to detect sites of active MM, both medullary and extramedullary, was as high as 92%. Following transplantation, 15 patients had negative PET-CT scans (including 13 with a very good partial response or at least a near complete response), but only 8 had normal MRI. INTERPRETATION AND CONCLUSIONS: MRI of the spine and pelvis still remains the gold standard imaging technique for the detection of bone marrow involvement in MM. 18F-FDG PET-CT provides additional and valuable information for the assessment of myeloma bone disease in areas not covered by MRI.

PMID: 17229635 [PubMed - indexed for MEDLINE]


Few diagnostic procedures are available to determine the degree of bone marrow cellularity and the numbers of cycling cells in patients with bone marrow disorders. Noninvasive imaging of the bone marrow compartment may be helpful. The PET tracer 3'-fluoro-3'-deoxy-L-thymidine (18F-FLT) has been developed recently. 18F-FLT uptake is related to the rate of DNA synthesis and increases with higher proliferation rates in many types of cancer. Background uptake of 18F-FLT in bone marrow is common. 18F-FLT PET might, therefore, visualize the high cycling activity of hematopoietic cells in the bone marrow compartment. Therefore, we investigated the feasibility of visualization and quantification of the activity of the bone marrow compartment with 18F-FLT PET to distinguish different hematologic disorders. METHODS:
Clinical and laboratory data of 18 patients with myelodysplasia (MDS), chronic myeloproliferative disorders, myelofibrosis, aplastic anemia, or multiple myeloma were correlated with the results of 18F-FLT PET using visual analysis and the standardized uptake value (SUV). Findings were compared with those of healthy control subjects (n = 14). RESULTS: With SUV and visual analysis, a distinction could be made between MDS (n = 9), chronic myeloproliferative disorders (n = 3), and myelofibrosis (n = 3) compared with healthy control subjects. A significant increase in 18F-FLT uptake was observed in all of the studied patients with MDS and myeloproliferative disorders. In contrast, patients with myelofibrosis and aplastic anemia (n = 1) demonstrated a decline in bone marrow 18F-FLT uptake compared with healthy control subjects. Comparable results were observed in osteolytic lesions of patients with multiple myeloma (n = 2). CONCLUSION: 18F-FLT PET can be used to visualize the proliferative activity of the bone marrow compartment and may be helpful to distinguish separate hematologic disorders.

PMID: 17015893


The purpose of this study was to evaluate the clinical utility of whole-body PET with (18)F-FDG in patients with multiple myeloma and related monoclonal diseases. METHODS: Between July 1, 1996, and July 2000, 98 (18)F-FDG PET scans were obtained for 66 patients, with 25 patients having 2 or more scans. The results were compared with routine clinical and staging information, including CT and MRI scans, as indicated. Of the 66 patients, 16 had previously untreated active myeloma, 14 had monoclonal gammopathy of undetermined significance (MGUS), 10 had disease in remission, and 26
had relapsing disease. RESULTS: Negative whole-body (18)F-FDG PET findings reliably predicted stable MGUS. Of the 14 MGUS patients with follow-up of 3-43+ mo, myeloma has developed in only 1 (7%), at 8 mo. Conversely, the 16 previously untreated patients with active myeloma all had focal or diffusely positive scan findings. Four (25%) of 16 previously untreated patients with positive (18)F-FDG PET findings had negative full radiologic surveys. Another 4 (25%) of 16 patients had focal extramedullary disease. This was confirmed by biopsy or other imaging techniques.

Extramedullary uptake also occurred in 6 (23%) of 26 patients with relapse. This extramedullary uptake was a very poor prognostic factor both before treatment and at relapse. For example, median survival was 7 mo for patients with disease relapse. Persistent positive (18)F-FDG PET findings after induction therapy predicted early relapse. In 13 (81%) of 16 patients with relapsing disease, new sites of disease were identified. The (18)F-FDG PET results were especially helpful in identifying focal recurrent disease in patients with nonsecretory or hyposecretory disease amenable to local irradiation therapy, which was used in 6 patients. CONCLUSION: Whole-body (18)F-FDG PET provides important prognostic information, which is clinically useful and complementary to conventional methods of evaluating plasma cell disorders. (18)F-FDG PET is a unique tool for evaluation of nonsecretory myeloma. Residual or recurrent disease after therapy, especially extramedullary disease, is a poor prognostic factor.

PMID: 12411548 [PubMed - indexed for MEDLINE]
Section — III

Hepatobiliary and Gastrointestinal Malignancies
Gastric Carcinoma

Introduction:
95% of gastric cancers are adenocarcinomas. Lymphoma, leiomyosarcoma, carcinoid, adenoacanthoma, and squamous cell carcinomas account for the remaining 5%.

Current staging/imaging:
Endoscopy is now the preferred initial diagnostic test, because it allows direct tumor visualization, cytologic testing, and histologic biopsy that yield the diagnosis in 90% or more of patients with exophytic lesions. Ulcerated cancers and linitis plastica lesions may be harder to diagnose endoscopically, but multiple biopsies and washings enhance the probability of accurate diagnosis. Endoscopic ultrasonography (EUS) has a high degree of accuracy in determining depth of tumor invasion, but is less accurate in detecting regional nodal metastasis. Ultrasound-guided fine-needle aspiration for cytologic test allows the assessment of regional lymph nodes and some distant metastatic sites (e.g., liver), further enhancing the ability of EUS to determine tumor stage and resectability. Abdominal CT scan is valuable in determining the abdominal extent of disease with regard to larger liver metastasis (1 cm or greater),
involvement of celiac or periaortic nodes, or extragastric extension (may help determine which lesions extend to surgically unresectable structures). Diagnostic laparoscopy allows visualization of small serosal or liver metastases and may give added information with regard to the amount of direct extension of the primary tumor. Distant metastases should be ruled out with a chest radiograph, serum liver chemistries, and abdominal CT scan. If a proximal gastric tumor extends to involve the esophagus; CT scan of the chest is useful in determining mediastinal node involvement or parenchymal lung metastases.

**Summary of Evidence for PET:**
FDG PET is not a reliable screening test for gastric carcinoma. The uptake and detectability is less in superficial lesions. Gastric adenocarcinoma express GLUT receptors and hence are FDG avid. However there is normal physiological uptake of FDG in the stomach also. The accuracy of FDG PET is similar to that of CECT in the detectability of primary tumor. While CECT is more sensitive in detecting nodes, the specificity of FDG for nodes is higher with PET. The accuracy of integrated CECT-PET is therefore the highest. Distant metastases are best detected on FDG PET, while serosal mets are best detected by CT. However FDG PET accuracy for serosal lesions remains higher. There is growing evidence in the detection of recurrent disease and assessing treatment response with Chemo radiation.
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**Selected Abstracts:**


OBJECTIVE: (18)F-2-deoxy-2-fluoro-D-glucose positron emission tomography (FDG-PET) is a promising screening modality targeting whole body. However, the validity of PET cancer screening remains to be assessed. Even the screening accuracy for whole-body screening using FDG-PET has not been evaluated. In this study, we investigated the screening accuracy of PET cancer screening. METHODS: A total of 2911 asymptomatic participants (1629 men and 1282 women, mean age 59.79 years) underwent both FDG-PET and other thorough examinations for multiple organs (gastrofiberscopy, total colonfiberscopy or barium enema, low-dose thin section computed tomography and sputum cytology, abdominal ultrasonography, an assay of prostate-specific antigen, mammography, mammary ultrasonography, Pap smear for the
uterine cervix, and magnetic resonance imaging for the endometrium and ovaries) between February 2004 and January 2005, and followed sufficiently. The detection rate, sensitivity, specificity, and positive predictive value of FDG-PET were calculated using cancer data obtained from all examinations along with a 1 year follow-up. RESULTS: From among 2911 participants FDG-PET found 28 cancers, 129 cancers were PET negative. PET-positive cancers comprised seven colorectal cancers, four lung cancers, four thyroid cancers, three breast cancers, two gastric cancers, two prostate cancers, two small intestinal sarcomas (gastrointestinal stromal tumors), one malignant lymphoma, one head and neck malignancy (nasopharyngeal carcinoid tumor), one thymoma, and one hepatocellular carcinoma. PET-negative cancers included 22 gastric cancers and 20 prostate cancers that were essentially difficult to detect using FDG-PET. The overall detection rate, sensitivity, specificity, and positive predictive value were estimated to be 0.96%, 17.83%, 95.15%, and 11.20%, respectively. CONCLUSIONS: FDG-PET can detect a variety of cancers at an early stage as part of a whole-body screening modality. The detection rate of PET cancer screening was higher than that of other screening modalities, which had already shown evidence of efficacy. However, the sensitivity of PET cancer screening was lower than that of other thorough examinations performed at our institute. FDG-PET has some limitations, and cancer screening using only FDG-PET is likely to miss some cancers.

PMID: 18600415 [PubMed - indexed for MEDLINE]

OBJECTIVE: Variable uptake of 2-deoxy-2-[18F]fluoro-D-glucose (FDG) has been noticed in positron emission tomography (PET) studies of gastric carcinoma patients, with low uptake occurring especially in some particular histological subtypes and early carcinomas. But this phenomenon has not been adequately explained. The aim of the present study is to clarify FDG uptake in gastric carcinomas especially focusing on histological subtypes, the depth of tumor invasion, and glucose transporter-1 (GLUT-1) expression which is considered to be one of the major factors for higher FDG uptake in human malignant tumors. METHODS: FDG-PET was performed on 35 preoperative patients with gastric carcinoma. Forty macroscopically distinguishable lesions on a surgical specimen were histologically classified into two subtypes: Cohesive type (papillary adenocarcinoma, tubular adenocarcinoma, and solid type poorly differentiated adenocarcinoma) or Noncohesive type (signet-ring cell carcinoma and non-solid type poorly differentiated carcinoma). GLUT-1 expression was immunohistochemically determined. Histological parameters (GLUT-1 expression, histological subtypes, the depth of invasion, lymphatic permeation, venous invasion and tumor size) were evaluated, and factors for FDG uptake (detectability and the degree) and GLUT-1 overexpression were determined by multiple regression analysis. RESULTS: Nineteen of 40 gastric carcinomas showed detectable FDG uptake (48%), multiple regression analysis revealed that both the depth of invasion and histological subtypes are independent factors that influence the detectable FDG uptake in gastric carcinoma (R2 = 0.66).
GLUT-1 expression was seen from an early cancer stage and the cohesive type was an independent factor influencing the overexpression of GLUT-1 (R2 = 0.66). GLUT-1 expression was the most influential factor for the degree of FDG uptake in gastric carcinoma (R2 = 0.68). CONCLUSIONS: This study provided important information on the clinical application of FDG-PET in gastric carcinoma that early or non-cohesive gastric carcinoma may show lower FDG uptake. Therefore, the usefulness of FDG-PET for the detection of gastric carcinoma is limited. But there is a possibility that FDG uptake associated with GLUT-1 expression may serve as a prognostic factor of gastric carcinoma representing tumor metabolism.

PMID: 17294670


PURPOSE: The aim of this study was to assess the diagnostic accuracy of (18)F-fluoro-2-deoxyglucose (FDG) positron emission tomography (PET) with respect to lymph node (LN) metastasis in patients with advanced gastric cancer, and to ascertain the factors that affect this accuracy. METHODS: Seventy-three patients with advanced gastric cancer, verified in all cases by endoscopic biopsy, were enrolled in this prospective study. We conducted FDG PET and other routine preoperative studies, including abdominal computed tomography (CT). Patients underwent either curative-intent gastrectomy and lymphadenectomy (n = 67) or exploratory laparotomy. The Japanese system for the classification of gastric cancer was used for LN assessment. RESULTS: FDG PET was able to detect primary lesions in 70 of the 73 cases. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value of FDG PET for LN metastasis
were 40\%, 95\%, 91\% and 56\%, respectively. Signet-ring cell carcinoma was associated with the lowest sensitivity (15\%), whereas other cell types could be detected with moderate sensitivity (30-71\%) and high specificity (93-100\%).

According to multiple logistic regression, the standardised uptake value for primary tumours was the only independent variable to be significantly related to sensitivity for LN metastasis (p = 0.02, odds ratio = 1.14). CT was superior to PET in terms of sensitivity (p < 0.0001), and PET was superior to CT in terms of specificity (p < 0.0001) and PPV (p = 0.05).

CONCLUSION: FDG PET exhibits good specificity for LN staging of gastric cancer, and FDG uptake in the primary tumour is significantly related to the accuracy of FDG PET. Despite some clear limitations, FDG PET proved useful in the LN staging of FDG-avid gastric cancer.

PMID: 16228236 [PubMed - indexed for MEDLINE]


BACKGROUND: The aim of the study was to evaluate whether the therapy-induced reduction of the (18)F-fluorodeoxyglucose positron emission tomography (18F-FDG-PET) maximum standardized uptake value in patients with advanced gastric adenocarcinoma treated with chemotherapy plus cetuximab could predict the objective response and outcome early during the treatment. METHODS: The study was performed as a part of a phase II trial evaluating cetuximab plus the leucovorin/5-fluorouracil/irinotecan (FOLFIRI) regimen. The objective response was evaluated according to the response evaluation criteria in solid tumors (RECIST) every 6 weeks. The early metabolic response evaluated by 18F-FDG-PET was assessed according to our own evaluated
cutoff value (<35%) after receiver operating characteristic (ROC) analysis. RESULTS: Twenty of 22 patients had positive baseline 18F-FDG-PET. The best RECIST response was: complete response (CR), 3; partial response (PR), 9; stable disease (SD), 8. Twelve patients (60%) were classified as metabolic responders and 8 (40%) as nonresponders. At the median follow-up time of 11 months, median time to disease progression (TTP) and overall survival (OS) for early metabolic responders versus nonresponders were 11 versus 5 months (P = 0.0016) and 16 versus 6 months (P = 0.1493), respectively. CONCLUSION: The early metabolic response evaluated by 18F-FDG-PET predicted the clinical outcome in this series of patients with advanced gastric cancer treated with chemotherapy plus cetuximab.

PMID: 18095077


AIM: To evaluate the clinical role of (18)F-fluorodeoxyglucose positron emission and computed tomography ((18)F-FDG PET/CT) in detection of gastric cancer recurrence after initial surgical resection. METHODS: In the period from January 2007 to May 2008, 23 patients who had previous surgical resection of histopathologically diagnosed gastric cancer underwent a total of 25 (18)F-FDG PET/CT scans as follow-up visits in our center. The standard of reference for tumor recurrence consisted of histopathologic confirmation or clinical follow-up information for at least 5 mo after PET/CT examinations. RESULTS: PET/CT was positive in 14 patients (61%) and negative in 9 (39%). When correlated with final diagnosis, which was confirmed by histopathologic evidence
of tumor recurrence in 8 of the 23 patients (35%) and by clinical follow-up in 15 (65%), PET/CT was true positive in 12 patients, false positive in 2, true negative in 8 and false negative in 2. Overall, the accuracy of PET/CT was 82.6%, the negative predictive value (NPV) was 77.7%, and the positive predictive value (PPV) was 85.7%. The 2 false positive PET/CT findings were actually chronic inflammatory tissue lesions. For the two patients with false negative PET/CT, the final diagnosis was recurrence of mucinous adenocarcinoma in the anastomosis in one patient and abdominal wall metastasis in the other. Importantly, PET/CT revealed true-positive findings in 11 (47.8%) patients who had negative or no definite findings by CT. PET/CT revealed extra-abdominal metastases in 7 patients and additional esophageal carcinoma in one patient. Clinical treatment decisions were changed in 7 (30.4%) patients after introducing PET/CT into their conventional post-operative follow-up program. CONCLUSION: Whole body (18)F-FDG PET/CT was highly effective in discriminating true recurrence in post-operative patients with gastric cancer and had important impacts on clinical decisions in a considerable portion of patients.

PMID: 18698676


INTRODUCTION: The usefulness of tumour markers CEA, CA19.9 and CA72.4 in association with FDG-PET/TG were prospectively evaluated in the post-operative follow-up of gastric cancer patients. MATERIAL AND METHODS: Fifty one consecutive patients were enrolled in a follow-up programme entailing with periodical clinical evaluations, instrumental examinations and tumour markers assay FDG-
PET/TC was performed only in cases of suspected recurrence. RESULTS: Sensitivity of CEA, CA19.9 and CA72.4 during the follow-up period was respectively: 16%, 33.3% and 50%. Overall sensitivity was 66.6%. Specificity was 100% for CEA, 93.3% for CA19.9, 100% for CA72.4, with an overall specificity of 96.2%. FDG-PET/TC had a sensitivity of 100%.

CONCLUSIONS: Tumour markers in association with FDG-PET/TC allow an early identification of recurrences after surgery, with the advantage to start chemotherapy or surgical protocols before the tumour has reached an advanced stage.

PMID: 18510026 [PubMed - indexed for MEDLINE]
Colorectal Cancer

Introduction
Colorectal cancer (CRC) is one of the leading causes of cancer morbidity and mortality worldwide. Diagnosis of CRC is generally based on colonoscopy and biopsy. Prognosis of CRC closely relates to initial stage of the disease at diagnosis and the ability to achieve surgical clearance. Accurate pre-operative staging is important for optimal therapeutic planning which includes surgery, radiation therapy or chemotherapy. Early detection of recurrence can lead to better survival if the sites of recurrence are localized and amenable to surgical excision. Accurate imaging plays a very important role and needs to be performed for routine surveillance and if recurrence is clinically suspected.

Conventional Imaging
Conventional pre-operative imaging of CRC is performed with ultrasound, CT scan and MRI. There is no ideal imaging modality in terms of diagnostic accuracy and staging due to the potential limitations of these modalities. CT is the most widely used modality in the diagnosis and staging of CRC with accuracy ranging between 64% and 81%. CT plays an
important role in detection of early recurrence however it is limited by reliance on size criteria to diagnose malignancy. Endoluminal ultrasound seems to have the highest accuracy for tumor infiltration of the bowel wall and the adjacent fatty tissue. But depth of invasion of the bowel wall and spread to regional lymph nodes is frequently obtained intraoperatorively and histopathologically.

**Summary of evidence for FDG PET**

In the *primary staging* of CRC, small studies have shown that FDG PET-CT is more accurate in tumor-node-metastases staging compared with CT scan & FDG PET alone. Another study of 44 patients which compared the accuracy of MDCT and FDG PET with respect to primary tumor detectability, lymph node involvement and distant metastases, FDG PET was not found to be superior to MDCT in primary staging of CRC. The low sensitivity of FDG PET for small lesions (less than 1 cm) and the chance of false positives in inflammatory bowel lesions could explain the current lack of evidence to indicate FDG PET as part of routine screening or initial staging of patients. FDG PET imaging can lead to a management change in 2-36% patients of CRC undergoing initial staging. But there is a small body of evidence to support this and in addition a lack of cost–benefit analysis has not led to an impact on general clinical practice particularly in nations where resources are limited. The primary staging of rectal cancers is one specific indication where FDG PET-CT is likely to make an impact on management decisions. Though MRI has an established role in rectal tumor staging by facilitating accurate assessment of local tumor extension, addition of PET can provide more accurate assessment of nodal & metastatic disease. A recent study of 83 patients concluded that FDG PET impacts management of patients of rectal cancer and influences staging/therapy in one third of patients and should be a component of rectal cancer work up.
Surgery remains the only option for potential cure in patients with recurrent CRC. For evaluation of disease recurrence PET has an established role in the standard of care of patients with suspected recurrence either due to clinical symptoms or rising tumor marker levels. A meta-analysis by Huebner et al found that FDG PET has a sensitivity and specificity of 97% and 76% in the detection of recurrent CRC which led to management change in 29% patients. This number is similar to the 32% management change demonstrated by Gambhir et al. A prospective blinded comparison by Valk et al between FDG PET and CT has shown a sensitivity and specificity of 93% and 98% for FDG PET and 96% and 69% for CT. FDG PET can be particularly useful in detecting subtle peritoneal and omental disease which can be difficult on CT scan alone. It is very useful in proper selection of patients who are suitable for surgery for recurrent disease.

One of the most compelling indication of FDG PET in CRC is to look for occult extrahepatic disease before planning a metastatectomy. Two meta analyses have shown a pooled sensitivity and specificity of 91.5 % and 95.5% versus 61 % and 91% for CT in this setting.

FDG PET has been used in assessing response at the completion of radiotherapy, chemoradiation or local ablative therapy. When performed at an appropriate time interval after treatment it can provide information on presence of viable tumor, differentiate disease from fibrosis/scar and also helps predict survival. There are a few prospective studies in literature which have looked at the role of FDG PET after radiation therapy in the prognostic stratification in patients with locally advanced rectal cancer. They concluded that a significant survival benefit was observed in patients with low FDG uptake after pre-operative radiotherapy in locally advanced tumors of the rectum. A few prospective studies have
shown that FDG PET reveals RFA treatment failure as well as detection of local recurrence earlier than CT scan.

For radiation therapy planning a few small studies indicate that tumor target volume assessment can be improved by the addition of FDG PET-CT with 17% of patients requiring change in treatment fields and 26% patients needing management change.

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Selected abstracts


PURPOSE: 18-Fluorodeoxyglucose positron emission tomography-computed tomography (FDG PET-CT) has a role
in recurrent colorectal cancer. This study was designed to assess the impact of PET-CT on management of primary rectal cancer. METHODS: Eighty-three patients with rectal cancer underwent PET-CT scan between 2002 and 2005. Referring physicians prospectively recorded stage and management plan after conventional imaging before PET-CT scan, which were compared to subsequent stage and management after PET-CT. RESULTS: Staging PET-CT caused a change in stage from conventional imaging in 26 patients (31 percent). Twelve (14 percent) were upstaged (7 change in N stage; 4 change in M stage; 1 change in N and M stage), and 14 (17 percent) were downstaged (10 change in N stage; 3 change in M stage; 1 change in N and M stage). PET-CT scan altered management intent in seven patients (8 percent) (curative to palliative 6 patients; palliative to curative 1 patient). Management was altered in ten patients (12 percent). There was no difference in impact with respect to tumor height. CONCLUSIONS: PET-CT scan impacts the management of patients with primary rectal cancer and influences staging/therapy in a third of patients and should be a component of rectal cancer workup.


BACKGROUND: The role of positron emission tomography with the glucose analogue [18F] fluoro-2-deoxy-D-glucose (FDG-PET) in the initial staging of disease in patients with primary colorectal cancer (CRC) has not been adequately assessed. AIMs: To evaluate the additional value of FDG-PET as a staging modality, complementary to routine multidetector row computed tomography (MDCT) in patients with CRC. METHODS: Forty four patients with CRC
underwent preoperative MDCT and FDG-PET. The accuracy of intraoperative macroscopic staging was also investigated compared with histopathological diagnosis. All FDG-PET images were evaluated with respect to detectability of the primary tumour, lymph node involvement, and distant metastases. Both MDCT and FDG-PET diagnoses and treatment plan were compared with surgical and histopathological results. RESULTS: Thirty seven patients underwent surgery. Tumour detection rate was 95% (42/44) for MDCT, 100% (44/44) for FDG-PET, and 100% (37/37) for intraoperative macroscopic diagnosis. Pathological diagnosis of T factor was T1 in five, T2 in four, T3 in 24, and T4 in four cases. Concordance rate with pathological findings of T factor was 57% (21/37) for MDCT and 62% (23/37) for macroscopic diagnosis. Lymph node involvement was pathologically positive in 19 cases. Regarding N factor, overall accuracy was 62% (23/37) for MDCT, 59% (22/37) for FDG-PET, and 70% (26/37) for macroscopic diagnosis. For all 44 patients, FDG-PET findings resulted in treatment changes in only one (2%) patient. CONCLUSION: FDG-PET is not superior to routine MDCT in the initial staging of primary CRC.


The aims of our study were to examine the impact of PET in changing management in patients with proven or suspected colorectal cancer recurrence and to assess the impact of management change on disease-free survival. METHODS: Symptomatic patients with a residual structural lesion suggestive of recurrent tumor (group A) or patients with
pulmonary or hepatic metastases considered to be potentially resectable (group B) underwent PET scans. Pre-PET management plans were documented by referring clinicians unaware of the PET results, and follow-up to 12 mo was performed to determine actual management and clinical outcomes. RESULTS: A total of 191 patients (118 men and 73 women; mean age, 66 y) were studied. PET detected additional sites of disease in 48.4% of patients in group A and in 43.9% of patients in group B. A change in planned management was documented in 65.6% of group A and in 49.0% of group B patients. These management plans were implemented in 96% of patients. Follow-up data in group A showed progressive disease in 60.5% of patients with additional lesions detected by PET, compared with conventional imaging, and in 36.2% of patients with no additional lesions detected by PET (P=0.04). In group B, progressive disease was identified in 65.9% of patients with additional lesions detected by PET and in 39.2% of patients with no additional lesions detected by PET (P=0.01). PET also provided valuable prognostic information on patients stratified into curative- or palliative-intent groups. CONCLUSION: These data demonstrate the significant impact of PET on management and outcomes in patients with suspected recurrent colorectal cancer.


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management change on disease-free survival. METHODS: Symptomatic patients with a residual structural lesion suggestive of recurrent tumor (group A) or patients with pulmonary or hepatic metastases considered to be potentially resectable (group B) underwent PET scans. Pre-PET management plans were documented by referring clinicians unaware of the PET results, and follow-up to 12 mo was performed to determine actual management and clinical outcomes. RESULTS: A total of 191 patients (118 men and 73 women; mean age, 66 y) were studied. PET detected additional sites of disease in 48.4% of patients in group A and in 43.9% of patients in group B. A change in planned management was documented in 65.6% of group A and in 49.0% of group B patients. These management plans were implemented in 96% of patients. Follow-up data in group A showed progressive disease in 60.5% of patients with additional lesions detected by PET, compared with conventional imaging, and in 36.2% of patients with no additional lesions detected by PET (P=0.04). In group B, progressive disease was identified in 65.9% of patients with additional lesions detected by PET and in 39.2% of patients with no additional lesions detected by PET (P=0.01). PET also provided valuable prognostic information on patients stratified into curative- or palliative-intent groups. CONCLUSION: These data demonstrate the significant impact of PET on management and outcomes in patients with suspected recurrent colorectal cancer.

PURPOSE: Surgery remains the only option for potential cure in patients with recurrent colorectal cancer. Accurate staging modalities aid in the avoidance of futile surgery, which may
result in considerable morbidity in patients with incurable disease. Current imaging techniques used in disease staging often are not sensitive enough to identify low-volume metastatic disease. This study reviews the role of positron emission tomography in the assessment of patients with suspected recurrent colorectal cancer. METHODS: A literature search using the PubMed, MEDLINE, and Embase database was performed, locating English language articles on positron emission tomography, positron emission tomography, recurrent colon, and/or rectal cancer. The references of these papers were searched manually for further references. RESULTS: Positron emission tomography is more sensitive and more specific than conventional diagnostic imaging for metastatic disease and local recurrence respectively. Studies confirm the superior ability of positron emission tomography scans compared with conventional diagnostic imaging in differentiating between scar tissue and invasive tumor. Positron emission tomography scanning is more sensitive and specific for the assessment of liver metastases (and probably in patients with lung metastasis) than conventional diagnostic imaging. Positron emission tomography is superior to conventional diagnostic imaging in the investigation of raised carcinoembryonic antigen in the postoperative patient and alters management in approximately 37 percent of patients with recurrent colorectal cancer. The limitations and cost effectiveness of positron emission tomography are discussed. CONCLUSIONS: Positron emission tomography scanning is emerging as the imaging modality of choice for patients being considered for surgery for locally recurrent colorectal cancer. Positron emission tomography has the greatest impact by detecting unresectable disease and thereby averting inappropriate surgery. Despite the high set-up costs, its use seems to be cost effective.

Accurate detection of recurrent colorectal carcinoma remains a diagnostic challenge. The purposes of this study were to evaluate the diagnostic value of Positron emission tomography (PET) using fluor-18-deoxyglucose (FDG) in recurrent colorectal carcinoma with a meta-analysis. All the published studies in English relating the diagnostic value of FDG-PET in the detection of recurrent colorectal carcinoma were collected. Methodological quality of the included studies was evaluated. Pooled sensitivity, specificity and diagnostic odds ratio and SROC (summary receiver operating characteristic curves) were obtained by the statistical software. Twenty-seven studies were included in the meta-analysis. The pooled sensitivity and specificity for FDG-PET detecting distant metastasis or whole body involvement in recurrent colorectal carcinoma were 0.91 (95% CI 0.88-0.92) and 0.83 (95% CI 0.79-0.87), respectively. The pooled sensitivity and specificity for FDG-PET detecting hepatic metastasis were 0.97 (95% CI 0.95-0.98) and 0.98 (95% CI 0.97-0.99). The pooled sensitivity and specificity for pelvic metastasis or local regional recurrence were 0.94 (95% CI 0.91-0.97) and 0.94 (95% CI 0.92-0.96). FDG-PET is valuable for the assessment of recurrent colorectal carcinoma.


PURPOSE: Focal metastasis may be treated with radiofrequency ablation (RFA), a low invasive method yet
limited by the lack of direct evidence of radicality of treatment. We, hereby, aimed at assessing the role of positron emission tomography-computed tomography (PET/CT) with fluoride radiolabeled deoxy-glucose ([18]F]FDG) in RFA treatment success evaluation and early diagnosis of local relapse of liver metastasis after RFA procedure. METHODS: RFA was performed in nine patients on 12 liver metastasis, serially imaged through [(18)F]FDG-PET/CT and multidetector CT (MDCT) at 1, 3, 6, and 9 months after treatment. Eight lesions were also scanned with [(18)F]FDG-PET/CT at 1 week after treatment. Imaging analyses were performed on 47 [(18)F]FDG-PET/CT and 51 MDCT. Imaging reading outcomes were compared to each other and to biopsy tissue results when available. RESULTS: In one case, [(18)F]FDG-PET/CT revealed radiotracer uptake at RFA site a week after procedure. Negative concordant outcome was obtained on eight lesions at 1 month after RFA, on eight cases at 3 months, on four at 6 months, and on two cases at 9 months. Extra-liver (peritoneal) disease was detected in one case by both [(18)F]FDG-PET/CT and MDCT. In seven cases, [(18)F]FDG-PET/CT revealed the presence of local recurrence earlier than MDCT. In no cases did MDCT detect local relapse earlier than [(18)F]FDG-PET/CT. CONCLUSION: [(18)F]FDG-PET/CT may detect RFA treatment failure as well as local relapse after RFA earlier than MDCT.


The purpose of this study was to assess the diagnostic accuracy of whole-body MRI (WB-MRI) at 1.5 T or 3 T compared with FDG-PET-CT in the follow-up of patients suffering from colorectal cancer. In a retrospective study, 24 patients with a
history of colorectal cancer and suspected tumour recurrence underwent FDG-PET-CT and WB-MRI with the use of parallel imaging (PAT) for follow-up. High resolution coronal T1w-TSE and STIR sequences at four body levels, HASTE imaging of the lungs, contrast-enhanced T1w- and T2w-TSE sequences of the liver, brain, abdomen and pelvis were performed, using WB-MRI at either 1.5 T (n = 14) or 3 T (n = 10). Presence of local recurrent tumour, lymph node involvement and distant metastatic disease was confirmed using radiological follow-up within at least 5 months as a standard of reference. Seventy seven malignant foci in 17 of 24 patients (71%) were detected with both WB-MRI and PET-CT. Both investigations concordantly revealed two local recurrent tumours. PET-CT detected significantly more lymph node metastases (sensitivity 93%, n = 27/29) than WB-MRI (sensitivity 63%, n = 18/29). PET-CT and WB-MRI achieved a similar sensitivity for the detection of organ metastases with 80% and 78%, respectively (37/46 and 36/46). WB-MRI detected brain metastases in one patient. One false-positive local tumour recurrence was indicated by PET-CT. Overall diagnostic accuracy for PET-CT was 91% (sensitivity 86%, specificity 96%) and 83% for WB-MRI (sensitivity 72%, specificity 93%), respectively. Examination time for WB-MRI at 1.5 T and 3 T was 52 min and 43 min, respectively; examination time for PET-CT was 103 min. Initial results suggest that differences in accuracy for local and distant metastases detection using FDG-PET-CT and WB-MRI for integrated screening of tumour recurrence in colorectal cancer depend on the location of the malignant focus. Our results show that nodal disease is better detected using PET-CT, whereas organ disease is depicted equally well by both investigations.
Hepatocellular Carcinoma & PET/CT

Introduction:
HCC is commonly associated with macronodular cirrhosis in South East Asia and micronodular cirrhosis in Europe and United States. Viral hepatitis, alcoholic hepatitis, chronic active hepatitis, nonalcoholic fatty liver disease are associated with HCC.

Current staging/imaging:
Ultrasound of the liver is an excellent screening tool. A 3 phase CECT and MRI are the current imaging modalities of choice. CECT guided biopsy helps clinch the diagnosis. The location, number of masses, evidence of extra hepatic spread, and patency of vessels, are the important questions to be answered by imaging.

Summary of Evidence for PET:
It is seen that FDG PET does not concentrate in all HCCs. Several case reports mention the advantage of FDG uptake, identifying the loco regional metastases and portal vein thrombosis, adding to the specificity of the CECT. In a prospective study of 18F-FDG, the sensitivities according to
tumor size (1-2, 2-5, and >/=5 cm) were 27.2%, 47.8%, and 92.8%, respectively; for (11)C-acetate, these respective values were 31.8%, 78.2%, and 95.2%. (18)F-FDG was more sensitive in the detection of poorly differentiated HCC. There are several case reports that have shown FDG uptake in hepatic and extra hepatic lesions including tumor thrombus. Animal studies have shown that FDG does not concentrate in well differentiated and moderately differentiated HCC more than that of the normal liver tissue. 11 C Acetate is a better agent for well differentiated HCC but does not perform better than FDG in extra hepatic lesions.

A combination of three phase CT scan along with FDG PET as a single study could provide the highest sensitivity and add prognostic information.

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Selected Abstracts:


AIM: This study was designed to investigate the performance of positron emission tomography (PET) imaging for hepatocellular carcinoma (HCC) on a hepatitis viral infection-induced woodchuck model using existing tracers such as 2-deoxy-2-\[(18)F\]fluoro-D-glucose (2FDG), 6-deoxy-6-\[(18)F\]fluoro-D-glucose (6FDG), [(1-11)C]acetate (acetate) and [N-methyl-(11)C]choline (choline).

METHODS: Fourteen woodchucks with HCC were imaged with different radiotracers: 13 (10 with HCC and 3 controls) with 2FDG; 4 (3 with HCC and 1 control) with 6FDG; 13 (10 with HCC and 3 controls) with acetate; 4 (2 with HCC and 2 controls) with choline. The woodchucks were euthanized after imaging experiments and liver tissues were harvested for histology, for enzymatic activities including hexokinase (HK), glucose-6-phosphatase, acetyl-CoA synthetase (ACAS) and choline kinase (CK), and for differential gene expressions between the HCCs and the surrounding hepatic tissues.

RESULTS: 2FDG detected 7/13 tumors with a tumor-to-liver uptake ratio (T/L) of 1.36+/−0.13. Five of these HCCs were moderately- or poorly-differentiated. The HK/glucose-6-phosphatase ratio was significantly higher in HCCs compared to the surrounding liver tissues (P=0.05). None of the HCCs imaged with 6FDG were detected by PET (T/L=1.01+/−0.11). Acetate detected 16/17 HCCs (T/L=2.02+/−0.7). ACAS activity was significantly higher in HCCs (P=0.01) and lipids-related genes were found up-regulated. Choline imaging detected all HCCs (T/L=1.63+/−0.34). CK activity was significantly higher in HCCs (P=0.001).

CONCLUSION: Well-differentiated and
some moderately-differentiated HCCs do not uptake 2FDG more than the surrounding liver tissues, but display increased acetate uptake. There is no contrast between HCCs and the surrounding liver tissues on the 6FDG PET images. Despite elevated background signal from the liver, choline uptake seems to be detectable in the HCCs scanned in this study.

PMID: 19039303


Because (18)F-FDG PET has insufficient sensitivity for the detection of hepatocellular carcinoma (HCC), (11)C-acetate PET has been proposed as another technique for this use. We prospectively evaluated the value of PET/CT using these 2 tracers for the detection of primary and metastatic HCC.

METHODS: One hundred twelve patients (99 with HCC, 13 with cholangiocellular carcinoma) underwent biopsy and (18)F-FDG and (11)C-acetate PET/CT. RESULTS: The overall sensitivities of (18)F-FDG, (11)C-acetate, and dual-tracer PET/CT in the detection of 110 lesions in 90 patients with primary HCC were 60.9%, 75.4%, and 82.7%, respectively. Elevated serum alpha-fetoprotein levels, an advanced tumor stage, portal vein tumor thrombosis, large tumors, and multiple tumors were significantly associated with positive (18)F-FDG PET/CT results. Uptake of (11)C-acetate was associated with large and multiple tumors. For (18)F-FDG, the sensitivities according to tumor size (1-2, 2-5, and >/=5 cm) were 27.2%, 47.8%, and 92.8%, respectively; for (11)C-acetate, these respective values were 31.8%, 78.2%, and 95.2%. (18)F-FDG was more sensitive in the detection of poorly differentiated HCC. Overall survival was lower in patients with (18)F-FDG PET/CT positive for all indexed
lesions than in those with FDG negative or partially positive through the entire follow-up period. In analysis based on biopsied lesions, the sensitivity of (18)F-FDG PET/CT was 64.4% for primary HCC and 84.4% for (11)C-acetate PET/CT. The overall sensitivities of (18)F-FDG, (11)C-acetate, and dual-tracer PET/CT for 35 metastatic HCCs were 85.7%, 77.0%, and 85.7%, respectively. There was no significant difference in the sensitivity of tracers according to metastatic tumor size, location, or differentiation. CONCLUSION: The addition of (11)C-acetate to (18)F-FDG PET/CT increases the overall sensitivity for the detection of primary HCC but not for the detection of extrahepatic metastases. (18)F-FDG, (11)C-acetate, and dual-tracer PET/CT have a low sensitivity for the detection of small primary HCC, but (18)F-FDG PET/CT has a relatively high sensitivity for the detection of extrahepatic metastases of HCC.

PMID: 18997056

**Clinical implication of glucose transport and metabolism evaluated by 18F-FDG PET in hepatocellular carcinoma.**


Hepatocellular carcinoma (HCC) has variable 18F-fluoro-2-deoxy-D-glucose (18F-FDG) uptake and the relationship between 18F-FDG uptake with the expression of glucose transporters (Gluts) and hexokinase II (HK-II) has not been extensively examined. Present study explored the role of 18F-FDG positron emission tomography (PET) as a clinical significance and the association with Gluts and HK-II in patients with HCC. Whole body 18F-FDG PET, immunohistochemistry and western blot analysis of Glut-1 to Glut-5 and HK-II were performed in 31 patients (24 male and 7 female, range 48-75 years) with HCC. Significant correlation was found between 18F-FDG uptake and overall expression
of Glut-2 (rho=0.55, p=0.002) and HK-II (rho=0.37, p=0.04). Expression of HK-II was correlated with Glut-2 (rho=0.57, p=0.0009) but not with other Gluts, which indicated that Glut-2 is a major glucose transporter. The prognosis of patients with SUV $\geq 2$ and positive Glut-2 were significantly worse than that with SUV $< 2$ and negative Glut-2 (p=0.005 and p=0.03), respectively. Multivariate analysis showed that SUV and lymph node metastasis were independent prognostic factors. The present study indicated that combined evaluation of 18F-FDG uptake and expression of Glut-2 might have an important role for management of patients with HCC.

PMID: 18949368

**Detection of hepatocellular carcinoma using 11C-choline PET: comparison with 18F-FDG PET.**


The purpose of this study was to retrospectively investigate the feasibility of 11C-choline PET, compared with 18F-FDG PET, for the detection of hepatocellular carcinoma (HCC).

**METHODS:** A total of 16 HCC lesions in 12 patients were examined with both 11C-choline PET and 18F-FDG PET. Tumor lesions were identified as areas of focally increased uptake, exceeding that of surrounding noncancerous liver tissue. For semiquantitative analysis, the tumor-to-liver (T/L) ratio was calculated by dividing the maximal standardized uptake value (SUV) in HCC lesions by the mean SUV in noncancerous liver tissue.

**RESULTS:** 11C-choline PET showed a slightly higher detection rate than did 18F-FDG PET for detection of HCC (63% vs. 50%, respectively), although this difference was not statistically significant. 11C-choline PET had a better detection rate for moderately differentiated HCC lesions but not for those poorly differentiated (75% vs. 25%, respectively). In contrast, 18F-FDG PET exhibited the
opposite behavior, with corresponding detection rates of 42% and 75%, respectively. The mean 11C-choline SUV and T/L ratio in moderately differentiated HCC lesions were higher than those in poorly differentiated HCC lesions. In contrast, the mean 18F-FDG SUV and T/L ratio in poorly differentiated HCC were higher than those in moderately differentiated HCC. These differences, however, were also not statistically significant. CONCLUSION: 11C-choline PET had a better detection rate for moderately differentiated HCC lesions but not for poorly differentiated HCC lesions, whereas 18F-FDG PET produced the opposite result. 11C-choline is a potential tracer to complement 18F-FDG in detection of HCC lesions.

PMID: 18632827
Cholangiocarcinoma

Introduction
Cholangiocarcinomas form 3% of the GI tumors and could be intrahepatic or extra hepatic. More than 90% of CC are well to moderately differentiated adenocarcinomas, that present as solid masses or infiltrate surrounding tissues, grow intraductally, or have mixed characteristics. Elevation of serum tumor markers (Ca 19-9 and CEA) supports diagnosis of CC, although none of them is diagnostic. Levels of Ca 19-9 seem to correlate with the stage of the disease, as serum levels of Ca 19-9 >100 U/mL have shown to have 33% sensitivity to detect resectable tumors compared with 72% for unresectable tumors

Conventional Staging:
Ultrasonography (US) is usually the initial test to evaluate biliary obstruction. Sensitivity and accuracy of US for ECC is 89% and 80% to 95%, respectively.

Use of duplex US with color Doppler technology has 93% sensitivity and 99% specificity in assessing portal venous or hepatic artery invasion.
Triple-phase CT scan is used to assess local spread, vascular and lymph node involvement, and presence of distant metastases. Sensitivity of triple-phase helical CT for detection of CC ranges between 90% and 100%. Overall accuracy of CT in determining resectability of CC is in the range of 60% to 85%.

CT cholangiography has been shown to be superior to conventional CT and comparable with ERCP for diagnosis of KCC because the sensitivity and specificity of CT cholangiography are 94%.

Magnetic resonance cholangiopancreatography has a overall sensitivity of 88% and specificity of 95%; 66% accuracy for detection of lymph node metastases, 78% sensitivity and 91% specificity for portal vein invasion, 58% sensitivity and 93% specificity for arterial invasion.

**Summary Of Evidence for PET:**

**Diagnosis** – the Ability to differentiate malignant from benign stricture of the biliary tree:

One prospective trial of 37 patients who underwent dual point imaging FDG PET study at two time intervals and the delayed scan when compared to histology yielded Sensitivity: 86%, specificity -86.5%, accuracy- 86%  Delayed imaging with FDG PET hence can be used to differentiate malignant from benign stricture. The overall accuracy of FDG PET to detect malignancy in biliary tree is 89% against 82% of CECT.

**Staging**: Three prospective and two retrospective studies have examined this indication.

First Prospective study of 123 patients, potentially operable cholangiocarcinoma were valuated with FDG PET/CT. The overall values for sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy
of PET-CT in primary tumor detection were 84.0%, 79.3%, 92.9%, 60.5%, and 82.9%, respectively. PET-CT demonstrated no statistically significant advantage over CT and MRI/MRCP in the primary tumor evaluation. PET-CT revealed significantly higher accuracy over CT in the diagnosis of regional lymph nodes metastases (75.9% vs 60.9%, P= 0.004) and distant metastases (88.3% vs 78.7%, P= 0.004). Additional use of PET-CT for assessing resectability correctly showed different results from those determined by conventional imaging in 15 (15.9%) of 94 patients with cholangiocarcinoma. Another study examined the role of SUV & FDG PET findings’ on P Glycoprotein expression, involved nodes and survival. Patients also underwent routine CT and MRI study. The diagnostic accuracies of FDG-PET, CT, and MRI for detection of lymph node metastasis were 86%, 68%, and 57%, the sensitivities were 43%, 43% and 43%, and the specificities were 100%, 76%, and 64%, respectively. A negative correlation was found between SUV and P-g p expression. The disease-free survival rates in the high SUV group were significantly lower than in the low SUV group, and a high SUV was an independent predictor of postoperative recurrence. In a retrospective study FDG PET was found to alter treatment choice in 20%, both in pre treatment and in post treatment staging. For detecting recurrence, retrospective study by P Conti et al showed a sensitivity and specificity of (PET alone and combined with CT) were 94% and 100% and, for CT alone, were 82% and 43%, respectively. This suggests that FDG PET/CT is useful in detecting suspected recurrence. FDG PET/CT has similar performance in the evaluation of T stage is superior to CT/MRI in the evaluation of N and M stage.
### Timing of the PET/CT

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## Selected Abstracts:


**OBJECTIVE:** We assessed whether delayed FDG PET imaging is more useful for the evaluation of biliary stricture in differential diagnosis of malignancy from benign disease.

**METHODS:** Thirty-seven patients who underwent FDG PET for differential diagnosis of the disease causing biliary stricture were included. FDG PET imaging was performed at 70 +/- 12 min (early) post FDG injection and repeated 188 +/- 27 min (delayed) after injection only in the abdominal region. Image analysis was performed with visual interpretation and using a semi-quantitative method if lesion was visible on the PET image. The semi-quantitative analysis using the standardized uptake value (SUV) was determined for both early and delayed images (SUVearly and SUVdelayed, respectively). The tumour-to-normal liver (T/L) ratio was also calculated.
RESULTS: The final diagnosis was cholangiocarcinoma in 29 and benign disease in eight patients. In cases of cholangiocarcinoma, visual analysis of FDG PET using the delayed images, improve the diagnosis with one more patient correctly identified. For early and delayed FDG PET, sensitivities were 82.8% and 86.2%, respectively; specificities were 87.5% for both; and accuracies were 83.8% and 86.5%, respectively. Both SUV and T/L ratio derived from delayed images were significantly higher than those derived from early images for cholangiocarcinoma (P<0.0002 and P<0.0001, respectively). CONCLUSION: FDG PET could be useful for differential diagnosis of malignancy from benign disease in patients with biliary stricture. Especially, the delayed targeted FDG PET imaging can be recommended in those patients when early imaging is negative or equivalent, because of increased lesion uptake and increased lesion to background contrast ratio.


OBJECTIVES: This study was conducted to evaluate the clinical role of integrated positron emission and computed tomography (PET-CT) in patients with suspected and potentially operable cholangiocarcinoma. METHODS: Between October 2005 and May 2007, 123 patients with suspected cholangiocarcinoma were enrolled in this study after diagnostic workup, including biliary dynamic computed tomography (CT) and magnetic resonance imaging/magnetic resonance cholangiopancreatography (MRI/MRCP) with magnetic resonance (MR) angiography. Patients with overt unresectable cholangiocarcinoma or gallbladder cancer diagnosed via conventional imaging were excluded.
Consecutively, each enrolled patient underwent PET-CT. Data were prospectively collected and analyzed in comparison with CT and MRI/MRCP. RESULTS: The overall values for sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of PET-CT in primary tumor detection were 84.0%, 79.3%, 92.9%, 60.5%, and 82.9%, respectively. PET-CT demonstrated no statistically significant advantage over CT and MRI/MRCP in the diagnosis of primary tumor. According to different morphologic characteristics of cholangiocarcinoma, PET-CT showed no significant difference in detecting those of mass-forming, periductal-infiltrating, and intraductal-growing types. PET-CT revealed significantly higher accuracy over CT in the diagnosis of regional lymph nodes metastases (75.9% vs 60.9%, P= 0.004) and distant metastases (88.3% vs 78.7%, P= 0.004). Additional use of PET-CT for assessing resectability correctly showed different results from those determined by conventional imaging in 15 (15.9%) of 94 patients with cholangiocarcinoma. CONCLUSIONS: PET-CT improved the accuracy of preoperative staging in patients with cholangiocarcinoma planning to undergo curative resection. Thus, PET-CT had an important clinical impact on the selection of proper treatment.


BACKGROUND: Patients with intrahepatic cholangiocarcinoma (ICC) have a poor prognosis, and lymph node metastasis is an important prognostic factor. In this study, we investigated the usefulness of fluorodeoxyglucose positron
emission tomography (FDG-PET) as a marker for lymph node metastasis, P-glycoprotein (P-gp) expression, and recurrence in ICC. METHODS: The subjects were 35 patients who underwent FDG-PET. Detectability of lymph node metastasis using FDG-PET was compared with that using computed tomography (CT) or magnetic resonance imaging (MRI). In patients who underwent resection, expression of P-gp was examined immunohistochemically, and the relationship between P-gp expression and the standardized uptake value (SUV) in FDG-PET was investigated. Survival rates were analyzed using clinical and pathologic factors. RESULTS: Of the 35 patients, 5 did not undergo surgery based on FDG-PET findings (2 with extrahepatic metastasis, and 3 with para-aortic lymph node metastasis) and 3 underwent laparotomy only (2 with peritoneal dissemination and 1 with para-aortic lymph node metastasis). The diagnostic accuracies of FDG-PET, CT, and MRI for detection of lymph node metastasis were 86%, 68%, and 57%, the sensitivities were 43%, 43% and 43%, and the specificities were 100%, 76%, and 64%, respectively. A negative correlation was found between SUV and P-gp expression (P = .002; r = -0.62). The disease-free survival rates in the high SUV group (≥8.5) were significantly lower than in the low SUV group (<8.5; P = .04), and a high SUV was an independent predictor of postoperative recurrence in multivariate analysis (risk ratio, 1.3; P = .03). CONCLUSIONS: FDG-PET is useful for prediction of lymph node metastasis, P-gp expression and recurrence in ICC.


BACKGROUND: The purpose of the current study was to evaluate the accuracy of (18)F-FDG PET/CT in staging hilar cholangiocarcinoma. MATERIALS AND METHODS: From
June 2004 to December 2007, patients evaluated for surgical treatment of hilar cholangiocarcinoma were entered into a prospective database. Dual modality (18)F-FDG PET/CT was performed before surgery. The report was reviewed with comparison to the operative and pathological results in each case for tumour-node-metastasis staging. RESULTS: Seventeen patients (6 women, 11 men) of a median age of 62 years were included in the study. Radical tumour resection was performed on seven patients. Ten patients underwent surgical exploration. The sensitivity of PET/CT in detecting primary tumour was found to be 58.8% (25% in T2 tumour, 70% in T3 tumour, 66.7% in T4 tumour). The sensitivity/specificity of PET/CT in detecting lymph node metastasis and distant metastasis were 41.7%/80% and 55.6%/87.5%, respectively. Positive (18)F-FDG uptake in the bile duct was found to be associated with surgical non-resectability (P = 0.05). CONCLUSION: Dual-modality PET/CT imaging was found to have a high specificity in detection of lymph node and distant metastasis in hilar cholangiocarcinoma, with a limited value in correct judgement of surgical resectability for tumours in stadium UICC I-III. J. Surg. Oncol. (c) 2008 Wiley-Liss, Inc.


BACKGROUND: Although (18)F-fluorodeoxyglucose positron emission tomography (PET) has widespread clinical use, its role in cancers of the biliary tract is ill-defined. The aim of this study was to determine if preoperative PET provided additional staging information in patients with biliary tract cancer, beyond that obtained through conventional
anatomic imaging. The role of PET in detecting disease recurrence after resection was also examined. STUDY DESIGN: Between March 2001 and October 2003, 126 patients with biopsy-proved or presumed biliary tract cancer (intrahepatic or extrahepatic cholangiocarcinoma and gallbladder carcinoma) underwent PET in addition to standard imaging evaluation. Histologic confirmation of the diagnosis was used as the reference standard with which PET results were compared. Patient followup information and serial imaging were reviewed for progression of lesions detected by PET. RESULTS: Of the 126 study patients, 93 (74%) underwent preoperative staging PET scans, the results of which changed the stage and treatment in 22 patients (24%): 15 of 62 (24%) with cholangiocarcinoma and 7 of 31 (23%) with gallbladder carcinoma. When used to assess for cancer recurrence (n=33), PET identified disease in 86% of patients but altered treatment in only 9%. So, of the entire study group, the findings of PET influenced management in 20% of patients (24% preoperative staging and 9% cancer recurrence). The sensitivity of PET for identifying the primary tumor was 80% overall: 78% for cholangiocarcinoma, 86% for gallbladder carcinoma. CONCLUSIONS: Most biliary tract cancers are (18)F-fluorodeoxyglucose avid tumors. In patients with potentially resectable tumors based on conventional imaging, PET identified occult metastatic disease and changed management in nearly one-fourth of all patients. PET also helped confirm recurrent cancer after resection.


BACKGROUND AND AIM: (18)F-Fluoro-2-deoxy-d-glucose positron emission tomography ((18)FDG-PET) is
promising for diagnosis and treatment of various malignancies. The aim of this study was to evaluate the clinical usefulness of (18)FDG-PET in differential diagnosis and staging of cholangiocarcinomas according to the intrahepatic, perihilar and common bile duct lesions and to compare with computerized tomography (CT) scan. METHODS: From January 2000 to September 2003, 54 patients with suspected cholangiocarcinoma underwent abdominal CT scan and (18)FDG-PET within a 2-week period. The PET images were analyzed visually and semiquantitatively. RESULTS: The overall accuracy of (18)FDG-PET for discriminating malignant diseases of bile duct from benign conditions was slightly higher than that of CT scan (88.9% vs 81.5%). The sensitivity of (18)FDG-PET in perihilar cholangiocarcinoma was lower than the value of intrahepatic and common bile duct cancers (83.3% vs 91.3%, 90.9%); moreover, in cases of perihilar cancer, the sensitivity of (18)FDG-PET was lower than that of CT scans (83.3% vs 91.7%). (18)FDG-PET detected nine distant metastatic lesions not found by other imaging studies and excluded two patients who potentially had resectable condition in other imaging studies from unnecessary laparotomy. CONCLUSION: The clinical usefulness of (18)FDG-PET in differential diagnosis of bile duct cancers is related to the site of primary disease. Although it is a helpful method for differential diagnosis especially in cases of intrahepatic and common bile duct cancers, (18)FDG-PET can not provide confirmative clues in perihilar cholangiocarcinoma. (18)FDG-PET may hold promise in the detection of hidden distant metastasis and can play an additional role in the evaluation of resectability. (18)FDG-PET can be complementary to CT scan in diagnosing and staging of cholangiocarcinoma.

F-18]fluorodeoxyglucose positron emission tomography and positron emission tomography: computed tomography
OBJECTIVES: We retrospectively assessed the diagnostic utility of dedicated positron emission tomography (PET) and hybrid PET-computed tomography (CT) scans with [F-18]fluorodeoxyglucose (FDG) in the imaging evaluation of patients with known or suspected recurrent and metastatic cholangiocarcinoma. METHODS: The study group included 24 patients (13 males and 11 females; age range, 34-75 years) with known or suspected recurrent and metastatic cholangiocarcinoma. We performed 8 dedicated PET scans (Siemens 953/A, Knoxville, Tenn) in 8 patients and 24 hybrid PET-CT scans (Siemens Biograph, Knoxville, Tenn) in 16 patients. Four patients underwent both pretreatment and posttreatment scans. Nonenhanced CT transmission scans were obtained for attenuation correction after administration of oral contrast material. PET images were obtained 60 minutes after the intravenous administration of 15 mCi (555 MBq) FDG. Prior treatments included surgery alone in 12 patients, surgery and chemotherapy in 6 patients, and surgery and combined chemoradiation therapy in 6 patients. Diagnostic validation was conducted through clinical and radiologic follow-up (2 months to 8 years). RESULTS: PET and CT were concordant in 18 patients. PET-CT correctly localized a hypermetabolic metastatic lesion in the anterior subdiaphragmatic fat instead of within the liver and was falsely negative in intrahepatic infiltrating type cholangiocarcinoma. PET was discordant with CT in 6 patients. PET was negative in an enlarged right cardiophrenic lymph node on CT, which remained stable for 1 year. In 1 patient, PET-CT scan showed hypermetabolic peritoneal disease in the right paracolic gutter without definite corresponding structural abnormalities, which was subsequently confirmed on a follow-up PET-CT scan.
performed 6 months after the initial study, at which time peritoneal nodular thickening was evident on concurrent CT. PET-CT documented the progression of locally recurrent and metastatic disease in another patient based on interval appearance of several new hypermetabolic lesions and significant increase in the standardized uptake values of the known lesions despite little interval change in the size and morphologic character of lesions on concurrent CT. It was also helpful in excluding metabolically active disease in patients with contrast enhancement at either surgical margin of hepatic resection site or focally within hepatic parenchyma and in an osseous lesion. Overall, based on the clinically relevant patient basis for detection of recurrent and metastatic cholangiocarcinoma, the sensitivity and specificity of PET (alone and combined with CT) were 94% and 100% and, for CT alone, were 82% and 43%, respectively. CONCLUSIONS: FDG PET and PET-CT are useful in the imaging evaluation of patients with cholangiocarcinoma (except for infiltrating type) for detection of recurrent and metastatic disease and for assessment of treatment response. In particular, the combined structural and metabolic information of PET-CT enhances the diagnostic confidence in lesion characterization.
**Gall Bladder**

**Introduction**
80% of gall bladder cancers are adenocarcinomas. Less than 5% are squamous cancers and less than 10% are anaplastic. These tumors often involve hepatic parenchyma, most often portions of segments IV and V that directly abut the gallbladder fossa. Lymphatic spread is first to the cystic duct (Calot’s) node, then to pericholedochal and hilar nodes, and finally to peripancreatic, duodenal, periportal, celiac, and superior mesenteric artery nodes. Nodal disease in the porta hepatis can cause common bile duct obstruction with resultant jaundice, which is the first clinical symptom in 30% of patients. Jaundice may also be caused by tumors arising in the gallbladder infundibulum, which may spread directly to the cystic duct and common hepatic duct. Although peritoneal metastases are frequent, distant extraperitoneal metastases are not.

**Current staging/imaging**
Contrast enhanced CT, Ultrasound & Endoscopic ultrasound are used to stage gall bladder cancer. Primary gall bladder mass, adjacent liver, local and regional nodes are evaluated
by these modalities. MRI of the abdomen with Magnetic resonance cholangiopancreatography (MRCP) has evolved into a single noninvasive imaging modality that allows complete assessment of biliary, vascular, hepatic parenchymal, and nodal involvement, as well as involvement of adjacent organs; thus, this modality may be helpful in select cases.

**Summary of Evidence for PET:**

FDG PET has been studied for its efficiency in discriminating cholecystitis from carcinoma. A sensitivity of up to 90% and specificity of 80% has been reported when delayed FDG uptake had been considered with normal C reactive protein. Although CECT has been the mainstay for the staging of GB ca; when FDG PET has been used in addition, the specificity of the local and regional nodes has risen. Distant metastases are best picked by FDG PET. In pre operative restaging of incidental detected adenocarcinomas of gall bladder, FDG PET added to node staging and distant metastases. An approach of contrast enhanced CT with FDG PET as single study is likely to yield the highest accuracy for all T, N & M stages. Evidence for other indications in GB Ca does not exist.

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Selected Abstracts:


Conventional imaging techniques such as ultrasonography, CT, and MRI are able to detect gallbladder abnormalities but are not always able to differentiate a malignancy from other disease processes such as cholecystitis. The purpose of the present study was to evaluate the efficacy of dual-time-point (18)F-FDG PET for differentiating malignant from benign gallbladder disease. METHODS: The study evaluated 32 patients who were suspected of having gallbladder tumors. (18)F-FDG PET (whole body) was performed at 62 +/- 8 min (early) after (18)F-FDG injection and was repeated 146 +/- 14 min (delayed) after injection only in the abdominal region. We evaluated the (18)F-FDG uptake both visually and semiquantitatively. Semiquantitative analysis using the standardized uptake value (SUV) was performed for both early and delayed images (SUV(early) and SUV(delayed), respectively). The retention index (RI) was calculated according to the equation (SUV(delayed) - SUV(early)) x 100/SUV(early). The tumor-to-liver ratio was also calculated. Results: The final diagnosis was gallbladder carcinoma in 23 patients and benign disease in 9 patients. For visual analysis of gallbladder carcinoma, delayed (18)F-FDG PET images improved the specificity of diagnosis in 2 patients. When an SUV(early) of 4.5, SUV(delayed) of 2.9, and RI of -8 were chosen as arbitrary cutoffs for differentiating between malignant and benign conditions, sensitivity increased from 82.6% to 95.7% and 100% for delayed imaging and combined early and delayed imaging (i.e., RI), respectively. With the same criteria, specificity decreased from 55.6% to 44.4% for delayed imaging and combined early and delayed imaging, respectively. The specificity of (18)F-FDG PET improved to
80% in the group with a normal level of C-reactive protein (CRP) and decreased to 0% in the group with an elevated CRP level. For gallbladder carcinoma, both SUV and tumor-to-liver ratios derived from delayed images were significantly higher than the ratios derived from early images (P < 0.0001). CONCLUSION: Delayed (18)F-FDG PET is more helpful than early (18)F-FDG PET for evaluating malignant lesions because of increased lesion uptake and increased lesion-to-background contrast. However, the diagnostic performance of (18)F-FDG PET depends on CRP levels.

PMID: 16595497


BACKGROUND/AIMS: (1) To evaluate the diagnostic value of integrated positron emission and computed tomography (PET/CT) in comparison with contrast-enhanced CT (ceCT) to detect biliary tract tumors and associated distant and regional lymph node metastases and (2) to evaluate the impact of PET/CT on therapy management. METHODS: From January 2001 to March 2005, each patient who was treated for a malignancy of the biliary tract underwent PET/CT examination in addition to the standard work-up imaging. Data were prospectively collected and analyzed in comparison with ceCT. RESULTS: Sixty-one patients with malignancies of the biliary tract were included into the study. Diagnosis was proven in all patients either by histology or cytology. PET/CT detected all gallbladder cancers (n=14). PET/CT and ceCT provided a comparable accuracy for the primary intra- (n=14) and extra-hepatic cholangiocarcinomas (n=33). All distant metastases (12/12) were detected by PET/CT, but only 3/12 by ceCT
Regional lymph node metastases were detected by PET/CT and ceCT in only 12% vs. 24%. PET/CT findings resulted in a change of management in 17% of patients deemed resectable after standard work-up. CONCLUSIONS: PET/CT is particularly valuable in detecting unsuspected distant metastases which are not diagnosed by standard imaging. Thus, PET/CT staging has an important impact on selection of adequate therapy.


Background. Radical re-resection is offered to patients with non-metastatic, invasive, incidental gallbladder cancer. Data evaluating (18)F-fluorodeoxyglucose positron emission tomography-computed tomography ((18)F-FDG PET-CT) in patients with incidental gallbladder cancer is sparse. Aim. To evaluate the efficacy of integrated (18)F-FDG PET-CT in determining occult metastatic or residual local-regional disease in patients with incidental gallbladder cancer. Methods. Patients referred with incidental gallbladder cancer for radical re-resection were evaluated using multidetector computed tomography (MDCT) and PET-CT. Based on preoperative imaging, 24 out of 92 patients were found suitable for surgery. The two imaging modalities were evaluated with respect to residual and resectable disease. Results. In determining residual disease, MDCT had a sensitivity and positive predictive value (PPV) of 42.8%, each, while PET-CT had a sensitivity and PPV of 28.5 and 20%, respectively. In determining resectability, MDCT had a sensitivity, PPV, and accuracy of 100, 87.5, and 87.5%, respectively, as compared to PET-CT (sensitivity=100%, PPV=91.3%, accuracy=91.6%). Conclusions. From our study, it appears that in patients
with incidental gall bladder cancer without metastatic disease, PET-CT and MDCT seem to have roles complementing each other. PET-CT was able to detect occult metastatic or residual local-regional disease in some of these patients, and seems to be useful in the preoperative diagnostic algorithm of patients whose MDCT is normal or indicates locally advanced disease.

PMID: 19088931
Gastrointestinal Stromal Tumor (GIST)

Introduction
Gastrointestinal stromal tumors constitute less than 1% of all digestive tract tumors. They may be benign or malignant (30%), and occur in every part of the gastrointestinal tract, however the stomach is the most common site. They develop with the same prevalence in men and in women, usually above the age of 50 years. They originate from the myenteric ganglion cells, termed the interstitial Cajal cells. The majority, i.e. 95% of GIST, show expression of the membrane receptor protein CD117 with a tyrosine kinase activity c-kit.

Surgery is the mainstay for resectable nonmetastatic GISTs, but virtually all GISTs are associated with a risk of metastasis. Imatinib 400 mg/day with or without surgery is the recommended first-line treatment for recurrent or metastatic GIST. The malignant tumors metastasize most commonly to the liver and peritoneum. The metastases are rarely found in the lungs, pleura and bones.

Conventional Imaging
The detection of GIST is based on imaging, endoscopy, histological and immuno-histochemical examinations. Contrast-enhanced CT has conventionally been the method
of choice for the staging and treatment monitoring of GIST.

**Summary of Evidence for PET**

The role of Whole-body FDG-PET seems limited for staging because of the low rate of extra-abdominal tumoral involvement and lower sensitivity than CT. $^{18}$FDG-PET scanning is effective in restaging GIST and for evaluating therapeutic response to a variety of treatments including Imatinib mesylate.

FDG PET is a functional imaging study which reflects the status of tumor metabolism (glycolysis) at a particular time. A baseline FDG PET/CT (contrast enhanced) scan should always be obtained prior to initiating treatment. Conducting a baseline evaluation allows one to establish a denominator against which future studies or quantitative measurements (SUV or SUV$_{\text{max}}$) can be compared. This denominator is essential for characterizing the metabolic response when using the European Organization for Research and Treatment of Cancer (EORTC) criteria, which are based on the magnitude of the change in SUV relative to baseline.

There is now convincing evidence that serial FDG PET or PET/CT scan is more sensitive and reliable tool for determining treatment response to imatinib mesylate in patients of GIST. Metabolic response as depicted on FDG PET correlates well with clinical benefit and have shown to precede by weeks or months significant decrease in tumor size on computed tomography (CT). The earliest therapeutic response can be seen on FDG PET as early as 24 hours after initiation of imatinib therapy.

Traditional anatomic tumor response criteria (WHO/RECIST/SWOG) are based on uni- or bidimensional changes in tumor size, and do not take into account changes in tumor metabolism, tumor density, or decrease in the number of intratumoral
vessels. These changes are regarded as indicator of therapeutic response to imatinib. Conversely, lack of metabolic response on FDG-PET indicates primary resistance to the drug and may help identify patients who would benefit from another therapy, while re-emergence of metabolic activity within tumor sites following a period of therapeutic response indicates secondary resistance to the drug. Newly proposed CT criteria using either no growth in tumor size or a combination of tumor density and size criteria have shown a close correlation with the predictive value results of FDG-PET. Thus, the integration of FDG-PET and CT, as in the combined hybrid PET/CT scanner will not only optimize the evaluation of patients with GIST treated with molecularly targeted drugs.

**GIST**

<table>
<thead>
<tr>
<th>Timing of the PET/CT (FDG)</th>
<th>Hierarchy of Diagnostic Efficacy</th>
<th>Relevance of Test</th>
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<tr>
<td>RT planning</td>
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Abstracts


Traditional anatomic tumor response criteria are based on unidimensional changes in tumor size, and do not take into account changes in tumor metabolism, tumor density, or decrease in the number of intratumoral vessels. These changes are, however, all indicative of response to imatinib therapy in patients with gastrointestinal stromal tumor (GIST). In these patients, metabolic responses seen on positron emission tomography (PET) using fluorine-18-fluorodeoxyglucose (18FDG) have been shown to be closely related to clinical benefit. Furthermore, these metabolic changes precede by weeks or months significant decrease in tumor size on computed tomography (CT). Conversely, lack of metabolic response on FDG-PET indicates primary resistance to the drug and may help identify patients who would benefit from another therapy, while re-emergence of metabolic activity within tumor sites following a period of therapeutic response indicates secondary resistance to the drug. Newly proposed CT criteria using either no growth in tumor size or a combination of tumor density and size criteria have shown a close correlation with the predictive value results of FDG-PET. Thus, the integration of FDG-PET and CT, as in the combined hybrid PET/CT scanners now available, will not only optimize the evaluation of patients with GIST treated with molecularly targeted drugs, but may ultimately help shorten clinical trials, and accelerate drug development in this disease and other cancers as well.


Clinical management of patients with gastrointestinal stromal tumors (GISTs) has dramatically changed with the introduction of novel therapeutics, such as imatinib mesylate. This has
created a need to re-evaluate the existing criteria used to assess treatment response. The current Response Evaluation Criteria in Solid Tumors are based on unidimensional tumor size, and do not take into account changes in responding GISTs such as a decrease in tumor density and decrease in the number of intratumoral vessels with computed tomography (CT). Positron emission tomography (PET) has been found to be highly sensitive in detecting early response, and to be useful in predicting long-term response to imatinib in patients with metastatic GIST; however, widespread use of PET is limited because of a lack of scanner availability and cost constraints. Modified CT criteria using a combination of tumor density and tumor size are promising in early response evaluation, and have excellent prognostic value. Identifying appropriate treatment response criteria is essential to optimize treatment for patients with GIST.


The management of gastrointestinal stromal tumors (GISTs) has been revolutionized in recent years by two major developments: the introduction of imatinib mesylate as a targeted therapeutic agent and the dramatic change in the tumor metabolic activity following successful therapy making in fluorodeoxyglucose (FDG)-PET as the modality of choice for monitoring therapeutic response. In the present communication, we have explored the current role of PET/computed tomography (CT) imaging in GIST on the basis of a brief overview of the published studies and our experience on the subject gained in a large tertiary care setting. There is now convincing evidence that serial PET study is more sensitive and reliable for determining treatment response to imatinib mesylate in patients of GIST, when compared with
only conventional CT monitoring. This modality also appears to be of potential value in initial disease evaluation including prediction of malignant potential in recently diagnosed GIST and in selection of optimal dose of imatinib for therapy. The findings of detection of disease recurrence on discontinuing imatinib and acquired resistance to imatinib provide insight into the issue of therapeutic endpoint definition. On the basis of the experience gained in recent times, the future potential of this powerful modality in this setting is hypothesized.
Pancreatic Carcinoma

Introduction
It is mentioned as the fourth most common malignancy in both men and women. Adenocarcinomas account for 90% of the Malignancies. Endocrine tumors, cystic tumors, lymphomas and sarcomas account for the remaining 10%.

Two thirds of pancreatic tumors are located in the head of the pancreas; clinical features include vague pain, weight loss, fatigue, and jaundice. One third of pancreatic tumors are in the body or tail; clinical features include epigastric or back pain, weight loss, fatigue, and evidence of metastatic disease.

Current staging/imaging
Patients suspected of having a pancreatic malignancy generally are evaluated by thin-slice, contrast-enhanced CT scanning. This modality is of use in identifying the tumor mass, as well as in assessing the liver for metastasis. Vascular involvement of superior mesenteric vein, portal vein, and celiac and superior mesenteric arteries also can be determined by CT scanning. Ultrasonography is useful in identifying the primary tumor mass, particularly in the pancreatic head, but is less sensitive than CT and provides less information regarding local and
regional dissemination. MRI has not proved superior to CT scanning for assessment of the primary tumor, metastatic disease, or vascular encasement. Occasional patients with CT findings suggestive but not diagnostic of vascular encasement may benefit from preoperative visceral angiography, although improvements in CT methods, particularly the use of dynamic contrast infusion and helical (spiral) techniques, have largely supplanted angiography. Patients with jaundice but no mass on CT scans generally are evaluated with ERCP. This study may reveal an irregular or tapering biliary stricture characteristic of an obstructing periampullary tumor. Sometimes the biliary stricture is seen in conjunction with a pancreatic duct stricture—the “double duct” signs—which is highly suggestive of the presence of a malignancy. Irregular strictures of the pancreatic duct also may be seen in patients with pancreatic carcinoma. Such endoscopic findings, even in the absence of a pancreatic mass on CT scanning, justify proceeding to surgical resection. Endoscopic Ultrasonography (EUS) can assess tumor size, portal and mesenteric vein involvement, and regional nodal involvement. EUS also can allow obtaining tissue samples for histological analysis from virtually all pancreatic lesions and from suggestive lymph nodes located close to the stomach and duodenum.

**Summary of Evidence for PET**

**Diagnosis**

Pancreatic Carcinoma have been evaluated and found to be rich in GLUT receptors. Hence FDG PET is expected to do well in Pancreatic Carcinoma.

In animal model it was seen that amongst the PET radiopharmaceuticals Fluro Thymidine has the highest uptake in the pancreatic cancer model. However in a pilot study it was shown to have poor accuracy in humans. FDG remains
the agent of choice. In a prospective study FDG PET/CT showed a sensitivity of 89%, specificity of 74%, PPV of 83%, NPV of 84%. The accuracy while similar to that of endosonography, ERCP with intraductal ultrasonography and abdominal ultrasound, in depicting small pancreatic lesions, additional diagnostic information is obtained from whole body PET imaging. For diagnosing Pancreatic carcinoma, studies reported the sensitivity and specificity of FDG-PET for detecting malignant pancreatic tumors as being 71-100% and 64-90%, respectively. FDG-PET does not replace, but is complementary to morphologic imaging, and therefore, in doubtful cases, the method must be combined with other imaging modalities. FDG-PET is a useful tool for differentiating autoimmune pancreatitis from suspected pancreatic cancer, if the accumulation pattern and extrapancreatic involvement are considered. IgG4 measurement and other current image tests can further confirm the diagnosis. 18-FDG PET is more accurate than conventional imaging techniques (CT and MR) in distinguishing benign from malignant (invasive and noninvasive) Intraductal Papillary Mucinous Neoplasms. In the evaluation of malignancy in benign cystic lesions of the pancreas, role of FDG PET was evaluated through a retrospective study and found to be not useful as the sensitivity was only 57% and specificity was 85%. FDG PET and contrast enhanced MRI study have been performed, followed by FDG PET/MRI fusion. It helped improve the localization of the tumor.

**Staging & Restaging:**

FDG PET has been used to evaluate chemotherapy response. Overall detection sensitivity at diagnosis varies between 90% and 95% and specificity from 82% to 100%, whereas for staging, sensitivity data vary from 61% to 100% and specificity data from 67% to 100%. Neuro endocrine tumors of the pancreas are best evaluated by peptide based PET or SPECT
agents. 68Ga DOTA-TOC and 99mTc HYNIC-TOC being the commonest of them respectively.

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<td>RT planning</td>
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**Selected Abstracts:**


Our aim was to use PET/MRI to evaluate and compare the uptake of 18F-FDG, 3-deoxy-3-18F-fluorothymidine (18F-FLT), and 18F-fluorethylcholine (18F-FEC) in human pancreatic tumor cell lines after xenotransplantation into SCID mice and to correlate tumor uptake with gene expression of membrane transporters and rate-limiting enzymes for tracer uptake and tracer retention. METHODS: Four weeks after orthotopic inoculation of human pancreatic carcinoma cells (PancTuI, Colo357, and BxPC3) into SCID mice, combined imaging was performed with a small-animal PET scanner and
a 3-T MRI scanner using a dedicated mouse coil. Tumor-to-liver uptake ratios (TLRs) of the tracers were compared with gene expression profiles of the tumor cell lines and both normal pancreatic tissue and pancreatic tumor tissue based on gene microarray analysis and quantitative polymerase chain reaction. RESULTS: 18F-FLT showed the highest tumor uptake, with a mean TLR of 2.3, allowing correct visualization of all 12 pancreatic tumors. 18F-FDG detected only 4 of 8 tumors and had low uptake in tumors, with a mean TLR of 1.1 in visible tumors. 18F-FEC did not show any tumor uptake. Gene array analysis revealed that both hexokinase 1 as the rate-limiting enzyme for 18F-FDG trapping and pancreas-specific glucose transporter 2 were significantly downregulated whereas thymidine kinase 1, responsible for 18F-FLT trapping, was significantly upregulated in the tumor cell lines, compared with normal pancreatic duct cells and pancreatic tumor tissue. Relevant genes involved in the uptake of 18F-FEC were predominantly unaffected or downregulated in the tumor cell lines. CONCLUSION: In comparison to 18F-FDG and 18F-FEC, 18F-FLT was the PET tracer with the highest and most consistent uptake in various human pancreatic tumor cell lines in SCID mice. The imaging results could be explained by gene expression patterns of membrane transporters and enzymes for tracer uptake and retention as measured by gene array analysis and quantitative polymerase chain reaction in the respective cell lines. Thus, standard molecular techniques provided the basis to help explain model-specific tracer uptake patterns in xenotransplanted human tumor cell lines in mice as observed by PET.

PMID: 18632830

Diagnostic impact of (18)F-FDG PET-CT evaluating solid pancreatic lesions versus endosonography, endoscopic retrograde cholangio-pancreatography with intraductal

PURPOSE: This prospective single-centre phase II trial assessed the diagnostic impact of (18)F-FDG PET-CT in the evaluation of solid pancreatic lesions (slashed circle >= 10 mm) compared to endosonography (EUS), endoscopic retrograde cholangio-pancreatography (ERCP) with intraductal ultrasound (IDUS), abdominal ultrasound (US) and histopathological reference. METHODS: Forty-six patients (32 men/14 women, slashed circle 61.7 years) with suspected pancreatic neoplasms underwent PET-CT with contrast-enhanced biphasic multi-detector CT of the upper abdomen followed by a diagnostic work-up with EUS, ERCP with IDUS and US within 3 weeks. PET-CT data sets were analysed by two expert readers in a consensus reading. Histology from surgery, biopsy/fine-needle aspiration and/or clinical follow-up >=12 months served as standard of reference. RESULTS: Twenty-seven pancreatic malignancies were histopathologically proven; 19 patients had benign diseases: 36/46 lesions (78%) were detected in the head of the pancreas, 7/46 and 3/46 in the body and tail region, respectively. Sensitivity and specificity of PET-CT were 89% and 74%, respectively; positive predictive value (PPV) and negative predictive value (NPV) were 83% and 82%, respectively. Sensitivity (81-89%), specificity (74-88%), PPV (83-90%) and NPV (77-82%) achieved by EUS, ERCP and US were not significantly different. PET analysis revealed significantly higher maximum mean standardised uptake values (SUV(max) 6.5 +/- 4.6) in patients with pancreatic malignancy (benign lesions: SUV(max) 4.2 +/- 1.5; p < 0.05). PET-CT revealed cervical lymphonodal metastasis from occult bronchogenic carcinoma and a tubular colon adenoma with intermediate dysplasia on polypectomy, respectively. CONCLUSIONS:
F-FDG PET-CT achieves a comparably high diagnostic impact evaluating small solid pancreatic lesions versus conventional reference imaging modalities. Additional clinical diagnoses are derived from concomitant whole-body PET-CT imaging.

PMID: 18481063


The ability to diagnose pancreatic carcinoma has been rapidly improving with the recent advances in diagnostic techniques such as contrast-enhanced Doppler ultrasound (US), helical computed tomography (CT), enhanced magnetic resonance imaging (MRI), and endoscopic US (EUS). Each technique has advantages and limitations, making the selection of the proper diagnostic technique, in terms of purpose and characteristics, especially important. Abdominal US is the modality often used first to identify a cause of abdominal pain or jaundice, while the accuracy of conventional US for diagnosing pancreatic tumors is only 50-70%. CT is the most widely used imaging examination for the detection and staging of pancreatic carcinoma. Pancreatic adenocarcinoma is generally depicted as a hypo attenuating area on contrast-enhanced CT. The reported sensitivity of helical CT in revealing pancreatic carcinoma is high, ranging between 89% and 97%. Multi-detector-row (MD) CT may offer an improvement in the early detection and accurate staging of pancreatic carcinoma. It should be taken into consideration that some pancreatic adenocarcinomas are depicted as isoattenuating and that pancreatitis accompanied by pancreatic adenocarcinoma might occasionally result in the overestimation of staging. T1-weighted spin-echo images with fat suppression and dynamic gradient-echo MR images enhanced with gadolinium have been reported to be superior.
to helical CT for detecting small lesions. However, chronic pancreatitis and pancreatic carcinoma are not distinguished on the basis of degree and time of enhancement on dynamic gadolinium-enhanced MRI. EUS is superior to spiral CT and MRI in the detection of small tumors, and can also localize lymph node metastases or vascular tumor infiltration with high sensitivity. EUS-guided fine-needle aspiration biopsy is a safe and highly accurate method for tissue diagnosis of patients with suspected pancreatic carcinoma. (18)F-fluorodeoxyglucose (FDG) positron emission tomography (PET) has been suggested as a promising modality for noninvasive differentiation between benign and malignant lesions. Previous studies reported the sensitivity and specificity of FDG-PET for detecting malignant pancreatic tumors as being 71-100% and 64-90%, respectively. FDG-PET does not replace, but is complementary to morphologic imaging, and therefore, in doubtful cases, the method must be combined with other imaging modalities.

PMID: 18333085


**BACKGROUND:** Fluorine-18 fluorodeoxyglucose positron emission tomography (FDG-PET) has been widely used for the diagnosis of pancreatic cancer. Because autoimmune pancreatitis is easily misdiagnosed as pancreatic cancer and can be tested for by FDG-PET analysis based on the presence of suspected pancreatic cancer, we attempted to clarify the differences in FDG-PET findings between the two conditions. 

**METHODS:** We compared FDG-PET findings between 15 patients with autoimmune pancreatitis and 26 patients with
pancreatic cancer. The findings were evaluated visually or semiquantitatively using the maximum standardized uptake value and the accumulation pattern of FDG. RESULTS: FDG uptake was found in all 15 patients with autoimmune pancreatitis, whereas it was found in 19 of 26 patients (73.1%) with pancreatic cancer. An accumulation pattern characterized by nodular shapes was significantly more frequent in pancreatic cancer, whereas a longitudinal shape indicated autoimmune pancreatitis. Heterogeneous accumulation was found in almost all cases of autoimmune pancreatitis, whereas homogeneous accumulation was found in pancreatic cancer. Significantly more cases of pancreatic cancer showed solitary localization, whereas multiple localization in the pancreas favored the presence of autoimmune pancreatitis. FDG uptake by the hilar lymph node was significantly more frequent in autoimmune pancreatitis than in pancreatic cancer, and uptake by the lachrymal gland, salivary gland, biliary duct, retroperitoneal space, and prostate were seen only in autoimmune pancreatitis. CONCLUSIONS: FDG-PET is a useful tool for differentiating autoimmune pancreatitis from suspected pancreatic cancer, if the accumulation pattern and extrapancreatic involvement are considered. IgG4 measurement and other current image tests can further confirm the diagnosis.

PMID: 18306988


OBJECTIVE: To assess the reliability of 18-fluorodeoxyglucose positron emission tomography (18-FDG PET) in distinguishing benign from malignant intraductal papillary mucinous neoplasms (IPMNs) of the pancreas and
its contribution to surgical decision making. SUMMARY

BACKGROUND DATA: Pancreatic IPMNs are increasingly recognized, often as incidental findings, especially in people over age 70 and 80. Computed tomography (CT) and magnetic resonance (MR) are unreliable in discriminating a benign from a malignant neoplasm. 18-FDG PET as imaging procedure based on the increased glucose uptake by tumor cells has been suggested for diagnosis and staging of pancreatic cancer.

METHODS: From January 1998 to December 2005, 64 patients with suspected IPMNs were prospectively investigated with 18-FDG PET in addition to conventional imaging techniques [helical-CT in all and MR and magnetic resonance cholangiopancreatography (MRCP) in 60]. 18-FDG PET was analyzed visually and semiquantitatively using the standard uptake value (SUV). The validation of the diagnosis was made by a surgical procedure (n = 44), a percutaneous biopsy (n = 2), main duct cytology (n = 1), or follow-up (n = 17). Mean and median follow-up times were 25 and 27.5 months, respectively (range, 12-90 months). RESULTS: Twenty-seven patients (42%) were asymptomatic. Forty-two patients underwent pancreatic resection, 2 palliative surgery, and 20 did not undergo surgery. An adenoma was diagnosed in 13 patients, a borderline tumor in 8, a carcinoma in situ in 5, and an invasive cancer in 21; in 17 patients a tumor sampling was not performed and therefore the histology remained undetermined. Positive criteria of increased uptake on 18-FDG PET was absent in 13 of 13 adenomas and 7 of 8 borderline IPMNs, but was present in 4 of 5 carcinoma in situ (80%) and in 20 of 21 invasive cancers (95%). Conventional imaging technique was strongly suggestive of malignancy in 2 of 5 carcinomas in situ and in 13 of 21 invasive carcinomas (62%). Furthermore, conventional imaging had findings that would be considered falsely positive in 1 of 13 adenomas (8%) and in 3 of 8 borderline neoplasms (37.5%). Therefore, positive 18-FDG
PET influenced surgical decision making in 10 patients with malignant IPMN. Furthermore, negative findings on 18-FDG PET prompted us to use a more limited resection in 15 patients, and offered a follow-up strategy in 18 patients (3 positive at CT scan) for the future development of a malignancy. CONCLUSIONS: 18-FDG PET is more accurate than conventional imaging techniques (CT and MR) in distinguishing benign from malignant (invasive and noninvasive) IPMNs. 18-FDG PET seems to be much better than conventional imaging techniques in selecting IPMNs patients, especially when old and asymptomatic, for surgical treatment or follow-up.

PMID: 18043094


PURPOSE: The aim of this study was to evaluate the potential of (18)F-fluorothymidine (FLT) PET/CT for imaging pancreatic adenocarcinoma. METHODS: This was a pilot study of five patients (four males, one female) with newly diagnosed and previously untreated pancreatic adenocarcinoma. Patients underwent FLT PET/CT, (18)F-fluorodeoxyglucose (FDG) PET/CT, and contrast-enhanced CT scanning before treatment. The presence of cancer was confirmed by histopathological analysis at the time of scanning in all five patients. The degree of FLT and FDG uptake at the primary tumor site was assessed using visual interpretation and semi-quantitative SUV analyses. RESULTS: The primary tumor size ranged from 2.5 x 2.8 cm to 3.5 x 7.0 cm. The SUV of FLT uptake within the primary tumor ranged from 2.1 to 3.1. Using visual interpretation, the primary cancer could be detected from background activity in two of five patients (40%)
on FLT PET/CT. By comparison, FDG uptake was higher in each patient with a SUV range of 3.4 to 10.8, and the primary cancer could be detected from background in all five patients (100%). CONCLUSIONS: In this pilot study of five patients with primary pancreatic adenocarcinoma, FLT PET/CT scanning showed poor lesion detectability and relatively low levels of radiotracer uptake in the primary tumor.

PMID: 17960376


Previous studies have suggested that whole body positron-emission tomography (PET) can distinguish between benign and malignant cysts of the pancreas. Patients were identified (n = 68) who had undergone whole body PET imaging for a cystic lesion of the pancreas between Jan. 1997 and May 2005. Cross-sectional imaging studies were reviewed by a single blinded radiologist, and positive PET studies were reviewed by a blinded nuclear medicine physician. Operative resection was performed in 21 patients (31%), and 47 patients were managed with radiographic follow-up. F-18 Fluorodeoxyglucose (FDG)-avid lesions were identified in eight of the 68 patients (12%). Within the resected group of patients (n=21), four of the seven patients (57%) with either in situ or invasive malignancy (adenocarcinoma: 3 of 5, papillary mucinous carcinoma: 1 of 2) had positive PET imaging (mean SUV, 5.9; range 2.5-8.0), and 2 of the 14 patients (14%) with benign lesions had positive PET imaging (serous cystadenoma, n=1, SUV=3.3; pseudocyst n=1, SUV=2.7). All lesions proven to be malignant with increased FDG uptake had highly suspicious findings on cross-sectional imaging. Within the group of resected patients, the sensitivity
of PET for identifying malignant pathology was 57%, and the specificity was 85%. The sensitivity and specificity of PET for malignancy in this study was lower than previously reported, and PET findings did not identify otherwise occult malignant cysts. We do not believe whole body FDG-PET to be essential in the evaluation of cystic lesions of the pancreas.

PMID: 17175454


BACKGROUND: This study assessed the value of image fusion with (18)F-fluorodeoxyglucose-positron emission tomography (FDG-PET) and magnetic resonance imaging (MRI) in patients suspected of having pancreatic cancer. METHODS: 32 patients (12 women, 20 men; age 24-79 years; mean 56.6 years) were included. All patients underwent whole-body FDG-PET examinations and contrast-enhanced MRI. Image fusion used a semiautomatic voxel-based algorithm. Separate reading, side-by-side analysis and evaluation of fused PET/MRI images were performed. Results were correlated to histopathology (n = 30), or clinical follow-up (n = 2). RESULTS: 15/32 patients had pancreas cancer and 17/32 patients benign disease. The sensitivity and specificity for cancer detection by FDG-PET were 93 and 41% for visual and 86 and 58% for semiquantitative analysis whereas MRI achieved 100 and 76% respectively. Topographical assignment of PET foci by image fusion was superior to side-by-side analysis in 11/39 (28%) foci (in 8/32 patients). However, a true impact on therapeutic strategy was observed only in 1/8 patients as the presence of multiple metastases, irresectable primaries or medical reasons for inoperability prevented a curative setting. CONCLUSION: Compared to side-by-side analysis, PET/MRI image fusion improves the anatomical
assignment and interpretation of FDG foci. The therapeutic benefit for the patient however is limited in patients with multiple lesions or incurable primaries. Copyright 2006 S. Karger AG, Basel and IAP.

PMID: 17106215


GOALS: The aims of this study were to determine the clinical use of 18-fluorodeoxyglucose positron emission tomography (FDG-PET) in the differential diagnosis of patients with suspected pancreatic cancer and in the determination of tumor response after concurrent chemoradiotherapy for pancreatic cancer. BACKGROUND: Despite advances in diagnostic tools for pancreatic cancer, it is difficult to differentiate pancreatic cancer from mass-forming pancreatitis. Even with current imaging modalities, it is also difficult to assess tumor response to therapeutic intervention. STUDY: One hundred two patients with suspected pancreatic cancer were selected for this study. Dynamic computerized tomography (CT) scan and FDG-PET were used sequentially to diagnose pancreatic cancer. After diagnostic confirmation their diagnostic yields were compared. We also evaluated the treatment response in 15 patients who underwent chemoradiation therapy with dynamic CT scan and FDG-PET and compared their results. RESULTS: In 93 out of 102 patients, pancreatic cancer was confirmed. FDG-PET showed higher diagnostic accuracy than CT scan (95.1% vs. 76.5%). FDG-PET was also superior to CT in the detection of liver metastasis. FDG-PET detected treatment response in 5 out of 15 cases after chemoradiation therapy, whereas CT could
not detect any treatment response. Comparing responder and nonresponder, FDG-PET was able to predict significantly different prognosis (399 vs. 233 d, $P<0.05$). CONCLUSIONS: FDG-PET is a very useful tool in diagnosing pancreatic cancer. FDG-PET may be also used as an adjunct for determining the treatment modality of pancreatic cancer and evaluating tumor response to chemoradiation therapy.

PMID: 17063113 [PubMed - indexed for MEDLINE]
Section — IV

Genitourinary Malignancies
Renal Cell Carcinoma

Introduction
Renal cell carcinoma is the most common malignancy of the kidney and accounts for 2% of all cancers. Surgical resection remains the only curative treatment for renal cell carcinoma. Knowledge of the tumoral stage at the time of diagnosis is essential for prognosis and surgical planning. Numerous studies have shown that the anatomic extent of the tumor at the time of diagnosis is the single most important factor in determining prognosis. The 5-year survival rate of 60%–90% among patients with organ-confined disease falls to 5%–10% among those with distant metastases.

Current Imaging
CT remains the single most effective imaging modality for the diagnosis and staging of renal cell carcinoma. In the majority of patients, it is the only imaging test needed prior to surgical management. The CT scan has been reported to attain accuracy of 91% in pre-operative staging of renal cell carcinoma.

Summary of Evidence
Results of a meta-analysis of published literature has shown that 18-F FDG PET can be useful in restaging (Sn 87%) and
detection of metastatic disease (Sn 72%). However, the performance of 18F-FDG PET in the detection of primary disease is limited. The detection of renal cell carcinoma with PET imaging is hampered by the fact that most radiotracers are excreted via the kidneys. The renal elimination of FDG can in part be overcome by increasing diuresis with hydration or by administering diuretics.

The largest series so far included 66 patients who underwent 90 FDG-PET scans for suspected or known renal cell carcinoma. FDG-PET demonstrated a sensitivity of 60% compared to 91.7% for CT and was less sensitive in detecting primary tumours, retroperitoneal lymph node metastases, or distant metastases.

Lee et al evaluated the role of 18-FDG PET /CT for the surveillance of patients with renal cell carcinoma (RCC); who have a high risk of local recurrence or distant metastasis. They incorporated sixty-three patients of RCC in their study with variable pathological stages. The FDG PET/CT accurately classified the presence of a recurrence or metastasis in 56/63 (89%) patients. FDG PET/CT had an 89.5% sensitivity, 83.3% specificity, 77.3% positive predictive value, 92.6% negative predictive value, and 85.7% accuracy in detecting recurrence or metastasis, which was not significantly different from the results with conventional methods.

The assessment of renal masses and primary staging of renal cell carcinoma are the domain of helical CT. PET with FDG may be helpful in the evaluation of “equivocal findings” on conventional studies, including bone scan, and also in the differentiation between recurrence and post-treatment changes. The value of other PET tracers in renal cell carcinoma is under investigation. Recently, 124 I-cG250 PET has shown promising results in the detection of clear-cell renal carcinoma.
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**Selected Abstracts:**


AIM: Renal cell carcinoma is the most frequent solid kidney tumor. At present, PET is not the imaging test of choice, the helical CT being the best method to assess these patients. The aim of the study was to perform a meta-analysis of the literature to evaluate the performance and accuracy of 18F-FDG PET in the detection of primary disease, recurrence and metastasis of renal cell carcinoma. MATERIALS AND METHODS: A systematic search was done of the available literature in primary and secondary databases published until October 2004 indexed in MEDLINE and CANCERLIT. Exclusion/inclusion criteria were applied. Their quality was evaluated using the
Flynn criteria and joint estimators of sensitivity (S), specificity (Sp), likelihood ratios (LR), diagnostic odds ratio (DOR) and summary ROC (SROC) curve were obtained. The presence of the threshold effect was evaluated and the summary ROC (SROC) curve was calculated. RESULTS: Seven out of 46 studies fulfilled the inclusion criteria and were analyzed. Three studies evaluated the use of 18F-FDG PET in the differential diagnosis of renal masses. Two studies analyzed restaging and two analyzed the role of 18F-FDG PET in the detection of metastatic disease. All the selected studies were classified according to Flynn’s criteria. We found the highest S in restaging with S 0.87 (95 % CI, 0.75-0.95) and in metastases detection with S 0.72 (95 % CI, 0.56-0.85) as well as the high Sp in differential diagnosis of renal masses. CONCLUSIONS: The results of this meta-analysis suggest that 18F-FDG PET can be useful in restaging and detection of metastatic disease, based on its acceptable Sn and Sp. However, the performance of 18F-FDG PET in the detection of primary disease is limited, but this may improve with the new PET/CT systems.


Objectives: Positron emission tomography (PET) provides unique insights into molecular pathways of diseases. PET using [F-18]-fluorodeoxyglucose (FDG) has gained increasing acceptance for the diagnosis, staging, and treatment monitoring of various tumour types. The aim of this review is to provide an update on the current status of molecular PET and PET/CT imaging in urological malignancies. Methods: The current literature on PET and PET/CT imaging was reviewed and summarized for prostate cancer, bladder cancer, renal, cell carcinoma, and germ cell tumours. Results: Depending on the radiotracer used, PET offers diagnostic information based on
glucose, choline or amino acid metabolism and has also been applied to imaging tumour cell proliferation and tissue hypoxia in urological malignancies. The diagnostic performance of FDG-PET is hampered by the renal excretion of FDG and by the low metabolic activity often seen in tumours such as prostate cancer. However, new PET tracers including radiolabelled choline and acetate may offer an alternative approach. There is consistent evidence that FDG-PET provides important diagnostic information in detecting metastatic and recurrent germ cell tumours and it might offer additional information in the staging and restaging of bladder and renal cancer. Conclusions: Although PET imaging has been shown to be a clinically useful tool, its application in urological malignancies still needs to be fully determined by larger prospective trials. The introduction of novel PET radiopharmaceuticals along with the new technology of PET/CT will likely change the future role of molecular imaging in urological malignancies.


OBJECTIVES To evaluate the role of (18)F-fluorodeoxyglucose (FDG) positron-emission tomography (PET)/computed tomography (CT) for the surveillance of patients with renal cell carcinoma (RCC) who have a high risk of local recurrence or distant metastasis, by comparing the results with those of conventional imaging methods.

PATIENTS AND METHODS Sixty-three patients with RCC had conventional imaging studies and FDG PET/CT during the follow-up after surgical treatment. Their pathological stages were T2 in 28 patients, T3a in 14, T3b in 19 and T4 in two; lymph-node or distant metastases were present in 12 patients.
Suspicious recurrent or metastatic lesions were confirmed by histopathology or by clinical follow-up. The sensitivity, specificity, positive predictive value, negative predictive value and accuracy of conventional surveillance methods and FDG PET/CT were analysed. The difference in the accuracy of FDG PET/CT by nuclear grade and histological subtype of tumours was also assessed. RESULTS The FDG PET/CT accurately classified the presence of a recurrence or metastasis in 56 (89%) patients. FDG PET/CT had an 89.5% sensitivity, 83.3% specificity, 77.3% positive predictive value, 92.6% negative predictive value, and 85.7% accuracy in detecting recurrence or metastasis, which was not significantly different from the results with conventional methods. Moreover, the accuracy of the FDG PET/CT by nuclear grade and histological subtypes was not significantly different. CONCLUSION For the surveillance of high-risk RCC, FDG PET/CT had results that were as good as conventional methods and were not influenced by the nuclear grades of cancer cells. In addition, it was possible to examine all organ systems in one procedure, and there was no need for contrast agents, that can damage renal function. Therefore, FDG PET/CT might replace conventional methods.
Ca Prostate

Introduction
Prostate carcinoma (PCa) is the most common life threatening cancer in men. Small carcinomas are present in about 30% of men between 30 and 40 years old and in 64% between 60 and 70 years old.

Current Imaging
For initial T staging of prostate cancer, transrectal ultrasonography (US) and magnetic resonance (MR) imaging are the established imaging modalities. Computed tomography (CT) and MR imaging for N staging has limited value because of the low sensitivity in the detection of lymph node metastases. Bone Scintigraphy is sensitive tool to detect distant osteoblastic skeletal metastases.

Summary of Evidence
Studies have shown that FDG is generally not a suitable PET tracer for diagnosing prostate cancer. Unlike many other tumor types, prostate cancer often does not display increased glucose metabolism. The most important factor for the low sensitivity (65%) is the low metabolic activity and hence the low FDG accumulation in prostate cancer metastases.
Based on upregulated enzymes of phospholipid metabolism in prostate carcinoma, $^{11}$C/$^{18}$F Choline is preferentially incorporated into phosphatidylcholine of membrane lipids of prostate cancer cells. PET allows sensitive detection of the $^{11}$C/$^{18}$F Choline signal and PET/CT fusion imaging enables intraprostatic signal localisation. Most published studies report a high detection rate of prostate carcinoma with $^{11}$C/$^{18}$F Choline PET/CT. Differentiation of prostate carcinoma from benign hyperplasia and from focal chronic prostatitis may be difficult. Acute prostatitis also accumulates $^{11}$C/$^{18}$F Choline with an equal intensity comparable to prostate carcinoma.

$^{11}$C Acetate PET/CT have shown promising results in localization of primary in prostate with staging the disease in pelvic & abdominal nodes and detecting distant skeletal metastases.

PSA relapse frequently is the first sign of recurrent or metastatic disease after radical prostatectomy or radiation therapy. PET with FDG can identify local recurrence and distant metastases, and the probability for a positive test increases with PSA. However, essentially all studies have shown that the sensitivity for recurrent disease detection is higher with either acetate or choline as compared with FDG.

Several studies suggest that FDG uptake in metastatic prostate cancer lesions reflects the biologic activity of the disease. Accordingly, FDG can be used to monitor the response to chemotherapy and hormonal therapy. Androgen receptor imaging agents like fluorodihydrotestosterone (FDHT) are being explored to predict the biology of treatment response for progressive tumor in late stage disease in castrated patients.

The short half-life of C-11 labeled PET tracers (20 min) limits whole-body imaging as well as posing logistical problems. In contrast, F-18 labeling, with a half-life of 109.7 min, overcomes most of these limitations.
18-F fluoride may provide a more sensitive bone scan and will probably be most valuable when PSA is greater than 20 ng/mL in patients with high suspicion or documented osseous metastases. 18F-Fluoride PET/CT has proved accurate in the diagnosis of skeletal metastases from prostate carcinoma.

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PURPOSE: Appropriate imaging in uro-oncology is a crucial component at primary diagnosis, followup and recurrence to
achieve an accurate assessment of the disease and determine the most effective treatment. We summarize recent developments in positron emission tomography and positron emission tomography/computerized tomography for prostate, bladder and renal cancer. MATERIALS AND METHODS: The recent published literature on positron emission tomography and positron emission tomography/computerized tomography in uro-oncology was searched and reviewed. RESULTS: For prostate cancer 18F-fluorodeoxyglucose is not highly effective for primary diagnosis but it has a limited role in staging and recurrence detection. Promising results have been shown by 11C-choline, 18F-fluorocholine, 11C-acetate and 18F-fluoride. The role of 11C-methionine, 18F-fluoro-5-alpha-dihydrotestosterone and anti-1-amino-3-18F-fluorocyclobutane-1-carboxylic acid remains to be elucidated. For bladder cancer 18F-fluorodeoxyglucose positron emission tomography is useful for identifying distant metastases but not for detecting primary tumors due to the urinary excretion of 18F-fluorodeoxyglucose. The role of 11C-choline and 11C-methionine remains to be evaluated further in clinical studies. For renal cancer 18F-fluorodeoxyglucose is of limited use for primary diagnosis but it has a role in staging and restaging of the disease. More clinical data are needed to investigate the roles of 18F-fluoromisonidazole and 18F-fluorothymidine. CONCLUSIONS: Several advances in positron emission tomography and positron emission tomography/computerized tomography for urological cancer have been made in recent years. However, larger clinical trials are needed to establish the role of this imaging method for urological malignancy. In the near future the new radiotracers and further advancement in this imaging technique are expected to improve the performance of positron emission tomography/computerized tomography in uro-oncology.
Recent developments in urologic oncology: positron emission tomography molecular imaging. Bouchelouche K, Oehr P. Curr Opin Oncol. 2008 May; 20(3):321-6
PURPOSE OF REVIEW: Traditional morphologically based imaging modalities in uro-oncology are now being complemented by the functional and molecular imaging technique positron emission tomography (PET). This review highlights the most important recent developments. RECENT FINDINGS: Prostate cancer: PET imaging with the new radiotracers 11C-choline, 18F-fluorocholine, and 11C-acetate show promising results. The role of anti-1-amino-3-18F-fluorocyclobutane-1-carboxylic acid remains to be elucidated further. 18F-fluoride PET is useful for the detection of bone metastases. Bladder cancer: 18F-fluorodeoxyglucose (FDG) PET/CT with delayed images after a diuretic and oral hydration may improve detection of locally recurrent or residual bladder tumours. Both 18F-FDG PET and 11C-choline PET may be useful for staging of bladder cancer. Renal cancer: 18F-FDG PET has a role in staging and restaging of the disease. Recently, 124I-cG250 PET has shown promising results in the detection of clear-cell renal carcinoma. Testicular cancer: 18F-FDG PET is useful in staging and follow-up after treatment. There are no important recent developments with new radiopharmaceuticals in testicular cancer. SUMMARY: The utility of PET molecular imaging in uro-oncology expanded due to the new metabolic PET tracers with more favourable properties.

Prostate cancer, renal cancer, bladder, and other urothelial malignancies make up the common tumors of the male genitourinary tract. For prostate cancer, common clinical
scenarios include managing the patient presenting with 1) low-risk primary cancer; 2) high-risk primary cancer; 3) prostate-specific antigen (PSA) recurrence after apparently successful primary therapy; 4) progressive metastatic disease in the noncastrate state; and 5) progressive metastatic disease in the castrate state. These clinical states dictate the appropriate choice of diagnostic imaging modalities. The role of positron emission tomography (PET) is still evolving but is likely to be most important in determining early spread of disease in patients with aggressive tumors and for monitoring response to therapy in more advanced patients. Available PET tracers for assessment of prostate cancer include FDG, 11C or 18F choline and acetate, 11C methionine, 18F fluoride, and fluorodihydrotestosterone. Proper staging of prostate cancer is particularly important in high-risk primary disease before embarking on radical prostatectomy or radiation therapy. PET with 11C choline or acetate, but not with FDG, appears promising for the assessment of nodal metastases. PSA relapse frequently is the first sign of recurrent or metastatic disease after radical prostatectomy or radiation therapy. PET with FDG can identify local recurrence and distant metastases, and the probability for a positive test increases with PSA. However, essentially all studies have shown that the sensitivity for recurrent disease detection is higher with either acetate or choline as compared with FDG. Although more data need to be gathered, it is likely that these two agents will become the PET tracers of choice for staging prostate cancer once metastatic disease is strongly suspected or documented. 18F fluoride may provide a more sensitive bone scan and will probably be most valuable when PSA is greater than 20 ng/mL in patients with high suspicion or documented osseous metastases. Several studies suggest that FDG uptake in metastatic prostate cancer lesions reflects the biologic activity of the disease. Accordingly, FDG can be used to monitor the response to chemotherapy and hormonal therapy.
Androgen receptor imaging agents like fluorodihydrotestosterone are being explored to predict the biology of treatment response for progressive tumor in late stage disease in castrated patients. The assessment of renal masses and primary staging of renal cell carcinoma are the domain of helical CT. PET with FDG may be helpful in the evaluation of “equivocal findings” on conventional studies, including bone scan, and also in the differentiation between recurrence and posttreatment changes. The value of other PET tracers in renal cell carcinoma is under investigation. Few studies have addressed the role of PET in bladder cancer. Because of its renal excretion, FDG is not a useful tracer for the detection of primary bladder tumors. The few studies that investigated its role in the detection of lymph node metastases at the time of primary staging were largely disappointing. Bladder cancer imaging with 11C choline, 11C methionine, or 11C- acetate deserves further study.
FDG PET in Testicular Tumors

Introduction
Germ cell tumors of the testis (GCT) are the most common malignant tumors of males who are between 15 and 45 years of age. The various risk factors for development of GCT’s are past history of GCT, cryptorchidism, testicular dysgenesis, infertility and a positive family history. GCT’s are classified into seminomas (accounting approx 40%) and non-seminomatous germ cell tumors (accounting approx 60%). Nonseminomas are clinically more aggressive and include choriocarcinomas, yolk sac tumor, embryonal cell carcinoma and teratomas. Serum tumor markers like alpha feto protein, beta HCG and LDH are important in the diagnosis, prognosis and assessing treatment response in GCT’s. The type of treatment offered depends upon the accurate histological subtype of the GCT.

Conventional imaging
Testicular tumors are usually diagnosed clinically and pathologically at surgery. Ultrasonography is used to confirm the presence of an intratesticular mass if clinical features are uncertain. USG is also used in patients who present with
metastatic adenopathy in whom an occult primary is suspected in the testis and also to evaluate the contralateral testis to identify the small number of patients with bilateral synchronous tumors. Magnetic resonance imaging is not routinely used, but can be helpful when the clinical & USG findings cannot differentiate between an intra and extra testicular mass.

CT scan is the imaging technique of choice for staging testicular neoplasms. It can readily diagnose large volume metastatic disease, however small volume disease can be missed. Studies have shown that up to 25-30% patients harbour microscopic metastatic disease which can be missed on CT scan.

**Summary of evidence for FDG PET**

Only a few studies are published in literature about the role of FDG PET in the initial staging of GCT’s. Similarly its precise role in determining prognosis is also not very clear. The most common clinical setting where the utility of PET has been studied is the evaluation of post chemotherapy residual masses in both seminomatous and non-seminomatous germ cell tumors. There are prospective trials which state that FDG PET is a very good predictor of residual viable tumor in post chemotherapy seminoma masses and helps clinical decision making. In one study of 54 patients PET reported a sensitivity of 80% and specificity of 100% for detecting viable tumor. It has a good negative predictive value in excluding viable disease in residual masses > 3 cms. In a large German multicentre trial of 121 patients, the negative predictive value of PET was (78%) not sufficient to predict absence of disease in residual masses of NSGCT due to presence of vital tumor and mature teratoma in many cases. The trial concluded that PET is unable to give a clear benefit over standard modalities like CT scan and tumor markers in the prediction of tumor viability in residual NSGCT masses.
To summarise, FDG PET-CT is useful in the assessment of post chemotherapy residual masses in GCT's. Though there is no conclusive evidence in literature stating the value of PET in initial staging, it can be certainly be certain considered as a potential application requiring a few more larger studies for its validation.

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Selected abstracts


PURPOSE: In patients with metastatic nonseminomatous germ cell cancer (NSGCT), residual masses after chemotherapy (CTX) can consist of vital carcinoma, mature teratoma, or
This prospective trial has evaluated the accuracy of [(18)F]fluorodeoxyglucose positron emission tomography (FDG-PET) for the prediction of histology compared with computed tomography (CT) and serum tumor markers (STM).

**PATIENTS AND METHODS:** A total of 121 patients with stage IIC or III NSGCT scheduled for secondary resection after cisplatin-based CTX were included. FDG-PET was performed after completion of CTX. All results were confirmed by histopathology and correlated to STM and CT.

**RESULTS:** Prediction of tumor viability with FDG-PET was correct in 56%, which did not reach the expected clinically relevant level of 70%, and was not better than the accuracy of CT (55%) or STM (56%). Sensitivity and specificity of FDG-PET were 70% and 48%. The positive predictive values were not significantly different (55%, 61%, and 59% for CT, STM, and PET, respectively). Judging only vital carcinoma as a true malignant finding, the negative predictive value increased to 83% for FDG-PET.

**CONCLUSION:** The presence of vital carcinoma and mature teratoma is common (55%) in residual masses in patients with NSGCT, and CT and STM cannot reliably predict absence of disease. In contrast to prior studies, this prospective trial, which is the only with histologic confirmation in all patients, demonstrated that FDG-PET is unable to give a clear additional clinical benefit to the standard diagnostic procedures, CT and STM, in the prediction of tumor viability in residual masses.


**PURPOSE:** The aim of this study was to determine the predictive values of 2-[fluorine-18]fluoro-2-deoxy-D-glucose-
positron emission tomography (FDG-PET) in primary staging in patients with newly diagnosed non-seminomatous germ cell tumour (NSGCT) clinical stage I/II. PATIENTS AND METHODS: The hypothesis was that FDG-PET would improve the negative predictive value (NPV) from 70% to 90%, thus requiring a total of 169 patients. All scans underwent visual analysis by a reference team of nuclear medicine physicians. Results were validated by histology following retroperitoneal lymph node dissection. RESULTS: Only 72 of the planned 169 patients were included, due to poor accrual. The prevalence of nodal involvement was 26%. Correct nodal staging by FDG-PET was achieved in 83% compared with correct computed tomography (CT) staging in 71%. CT had a sensitivity and specificity of 41% and 95%, respectively. Positive predictive value (PPV) and NPV were 87% and 67%, respectively. FDG-PET had a sensitivity and specificity of 66% and 98%, respectively. PPV was 95%. The primary end point was not reached, with an NPV of 78%. CONCLUSION: FDG-PET as a primary staging tool for NSGCT yielded only slightly better results than CT. Both methods had a high specificity while false-negative findings were more frequent with CT. FDG-PET is mostly useful as a diagnostic tool in case of questionable CT scan.


PURPOSE: There are several management options for patients with clinical stage I (CS1) nonseminomatous germ cell tumors
(NSGCT); this study examined whether an 18fluorodeoxyglucose positron emission tomography (18FDG PET) scan could identify patients without occult metastatic disease for whom surveillance is an attractive option. METHODS: High-risk (lymphovascular invasion positive) patients with CS1 NSGCT underwent 18FDG PET scanning within 8 weeks of orchidectomy or marker normalization. PET-positive patients went off study; PET-negative patients were observed on a surveillance program. The primary outcome measure was the 2-year relapse-free rate (RFR) in patients with a negative PET scan (the negative predictive value). Assuming an RFR of 90% to exclude an RFR less than 80% with approximately 90% power, 100 PET-negative patients were required; 135 scanned patients were anticipated. RESULTS: Patients were registered between May 2002 and January 2005, when the trial was stopped by the independent data monitoring committee due to an unacceptably high relapse rate in the PET-negative patients. Of 116 registered patients, 111 underwent PET scans, and 88 (79%) were PET-negative (61% of preorchidectomy marker-negative patients v 88% of marker-positive patients; P = .002); 87 proceeded to surveillance, and one requested adjuvant chemotherapy. With a median follow-up of 12 months, 33 of 87 patients on surveillance relapsed (1-year RFR, 63%; 90% CI, 54% to 72%). CONCLUSION: Though PET identified some patients with disease not detected by computed tomography scan, the relapse rate among PET negative patients remains high. The results show that 18FDG PET scanning is not sufficiently sensitive to identify patients at low risk of relapse in this setting.
Section — V

Gynecological Malignancies
PET / PET- CT in Cervical Cancers

Introduction
Carcinoma Cervix is the commonest malignancy and a leading cause of cancer mortality seen in Indian women. At Tata Memorial Hospital, Carcinoma Cervix constitutes approximately 10% of all cancers. More than 2/3rd of the patients present with advanced stages (FIGO Stage II/III). The mainstay of treatment has traditionally been radical radiation therapy with 80-90% of patients requiring radiation in their lifetime and over decades the survival rates have achieved a plateau of 30 - 55% at 5 years. In patients with advanced stages (stages IIB to IVA), 15 - 38% have para-aortic lymph nodal metastases at presentation. Identification of para-aortic nodal status allows modification of radiation therapy fields to include this nodal disease, which, because of intestinal morbidity, is not routinely included in the treatment field by most of the Radiation Oncologists. Extended field radiation therapy that includes the para-aortic nodes is associated with a 31 - 50% 5 year-survival, depending on the location and extent of para-aortic nodal metastasis and the likelihood of controlling the pelvic disease. Therefore, in advanced cervical cancer, it has been reported that progression-free survival is significantly related to para-aortic lymph node metastasis. In a collective
series of Gynecologic Oncology Group protocols, Para aortic nodal status was the most significant indication of recurrence. Also, 15 - 45% of patients post treatment also fails in para-aortic nodal region. Identification of early isolated para-aortic nodal relapse and salvage treatment to a large extent offers excellent palliation, improves outcome and better quality of life.

**Current Status in Imaging including PET-CT**

**Primary Staging:** The accuracy of CT and MRI for the staging of cervical cancer has been reported as being from 63% to 69% for CT and from 77% to 90% for MRI. Many studies have evaluated the role of FDG–PET in the primary staging of cervical cancers. With an overall sensitivity of 97%, FDG–PET also plays an important role in the evaluation of primary cervical tumors. However, neither PET nor CT is an effective method for detecting parametrial disease, and either might fail to detect the primary tumor. However, there are no data comparing MRI and PET/CT for primary tumor evaluation, hence MRI remains the best imaging technique for initial primary tumour staging.

**Nodal Staging:** Cervix carcinoma usually spreads from the primary cervical lesion sequentially to pelvic lymph nodes, para-aortic lymph nodes, and supraclavicular lymph nodes, then ultimately to extranodal sites of distant metastasis. If metastasis in the para-aortic lymph nodes is detected, patients would benefit from extended-field radiotherapy or combined radiotherapy and chemotherapy protocols. Survival rates for patients with positive pelvic lymph nodes are reported to be decreased by about 50% compared with those with negative pelvic lymph nodes. The survival rate of patients with positive para-aortic lymph nodes is about 30%. The accuracy of detecting lymph node metastasis by CT or MRI is dependent on the size of the lymph node on the cross-sectional image.
and is based on distortion of normal lymph node architecture or lymph node enlargement. When lymph nodes measuring greater than 1 cm were considered abnormal, the reported sensitivity of MRI was 38-89%, whereas the specificity was 78-99% in surgically staged patients. A number of noninvasive modalities have been used to evaluate the status of para-aortic nodal metastasis. CT Scanning has been widely used for clinical staging, but its sensitivity for nodal metastasis is only 44%. In contrast to CT, FDG-PET can non-invasively assess metabolic activity in cancers and metastatic lesions. The differentiation capability for malignant lesions of FDG-PET is not compromised by using morphologic size criteria. Even malignant lesions less than 1 cm in diameter that manifest high FDG uptake can be differentiated from nonmalignant tissue by using PET. Therefore, FDG-PET can detect metastatic para-aortic lymph nodes in patients with advanced cervical cancer whose lymph nodes have not been abnormally enlarged. Havrilesky et al. found that the pooled sensitivity and specificity of FDG–PET for detecting pelvic lymph node metastasis were 79% (95%, CI 65–90%) and 99% (96–99%), respectively, compared with 72% (53–87%) and 96% (92–98%), respectively, for MRI.

Many published data have previously reported the clinical value of 18F FDG PET for imaging the primary tumor, staging the nodal and visceral involvement, and also detecting a recurrent disease. Rose et al. used FDG-PET for evaluating nodal metastasis in locally advanced cervical cancer before surgical staging, with a sensitivity of 75% and a specificity of 92% to detect the metastases of para-aortic lymph nodes. They found that the accuracy of FDG-PET was greater than that of CT in detecting the para-aortic lymph nodal metastasis. In a similar series, Wu et al. have reported a sensitivity of 85.7%, a specificity of 94.4%, and an accuracy of 92% with FDG PET to detect para-aortic lymph nodal metastasis in patients with advanced cervical cancer and negative abdominal CT
findings. Grigsby et al. demonstrated that FDG-PET detects more abnormal lymph node regions than does CT, and that FDG-PET findings are a better predictor of survival than those of CT in patients with cervical cancer.

Magnetic Resonance Imaging (MRI) has also been reviewed in evaluating both the primary disease at cervix and also para-aortic nodal staging. MRI has been recognized as an important imaging modality for the management of cervical cancer because of its multi-planar capability, distinct tissue contrast characteristics using various pulse sequences, and excellent tissue contrast, particularly between tumor and surrounding normal tissues. However, PET findings were most often compared to CT results, while MRI is nowadays considered as the modality of choice for staging the primary tumor. Only one study by Narayan et al. has compared the respective value of MRI and PET for staging loco-regionally advanced cervical cancer. Their study found that the primary tumor was similarly detected by the two imaging techniques with a sensitivity of 100%. On the other hand, except for small-volume metastases, PET had a sufficiently high positive predictive value (91%) in the pelvis and para-aortic region, to obviate lymph node sampling. More recent studies have shown that the 3D quantitative imaging-based method of tumor size assessment using MRI is highly accurate in determining actual tumor size and extent and may be superior to clinical palpation in predicting local tumor control. Conversely, MRI accuracy was insufficient for nodal management. If MRI remains the modality of choice for evaluating the loco-regional status of the primary tumor, metabolic imaging i.e FDG PET seems particularly useful for staging, in one session, extra pelvic nodal metastases. Thus, PET may have a significant impact on treatment decision-making.

Identification of para-aortic nodal status allows modification of radiation therapy fields to include this nodal disease.
Stehman et al. previously demonstrated the prognostic importance of para-aortic nodal status in locally advanced cervical carcinoma. In advanced cervical cancer, it has been reported that progression-free survival is significantly related to para-aortic lymph node metastasis. Recent studies have shown a survival benefit in patients with positive para-aortic nodes treated by extended-field irradiation and concurrent radio-sensitizing chemotherapy.

**Response Evaluation**

PET is also of great value for optimally confirming a complete remission and detecting a recurrence non-invasively in post-treatment follow-up. More recently, positron emission tomography (PET) with the glucose analogue, 18 F-fluorodeoxyglucose (FDG) has demonstrated promising results in evaluating tumor response and predicting survival after primary treatment with radiation therapy or chemotherapy for several tumor types, including head-and-neck cancer, breast cancer, seminoma, colorectal cancer, lymphoma, and lung cancer. Recently, Grigsby et al have reported the role of FDG PET in post-therapy surveillance monitoring in a series of 75 patients with cervical cancer. They have concluded that FDG-PET is a valuable tool to evaluate the response of both at primary and its lymph node disease after radiation therapy and chemotherapy and for the Post-Rx surveillance of patients to detect asymptomatic recurrence.

**Surveillance:** FDG–PET has been advocated as a useful tool for determining the optimal scope of salvage therapy in patients with recurrent cervical cancer. Approximately 70% of recurrences of cervical cancer are estimated to be distant or a combination of local and distant metastases. Several authors reported the ability of FDG–PET to diagnose cervical cancer recurrence in the pelvis, abdomen, and extra-abdominal sites, including inguinal lymph nodes, PALNs, peritoneum, liver,
spleen, transposed ovaries, mediastinal lymph nodes, bone, pleura, and lung. Earlier detection of recurrent disease may have the potential to improve effectiveness of treatment and survival, particularly in patients amenable to salvage surgery. FDG–PET in cervix cancer patients has rapidly expanded. Investigators have documented its usefulness in initial staging of cervix cancer patients. Preliminary reports suggest that PET/CT is effective in the lymph node staging of locally advanced cervix carcinoma with negative CT findings. It has been advocated that the maximal value of FDG uptake reflects tumour aggressiveness and is negatively associated with survival. In addition, FDG may help to customize radiotherapy planning, reduce unnecessary surgical interventions and change therapeutic approaches by modifying radiation fields. The value of hybridizing PET imaging with CT imaging has been reported for detection of cervical cancer metastases, which facilitates decision-making and radiation treatment planning. Although metabolic examination is less accurate in detecting microscopic disease and lesions smaller than 1.5 cm, PET/CT is an effective imaging technique in the evaluation of locally advanced cervix carcinoma. Grigsby recently recommended that routine FDG–PET/CT should be performed 3 months post-therapy, every 6 months for 3 years, every year for two additional years, and then as clinically indicated. However, further evaluation in prospective clinical trials will be required to assess the clinical benefit of this strategy.
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**Selected Abstracts**

**Havrilesky LJ, Kulasingam SL, Matchar DB, Myers ER.**  
FDG-PET for management of cervical and ovarian cancer.  
Gynecol Oncol 2005; 97: 183-91

Abstract: To assess the diagnostic performance of Positron Emission Tomography using fluorodeoxyglucose (FDG-PET) in comparison to conventional imaging modalities in the assessment of patients with cervical and ovarian cancer. Studies published between 1966 and 2003 were identified using an OVID search of the MEDLINE database. Inclusion criteria were use of a dedicated scanner, resolution specified, ≥12 human subjects, clinical follow-up ≥6 months or histopathology as reference standard, and sufficient data provided to construct a two-by-two table. Two reviewers independently abstracted data regarding sensitivity and specificity of PET. 25 studies (15 cervical cancer, 10 ovarian cancer) met inclusion criteria for full text review. For cervical
cancer, pooled sensitivity and specificity of PET for aortic node metastasis are 0.84 (95% CI 0.68–0.94) and 0.95 (0.89–0.98). Pooled sensitivity and specificity for detection of pelvic node metastasis are: PET, 0.79 (0.65–0.90) and 0.99 (0.96–0.99); MRI, 0.72 (0.53–0.87) and 0.96 (0.92–0.98). Pooled sensitivity for CT is 0.47 (0.21–0.73) (pooled specificity not available). Pooled sensitivity and specificity of PET for recurrent cervical cancer with clinical suspicion are 0.96 (0.87–0.99) and 0.81 (0.58–0.94). For ovarian cancer, pooled sensitivity and specificity to detect recurrence with clinical suspicion are: PET, 0.90 (0.82–0.95) and 0.86 (0.67–0.96); conventional imaging, 0.68 (0.49–0.83) and 0.58 (0.33–0.80); CA-125, 0.81 (0.62–0.92) and 0.83 (0.58–0.96). When conventional imaging and CA-125 are negative, pooled sensitivity and specificity of PET are 0.54 (0.39–0.69) and 0.73 (0.56–0.87), respectively. When CA-125 is rising and conventional imaging is negative, the pooled sensitivity and specificity of PET are 0.96 (0.88–0.99) and 0.80 (0.44–0.97).

Conclusions: There is good evidence that PET is useful for the pre-treatment detection of retroperitoneal nodal metastasis in cervical cancer. There is fair evidence that PET is useful for the detection of recurrent cervical cancer. PET is less useful for the detection of microscopic residual ovarian cancer but has fair sensitivity to detect recurrence in the setting of a rising CA-125 and negative conventional imaging studies. Available studies are limited by low numbers of patients and wide confidence intervals.


Abstract: Cervical cancer ranks among the top three cancer diagnoses in women worldwide. In the United States, the SEER Cancer Statistics Review identified cervical cancer as the third leading cause (following childhood cancers and testicular
cancer) of average years of life lost per person dying of cancer for all races and both genders. Approximately one-third of cervical cancer patients develop disease recurrence and the majority of these recurrences occur within the first 2 years after completion of therapy. Predictors of disease recurrence include stage and lymph node status at the time of initial diagnosis. The initial diagnosis and staging of cervical cancer has traditionally been achieved by history and physical examination and by use of selected imaging studies. Accurate staging is important both for selecting appropriate therapy and for prognosis. Computed tomography (CT) has been the most widely used imaging method for assessment of nodal involvement and detection of distant metastatic disease. Positron Emission Tomography (PET) has become an established imaging tool for cervical cancer. The functional information about regional glucose metabolism provided by fluorodeoxyglucose (FDG)-PET provides for greater sensitivity and specificity in most cancer imaging applications by comparison with CT and other anatomic imaging methods. PET is superior to conventional imaging modalities for evaluating patients with cervical cancer.


Abstract: Introduction: Positron Emission Tomography (PET) with F18 Flurodeoxyglucose (FDG) has been evaluated and found to be a useful diagnostic tool in a certain number of malignancies, particularly in providing crucial assessment of metabolic activity of the tumor. We here in review and discuss the place and role of FDG–PET scan in cervix carcinoma patients’ management. Materials and methods: Data for this review were identified by searches of Medline with and without MeSH database and Cancerlit. Studies were selected only if
they were randomised clinical trials or historical reports. References were also identified from reference lists in relevant previously published articles. Recent guidelines and meta-analyses were included. Only published articles were taken into consideration. Results: Although FDG–PET may be useful in the primary cervical tumors morphologic and metabolic evaluation, it seems to have limited place for disease staging in patients with early-stage disease (less than 4 cm). Hybrid PET/CT is an effective imaging technique in the lymph node staging of locally advanced cervix carcinoma with negative CT findings and may lead to substantial changes in treatment planning for several patients. FDG–PET provides meaningful information for the early evaluation of therapeutic response and long-term follow-up. Conclusion: Several reports have demonstrated the efficacy of FDG–PET in both pre-treatment staging and post-treatment evaluation of patients with cervical carcinoma. Further evaluation in prospective clinical trials will be required to assess the clinical benefit of this strategy.

The Standardized Uptake Value for F-18 Fluorodeoxyglucose Is a Sensitive Predictive Biomarker for Cervical Cancer Treatment Response and Survival


Abstract: BACKGROUND. The objective of this study was to evaluate cervical tumor uptake of F-18 fluorodeoxyglucose (FDG) measured as the maximal standardized uptake value (SUVmax) by positron emission tomography (PET) and its association with treatment response and prognosis in patients with cervical cancer. METHODS: The study population consisted of 287 patients with stage IA2 through IVB cervical cancer who underwent pretreatment FDG-PET studies. SUVmax, tumor volume, and sites of lymph node metastasis were recorded. Therapy included surgery, chemoradiation, or palliation. RESULTS: The mean SUVmax was 11.4 (range,
The mean tumor volume by stage was 42.1 cm$^3$ for stage I tumors (using International Federation of Gynecology and Obstetrics [FIGO] staging criteria), 63.7 cm$^3$ for stage II tumors, 129.2 cm$^3$ for stage III tumors, and 166.2 cm$^3$ for stage IV tumors. There was no correlation between tumor volume and SUVmax (correlation coefficient [R$^2$] = 0.01).

No significant difference in SUVmax was observed between squamous histology (n = 247 patients) and nonsquamous histology (n = 40 patients; P = 0.089). Higher SUVmax was associated with an increased risk of lymph node metastasis at diagnosis (P = 0.0009). A Cox proportional-hazards model for death from cervical cancer was used to evaluate tumor histology, lymph node metastasis, tumor volume, and SUVmax. The results indicated that SUVmax was the only significant independent factor (P = 0.0027). Three prognostic groups were established using SUVmax. The overall survival rates at 5 years were 95% for an SUVmax $\leq$ 5.2, 70% for an SUVmax $>$ 5.2 and $\leq$ 13.3, and 44% for an SUVmax $>$ 13.3 (P < 0.0001). Increasing SUVmax was associated with persistent abnormal FDG uptake in the cervix on 3-month FDG-PET studies in 238 patients who received curative chemoradiation (P = 0.04). CONCLUSIONS: The SUVmax of the cervical tumor at diagnosis was a sensitive biomarker of treatment response and prognosis for patients with cervical cancer.

**Prospective Clinical Trial of Positron Emission Tomography/ Computed Tomography Image-guided intensity-modulated radiation therapy for cervical carcinoma with positive para-aortic lymph nodes.**


**Abstract:** Purpose: To describe a more aggressive treatment technique allowing dose escalation to positive para-aortic lymph nodes (PALN) in patients with cervical cancer, by means
of positron emission tomography (PET)/computed tomography (CT)–guided intensity-modulated radiation therapy (IMRT). Here, we describe methods for simulation and planning of these treatments and provide objectives for target coverage as well as normal tissue sparing to guide treatment plan evaluation. Methods and Materials: Patients underwent simulation on a PET/CT scanner. Treatment plans were generated to deliver 60.0 Gy to the PET-positive PALN and 50.0 Gy to the PALN and pelvic lymph node beds. Treatment plans were optimized to deliver at least 95% of the prescribed doses to at least 95% of each target volume. Dose–volume histograms were calculated for normal structures. Results: The plans of 10 patients were reviewed. Target coverage goals were satisfied in all plans. Analysis of dose–volume histograms indicated that treatment plans involved irradiation of approximately 50% of the bowel volume to at least 25.0 Gy, with less than 10% receiving at least 50.0 Gy and less than 1% receiving at least 60.0. With regard to kidney sparing, approximately 50% of the kidney volume received at least 16.0 Gy, less than 5% received at least 50.0 Gy, and less than 1% received at least 60.0 Gy. Conclusions: We have provided treatment simulation and planning methods as well as guidelines for the evaluation of target coverage and normal tissue sparing that should facilitate the more aggressive treatment of cervical cancer.
PET / PET- CT in Endometrial Cancers

Introduction

Among the gynecological malignancies carcinoma uterine body is one of the common cancers in the west. Most women present with disease confined to the uterus, and many of these women have an excellent prognosis and outcome. Over 80% of primary endometrial cancers are endometrioid adenocarcinomas. Endometrial tumors spread by direct extension to the cervix, vagina and, via the fallopian tubes, to the ovaries and peritoneal cavity. Myometrial invasion is common and may lead to serosal and parametrial involvement. Lymphatic spread occurs to the external iliac, internal iliac and obturator regions of the pelvis and to the para-aortic nodes from the upper part of the uterus. Haematogenous spread results in lung metastases. Patterns of recurrences also imply a tendency to early systemic metastasis.

Surgery is the mainstay of treatment. The performance of full surgical staging for endometrial cancer has several possible advantages. First, it allows the treating physician to tailor adjuvant therapies to the location and volume of identified metastases. In addition, there is a growing body of data to suggest that more extensive pelvic and aortic
lymphadenectomy is associated with improved outcomes among women with high-risk early stage and advanced stage disease.

**Current Staging / Imaging:** Increasingly, Magnetic Resonance Imaging (MRI) is used in the preoperative imaging of women with endometrial cancer to assess the depth of myometrial invasion. Depth of invasion is closely related to the risk of lymph node involvement and may be used to aid decisions for selective lymphadenectomy. MRI is more sensitive than transvaginal ultrasound and computed tomography (CT) scanning for the assessment of depth of invasion and can identify cervical involvement. CT may be helpful in assessment of the upper abdomen if intra-abdominal metastases are suspected. Experience of FDG-PET in endometrial cancer is currently limited and is unlikely to contribute significantly to preoperative management. However, initial reports suggest that FDG-PET may be clinically useful in evaluating potential disease recurrence, with negative results correlating with a disease-free course. Despite the use of preoperative imaging as an aid to treatment planning, the staging of endometrial cancer remains surgico-pathological, relying both on a surgical assessment of intra-abdominal disease and in most cases, where disease is confined to the uterine corpus, on depth of myometrial invasion. There has been considerable debate concerning the surgical staging of endometrial cancer. It is generally accepted that, as a minimum, total hysterectomy with bilateral salpingo-oophorectomy, peritoneal cytology and inspection of the upper abdominal organs and peritoneal surfaces should be performed. Most endometrial cancer recurrences occur within the first 3 years after treatment. Follow-up is undertaken with the aim of detecting recurrence and identifying side-effects of treatment. Women who experience recurrence after treatment for early
endometrial cancer are managed according to the pattern of recurrence and overall fitness. MRI is useful for evaluating suspected pelvic recurrence, whereas CT is preferable for imaging suspected para-aortic recurrence. Chest X-ray will detect lung metastases, although CT is frequently employed for simultaneous assessment of both the abdomen and chest.

However, only few retrospective case series has investigated the role of PET/CT in the post-therapy surveillance of patients with uterine corpus cancer, and there have been no studies investigating the sensitivity and specificity of preoperative PET/CT in these patients. The principal benefit of PET/CT is its sensitivity in detecting distant metastases. Due to its high NPV in predicting LN metastases, PET/CT can also be useful in selected patients who are poor candidates for surgical staging. The low PPV of this method may be due to misinterpreting reactive lymphadenopathy after endometrial biopsy as malignant change. Larger prospective studies are needed to clarify the role of PET/CT in preoperative evaluation of uterine corpus cancer.

Torizuka T et al. compared PET & MRI for detecting myometrial invasion and found that FDG PET may be feasible for predicting invasion, especially when uterine atrophy makes it difficult to detect with MRI in post-menopausal patients and thereby avoid overestimation of invasion. There are still few issues regarding this. First is that these imaging need not change the treatment plan radically and surgery is still required. Secondly in our setting we need to be aware of the fact that infections may raise the SUV and this may affect the specificity.

Advanced disease form a heterogeneous group of patients whose survival ranges from 10 to >65 % . It is imperative to detect the subsets of the patients that will benefit from adjuvant radiotherapy. In this respect the imaging studies are evolving to help to identify accurately these patients. Lok KV et al in
their study showed the involvement of lymph node in pre
operative patients. By defining the lymphatic spread via
surgical staging, postoperative radiotherapy can be
recommended to patients with nodal metastases, while it can
be withheld from those patients with negative nodes. Thus the
management changes for these patients.

Horowitz NS et al also showed that FDG-PET is only
moderately sensitive (60%) in predicting lymph node
metastasis pre-operatively in patients with endometrial cancer.
This corresponds with the findings of Park et al. which
compared MRI & PET Scan showing better specificity and
accuracy of PET scan. The other benefit of PET scan is that it
can also pick up distant metastasis in the same study

PET Scan becoming negative also signifies important factor
for prognosis and patient remain disease free, in contrast to
patients with carcinoma ovary where negative PET Scan means
absence of macroscopic disease. This difference in the nature
of the diseases will help to utilized PET Scan as modality for
the follow of patients with carcinoma endometrium.

The early stage presentation of the carcinoma endometrium
patients is reflected in long term overall survival & disease
free status. Most of the recurrences occur within the first 3
years after treatment. The aim of follow up is to detect
recurrences early so that salvage treatment can be offered.
Imaging is usually done for symptomatic patients on follow
up. PET scan as an imaging modality during the follow up,
and for diagnosis of the recurrence is still emerging. Even in
the asymptomatic patients, PET Scan have shown better results
than the other imaging modalities.

Two studies have been published favoring the routine scan as
surveillance strategy. Belhocine have reported that use of PET-
CT in post therapy follow up is useful, as it help to identify
asymptomatic recurrences in almost 12% patients, thereby
helping salvage treatment and also avoiding unnecessary over treatment in few cases. Similar study was done for uterine sarcoma showed that PET CT is useful in post-treatment follow up of the uterine sarcoma. Recently published study by Kitajima K et al has shown that in cases of suspected recurrence PET CT was better than PET which is better than the CT alone. Based on PET/CT findings there was change of management in 42% patients which is a significant number.

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**Suggested Reading**


Abstract: OBJECTIVE: To compare positron emission
tomography/computed tomography (PET/CT) with magnetic resonance imaging (MRI) in the preoperative detection of primary lesions and lymph node (LN) and distant metastases in patients with uterine corpus cancer. METHODS: The patient cohort consisted of 53 women with uterine corpus cancer who underwent preoperative workup, including both MRI and PET/CT scans, and underwent surgical staging, including pelvic and/or paraaortic LN dissection, between October 2004 and June 2007 at Asan Medical Center, Seoul, Korea. Pathologic data from surgical staging were compared with the preoperative MRI and PET/CT results. For area specific analysis, LNs were divided into paraaortic, right pelvic and left pelvic areas. RESULTS: In detecting primary lesions, MRI and PET/CT showed no differences in sensitivity (91.5% vs. 89.4%), specificity (33.3% vs. 50.5%), accuracy (84.9% vs. 84.9%), positive predictive value (PPV) (91.5% vs. 93.3%) and negative predictive value (NPV) (33.3% vs. 37.5%). With MRI, the sensitivity, specificity, accuracy, PPV and NPV for detecting metastatic LNs on LN area-by-area analysis were 46.2%, 87.9%, 83.9%, 28.6% and 94.0%, respectively; With PET/CT, those were 69.2%, 90.3%, 88.3%, 42.9%, and 96.6%, respectively. PET/CT showed higher sensitivity, but it did not reach statistical significance (p=0.250). There were also no differences in specificity, accuracy, PPV and NPV. In detecting distant metastasis, the sensitivity, specificity, accuracy, PPV and NPV of PET/CT were 100%, 93.8%, 92.5%, 62.5% and 100%, respectively. CONCLUSION: In patients with uterine corpus cancer, PET/CT had moderate sensitivity, specificity and accuracy in detecting primary lesions and LN metastases, indicating that this method cannot replace surgical staging. The primary benefit of PET/CT is its sensitivity in detecting distant metastases. Because of its high NPV in predicting LN metastasis, PET/CT may also have advantages in selected patients who are poor candidates for surgical staging.

Abstract: OBJECTIVES: To estimate the sensitivity and specificity of positron emission tomography (PET) with 2-[(18)F]fluoro-2-deoxy-d-glucose (FDG) for detecting pelvic and para-aortic lymph node metastasis in patients with uterine corpus carcinoma before surgical staging. METHODS: Patients with newly diagnosed FIGO grade 2 or 3 endometrioid, papillary serous, or clear cell adenocarcinoma or uterine corpus sarcoma scheduled for surgical staging, including bilateral pelvic and para-aortic lymphadenectomy, were eligible. PET was performed within 30 days of surgery and interpreted independently by two nuclear medicine physicians. The imaging, operative, and pathologic findings for each patient and each nodal site were compared, and the sensitivity and specificity of FDG-PET in predicting nodal metastasis were determined. RESULTS: Twenty patients underwent FDG-PET before surgical staging. One patient found to have ovarian carcinoma on final pathology was excluded. Of the 19 primary intrauterine tumors, 16 (84%) exhibited increased FDG uptake. One patient did not undergo lymphadenectomy; her chest CT was suspicious for metastatic disease and FDG-PET showed uptake in multiple nodal and pulmonary foci. Metastatic disease was confirmed by percutaneous nodal biopsy. A total of three pathologically positive nodes were found in 2 of the 18 patients (11%). FDG-PET predicted that 3 patients would have positive lymph nodes (2 true positive and 1 false positive). Analyzed by lymph node regions, FDG-PET had 60% sensitivity and 98% specificity. The sensitivity and specificity by individual patient were 67% and 94%, respectively. CONCLUSIONS: FDG-PET is only moderately sensitive in predicting lymph node metastasis
pre-operatively in patients with endometrial cancer. This imaging modality should not replace lymphadenectomy, but may be helpful for patients in whom lymphadenectomy cannot be, or was not, performed.


Abstract: Objective. To estimate the potential cost-effectiveness of a hypothetical test to screen for lymph node metastases in women with newly diagnosed, apparent early stage endometrial cancer. Methods. A decision model was constructed to inform a choice between the following strategies: (1) Usual care, in which the probability of undergoing full surgical staging (29%) is based on literature review; (2) Noninvasive diagnostic testing for metastasis (Testing), in which patients with abnormal test results undergo full surgical staging; (3) 100% referral, in which all patients are referred for full surgical staging. Survival was modeled using Surveillance Epidemiology and End Results (SEER) database. Base case diagnostic test characteristic estimates (sensitivity 0.90, specificity 0.90) were varied for sensitivity analysis. Cost of the diagnostic test was set at $500 and varied; costs of treatment for endometrial cancer (surgery, adjuvant therapies, diagnosis of recurrence, salvage therapies and palliative care) were incorporated. Results. Usual care was the least expensive strategy, while Testing was more expensive and more effective, with an incremental cost-effectiveness ratio (ICER) of $18,785 per year of life saved (YLS) compared to Usual care. 100% referral was the most expensive and most effective strategy, with an ICER of $35,358 per YLS compared to Testing. Results are relatively sensitive to variation in test characteristics and the cost of the diagnostic test but insensitive
to cost of treatment and probability of adjuvant therapies. Testing remains cost-effective compared to Usual care unless the usual rate of referral to a Gynecologic Oncologist for full staging exceeds 90%. Conclusions. Given the current low rates of full surgical staging and/or referral to a Gynecologic Oncologist, a diagnostic test to detect nodal metastasis for endometrial cancer has potential to be cost effective when compared to usual care. Testing is also potentially cost-effective compared to 100% referral at very high test sensitivities and at the lower range of test costs.
Introduction

Ovarian neoplasms encompass a wide array of benign and malignant tumors with diverse histologic cell types, clinical features and hormone secreting tumors. On the basis of distinct pathologic and clinical features, ovarian cancer can be separated into three distinct histologic subtypes: epithelial tumors, germ cell tumors, and sex cord–stromal tumors. The epithelial tumors account for 60% of all ovarian neoplasm and for 80% to 90% of ovarian malignancies. The epithelial tumors arise from the surface epithelium or serosa of the ovary.

In the majority of cases, malignant epithelial ovarian tumors disseminate throughout the peritoneal cavity after exfoliation of malignant cells from the surface of the ovary. The typical circulation of the peritoneal fluid along the undersurface of the right hemi-diaphragm facilitates the frequently observed pattern of widespread dissemination of malignant tumor cells within the peritoneal cavity. In addition, the omentum frequently attracts these malignant cells and is thus a common site of metastasis. Tumor spread also occurs via the lymphatics from the ovary. A primary source of drainage follows the ovarian blood supply in the infundibulo-pelvic ligament to
lymph nodes around the aorta and vena cava to the level of
the renal vessels. There is also lymphatic drainage through
the broad ligament and parametrial channels; consequently,
pelvic sidewall lymphatics, including the external iliac,
obturator, and hypogastric chains, are also frequently involved.
Spread to lymph nodes is common. Approximately 10% of
patients with ovarian cancer that appears to be localized to
the ovaries have metastases to para-aortic lymph nodes, and
retroperitoneal lymph node involvement is found in the
majority of cases of advanced ovarian cancer. Hematogenous
metastases to extra-abdominal sites can occur but are relatively
uncommon. There can also be direct extension of the tumor
from the ovary to involve the adjacent peritoneal surfaces of
the bladder, recto-sigmoid, and pelvic peritoneum.

Most patients are not symptomatic until the disease has
progressed to advanced stages; hence, approximately 75–80%
of women with ovarian cancer have tumor spread beyond the
ovary at the time of diagnosis. Primary therapy of ovarian
cancer usually consists of surgical cytoreduction followed by
paclitaxel and platinum based chemotherapy or vice-versa.
Most women respond to primary therapy, with 75% of patients
achieving a complete clinical response. Despite good initial
response, the majority of ovarian cancer patients will ultimately
develop recurrent disease. Both chemotherapy and
radiotherapy or combinations of both are treatment modalities
of potential benefit. Although significant advances have been
made with the use of chemotherapy, the treatment of ovarian
carcinoma still remains a challenge. The clinical follow-up
includes close surveillance, periodic evaluation of serum
CA-125 levels and the use of imaging modalities.

**Current Staging / Imaging and Evidence:**

After initial evaluation and establishing disease confined to
abdomino-plevic cavity, staging is essentially by surgery. The
extent of surgery depends on resectability and is therapeutic
for early stage while diagnostic and to some extent therapeutic. Pre-operative imaging to a large extent maps the disease. Computed tomography (CT) and magnetic resonance (MRI) are anatomic, high-resolution imaging techniques are commonly used to guide the management of patients with epithelial ovarian cancers. They have limited role to resolve small volumes of disease and false positives due to their inability to distinguish between viable tumor masses and masses consisting of necrotic or scar tissue. Functional imaging methods such as positron emission tomography (PET) can establish the metabolic or functional parameters of tissue and may aid in these distinctions. The diagnostic test performance of FDG-PET as an adjunct to conventional imaging (e.g., CT, MRI) has been attempted for ovarian cancer in

1. Staging at the time of initial diagnosis
2. Detecting recurrent disease following treatment (surgery, radiation, chemotherapy, or combination) or in rising CA-125 levels and a negative CT?

**Staging:** Ovarian cancer is generally characterized by a marked increase in FDG uptake, but its use in the evaluation of primary ovarian masses is limited due to a relatively high rate of false positive findings. In advance disease at presentation, PET imaging has the potential to identify systemic disease and its distribution. It may also assist in identifying the sanctuary sites for tumor seedings in the peritoneal cavity like, sub-hepatic region, para-colic gutters, etc. However, its role in preoperative staging is yet to be established and needs systematic prospective studies in future.

**Recurrent Disease / Surveillance:** Although recurrent ovarian cancer is almost never curable, early detection of recurrence theoretically affords a better chance that salvage treatment will result in prolonged remission and sustained quality of life. Although CA-125 elevation is often useful in detecting
recurrence, it is not helpful in localizing the disease. Knowledge of the location of recurrence could guide tailored salvage treatment. Conventional imaging modalities often give nonspecific results and are suboptimal for the reliable detection of peritoneal recurrence of ovarian cancer. The identification of more accurate imaging modalities should improve management decisions for patients with recurrent ovarian cancer. Often, the suggestion of ovarian cancer recurrence by rising CA-125 levels is followed by radiological evaluation of patients to localize the disease, primarily by contrast enhanced computed tomography (CT). Although useful in many cases, CT has limitations in the accurate detection of intra-abdominal tumor recurrence due to difficulties in reliably identifying small tumor deposits and in separating bowel structures from adjacent tumor tissue. The anatomic localization of ovarian cancer recurrence is important for subsequent treatment planning and follow-up. Several studies however, demonstrated the effectiveness of FDG-PET in detecting recurrent ovarian cancer and have shown that it provides additional information over contrast enhanced CT. An important limitation of FDG-PET imaging of the abdomen is precise localization of tumor recurrence due to the lack of reliable anatomical landmarks and the limited spatial resolution of PET. Furthermore, variable physiologic FDG uptake in bowel and muscle tissue as well as the renal excretion of the radiotracer can confound image interpretation. Combined positron emission tomography and computed tomography (PET/CT) is a new imaging technology which merges the metabolic information from FDG-PET with the anatomical information from CT. There is limited information available so far describing the role of FDG-PET/CT in ovarian cancer patients.

Many studies have addressed the use of surveillance PET to detect recurrent or persistent ovarian cancer in the absence of
clinical suspicion. The pooled sensitivity of PET is 0.54 (95% CI 0.39–0.69) and pooled specificity is 0.73 (95% CI 0.56–0.87). In a prospective study, Rose et al. required a negative abdominal and pelvic CT and normal CA-125 prior to entry and performed a second look laparotomy with biopsies on all patients following the PET scan. The authors reported that PET has a relatively low sensitivity (0.18) and specificity (0.45) and concluded that PET is not sensitive for detection of small volume disease. Three studies have addressed the use of PET to detect recurrent ovarian cancer in the setting of a rising CA125 and negative or equivocal conventional imaging studies. The pooled sensitivity of PET is 0.96 (95% CI 0.88–0.99) and pooled specificity 0.80 (95% CI 0.44–0.97). Two studies were limited by lack of specified minimum clinical follow-up to confirm PET results. Six studies addressed the use of PET to detect recurrent ovarian cancer when clinical suspicion exists; Pooled PET sensitivity is 0.90 (95% CI 0.82–0.95) and specificity 0.86 (95% CI 0.67–0.96). All authors concluded that PET may be useful in the detection of recurrent ovarian cancer.

In a systematic review and meta-analysis with 34 included studies, CA 125 had the highest pooled specificity, 0.93 (95% CI: 0.89–0.95); PET–CT had highest pooled sensitivity, 0.91(95% CI: 0.88–0.94). The AUC of CA 125, PET alone, PET–CT, CT and MRI were 0.9219, 0.9297, 0.9555, 0.8845 and 0.7955, respectively.

PET does not appear to be useful in the routine surveillance of patients with a history of ovarian cancer, nor is it likely to improve the sensitivity of conventional modalities to detect microscopic intra-peritoneal disease. There is fair evidence to support the use of PET for the detection of recurrent ovarian cancer when the CA-125 is elevated and conventional imaging is negative or equivocal, although whether this results in improved patient outcomes is unclear. Future studies are
needed to address the impact of FDG-PET/CT on clinical patient management Vs. the cost effectiveness of such an approach.

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**Selected Abstract**


**Abstract:** To assess the diagnostic performance of Positron Emission Tomography using fluorodeoxyglucose (FDG-PET) in comparison to conventional imaging modalities in the assessment of patients with cervical and ovarian cancer. Studies published between 1966 and 2003 were identified using an OVID search of the MEDLINE database. Inclusion criteria were use of a dedicated scanner, resolution specified, ≥12 human subjects, clinical follow-up ≥6 months or histopathology as reference standard, and sufficient data provided to construct a two-by-two table. Two reviewers independently abstracted data regarding sensitivity and specificity of PET. 25 studies (15 cervical cancer, 10 ovarian
cancer) met inclusion criteria for full text review. For cervical cancer, pooled sensitivity and specificity of PET for aortic node metastasis are 0.84 (95% CI 0.68–0.94) and 0.95 (0.89–0.98). Pooled sensitivity and specificity for detection of pelvic node metastasis are: PET, 0.79 (0.65–0.90) and 0.99 (0.96–0.99); MRI, 0.72 (0.53–0.87) and 0.96 (0.92–0.98). Pooled sensitivity for CT is 0.47 (0.21–0.73) (pooled specificity not available). Pooled sensitivity and specificity for PET for recurrent cervical cancer with clinical suspicion are 0.96 (0.87–0.99) and 0.81 (0.58–0.94). For ovarian cancer, pooled sensitivity and specificity to detect recurrence with clinical suspicion are: PET, 0.90 (0.82–0.95) and 0.86 (0.67–0.96); conventional imaging, 0.68 (0.49–0.83) and 0.58 (0.33–0.80); CA-125, 0.81 (0.62–0.92) and 0.83 (0.58–0.96). When conventional imaging and CA-125 are negative, pooled sensitivity and specificity of PET are 0.54 (0.39–0.69) and 0.73 (0.56–0.87), respectively. When CA-125 is rising and conventional imaging is negative, the pooled sensitivity and specificity of PET are 0.96 (0.88–0.99) and 0.80 (0.44–0.97).

Conclusions. There is good evidence that PET is useful for the pre-treatment detection of retroperitoneal nodal metastasis in cervical cancer. There is fair evidence that PET is useful for the detection of recurrent cervical cancer. PET is less useful for the detection of microscopic residual ovarian cancer but has fair sensitivity to detect recurrence in the setting of a rising CA-125 and negative conventional imaging studies. Available studies are limited by low numbers of patients and wide confidence intervals.

Melissa M. Thrall, Julie A. DeLoia, Holly Gallion, Norbert Avril et al.

Clinical use of combined positron emission tomography and computed tomography (FDG-PET/CT) in recurrent ovarian cancer Gynecologic Oncology 105 (2007) 17–22

Abstract: Objective. The aim of this study was to evaluate the use of co-registered PET/CT using F-18 fluorodeoxyglucose
(FDG) for surveillance and follow-up of ovarian cancer patients to detect recurrent disease. Material and methods. A retrospective chart review was performed on 39 ovarian cancer patients who underwent a total of 59 FDG-PET/CT scans. The following information was obtained: clinical indication for FDG-PET/CT, the results of FDG-PET/CT particularly with regard to the additional diagnostic information, the localization of disease and subsequent clinical patient management.

Results. Twenty-four FDG-PET/CT were performed in 22 patients with previously negative or indeterminate CT scans but rising CA-125 levels providing a sensitivity of 90% for localizing disease. Nine FDG-PET/CT in 8 patients with clinical symptoms of recurrence but normal CA-125 levels detected all three patients who had recurrent disease confirmed within 6 months of follow-up. In addition, 4 FDG-PET/CT performed as routine follow-up with no clinical evidence of recurrent disease were true-negative in all cases. Fourteen FDG-PET/CT in 12 patients with recurrent disease already identified by conventional CT imaging were useful in guiding treatment decisions such as radiation therapy, surgery or chemotherapy by confirming the recurrence and more precisely localizing the site(s) of disease. Of note, FDG-PET/CT helped to avoid surgery in four patients who had additional disease detected in unresectable anatomic areas. A total of 51 FDG-PET/CT were performed in the patients described above with an overall sensitivity and specificity of 94.5% and 100%, respectively. Eight FDG-PET/CT scans in five patients performed for assessment of treatment response following chemotherapy or radiation were useful as the disease was not clearly visualized by conventional CT imaging at baseline.

Conclusions. In our experience, FDG-PET/CT has the greatest utility in settings of suspected ovarian cancer recurrence, particularly in patients with rising CA-125 levels and negative conventional imaging. FDG-PET/CT was specifically helpful in optimizing the selection of patients for site-specific
treatment, including radiation treatment planning, and aided in the selection of optimal surgical candidates. The co-registered metabolic–anatomic information from combined FDG-PET/CT holds promise in replacing the single imaging procedures.


Abstract Background and purpose: Ovarian cancer is the commonest tumor in female patients with a propensity for recurrence even after primary chemotherapy in early stage. The accuracy of CA 125, PET alone, PET–CT, CT and MRI in diagnosing the recurrent ovarian carcinoma has never been systematically assessed, and present systematic review was aimed at this issue. Methods: We searched for articles published from January 1995 to November 2007, inclusion criteria including: articles were reported in English or Chinese; CA 125, PET whether interpreted with or without the use of CT, CT or MRI was used to detect recurrent ovarian carcinoma; Histopathologic analysis and/or close clinical and imaging follow-up for at least 6 months. We extracted data to calculate sensitivity, specificity, SROC curves and AUC and to test for heterogeneity. Result: In 34 included studies, CA 125 had the highest pooled specificity, 0.93 (95% CI: 0.89–0.95); PET–CT had highest pooled sensitivity, 0.91 (95% CI: 0.88–0.94). The AUC of CA 125, PET alone, PET–CT, CT and MRI were 0.9219, 0.9297, 0.9555, 0.8845 and 0.7955, respectively. Results of pairwise comparison between each modality demonstrated AUC of PET, whether interpreted with or without the use of CT, was higher than that of CT or MR, p < 0.05. The pooled sensitivity, pooled specificity and AUC showed no statistical significance between PET alone and
PET–CT. There was heterogeneity among studies and evidence of publication bias. \textit{Conclusion:} PET–CT might be a useful supplement to current surveillance techniques, particularly for those patients with an increasing CA 125 level and negative CT or MR imaging. However, regarding to diagnostic accuracy, interpreted CT images may have limited additional value on PET in detecting recurrent ovarian cancer.
Section — VI

Bone and Soft Tissue Malignancies
Osteogenic Sarcoma

Introduction
Any primary bone-forming tumor is termed an osteogenic sarcoma (OGS) and this category technically includes fibrosarcoma, chondrosarcoma and osteosarcoma. For purposes of this review, only osteosarcomas are discussed. They are the third most common type of tumour in adolescents. They can be divided in multiple ways based on location in bone, degree of cellular differentiation, histologic composition, number of foci and underlying bone disease (such as Paget’s disease). Traditionally, conventional, gnathic, telangiectatic, small cell, intraosseous low grade, intracortical, surface (high grade, periosteal, parosteal) and multicentric are terms used to describe them.

Conventional staging
Traditionally, OGS is diagnosed on the basis of its location and plain radiographic appearance. Occasionally, it maybe diagnosed when it presents with early clinical symptoms based on another imaging test such as MRI or bone scintigraphy when the lesion is radiographically occult.

MRI is the modality of choice for assessing the extent of disease and the tumour is usually characterized based on a
surgical biopsy and histologic analysis.\textsuperscript{1} Skip metastases are rare (3\%) but the entire bone segment must be imaged. MRI has a high NPV of 96\% but due to the rarity of such lesions, a low PPV of only 14\%.\textsuperscript{2}

Bone scintigraphy and FDG PET-CT are felt to be more sensitive than anatomic imaging modalities in detecting distant especially osseous and unsuspected metastases while chest CT is the preferred modality for detecting pulmonary metastases.

Response to therapy, restaging and detection of recurrences is usually performed using the same imaging tools in the manner outlined above.

**Summary of evidence**

**Initial Diagnosis**

Plain radiographs and MRI form the mainstay of initial diagnosis of OGS.\textsuperscript{3} At this time, there is no role for PET-CT in initial diagnosis of OGS. Consideration could be made in the case of sarcomatous degeneration of Paget’s disease as FDG PET has been shown to have variable uptake in Paget’s disease and there are case reports of altered FDG uptake with metastases in patients with Paget’s disease.\textsuperscript{4, 5}

**Staging**

At this time, the superior anatomic detail provided by MRI makes it a preferred modality for assessing extent of disease and there is no literature favouring FDG-PET in this regard for now.\textsuperscript{6} FDG PET shows promise in assessing the grade of tumor based on its metabolic uptake and subsequent prognostic information.\textsuperscript{7-9} There is also role for PET-CT in directing biopsy of metabolically active lesions especially in large and heterogeneous lesions with necrotic tissue.\textsuperscript{10} In case of assessing osseous metastases, bone scintigraphy is still felt to be superior to FDG PET in identifying these for OGS.\textsuperscript{11} No
information is available regarding the efficacy of F-18 imaging over conventional bone scintigraphy. Chest CT continues to remain the investigation of choice while assessing pulmonary metastases however PET-CT is better than PET alone and when lung lesions less than 0.5 cm and lymph nodes greater than 1 cm are excluded, PET-CT maybe superior to CT alone.  

**Response Evaluation and Restaging**

FDG PET shows promise in initial grading of OGS based on increased initial uptake. Additionally, there is also promise regarding the role of FDG PET in assessing response to neoadjuvant chemotherapy with decrease in FDG uptake correlating with histologic necrosis. In a study by Sato et al, they showed that a higher post therapy SUV correlated with the expression of metastasis related glycolytic enzyme while pre therapy values did not, suggesting FDG PET may provide valuable information for the metastatic potential of tumours following treatment.  

FDG PET CT has been shown to be an accurate tool in detecting local disease and distant metastases as mentioned above in the staging section however bone scintigraphy is still felt to be better for osseous metastases and chest CT more sensitive for pulmonary metastases. The role of F-18 PET CT has not yet been fully assessed but there is some interest in the possibility that with tumour necrosis there is deactivation of the MYC gene which results in decreasing FDG uptake and increasing F-18 uptake.

**Suspected recurrence**

In a small study evaluating recurrence a variety of paediatric sarcomas, PET CT was found to be most effective in diagnosing local recurrence. Its role in assessing more distal metastases needs further investigation and it maybe used in combination with other conventional imaging tests.
Timing of the PET/CT | Hierarchy of Diagnostic Efficacy | Relevance of Test | Level of Evidence
---|---|---|---
Diagnosis | Level 1 | Probably inappropriate | 1 level 1 study
 Staging | Level 2 | Probably appropriate | 3 level 1 studies
 Response evaluation | Level 2 | Probably appropriate | 3 level 1 studies
 Restaging | Level 2 | Probably appropriate | 3 level 1 studies
 Suspected recurrence | Level 2 | Probably appropriate | 1 level 1 study
 Followup | Level 1 | NA | NA
 RT planning | Level 1 | NA | NA

**Summary**
The role of FDG PET in OGS is still to be defined. There may be some role for FDG PET in increasing biopsy yield by directing biopsy to the most metabolically active portion of the lesion. There is considerable potential in using FDG PET to prognosticate disease based on its initial SUV and assess its metastatic potential of OGS following neoadjuvant chemotherapy and using it as a non invasive tool in the assessment of response to therapy.

**Selected References**
Radiologic staging of primary bone sarcoma: MR imaging, scintigraphy, angiography, and CT correlated with pathologic examination. Bloem JL, Taminiau AH,

The relative value of magnetic resonance (MR) imaging, computed tomography (CT), technetium-99m bone scintigraphy, and angiography in local tumor staging was prospectively evaluated in 56 patients with primary bone sarcoma. The results of imaging were correlated with findings at surgery and at dissection of the resected specimens. MR imaging was significantly superior to CT and scintigraphy in defining intraosseous tumor length and was as accurate as CT in demonstrating cortical bone and joint involvement. It was definitely superior to CT in demonstrating involvement of muscle compartments. MR imaging was also the best modality in exhibiting the relationship between tumor and major neurovascular bundles; however, these differences were not significant. It is concluded that MR imaging is the modality of choice for local staging of primary bone sarcoma.


PURPOSE: To assess the relative accuracies of computed tomography (CT) and magnetic resonance (MR) imaging in the local staging of primary malignant bone and soft-tissue tumors. MATERIALS AND METHODS: At four institutions, 367 eligible patients (aged 6-89 years) with malignant bone or soft-tissue neoplasms in selected anatomic sites were enrolled. Patients underwent both CT and MR imaging within 4 weeks before surgery. In each patient, CT scans were interpreted independently by two radiologists and MR images by two other radiologists at the enrolling institution. The CT and MR images were then interpreted together by two of those
radiologists and subsequently reread at the other institutions. Imaging and histopathologic findings were compared and were supplemented when needed with surgical findings. Receiver operating characteristic curve analysis and descriptive statistical analysis were performed. RESULTS: Cases were analyzable in 316 patients: 183 had primary bone tumors; 133 had primary soft-tissue tumors. There was no statistically significant difference between CT and MR imaging in determining tumor involvement of muscle, bone, joints, or neurovascular structures. The combined interpretation of CT and MR images did not statistically significantly improve accuracy. Interreader variability was similar for both modalities. CONCLUSION: CT and MR imaging are equally accurate in the local staging of malignant bone and soft-tissue neoplasms in the specific anatomic sites studied.


Bone and soft tissue tumours are rare neoplasms. There are five major roles of imaging in the management of primary musculoskeletal tumours, that is, to differentiate between benignity and malignancy, to evaluate for local tumour extension, to screen for metastases, to judge the effect of chemotherapy, and to monitor for recurrence. To accomplish this, multiple modalities are required because no single examination is able to complete all these tasks. These modalities include plain radiography, CT, MRI, conventional nuclear medicine as well as positron emission tomography (PET) imaging. Elsewhere, PET imaging has been discussed at length, because it is likely to be superior in the assessment of bone and soft tissue tumours over conventional nuclear medicine procedures. However, conventional nuclear medicine may be of value when PET is unavailable. In this review, an
overview of anatomical imaging will be given and the role of non-PET functional imaging will be discussed in detail. A variety of illustrative cases will be presented.


The authors imaged a lung cancer patient with an enlarging solitary pulmonary nodule and incidentally found intense activity in the right proximal humerus consistent with known Paget disease confirmed via plain film and computed tomography (CT) without change in the CT appearance or symptoms during the next 7 months. The alkaline phosphatase and alanine amino transferase (ALT) levels were in the normal ranges. Their findings of high uptake with normal alkaline phosphatase and ALT are contradictory to previous reports. The authors present a case of Paget disease that appeared “hot” on positron emission tomography initially thought to be a malignant transformation that typically demonstrated high uptake.


Paget’s disease of bone is common in the elderly and is associated with increased osteoblastic and osteoclastic activity at affected sites in the skeleton. It is not known whether this high metabolic activity is associated with increased glycolysis and, hence, uptake of [18F]FDG. The appearances of Paget’s disease with [18F]FDG PET have not been described and it is not known whether Paget’s may cause false-positive studies in those undergoing oncological staging or whether [18F]FDG PET can reliably differentiate benign pagetic change from osteosarcoma that may complicate Paget’s disease. We reviewed [18F]FDG PET scans in patients with uncomplicated
Paget’s disease and documented its appearances. METHODS: Eighteen patients with established Paget’s disease and typical radiological features had 99mTc-MDP bone scans and [18F]FDG PET scans performed. Serum alkaline phosphatase (ALP) was also measured. RESULTS: All patients showed high uptake of MDP in affected bones. Of the 18 patients only six showed any uptake of [18F]FDG. This occurred in some but not all bones shown to be involved on MDP bone scans. Three patients demonstrated low-grade uptake and three showed marked accumulation of [18F]FDG. The [18F]FDG-positive group had higher serum ALP levels than the [18F]FDG-negative patients (p < 0.05). CONCLUSION: Paget’s disease of bone is not associated with abnormal [18F]FDG uptake in the majority of patients and, therefore, there is potential for discriminating between benign Paget’s disease and associated Paget’s sarcoma. However, low-grade uptake may be seen in patients with more active disease as measured by ALP. Rarely, marked uptake of [18F]FDG may be seen and Paget’s disease should be included as a possible cause of false-positive scans in elderly patients who are being assessed for metastatic disease.


This review focuses on imaging of osteosarcoma and Ewing’s sarcoma of the long bones in children during preoperative neoadjuvant chemotherapy. Morphological criteria on plain films and conventional static MRI are insufficiently correlated with histological response. We review the contribution of dynamic MRI, diffusion-weighted MR and nuclear medicine ([18FDG-PET) to monitor tumoural necrosis. MRI is currently the best method to evaluate local extension prior to tumour
resection, especially to assess the feasibility of conservative surgery. Quantitative models in dynamic MRI and 18FDG-PET are currently being developed in order to find new early prognostic criteria, but for the time being, treatment protocols are still based on the gold standard of histological response.


The purpose of this study was to determine the relationship between sarcoma tumor grade and the quantitative tumor metabolism value for [F-18]fluorodeoxyglucose (FDG) determined by positron emission tomography (PET) imaging. Seventy patients with bone or soft-tissue sarcomas underwent PET scanning with quantitative determination of tumor FDG metabolic rate (MRFDG) before treatment. MRFDG (micromol/g/min) for each tumor was compared with National Cancer Institute tumor grade, S-phase percentage, and percentage of aneuploidy of the tumor population. The pretreatment quantitative determination of tumor MRFDG by PET correlates strongly with tumor grade but not with the other selected histopathological tumor correlates. In addition, overlap of MRFDG PET values with tumor grade suggests that PET, an objective tumor measurement, may provide an alternative means of assessing tumor biological potential or may have the potential to overcome some of the limitations of traditional pathological evaluation. FDG PET can uniquely provide a metabolic profile of a diverse group of sarcomas noninvasively and provide clinically relevant tumor biological information.

Prognostic significance of (18)F-FDG and (99m) Tc-methylene diphosphonate uptake in primary osteo-sarcoma. Franzius C, Bielack S, Flege S, Sciuk J,

The purpose of this retrospective analysis was to evaluate the prognostic significance of both initial glucose metabolism as measured by (18)F-FDG PET and osteoblastic activity as measured by (99m)Tc-methylene diphosphonate (MDP) bone scintigraphy in osteosarcoma. METHODS: In 29 patients (18 male, 11 female; age range, 5-41 y) with primary osteosarcoma, (18)F-FDG uptake and (99m)Tc-MDP uptake were measured semiquantitatively (average and maximum tumor-to-nontumor ratios [T/NT(av) and T/NT(max), respectively]) using PET and bone scintigraphy at the time of diagnosis. After chemotherapy, the patients underwent surgery for their primary tumor, and the response was determined histologically. Cumulative overall survival and event-free survival were determined by clinical and imaging follow-up of 7-72 mo (median, 28 mo). RESULTS: Clinical and imaging follow-up revealed that the disease relapsed or failed to achieve complete remission in 9 patients and that 6 patients died of the disease. Both overall and event-free survival were significantly better in patients with a low (18)F-FDG T/NT(max) (less than the median) than in patients with a high (18)F-FDG T/NT(max) (at least the median). The negative relationship of (18)F-FDG T/NT(av), (99m)Tc-MDP T/NT(max), and (99m)Tc-MDP T/NT(av) with overall and event-free survival did not reach a level of significance. (18)F-FDG uptake values correlated moderately and positively with (99m)Tc-MDP uptake values, but a level of significance was reached only between (18)F-FDG T/NT(max) and (99m)Tc-MDP T/NT(av). CONCLUSION: The initial glucose metabolism of primary osteosarcoma as measured by (18)F-FDG PET using T/NT(max) provides prognostic information. High (18)F-FDG uptake correlates with poor outcome. Thus, (18)F-FDG uptake may be complementary to other well-known factors in judging the prognosis in osteosarcoma.

Clinical diagnosis of skeletal tumors can be difficult, because such lesions compose a large, heterogeneous group of entities with different biologic behaviors. The aim of this prospective study was to assess the value of PET in grading tumors and tumorlike lesions of bone. METHODS: Two hundred two patients with suspected primary bone tumors were investigated using FDG PET. Uptake of FDG was evaluated semiquantitatively by determining the tumor-to-background ratio (T/B). All patients underwent biopsy, resulting in the histologic detection of 70 high-grade sarcomas, 21 low-grade sarcomas, 40 benign tumors, 47 tumorlike lesions, 6 osseous lymphomas, 6 plasmacytomas, and 12 metastases of an unknown primary tumor. RESULTS: All lesions, with the exception of 3 benign tumors, were detected by increased FDG uptake. Although sarcomas showed significantly higher T/Bs than did latent or active benign lesions (P < 0.001), aggressive benign lesions could not be distinguished from sarcomas. Using a T/B cutoff level for malignancy of 3.0, the sensitivity of FDG PET was 93.0%, the specificity was 66.7%, and the accuracy was 81.7%. CONCLUSION: FDG PET provides a promising tool for estimating the biologic activity of skeletal lesions, implicating consequences for the choice of surgical strategy.


Positron emission tomography (PET)-computed tomography (CT) is a useful device in identifying musculoskeletal lesions that require biopsy. It can be used to localize the primary lesion, identify a site to biopsy, and evaluate metastatic lesions that
require follow-up biopsies. Not all malignant tumors have hypermetabolic activity, and there are many benign lesions and physiologic processes that do have increased F-18 fluorodeoxyglucose uptake. Knowledge of these issues is important when reviewing PET-CT and directing subsequent musculoskeletal biopsies.


The purpose of this study was to compare positron emission tomography using fluorine-18 fluorodeoxyglucose (FDG-PET) and technetium-99m methylene diphosphonate (MDP) bone scintigraphy in the detection of osseous metastases from malignant primary osseous tumours. In 70 patients with histologically proven malignant primary bone tumours (32 osteosarcomas, 38 Ewing’s sarcomas), 118 FDG-PET examinations were evaluated. FDG-PET scans were analysed with regard to osseous metastases in comparison with bone scintigraphy. The reference methods for both imaging modalities were histopathological analysis, morphological imaging [additional conventional radiography, computed tomography (CT) or magnetic resonance imaging (MRI)] and/or clinical follow-up over 6-64 months (median 20 months). In 21 examinations (18%) reference methods revealed 54 osseous metastases (49 from Ewing’s sarcomas, five from osteosarcomas). FDG-PET had a sensitivity of 0.90, a specificity of 0.96 and an accuracy of 0.95 on an examination-based analysis. Comparable values for bone scintigraphy were 0.71, 0.92 and 0.88. On a lesion-based analysis the sensitivity of FDG-PET and bone scintigraphy was 0.80 and 0.72, respectively. Analysing only Ewing’s sarcoma patients, the sensitivity, specificity and accuracy of FDG-PET and bone scan were 1.00, 0.96 and 0.97 and 0.68, 0.87 and 0.82,
respectively (examination-based analysis). None of the five osseous metastases from osteosarcoma were detected by FDG-PET, but all of them were true-positive using bone scintigraphy. In conclusion, the sensitivity, specificity and accuracy of FDG-PET in the detection of osseous metastases from Ewing’s sarcomas are superior to those of bone scintigraphy. However, in the detection of osseous metastases from osteosarcoma, FDG-PET seems to be less sensitive than bone scintigraphy.


OBJECTIVE: The objective of this retrospective study was to compare the diagnostic value of 2-[(18)F]fluoro-2-deoxy-D-glucose positron emission tomography ((18)F-FDG PET)/CT versus (18)F-FDG PET and CT alone for staging and restaging of pediatric solid tumors. METHODS: Forty-three children and adolescents (19 females and 24 males; mean age, 15.2 years; age range, 6-20 years) with osteosarcoma (n = 1), squamous cell carcinoma (n = 1), synovial sarcoma (n = 2), germ cell tumor (n = 2), neuroblastoma (n = 2), desmoid tumor (n = 2), melanoma (n = 3), rhabdomyosarcoma (n = 5), Hodgkin’s lymphoma (n = 7), non-Hodgkin-lymphoma (n = 9), and Ewing’s sarcoma (n = 9) who had undergone (18)F-FDG PET/CT imaging for primary staging or follow-up of metastases were included in this study. The presence, location, and size of primary tumors was determined separately for PET/CT, PET, and CT by two experienced reviewers. The diagnosis of the primary tumor was confirmed by histopathology. The presence or absence of metastases was confirmed by histopathology (n = 62) or clinical and imaging follow-up (n = 238). RESULTS: The sensitivities for the detection of solid primary tumors using integrated (18)F-FDG PET/CT (95%), (18)F-FDG PET alone (73%), and CT alone (93%)
were not significantly different (p > 0.05). Seventeen patients showed a total of 153 distant metastases. Integrated PET/CT had a significantly higher sensitivity for the detection of these metastases (91%) than PET alone (37%; p < 0.05), but not CT alone (83%; p > 0.05). When lesions with a diameter of less than 0.5 cm were excluded, PET/CT (89%) showed a significantly higher specificity compared to PET (45%; p < 0.05) and CT (55%; p < 0.05). In a sub-analysis of pulmonary metastases, the values for sensitivity and specificity were 90%, 14%, 82% and 63%, 78%, 65%, respectively, for integrated PET/CT, stand-alone PET, and stand-alone CT. For the detection of regional lymph node metastases, (18)F-FDG PET/CT, (18)F-FDG PET alone, and CT alone were diagnostically correct in 83%, 61%, and 42%. A sub-analysis focusing on the ability of PET/CT, PET, and CT to detect osseous metastases showed no statistically significant difference between the three imaging modalities (p > 0.05).

CONCLUSION: Our study showed a significantly increased sensitivity of PET/CT over that of PET for the detection of distant metastases but not over that of CT alone. However, the specificity of PET/CT for the characterization of pulmonary metastases with a diameter > 0.5 cm and lymph node metastases with a diameter of <1 cm was significantly increased over that of CT alone.


BACKGROUND: Response to neoadjuvant chemotherapy is a significant prognostic factor for osteosarcoma (OS) and the Ewing sarcoma family of tumors (ESFT). Conventional radiographic imaging does not discriminate between responding and nonresponding osseous tumors. [F-18]-fluorodeoxy-D-glucose (FDG) positron emission tomography
(PET) is a noninvasive imaging modality that accurately predicts histopathologic response in patients with various malignancies. To describe the FDG PET imaging characteristics and to determine the correlation between FDG PET imaging and chemotherapy response in children with bone sarcomas, we reviewed our single institution experience.

METHODS: Thirty-three pediatric patients with OS or ESFT with osseous primary sites were evaluated by FDG PET. All patients received standard neoadjuvant chemotherapy. FDG PET standard uptake values before (SUV1) and after (SUV2) chemotherapy were analyzed and correlated with chemotherapy response assessed by histopathology in surgically excised tumors. Twenty-six patients had SUV1, SUV2, and surgical excision. RESULTS: Although the mean SUV1 in children with OS or ESFT were similar (8.2 vs. 5.3, P = 0.13), mean SUV2 for OS patients was greater than the values for ESFT patients (3.3 vs. 1.5, P = 0.01). All ESFT patients and 28% of OS patients had a favorable histologic response to chemotherapy (> or= 90% necrosis). Combining ESFT and OS patients, both SUV2 and the ratio of SUV2 to SUV1 (SUV2:SUV1) were correlated with histologic response (P = 0.01 for both comparisons). CONCLUSION: FDG PET evaluation of pediatric bone sarcomas demonstrated significant alteration in response to neoadjuvant chemotherapy. SUV2 and SUV2:SUV1 correlated with histopathologic assessment of response and potentially could be used as a noninvasive surrogate to predict response in patients.

surgical removal of the tumor, particularly if a limb salvage procedure is intended. In addition, response to neoadjuvant chemotherapy is considered as an important prognostic indicator. The aim of this prospective study was to assess the usefulness of 2-(18F) fluoro-2-deoxy-D-glucose (FDG) PET in the noninvasive evaluation of neoadjuvant chemotherapy response in osteosarcoma.

METHODS: In 27 patients with osteosarcoma, we determined tumor-to-background ratios (TBRs) of FDG uptake with PET, before and after neoadjuvant chemotherapy according to COSS 86c or COSS 96 protocols, respectively. We compared changes in glucose metabolism of osteosarcomas with the histologic grade of regression in the resected specimen, according to Salzer-Kuntschik, discriminating responders (grades I-III; n = 17) and nonresponders (grades IV-VI; n = 10).

RESULTS: The decrease of FDG uptake in osteosarcomas expressed as a ratio of posttherapeutic and pretherapeutic TBRs showed a close correlation to the amount of tumor necrosis induced by polychemotherapy (P < 0.001; Spearman). With a TBR ratio cutoff level of 0.6, all responders and 8 of 10 nonresponders could be identified by PET. In addition, lung metastases of osteosarcoma were detected with FDG PET in 4 patients.

CONCLUSION: FDG PET provides a promising tool for noninvasive evaluation of neoadjuvant chemotherapy response in osteosarcoma. This could imply consequences for the choice of surgical strategy, because a limb salvage procedure cannot be recommended in patients nonresponsive to preoperative chemotherapy unless wide surgical margins can safely be achieved.


Objective: Positron emission tomography (PET) using fluorine-18-fluoro-2-D-deoxyglucose (FDG) is increasingly
being used to evaluate and manage oncology patients. Several reports have documented its utility in diagnosis, staging, response to treatment, and tumor viability assessment. There is, however, a paucity of literature on PET scanning in patients with osteosarcoma. We report results of serial F-18 FDG-PET scans in 16 untreated patients with osteosarcoma who underwent chemotherapy prior to surgical resection of the primary tumor site.

Procedure: Changes in tumor fluoro-2-D-deoxyglucose (FDG) uptake were correlated with percent tumor necrosis on histopathology. PET studies were analyzed by visual assessment of tumor uptake of FDG by 3 independent observers, calculating a tumor to normal background activity ratio (TBR) by drawing regions of interest (ROIs) around the tumor and background activity in the contralateral normal limb, and percent change in TBR values between baseline and presurgical study.

Results: All patients had positive baseline scans. Baseline TBRs ranged between 2.5-8.7 and visual assessment of intensity of FDG uptake was 2-3 on a scale of 0-3. At histopathologic examination, 8 patients were classified as good responses with more than 90% tumor necrosis and 8 patients as poor responses with less than 90% necrosis. Tumor necrosis was accurately predicted on PET scan in 15/16 patients by visual assessment, 14/15 patients by final TBR value on presurgery scans, and 7/15 patients using percent change of TBR on serial scans.

Conclusions: The results of this small series suggest that FDG-PET scanning is fairly accurate in evaluating the response of osteosarcoma to chemotherapy. Visual assessment and TBR are more accurate in predicting tumor necrosis than percent change in TBR on serial scans.

(18)F and (18)FDG PET imaging of osteosarcoma to non-invasively monitor in situ changes in cellular proliferation and bone differentiation upon MYC inactivation. Arvanitis
Osteosarcoma is one of the most common pediatric cancers. Accurate imaging of osteosarcoma is important for proper clinical staging of the disease and monitoring of the tumor’s response to therapy. The MYC oncogene has been commonly implicated in the pathogenesis of human osteosarcoma. Previously, we have described a conditional transgenic mouse model of MYC-induced osteosarcoma. These tumors are highly invasive and are frequently associated with pulmonary metastases. In our model, upon MYC inactivation osteosarcomas lose their neoplastic properties, undergo proliferative arrest, and differentiate into mature bone. We reasoned that we could use our model system to develop non-invasive imaging modalities to interrogate the consequences of MYC inactivation on tumor cell biology in situ. We performed positron emission tomography (PET) combining the use of both (18)F-fluorodeoxyglucose ((18)FDG) and (18)F-flouride ((18)F) to detect metabolic activity and bone mineralization/remodeling. We found that upon MYC inactivation, tumors exhibited a slight reduction in uptake of (18)FDG and a significant increase in the uptake of (18)F along with associated histological changes. Thus, these cells have apparently lost their neoplastic properties based upon both examination of their histology and biologic activity. However, these tumors continue to accumulate (18)FDG at levels significantly elevated compared to normal bone. Therefore, PET can be used to distinguish normal bone cells from tumors that have undergone differentiation upon oncogene inactivation. In addition, we found that (18)F is a highly sensitive tracer for detection of pulmonary metastasis. Collectively, we conclude that combined modality PET/CT imaging incorporating both (18)FDG and (18)F is a highly sensitive means to non-invasively measure osteosarcoma growth and the therapeutic response, as well as to detect tumor cells that have undergone differentiation upon oncogene inactivation.

BACKGROUND: Combined positron emission tomography with (18)fluoro-deoxyglucose and computed tomography (FDG-PET/CT) has been used in the diagnosis and staging of various malignancies, but their use in the management of pediatric sarcomas is less well defined. The potential role of FDG-PET/CT in the diagnosis of local recurrence and distant metastases of pediatric sarcomas was investigated.

PROCEDURE: Nineteen children (aged 2-21) with sarcoma (9 Ewing sarcoma, 3 osteogenic sarcoma, 7 rhabdomyosarcoma) were evaluated between January 2000 and December 2005 by FDG-PET/CT for suspected local relapse or distant metastases. The results of 21 FDG-PET studies, 16 CT scans, 9 magnetic resonance imaging (MRI) studies, and 7 bone scans (BSs) were compared with surgical pathology or clinical follow-up for at least 3 months.

RESULTS: FDG-PET detected local relapse in all seven patients and distant metastases in 10/13 (77%). FDG-PET/CT and CT/MRI/BS results were discordant in eight patients. FDG-PET/CT was the only modality that detected distant metastases in two patients. PET/CT was true negative and excluded disease in three patients with abnormal CT/BSs and was false negative in three patients with distant metastases.

CONCLUSION: FDG-PET/CT may be useful and complementary to other imaging modalities for the detection of recurrent pediatric sarcomas, especially at the primary site. Its potential advantages and limitations compared with conventional imaging modalities need to be further investigated in larger homogenous patient groups.
Ewing’s Sarcoma and Primitive Neuroectodermal Tumours (PNET)

Introduction
At present, histologically Ewing’s sarcoma is felt to be a type of extremely malignant primitive neuroectodermal tumour (PNET). Collectively, Ewing’s sarcoma and PNET are known as the Ewing’s family of tumours. Genetically, 90% are associated with t(11, 22) translocations. They typically affect patients between 10 and 20 years of age with a 3:2 male predominance while affecting Caucasians much more than Asians or Blacks. Clinically, they present with constitutional symptoms mimicking infection (fever, local heat, anaemia leukocytosis etc). The tumour occurs most commonly in the meta-diaphyses of the long bones (femur 25% and humerus 8%). When flat bones are involved, the pelvis (20%) and ribs (11%) are most commonly involved. Upto 10% can be multiple at presentation and 30% present with metastases initially (lung 85%, bones 69%, pleura 46% and CNS 12%). Five-year survival for patients with metastases at presentation is 55-70%. Treatment is usually with surgery, chemo and radiation therapy.
Conventional staging

Ewing’s sarcoma is usually diagnosed based on its radiographic appearance. MRI and CT are used to assess the extent of osseous and adjacent soft tissue involvement. Biopsy is the method of choice for grading the tumour. Bone scintigraphy demonstrates increased uptake and is preferred to detect additional osseous metastases. Chest CT and brain MRI are used to assess pulmonary and CNS lesions. MRI has an inconsistent appearance when assessing response to therapy and radiographs are relatively insensitive. Recurrence is currently diagnosed based on differences in the anatomic appearance on radiographs, CT or MRI.

Summary of Evidence

Initial Diagnosis

The characteristic plain radiographic (onion skin periosteal reaction and classic location) and MRI appearance followed by biopsy are the modalities of choice in initial diagnosis. Local extent of disease is also best seen on MRI with some role for CT in assessing osseous involvement.\(^1\) The role of FDG PET in initial diagnosis is non-specific given the variety of conditions, both benign and malignant that can also show considerably increased uptake.

Staging

Extent of the primary tumour is best assessed using MRI due to the excellent anatomic detail it provides.\(^1\) Large necrotic lesions can be troublesome to biopsy as negative results are not rare. FDG PET imaging has been found to be useful in guiding biopsy to the metabolically active portion of the mass.\(^2\) FDG PET has shown promise in grading tumours based on the degree of uptake, with more aggressive lesions demonstrating greater uptake.\(^3\) In the evaluation of adjacent local osseous lesions (multicentric Ewing’s sarcoma) and
distant osseous metastases, FDG PET has been shown to be superior to bone scintigraphy and MRI. 4-6 Chest CT is still the preferred method to identify pulmonary metastases but when lung lesions less than 0.5 cm and mediastinal nodes greater than 1 cm are excluded PET CT tends to be more specific. 6-8 PET CT in addition to the other conventional methods adds significant information that has a relevant impact on therapy planning. 9 PET-CT is found to be superior to PET alone in terms of sensitivity, specificity and accuracy of detecting lesions. 10

Response Evaluation
Response to neoadjuvant chemotherapy is a significant prognostic factor in these tumors and recent work suggests that a decrease in post therapy standardized uptake value (SUV) by greater than 30% correlates well with good response histologically, while bone scintigraphy is less representative.11 Post therapy SUV and the ratio of pre and post therapy SUV correlate well with histologic response and could be used as a non invasive surrogate to predict response. 12

Suspected Recurrence
In a small study evaluating recurrence a variety of paediatric sarcomas, PET CT was found to be most effective in diagnosing local recurrence. Its role in assessing more distal metastases needs further investigation and it maybe used in combination with other conventional imaging tests.13

Summary
The role of FDG PET in Ewing’s sarcoma and PNET is not yet fully defined. There is a role for it in identifying the most metabolically active portion of the tumour in order to increase the yield from biopsy. Some data suggests it is superior to bone scintigraphy and even MRI in detecting additional osseous lesions but corroborative imaging is still needed for
most accurate staging especially for pulmonary lesions. The most encouraging area for PET CT in this group seems to be in non invasively assessing treatment response.

**Selected references**


This review focuses on imaging of osteosarcoma and Ewing’s sarcoma of the long bones in children during preoperative neoadjuvant chemotherapy. Morphological criteria on plain films and conventional static MRI are insufficiently correlated with histological response. We review the contribution of dynamic MRI, diffusion-weighted MR and nuclear medicine (18FDG-PET) to monitor tumoural necrosis. MRI is currently the best method to evaluate local extension prior to tumour resection, especially to assess the feasibility of conservative surgery. Quantitative models in dynamic MRI and 18FDG-PET are currently being developed in order to find new early prognostic criteria, but for the time being, treatment protocols are still based on the gold standard of histological response.


Positron emission tomography (PET)-computed tomography (CT) is a useful device in identifying musculoskeletal lesions that require biopsy. It can be used to localize the primary lesion, identify a site to biopsy, and evaluate metastatic lesions that require follow-up biopsies. Not all malignant tumors have hypermetabolic activity, and there are many benign lesions
and physiologic processes that do have increased F-18 fluorodeoxyglucose uptake. Knowledge of these issues is important when reviewing PET-CT and directing subsequent musculoskeletal biopsies.


Clinical diagnosis of skeletal tumors can be difficult, because such lesions compose a large, heterogeneous group of entities with different biologic behaviors. The aim of this prospective study was to assess the value of PET in grading tumors and tumorlike lesions of bone. METHODS: Two hundred two patients with suspected primary bone tumors were investigated using FDG PET. Uptake of FDG was evaluated semiquantitatively by determining the tumor-to-background ratio (T/B). All patients underwent biopsy, resulting in the histologic detection of 70 high-grade sarcomas, 21 low-grade sarcomas, 40 benign tumors, 47 tumorlike lesions, 6 osseous lymphomas, 6 plasmacytomas, and 12 metastases of an unknown primary tumor. RESULTS: All lesions, with the exception of 3 benign tumors, were detected by increased FDG uptake. Although sarcomas showed significantly higher T/Bs than did latent or active benign lesions (P < 0.001), aggressive benign lesions could not be distinguished from sarcomas. Using a T/B cutoff level for malignancy of 3.0, the sensitivity of FDG PET was 93.0%, the specificity was 66.7%, and the accuracy was 81.7%. CONCLUSION: FDG PET provides a promising tool for estimating the biologic activity of skeletal lesions, implicating consequences for the choice of surgical strategy.

**FDG-PET for detection of osseous metastases from malignant primary bone tumours: comparison with bone scintigraphy.** Franzius C, Sciuk J, Daldrup-Link HE,
The purpose of this study was to compare positron emission tomography using fluorine-18 fluorodeoxyglucose (FDG-PET) and technetium-99m methylene diphosphonate (MDP) bone scintigraphy in the detection of osseous metastases from malignant primary osseous tumours. In 70 patients with histologically proven malignant primary bone tumours (32 osteosarcomas, 38 Ewing’s sarcomas), 118 FDG-PET examinations were evaluated. FDG-PET scans were analysed with regard to osseous metastases in comparison with bone scintigraphy. The reference methods for both imaging modalities were histopathological analysis, morphological imaging [additional conventional radiography, computed tomography (CT) or magnetic resonance imaging (MRI)] and/or clinical follow-up over 6-64 months (median 20 months). In 21 examinations (18%) reference methods revealed 54 osseous metastases (49 from Ewing’s sarcomas, five from osteosarcomas). FDG-PET had a sensitivity of 0.90, a specificity of 0.96 and an accuracy of 0.95 on an examination-based analysis. Comparable values for bone scintigraphy were 0.71, 0.92 and 0.88. On a lesion-based analysis the sensitivity of FDG-PET and bone scintigraphy was 0.80 and 0.72, respectively. Analysing only Ewing’s sarcoma patients, the sensitivity, specificity and accuracy of FDG-PET and bone scan were 1.00, 0.96 and 0.97 and 0.68, 0.87 and 0.82, respectively (examination-based analysis). None of the five osseous metastases from osteosarcoma were detected by FDG-PET, but all of them were true-positive using bone scintigraphy. In conclusion, the sensitivity, specificity and accuracy of FDG-PET in the detection of osseous metastases from Ewing’s sarcomas are superior to those of bone scintigraphy. However, in the detection of osseous metastases from osteosarcoma, FDG-PET seems to be less sensitive than bone scintigraphy.

OBJECTIVE: The purpose of this study was to compare the diagnostic accuracy of whole-body MR imaging, skeletal scintigraphy, and 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET) for the detection of bone metastases in children. SUBJECTS AND METHODS: Thirty-nine children and young adults who were 2—19 years old and who had Ewing’s sarcoma, osteosarcoma, lymphoma, rhabdomyosarcoma, melanoma, and Langerhans’ cell histiocytosis underwent whole-body spin-echo MR imaging, skeletal scintigraphy, and FDG PET for the initial staging of bone marrow metastases. The number and location of bone and bone marrow lesions diagnosed with each imaging modality were correlated with biopsy and clinical follow-up as the standard of reference. RESULTS: Twenty-one patients exhibited 51 bone metastases. Sensitivities for the detection of bone metastases were 90% for FDG PET, 82% for whole-body MR imaging, and 71% for skeletal scintigraphy; these data were significantly different (p < 0.05). False-negative lesions were different for the three imaging modalities, mainly depending on lesion location. Most false-positive lesions were diagnosed using FDG PET. CONCLUSION: Whole-body MR imaging has a higher sensitivity than skeletal scintigraphy for the detection of bone marrow metastases but a lower sensitivity than FDG PET.


AIM: High-grade Ewing sarcomas and Primitive neuroectodermal tumours (PNET) make up the tumours of
the Ewing family. Our purpose was to evaluate the value of [18F]fluorodeoxyglucose positron emission tomography (FDG PET) in patients with Ewing tumours. PATIENTS AND METHODS: Twenty-four patients who had PET because of a suspected Ewing tumour during a 5-year period were included in this retrospective study. The images of 33 whole-body FDG PET investigations performed in primary or secondary diagnostics were analysed visually and semi-quantitatively by using standardized uptake values (SUVs). In 14 cases, PET was compared to bone scintigraphy regarding bone lesions. The final diagnosis was based on histology, imaging and follow-up. RESULTS: Histologically, the primary lesions were 10 Ewing sarcoma, 13 PNET and one osteomyelitis. The sensitivity and specificity of an examination-based analysis (presence of Ewing tumour and/or its metastases) were 96 and 78%, respectively. Altogether, 163 focal lesions were evaluated. Sensitivity and specificity regarding individual lesions were 73 and 78%. This lower sensitivity is mainly due to small lesions. In true-positive cases, the mean SUV was 4.54 +/- 2.79, and the SUVs in two false-positive cases were 4.66 and 1.60. True-positive and false-positive cases could not be differentiated definitively based on SUVs because of overlap and low values in true-positive lesions. In four cases, PET depicted 70 while bone scintigraphy depicted only eight bone metastases. CONCLUSION: An FDG PET investigation is a valuable method in the case of Ewing tumours. PET is superior to bone scintigraphy in the detection of bone metastases of Ewing tumours. For the depiction of small lesions, mainly represented by pulmonary metastases, PET is less sensitive than helical computed tomography. Determination of the role of whole-body FDG PET in diagnostic algorithm needs further investigation.

OBJECTIVE: The objective of this retrospective study was to compare the diagnostic value of 2-[(18)F]fluoro-2-deoxy-D-glucose positron emission tomography ((18)F-FDG PET)/CT versus (18)F-FDG PET and CT alone for staging and restaging of pediatric solid tumors. METHODS: Forty-three children and adolescents (19 females and 24 males; mean age, 15.2 years; age range, 6-20 years) with osteosarcoma (n = 1), squamous cell carcinoma (n = 1), synovial sarcoma (n = 2), germ cell tumor (n = 2), neuroblastoma (n = 2), desmoid tumor (n = 2), melanoma (n = 3), rhabdomyosarcoma (n = 5), Hodgkin’s lymphoma (n = 7), non-Hodgkin-lymphoma (n = 9), and Ewing’s sarcoma (n = 9) who had undergone (18)F-FDG PET/CT imaging for primary staging or follow-up of metastases were included in this study. The presence, location, and size of primary tumors was determined separately for PET/CT, PET, and CT by two experienced reviewers. The diagnosis of the primary tumor was confirmed by histopathology. The presence or absence of metastases was confirmed by histopathology (n = 62) or clinical and imaging follow-up (n = 238). RESULTS: The sensitivities for the detection of solid primary tumors using integrated (18)F-FDG PET/CT (95%), (18)F-FDG PET alone (73%), and CT alone (93%) were not significantly different (p > 0.05). Seventeen patients showed a total of 153 distant metastases. Integrated PET/CT had a significantly higher sensitivity for the detection of these metastases (91%) than PET alone (37%; p < 0.05), but not CT alone (83%; p > 0.05). When lesions with a diameter of less than 0.5 cm were excluded, PET/CT (89%) showed a significantly higher specificity compared to PET (45%; p < 0.05) and CT (55%; p < 0.05). In a sub-analysis of pulmonary metastases, the values for sensitivity and specificity were 90%,
14%, 82% and 63%, 78%, 65%, respectively, for integrated PET/CT, stand-alone PET, and stand-alone CT. For the detection of regional lymph node metastases, (18)F-FDG PET/CT, (18)F-FDG PET alone, and CT alone were diagnostically correct in 83%, 61%, and 42%. A sub-analysis focusing on the ability of PET/CT, PET, and CT to detect osseous metastases showed no statistically significant difference between the three imaging modalities (p > 0.05).

CONCLUSION: Our study showed a significantly increased sensitivity of PET/CT over that of PET for the detection of distant metastases but not over that of CT alone. However, the specificity of PET/CT for the characterization of pulmonary metastases with a diameter > 0.5 cm and lymph node metastases with a diameter of <1 cm was significantly increased over that of CT alone.


BACKGROUND: The purpose was the comparison of positron emission tomography using F-18-fluorodeoxy-glucose (FDG-PET) and spiral thoracic CT to detect pulmonary metastases from malignant primary osseous tumors. PATIENTS AND METHODS: In 71 patients with histologically confirmed malignant primary bone tumors (32 osteosarcomas, 39 Ewing’s sarcomas) 111 FDG-PET examinations were evaluated with regard to pulmonary/pleural metastases in comparison with spiral thoracic CT. Reference methods were the clinical follow-ups for 6-64 months (median 20 months) or a histopathologic analysis. RESULTS: In 16 patients (23%) reference methods revealed a pulmonary/pleural metastatic disease. FDG-PET had a sensitivity of 0.50, a specificity of 0.98, and an accuracy of 0.87 on a patient based analysis. Comparable values for spiral CT were 0.75, 1.00, and 0.94. It was shown that no
patient who had a true positive FDG-PET had a false negative CT scan, nor was a pulmonary metastases detected earlier by FDG-PET than by spiral CT. CONCLUSIONS: There seems to be a superiority of spiral CT in the detection of pulmonary metastases from malignant primary bone tumors as compared with FDG-PET. Therefore, at present a negative FDG-PET cannot be recommended to exclude lung metastases. However, as specificity of FDG-PET is high, a positive FDG-PET result can be used to confirm abnormalities seen on thoracic CT scans as metastatic.


PURPOSE: The objective of this study was to evaluate the impact of positron emission tomography (PET) using fluorine-18-fluorodeoxyglucose (FDG) for initial staging and therapy planning in pediatric sarcoma patients. PATIENTS AND METHODS: In this prospective multicenter study, 46 pediatric patients (females, n = 22; males, n = 24; age range, 1 to 18 years) with histologically proven sarcoma (Ewing sarcoma family tumors, n = 23; osteosarcoma, n = 11; rhabdomyosarcoma, n = 12) were examined with conventional imaging modalities (CIMs), including ultrasound, computed tomography (CT), magnetic resonance imaging, and bone scintigraphy according to the standardized algorithms of the international therapy optimization trials, and whole-body FDG-PET. A lesion- and patient-based analysis of PET alone and CIMs alone and a side-by-side (SBS) analysis of FDG-PET and CIMs were performed. The standard of reference consisted of all imaging material, follow-up data (mean follow-up time, 24 +/- 12 months), and histopathology and was determined by an interdisciplinary tumor board. RESULTS: FDG-PET and CIMs were equally effective in the detection of primary
tumors (accuracy, 100%). PET was superior to CIMs concerning the correct detection of lymph node involvement (sensitivity, 95% v 25%, respectively) and bone manifestations (sensitivity, 90% v 57%, respectively), whereas CT was more reliable than FDG-PET in depicting lung metastases (sensitivity, 100% v 25%, respectively). The patient-based analysis revealed the best results for SBS, with 91% correct therapy decisions. This was significantly superior to CIMs (59%; P < .001). CONCLUSION: In staging pediatric sarcoma, subsidiary FDG-PET scanning depicts important additional information and has a relevant impact on therapy planning when analyzed side-by-side with CIMs.


Hybrid PET/CT was compared with PET alone in the staging and restaging of patients with Ewing tumor to assess the benefit of the combined imaging technique. METHODS: A total of 163 (18)F-FDG PET/CT studies performed in 53 patients (age: range, 4-38 y; median, 16.5 y) with histopathologically confirmed Ewing tumor were evaluated retrospectively. All PET/CT studies included low-dose CT for attenuation correction; in 91 examinations, additional diagnostic chest CT was performed. PET and CT data were assessed independently by 2 nuclear medicine physicians and 2 radiologists, respectively. Finally, both datasets were fused by use of software and analyzed by all 4 reviewers (consensus reading). Each lesion was scored with a 5-point scale. Biopsy, imaging, or clinical follow-up served as a standard of reference. Receiver operating characteristic (ROC) analyses were performed to evaluate PET and PET/CT performance characteristics. To measure the abilities to detect and correctly
localize tumor foci, localization ROC (L-ROC) curves were generated for PET. RESULTS: A total of 609 lesions were detected by PET alone. The hybrid PET/CT technique resulted in a change of score in 160 of these lesions (26%): higher scores in 23 lesions (4%) and lower scores in 137 lesions (23%). In 49 lesions detected by PET (8%), the localization had to be changed after image fusion. Additionally, 124 (21%) more lesions were found by PET/CT than by PET alone, resulting in a total of 733 lesions. As determined by lesion-based analysis, the sensitivity, specificity, and accuracy of PET were 71%, 95%, and 88%, respectively; the corresponding values for the hybrid PET/CT technique were 87%, 97%, and 94% (P < 0.0001). The areas under the curve in the ROC analysis were 0.82 for PET and 0.92 for PET/CT (P < 0.0001), and that in the L-ROC analysis was 0.66 for PET. CONCLUSION: PET/CT is significantly more accurate than PET alone for the detection and localization of lesions and improves staging for patients with Ewing tumor. The hybrid technique is superior to PET alone in terms of sensitivity, specificity, and accuracy, mainly because of the detection of new lesions.


PURPOSE: The purpose of this study was to evaluate the potential of positron emission tomography using F-18-fluoro-2-deoxy-D-glucose (FDG PET) to assess the chemotherapy response of primary osseous tumors compared with the degree of necrosis determined histologically. PATIENTS AND METHODS: Seventeen patients with primary bone tumors (11 osteosarcomas, 6 Ewing’s sarcomas) were examined using FDG PET and planar bone scintigraphy before neoadjuvant
chemotherapy and before surgery. Tumor response was classified histologically according to Salzer-Kuntschik (grades I-II: good response; grades IV-VI: poor response). In both imaging methods, quantification was performed using tumor to nontumor ratios (T:NT). RESULTS: Histologically, 15 patients were classified as having good responses (grade I, n = 1; grade II, n = 6; grade III, n = 8) and two as having poor responses (grades IV and V). FDG PET showed more than a 30% decrease in T:NT ratios in all patients who had good responses. However, three of these patients had increasing bone scintigraphy T:NT ratios, and another five had decreasing ratios of less than 30%. The patients with poor responses had increasing T:NT ratios and decreasing ratios of less than 30%, respectively, using both imaging methods. CONCLUSIONS: FDG PET seems to be a promising tool for evaluating the response of primary osseous tumors to chemotherapy. In this preliminary study, FDG PET was superior to planar bone scintigraphy.


BACKGROUND: Response to neoadjuvant chemotherapy is a significant prognostic factor for osteosarcoma (OS) and the Ewing sarcoma family of tumors (ESFT). Conventional radiographic imaging does not discriminate between responding and nonresponding osseous tumors. [F-18]-fluorodeoxy-D-glucose (FDG) positron emission tomography (PET) is a noninvasive imaging modality that accurately predicts histopathologic response in patients with various malignancies. To describe the FDG PET imaging characteristics and to determine the correlation between FDG PET imaging and chemotherapy response in children with bone
sarcomas, we reviewed our single institution experience. METHODS: Thirty-three pediatric patients with OS or ESFT with osseous primary sites were evaluated by FDG PET. All patients received standard neoadjuvant chemotherapy. FDG PET standard uptake values before (SUV1) and after (SUV2) chemotherapy were analyzed and correlated with chemotherapy response assessed by histopathology in surgically excised tumors. Twenty-six patients had SUV1, SUV2, and surgical excision. RESULTS: Although the mean SUV1 in children with OS or ESFT were similar (8.2 vs. 5.3, P = 0.13), mean SUV2 for OS patients was greater than the values for ESFT patients (3.3 vs. 1.5, P = 0.01). All ESFT patients and 28% of OS patients had a favorable histologic response to chemotherapy (>or= 90% necrosis). Combining ESFT and OS patients, both SUV2 and the ratio of SUV2 to SUV1 (SUV2:SUV1) were correlated with histologic response (P = 0.01 for both comparisons). CONCLUSION: FDG PET evaluation of pediatric bone sarcomas demonstrated significant alteration in response to neoadjuvant chemotherapy. SUV2 and SUV2:SUV1 correlated with histopathologic assessment of response and potentially could be used as a noninvasive surrogate to predict response in patients.


BACKGROUND: Combined positron emission tomography with (18)fluoro-deoxyglucose and computed tomography (FDG-PET/CT) has been used in the diagnosis and staging of various malignancies, but their use in the management of pediatric sarcomas is less well defined. The potential role of FDG-PET/CT in the diagnosis of local recurrence and distant metastases of pediatric sarcomas was investigated.
PROCEDURE: Nineteen children (aged 2-21) with sarcoma (9 Ewing sarcoma, 3 osteogenic sarcoma, 7 rhabdomyosarcoma) were evaluated between January 2000 and December 2005 by FDG-PET/CT for suspected local relapse or distant metastases. The results of 21 FDG-PET studies, 16 CT scans, 9 magnetic resonance imaging (MRI) studies, and 7 bone scans (BSs) were compared with surgical pathology or clinical follow-up for at least 3 months.

RESULTS: FDG-PET detected local relapse in all seven patients and distant metastases in 10/13 (77%). FDG-PET/CT and CT/MRI/BS results were discordant in eight patients. FDG-PET/CT was the only modality that detected distant metastases in two patients. PET/CT was true negative and excluded disease in three patients with abnormal CT/BSs and was false negative in three patients with distant metastases.

CONCLUSION: FDG-PET/CT may be useful and complementary to other imaging modalities for the detection of recurrent pediatric sarcomas, especially at the primary site. Its potential advantages and limitations compared with conventional imaging modalities need to be further investigated in larger homogenous patient groups.
Soft Tissue Sarcomas

Introduction

Soft tissue sarcomas are a varied group of tumours with considerable challenges in diagnosis, therapy and follow up. Fibrous histiocytomas are most common (28%) followed by liposarcoma (15%), leiomyosarcoma (12%), synovial cell sarcoma (10%), malignant peripheral nerve sheath tumours (6%) and rhabdomyosarcomas (5%). It should be kept in mind that individual sarcomas have specific considerations, which cannot be comprehensively covered in this review.

Conventional staging

Due to their rapid yet innocuous growth in locations that allow them to reach large proportions before detection, these tumours are usually detected clinically. Anatomic imaging, most importantly MRI is used to assess the extent of the lesion and involvement of adjacent structures. CT is usually used to detect additional metastatic disease. Response to therapy is usually based on the morphological changes on CT and MRI. Local recurrence is usually assessed by MRI and CT, while distant metastases are usually detected on CT. Staging is based on a combination of histologic grade and extent of primary disease and presence of metastases.
Summary of Evidence

Initial diagnosis, staging and restaging
There is no role for FDG PET in the initial diagnosis of soft tissue sarcomas although it is able to identify the large lesions. Some data suggests that on the basis of increased uptake in the lesion, one could increase the degree of suspicion for a malignant lesion but differentiation between benign and low-grade lesions is not possible. \(^1,^2\) More importantly, although FDG PET cannot serve as a substitute for histologic diagnosis, the initial semiquantitative uptake in the lesion has been shown to correlate with tumor grade and be predictive of recurrence free, overall 5 year and disease free survival rates. \(^3,^4\) There is potential utility for FDG PET in directing biopsy to the most metabolically active and potentially malignant portion of the mass. \(^5\) There is no literature available at this time on the use of FDG PET in staging or restaging soft tissue sarcomas.

Response Assessment
There are several studies citing the utility of FDG PET in assessing the response to therapy in soft tissue sarcomas. In a study of 46 patients with high grade soft tissue sarcomas by Schuetze et al in 2005, patients with baseline SUVmax \(\geq 6\) and < 40% decrease in SUVmax following neoadjuvant chemotherapy had an estimated disease recurrence rate of 90% at 4 years. Patients with >40% decrease in SUV had significantly better prognoses. \(^6\) There are few reports on the change in management of soft tissue sarcomas based on PET CT findings and numbers vary between 3 and 50%. \(^7,^8\)

Summary
At this time, FDG PET’s major roles in soft tissue sarcomas pertain to identifying the most metabolically active portion of the tumor to increase yield from biopsy and in assessing
treatment response and prognosis. No significant role is seen in staging or restaging.

<table>
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Selected References


The purpose of this review is to underscore the value of positron emission tomography (PET) in the management of patients with soft tissue sarcomas. Although the most essential step in the diagnostic evaluation of soft tissue sarcomas is tumor biopsy, functional imaging techniques is growing and becoming more popular than before. PET scan traces molecular and cellular activities of normal and tumor cells through the use of radiotracers that engage in cell metabolism. The most important and widely used tracer is fluorodeoxyglucose (18FDG). PET scan usefulness is not limited to its ability to differentiate benign from malignant lesions. The scan can detect intrallesional morphologic
variation which is especially true in soft tissue sarcomas, it can predict tumor grade, and it is of value in staging, restaging and prognosis. As for the time, PET is not meant to replace tissue biopsy but rather complement the biopsy to better understand the biological behavior of soft tissue sarcomas.


BACKGROUND: Sarcomas represent a significant diagnostic and therapeutic challenge that requires techniques to provide better assessment of the disease than provided by traditional means. FDG-PET depicts the increased metabolism in abnormal tissues, enabling visualisation and quantification in vivo. The objective of this review was to assess the diagnostic value of FDG-PET in the detection, grading and therapy response of soft tissue and bone sarcomas. METHODS: A systematic review and meta-analysis of clinical studies on FDG-PET and sarcomas was conducted. Databases of PubMed, Embase and Cochrane were searched for studies. Besides that, the references of identified studies were reviewed. Three reviewers independently assessed the methodological quality. Statistical pooling was possible for studies concerning detection and grading of studies with mixed sarcomas (soft tissue and bone) and studies with soft tissue sarcomas only. RESULTS: Twenty-nine studies met the inclusion criteria. There was disagreement between the reviewers in 21.5% of the questions from the criteria list. The methodological quality of most of the included studies was poor. Pooled sensitivity, specificity and accuracy of PET for the detection of sarcomas were 0.91, 0.85 and 0.88, respectively. The difference between the mean Standard Uptake Value (SUV) in malignant and benign tumours for the studies concerning mixed and soft tissue
sarcomas was statistically significant, as well as the difference in FDG uptake between low and high grade mixed sarcomas.

CONCLUSIONS: The meta-analysis in this study was limited by the fact that only a few studies had mutual comparable outcome parameters. Moreover, the methodological quality of the studies was generally poor. Nevertheless, our results indicate that FDG-PET can discriminate between sarcomas and benign tumours and low and high grade sarcomas based on the mean SUV. The diagnostic implications of these results have to be investigated, especially the discrimination between benign tumours and low grade sarcomas. Based on this meta-analysis, there is no indication to use FDG-PET in the standard treatment of sarcomas. In the future PET imaging in bone and soft tissue sarcomas should be directed to the clinical implication for the detection and grading of sarcomas and the treatment evaluation of locally advanced sarcomas.


OBJECTIVE: The objective of this study was to evaluate the prognostic significance of preoperative positron emission tomography (PET) using 2-fluoro-2-deoxy-D-glucose (FDG) by calculating the mean standardized uptake values (SUV) in patients with resectable soft tissue sarcomas (STS).

SUMMARY AND BACKGROUND DATA: FDG-PET might be used as an adjunctive tool (in addition to biopsy and radiologic tomography) in the preoperative prognostic assessment of resectable STS. METHODS: A total of 74 adult patients with STS underwent preoperative FDG-PET imaging with calculation of the SUV. Clinicopathologic data and the SUV were analyzed for an association with the clinical outcome. The first and the third quartiles of the SUV
distribution function were used as cutoff values (1.59 and 3.6). Survival was estimated by the Kaplan-Meier method. Univariate and multivariate analyses were performed using log-rank test and the Cox proportional hazards regression model. RESULTS: In 55 cases, STS were completely resected (follow up 40 months): 5-year recurrence-free survival rates in patients with SUV <1.59, 1.59 to <3.6, and > or =3.6 were 66%, 24%, and 11%, respectively (P = 0.0034). SUV was a predictor for overall survival (5-year rates: 84% [SUV <1.59], 45% [SUV 1.59 to <3.6], and 38% [SUV > or =3.6]; P = 0.057) and local tumor control (5-year rates: 93% [SUV <1.59], 43% [SUV 1.59 to <3.6], and 15% [SUV > or =3.6]; P = 0.0017). By multivariate analysis, SUV was found to be predictive for recurrence-free survival. The prognostic differences with respect to the SUV were associated with tumor grade (P = 0.002). CONCLUSION: The semiquantitative FDG uptake, as measured by the mean SUV on preoperative PET images in patients with resectable STS, is a useful prognostic parameter. SUV with cutoff values at the first and the third quartiles of the SUV distribution predicted overall survival, recurrence-free survival, and local tumor control. Therefore, FDG-PET can be used to improve the preoperative prognostic assessment in patients with resectable STS.


The purpose of this study was to determine the relationship between sarcoma tumor grade and the quantitative tumor metabolism value for [F-18]fluorodeoxyglucose (FDG) determined by positron emission tomography (PET) imaging. Seventy patients with bone or soft-tissue sarcomas underwent PET scanning with quantitative determination of tumor FDG metabolic rate (MRFDG) before treatment. MRFDG
(micromol/g/min) for each tumor was compared with National Cancer Institute tumor grade, S-phase percentage, and percentage of aneuploidy of the tumor population. The pretreatment quantitative determination of tumor MRFDG by PET correlates strongly with tumor grade but not with the other selected histopathological tumor correlates. In addition, overlap of MRFDG PET values with tumor grade suggests that PET, an objective tumor measurement, may provide an alternative means of assessing tumor biological potential or may have the potential to overcome some of the limitations of traditional pathological evaluation. FDG PET can uniquely provide a metabolic profile of a diverse group of sarcomas noninvasively and provide clinically relevant tumor biological information.


Magnetic resonance imaging (MRI) has been the most useful tool in the anatomical definition of soft tissue sarcoma, although there remains the problem of defining the lesions as benign or malignant. The management of such lesions requires biopsy prior to surgical resection. If the most malignant area could be defined more accurately, then this area could be targeted for biopsy. Fluorodeoxyglucose positron emission tomography (FDG PET) has been found to be useful in identifying malignancy and variations in grade in soft tissue masses. The aim of this study was to assess the use of FDG PET scanning with or without co-registered MRI to indicate the most appropriate biopsy site. Twenty consecutive patients presented with soft tissue masses with clinical signs of malignancy. All patients underwent MRI and FDG PET scanning and the two images were co-registered. A biopsy site that was the most likely to be malignant was defined on the
PET scan. All patients underwent an initial biopsy and then complete surgical resection of the mass. The histological results from the mass were compared with those from the biopsy specimen obtained from the site suggested by the PET scan. In malignant masses the biopsy site suggested by the FDG PET scan was found to be representative of the most malignant site on the whole mass histology. Benign lesions had low or no FDG uptake. In no case did the co-registered image add significantly to the appropriate biopsy site. FDG PET can be used to appropriately direct biopsy in soft tissue sarcoma and potentially may lead to computed tomography/MRI directed outpatient biopsy prior to definitive treatment.


BACKGROUND: Patients with high-grade soft tissue sarcomas are at high risk of developing local disease recurrence and metastatic disease. [F-18]-fluorodeoxy-D-glucose (FDG) positron emission tomography (PET) scans are hypothesized to detect histopathologic response to therapy and to predict risk of tumor progression in patients with various malignancies. Serial FDG-PET scans were taken to determine the correlation between FDG uptake and patient outcomes in patients receiving multimodality treatment of extremity sarcomas. METHODS: Forty-six patients with high-grade localized sarcomas were studied. The maximum standardized uptake values (SUVmax) of tumors were measured before receipt of neoadjuvant chemotherapy and again before surgery. Resected specimens were examined for residual viable tumor. Patients were followed up at least annually for evidence of local and distant recurrence of disease and survival. RESULTS: Patients with a baseline tumor SUVmax >/= 6 and < 40% decrease in FDG uptake were at high risk of systemic disease recurrence.
estimated to be 90% at 4 years from the time of initial diagnosis. Patients whose tumors had a ≥ 40% decline in the SUVmax in response to chemotherapy were at a significantly lower risk of recurrent disease and death after complete resection and adjuvant radiotherapy. CONCLUSIONS: The FDG-PET scan was found to be a useful method with which to predict the outcomes of patients with high-grade extremity soft tissue sarcomas treated with chemotherapy. The pretreatment tumor SUVmax and change in SUVmax after neoadjuvant chemotherapy independently identified patients at high risk of tumor recurrence. The FDG-PET scan showed promise as a tool to identify the patients with sarcoma who are most likely to benefit from chemotherapy.


PURPOSE: Limited information is available on the use of positron emission tomography (PET) in paediatric oncology. The aim of this study was to review the impact of PET on the management of paediatric patients scanned over a 10-year period. METHODS: One hundred and sixty-five consecutive oncology patients aged 11 months to 17 years were included. Two hundred and thirty-seven scans were performed. Diagnoses included lymphoma (60 patients), central nervous system (CNS) tumour (59), sarcoma (19), plexiform neurofibroma with suspected malignant change (13) and other tumours (14). A questionnaire was sent to the referring clinician to determine whether the PET scan had altered management and whether overall the PET scan was thought to be helpful. RESULTS: One hundred and eighty-nine (80%) questionnaires for 126 patients were returned (63 relating to lymphoma, 62 to CNS tumours, 30 to sarcoma, 16 to plexiform neurofibroma
and 18 to other tumours). PET changed disease management in 46 (24%) cases and was helpful in 141 (75%) cases. PET findings were verified by histology, clinical follow-up or other investigations in 141 cases (75%). The returned questionnaires indicated that PET had led to a management change in 20 (32%) lymphoma cases, nine (15%) CNS tumours, four (13%) sarcomas, nine (56%) plexiform neurofibromas and four (22%) cases of other tumours. PET was thought to be helpful in 47 (75%) lymphoma cases, 48 (77%) CNS tumours, 24 (80%) sarcomas, 11 (69%) neurofibromas and 11 (61%) cases of other tumours. PET findings were verified in 44 (70%) lymphoma cases, 53 (85%) CNS tumours, 21 (70%) sarcomas, 12 (75%) neurofibromas and 11 (61%) other tumour cases.

CONCLUSION: PET imaging of children with cancer is accurate and practical. PET alters management and is deemed helpful (with or without management change) in a significant number of patients, and the results are comparable with the figures published for the adult oncology population.


AIM OF THE STUDY: To assess the impact of repeated F-18 FDG studies on the management of patients with bone and soft tissue (B&S) sarcomas. MATERIAL AND METHODS: Twenty patients with B&S tissue tumors (11 M and 9 F age 17-72 years) had 52 F-18 FDG Dual Head Coincidence Imaging (DHCI) studies. 7 patients were followed for 6 months to 2 years clinically after removal of the primary tumor. Thirteen patients were evaluated for suspected recurrences. Patient’s preparation, F-18 FDG injection and imaging procedure were done according to department protocol. Attenuation corrected images were interpreted visually by 3 trained physicians. Tumor to background ratios were calculated
for all lesions. RESULTS: In 13 patients having both studies, baseline FDG and CT/MRI were concordant in 8 patients, FDG detected more lesions in 3 patients but it did not detect 4 metastatic pulmonary nodules in 2 patients. Follow up studies showed stable disease in 10 patients while 6 patients who showed worsening disease needed to change their chemotherapy. Surgery was avoided in 2 patients and 2 patients showed improved response. CONCLUSION: Repeated F-18 FDG DHCI examinations proved to have an impact on the clinical management of patients with malignant bone and soft tissue sarcoma. It helps to differentiate postoperative changes from local recurrence.
Melanoma

Introduction
Melanoma is a common skin tumour, seen most commonly in fair skinned individuals with excessive exposure to sunlight. It is presently the 9th most common cancer in the United States with a rising incidence, accounting for 3.5% of cancers and 1.4% of cancer deaths. Four clinical histopathologic subtypes of cutaneous melanoma are described: superficial spreading, lentigo maligna, acral lentiginous and nodular melanoma.

Conventional staging
Systems by Clarke (where extent is based on anatomic landmarks in skin) and Breslow (where extent is based on measured thickness of extension) have been used to assess the local extent of disease and presently, the Breslow depth is preferred as it provides greater prognostic information. Staging of the disease is based on the TNM classification based on local extent of disease (I and II), local node involvement (III) and distant metastases (IV). The most current staging system used is the one proposed by the American Joint Committee on Cancer (AJCC) from 2002 which incorporate aspects of all the above mentioned staging systems.

Lesions are initially suspected on physical examination and confirmed by biopsy. Depending on the histologic results,
higher risk patients undergo wider excision and sentinel node biopsy and subsequent staging with chest radiographs and serum LDH which if positive are poor prognostic indicators. CT is felt to be optional due to its low yield. S-100 is a serum marker that is used to detect melanoma with some success.

Summary of Evidence

Initial Diagnosis, Staging and Restaging

At this time, there is a limited role for PET in the initial diagnosis or staging of stage I or II cutaneous melanoma and skin and sentinel node biopsy are still the favoured choice. In a prospective nonrandomized control study of 144 patients in early stage melanoma PET revealed a low sensitivity of 21% for regional node involvement and 11% sensitivity for predicting the first site of recurrence. Furthermore, none of the distant sites suspected by PET were found to have tumour by biopsy or conventional imaging. In a more recent study, PET demonstrated a sensitivity of 14.3% and positive predictive value (PPV) of 50% for localizing subclinical nodal metastases. Specificity, net present value and accuracy were 94.7, 75 and 73% respectively. A meta-analysis of 28 studies revealed that FDG PET has an adjunctive role, especially in stage III and IV cutaneous melanoma for detecting deep soft tissue, nodal and visceral metastases and PET CT was felt to be more precise than PET alone. Another recent meta-analysis suggests level IV evidence supports the use of FDG PET (PET-CT with dedicated CT interpretation preferably) in AJCC stage III and IV disease. The sensitivity, specificity and accuracy of PET-CT in detecting metastases in high risk patients were 85, 96, 91% while for PET-CT with dedicated CT interpretation were 98, 94 and 96% respectively. PET CT has been found to change management in approximately 30% of patients with melanoma. In terms of prognosis, patients with high
standardized uptake values (SUV) in metastatic nodes have shorter disease free survival than those with lower SUVs but this difference does not appear to translate into overall survival. 

Briefly, PET maybe more sensitive than CT in detecting skin, bowel, skeletal and nodal metastases but CT is better for pulmonary lesions while MRI is the mainstay for brain metastases. The sensitivity of PET is limited for small lesions while clinical correlation and corroborative anatomical imaging increase the specificity of FDG PET abnormalities.

**Response Assessment**

S-100B is a tumour marker that has been found to be useful in some cases of melanoma in detecting recurrence and assessing treatment response. In these patients, recent data suggests that FDG PET-CT can be used to assess treatment response as the change in tumor maximum standardized uptake value (SUVmax) correlates well with change in serum S-100B values. 

**Suspected Recurrence**

Monitoring high-risk melanoma patients is a challenging and FDG PET CT has shown promise in a small study by detecting metastases with a sensitivity, specificity and accuracy of 97, 100 and 98% respectively in patients with truly elevated S-100B. Early work also suggests that FDG PET-CT is accurate in detecting clinically occult disease recurrence and patients who are PET negative go on to have disease free states for 12-48 months subsequently.

**Impact on Patient Management**

Various studies have shown that FDG PET has had an impact on patient management by changing treatment plan between 11 and 49% of the time. 

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Timing of the Hierarchy of Relevance of Level of PET/CT Diagnostic Test Evidence

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**Summary**

FDG PET is a sensitive and specific technique for patients with melanoma but has limitations with small (less than 1 cm), pulmonary (chest CT) and brain (MRI) metastases. It is felt to be superior to CT alone in detecting abdominal, nodal, subcutaneous and skins sites. It is useful in assessing extent of disease in patients with surgically resectable disease by conventional methods as it may render them unresectable in a considerable population.

**Selected References**


BACKGROUND: The purpose of the current study was to determine the sensitivity and specificity of initial F-18
fluorodeoxy-D-glucose-positron emission tomography (FDG-PET) scanning for detection of occult lymph node and distant metastases in patients with early-stage cutaneous melanoma. METHODS: The authors conducted a prospective nonrandomized clinical trial. Inclusion criteria were patients with cutaneous melanoma tumors > 1.0 mm Breslow thickness, local disease recurrence, or solitary intransit metastases without regional lymph or distant metastases by standard clinical evaluation. All patients underwent whole-body FDG-PET scanning before surgical therapy. Abnormal PET findings were studied by targeted conventional imaging and/or biopsy. FDG-PET scans were interpreted in a blinded fashion. Regional lymph node basins were staged by sentinel lymph node biopsy (SLNB). PET scan findings in regional lymph nodes were compared with histology of SLNB specimens. Abnormal distant PET scan findings were studied with repeat conventional scan imaging at 3-6 months and were correlated with the first site(s) of clinical disease recurrence. Blinded PET scan findings were correlated with all information to determine sensitivity and specificity. RESULTS: There were 144 assessable patients with a mean tumor depth of 2.8 mm. The median follow-up for these patients was 41.4 months. Blinded interpretations of FDG-PET scan images showed that 31 patients (21%) had signs of metastatic disease, 13 patients had probable regional lymph node metastases, and 18 patients had 23 sites of possible distant metastases. SLNB and/or follow-up demonstrated regional lymph node metastases in 43 of 184 lymph node basins in 40 patients (27.8%). Compared with all clinical information, FDG-PET scan sensitivity for detection of regional lymph node metastases was 0.21 (95% confidence [CI], 0.10-0.36) and specificity was 0.97 (95% CI, 0.93-0.99). No distant sites were confirmed to be true positive by targeted conventional imaging/biopsy at the time of presentation. Thirty-four patients (23.6%) presented with 54 foci of metastatic disease at initial disease recurrence.
FDG-PET scan sensitivity for prediction of the first site(s) of clinical disease recurrence was 0.11 (95% CI, 0.04-0.23). Excluding patients with brain metastases, FDG-PET scan sensitivity for detection of occult Stage IV disease in patients was 0.04 (95% CI, 0.001-0.20) and specificity was 0.86 (95% CI, 0.79-0.92). CONCLUSIONS: FDG-PET scanning did not impact the care of patients with early-stage melanoma already staged by standard techniques. Routine FDG-PET scanning was not recommended for the initial staging evaluation in this population.


The objective of this study was to evaluate the role of preoperative 18F-fluorodeoxyglucose-positron emission tomography/computed tomography scanning, preoperative lymphoscintigraphy (LS), and sentinel lymph node biopsy in patients with malignant melanoma. Fifty-two patients (36 men: 16 women; mean age 55.0 +/- 13.0 years; median age 61 years; range 17-76 years) with malignant melanoma were selected. According to the latest version of the American Joint Committee on Cancer staging system, the disease in the study patients was initially classified as either stage I or II. The other primary tumor characteristics were mean Breslow depth=2.87 mm and median=2 mm; range 1-12.0 mm and Clarks levels III-V. None of the study patients had clinical or radiological evidence of regional lymph node metastatic disease. At least one sentinel node was identified in all patients. Preoperative LS detected a total of 111 sentinel lymph nodes (average 2.13 sentinel lymph node per patient) and demonstrated a single nodal draining basin in 38 (73%) patients and multiple (2-3 draining basins) in the remaining 14 (27%) patients. Fourteen out of the 52 patients (27%) had at least

PURPOSE: To calculate summary estimates of the diagnostic performance of fluorine 18 fluorodeoxyglucose (FDG) positron emission tomographic (PET) imaging in the initial staging of cutaneous malignant melanoma (CMM), following the new American Joint Committee on Cancer (AJCC) staging classification on per-patient and per-lesion bases.

MATERIALS AND METHODS: MEDLINE, EMBASE, Web of Science, and Cochrane Database of Systematic Reviews databases, and reference lists of reviews and included papers were searched, without any language restrictions, for relevant articles published before March 2007. Two reviewers independently assessed study eligibility and methodologic quality by using the quality assessment of diagnostic accuracy studies checklist. A pooled random effect was estimated and a fixed coefficient regression model was used to explore the existing heterogeneity.

RESULTS: Twenty-eight studies involving 2905 patients met the inclusion criteria. The pooled
estimates of FDG PET for the detection of metastasis in the initial staging of CMM were sensitivity, 83% (95% confidence interval [CI]: 81%, 84%); specificity, 85% (95% CI: 83%, 87%); positive likelihood ratio (LR), 4.56 (95% CI: 3.12, 6.64); negative LR, 0.27 (95% CI: 0.18, 0.40); and diagnostic odds ratio, 19.8 (95% CI: 10.8, 36.4). Results from eight studies suggested that FDG PET was associated with 33% disease management changes (range, 15%-64%). CONCLUSION: There is good preliminary evidence that FDG PET is useful for the initial staging of patients with CMM, especially as adjunctive role in AJCC stages III and IV, to help detect deep soft-tissue, lymph node, and visceral metastases. FDG PET-computed tomographic imaging seemed to be more precise than PET alone, as suggested by four eligible studies. Further evaluation by using a well-designed prospective study, with clinical outcome-focused measures and cost effectiveness analysis, is needed to clarify the appropriate role of FDG PET in CMM staging. SUPPLEMENTAL MATERIAL: http://radiology.rsna.org/cgi/content/full/249/3/836/DC1.

Cutaneous melanoma (CM) is a common malignancy and imaging, particularly lymphoscintigraphy (LS), positron-emission tomography with 2-fluoro-2-deoxyglucose (FDG-PET), ultrasound, radiography computed tomography (CT) and magnetic resonance imaging have important roles in staging and restaging, surgical guidance, surveillance and assessment of recurrent disease. This review aims to summarize the available data regarding these and other imaging modalities in CM and provide the basis for subsequent formulation of guidelines regarding the use of imaging in CM. PubMed and Medline searches were performed and reference lists from
publications were also searched. The published data were reviewed and tabulated. There is level I evidence supporting the use of LS and sentinel lymph node biopsy in nodal staging for CM. There is level III evidence demonstrating the superiority of ultrasound to palpation in the assessment of lymph nodes in CM. There is level IV evidence supporting FDG-PET in American Joint Committee on Cancer stage III/IV and recurrent CM and that FDG-PET/CT may be superior to FDG-PET. Level IV evidence also supports the use of CT in the same group of patients and the role of CT appears to be complementary to FDG-PET. Various imaging modalities, especially LS/sentinel lymph node biopsy and FDG-PET/CT, add incremental information in the management of CM and the various modalities have complementary roles depending on the clinical situation.


PURPOSE: To prospectively determine the accuracy of positron emission tomography (PET)/computed tomography (CT) with added CT morphologic information for depiction of metastases in patients with high-risk melanoma and negative findings for metastases at PET, by using histologic findings or additional imaging and/or follow-up findings as reference standard. MATERIALS AND METHODS: Institutional review board approval was obtained. Informed consent was obtained from patients. One hundred twenty-four consecutive high-risk melanoma patients (65 female, 59 male; mean age, 54.4 years; range, 15-82 years) were included. Fluorine 18 fluorodeoxyglucose (FDG) PET/CT was performed. First, PET/CT scans were evaluated for presence of metastases with increased FDG uptake; CT anatomic location was determined.
Lesions were considered metastases if there was focal uptake higher than that of background tissue. Second, coregistered CT images of combined PET/CT scans were evaluated for presence of lesions without FDG uptake. Findings were compared with reference standard findings to determine the accuracy of each evaluation. McNemar test was used to assess statistical differences in accuracy. RESULTS: In 53 of 124 patients, metastases were found. In 46 of 53 patients with metastases, lesions had increased FDG uptake. In seven patients with metastatic disease, metastases did not have increased FDG uptake (maximum standard uptake value [SUV], <1.5; n = 5) or had faint FDG uptake (maximum SUV, 2.5 and 2.9; n = 2)-findings that were inconclusive with PET alone. These lesions were interpreted as metastases only with coregistered CT images. Lesions missed with PET were located in the lungs, iliac lymph nodes, subcutis, and psoas muscle. Sensitivity, specificity, and accuracy, respectively, of PET/CT for depiction of metastases were 85%, 96%, and 91%, and those of PET/CT with dedicated CT interpretation were 98%, 94%, and 96% (P = .016). CONCLUSION: Dedicated analysis of coregistered CT images significantly improves the accuracy of integrated PET/CT for depiction of metastases in patients with high-risk melanoma.


PURPOSE: To investigate the accuracy of different interpretative approaches and to evaluate the management implications of fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) in cutaneous malignant melanoma. METHODS: We retrospectively identified 60 consecutive patients who underwent 76 PET/CT scans for cutaneous malignant melanoma. PET/CT reports were classified as positive,
negative, or equivocal for regional and distant disease. Scan indication (staging, restaging, surveillance, or therapeutic monitoring), tumour stage, presence or absence of regional or distant disease, and post-scan management changes were determined by review of all available medical records. Maximum standardized uptake values (SUV(max)) of all findings were noted. Diagnostic accuracy of PET/CT was compared using either a high or low threshold interpretation (i.e. subtle, but indeterminate findings coded negative or positive, respectively). The frequency of management changes was compared between patient subgroups (stratified by tumour stage or indication). RESULTS: Using a high threshold interpretative approach, the overall accuracy of PET/CT for disease was 72.4% (55/76), which was significantly (P<0.05) greater than the accuracy of 53.9% (41/76) seen when using a low threshold approach. Per scan accuracy by staging site was 92.1% (70/76) for regional and 76.3% (58/76) for distant disease. PET/CT changed management in 21 of 76 studies (27.6%). When stratified by stage and indication, management changes occurred in all patient subgroups, except for stage I patients (0 of 5). CONCLUSION: When interpreted with a high threshold approach, PET/CT demonstrates high accuracy for the diagnosis of both regional and distant disease in cutaneous malignant melanoma and frequently changes management in patients with stage II-IV disease referred for a variety of indications.


BACKGROUND: The incidence of malignant melanoma has increased. Identification of additional prognostic factors may allow the development of individualized strategies. This
Multivariate analysis was undertaken to evaluate the potential role of the standard uptake value (SUV) in predicting disease-free and overall survival in melanoma patients with lymph node metastases. METHODS: All melanoma patients with palpable lymph node metastases who where referred for a fluorodeoxyglucose positron emission tomography scan were eligible. The SUV in the lymph node metastasis was calculated. Data were analyzed (Kaplan-Meier), and differences in cumulative survival and the disease-free rate were assessed (log-rank test). Univariate and multivariate analyses (Cox proportional hazard model) were performed to determine independent prognostic factors. RESULTS: There was no statistical difference in survival for the 38 patients with a high or low SUVmean (P = .11). However, a significant difference was found in disease-free survival (P = .03). Ulceration of the primary melanoma (P = .023) was an independent predictor of survival. For the disease-free survival, multivariate Cox regression showed adjuvant radiation (P = .001), localization of the primary melanoma (P = .017), and a high SUVmean (P = .009) as independent prognostic factors. CONCLUSIONS: Disease-free survival of melanoma patients was prolonged in those with a low SUVmean value (P = .03) in their lymph node metastasis, as compared with those with a high SUVmean. However, this difference was not found for overall survival. In multivariate analysis, high SUVmean was an independent prognostic factor (P = .009) for disease-free survival. Prospective research should determine whether patients with a high FDG uptake in melanoma lymph node metastases could benefit from adjuvant radiation treatment or chemotherapy.

OBJECTIVE: To compare the value of the tumor marker S-100B protein and fluorodeoxyglucose positron emission
tomography/computed tomography (FDG-PET/CT) in patients treated for melanoma metastases. METHODS: In 41 patients with proven melanoma metastases, S-100B measurements and FDG-PET/CT were performed before and after therapy. The change of S-100B levels (DeltaS-100B) was assessed. In all patients, therapy response was assessed with PET/CT using visual criteria and change of maximal standard uptake value (DeltaSUV(max.)) or total lesion glycolysis (DeltaTLG). RESULTS: In 15 of 41 patients (37%), S-100B values were not suitable because they were normal before and after therapy. In 26 patients, S-100B was suitable for therapy response assessment. PET/CT was suitable for response assessment in all patients. Correlations between DeltaS-100B and DeltaTLG (r = 0.850, p < 0.001) and between DeltaS-100B and DeltaSUV(max.) (r = 0.818, p < 0.001) were both excellent. A complete agreement between S-100B and PET/CT response assessment was achieved in 22 of 26 patients. In 4 patients, therapy response differed between the S-100B and PET/CT findings, but subsequent S-100B measurements realigned the S-100B results with the later PET/CT findings. CONCLUSION: In a third of our patients with metastases, the S-100B tumor marker was not suitable for therapy assessment. In these patients, imaging techniques remain necessary, and FDG-PET/CT can be used for response assessment.


PURPOSE: To evaluate the usefulness of PET/CT in melanoma patients with an elevated serum S-100B tumour marker level. METHODS: Out of 165 consecutive high-risk melanoma patients referred for PET/CT imaging, 47 had elevated (>0.2 microg/l) S-100B serum levels and a
contemporaneous 18F-FDG PET/CT scan. PET/CT scans were evaluated for the presence of metastases. To produce a composite reference standard, we used cytological, histological, MRI and PET/CT follow-up findings as well as clinical and S-100B follow-up. RESULTS: Among the 47 patients with increased S-100B levels, PET/CT correctly identified metastases in 38 (30 distant metastases and eight lymph node metastases). In one patient with cervical lymph node metastases, PET/CT was negative. Eight patients had no metastases and PET/CT correctly excluded metastases in all of them. Overall sensitivity for metastases was 97% (38/39), specificity 100% (8/8) and accuracy 98% (46/47). S-100B was significantly higher in patients with distant metastases (mean 1.93 microg/l, range 0.3-14.3 microg/l) than in patients with lymph node metastases (mean 0.49 microg/l, range 0.3-1.6 microg/l, p=0.003) or patients without metastases (mean 0.625 microg/l, range 0.3-2.6 microg/l, p=0.007). However, 6 of 14 patients with a tumour marker level of 0.3 microg/l had no metastases. CONCLUSION: In melanoma patients with elevated S-100B tumour marker levels, FDG-PET/CT accurately identifies lymph node or distant metastases and reliably excludes metastases. Because of the significant number of false positive S-100B tumour marker determinations (17%), we recommend repetition of tumour marker measurements if elevated S-100B levels occur before extensive imaging is used.

Whole body positron emission tomography in follow-up of high risk melanoma. Koskivuo IO, Seppanen MP, Suominen EA, Minn HR. Acta Oncol. 2007;46(5):685-690. The aim of this study was to determine the clinical impact of whole body positron emission tomography (FDG PET) to detect clinically silent metastases in the follow-up of patients with high risk melanoma. FDG PET was performed to 30 asymptomatic melanoma patients (AJCC stage IIB-IIIC)
7-24 months after the primary surgery and sentinel node biopsy. FDG PET was able to detect six of seven recurrences, constituting 20% of all study patients. One patient presented with a negative FDG PET finding at the very first scanning, but was positive later in a repeated scan after manifestation of palpable mass in the axilla. The positive PET finding had an impact on treatment decisions in every case: three patients underwent surgical resection and four patients received chemotherapy or interferon. The mean follow-up time was 27 months (range, 12-48 months) and during that time the other 23 patients with true negative FDG PET were disease-free. One of the seven recurrences was in remission after surgical metastasectomy. In conclusion, whole body FDG PET is a valuable follow-up tool in high risk melanoma to diagnose recurrences and to select the patients, who are suitable for surgical metastasectomy.


We have undertaken a retrospective analysis of all positron emission tomography (PET) scans carried out at St Thomas’ Hospital, London, since 1994 to establish the sensitivity and specificity of this radiologic technique in cutaneous malignant melanoma. In particular, we have identified those patients with primary cutaneous malignant melanoma in whom PET scanning revealed in-transit or regional spread to nodes and those patients with known regional spread in whom PET scanning revealed distant metastases. We defined our false-negative results as a negative scan result with positive histology or subsequent clinical progression of disease. False-positive results were defined as a suspect scan with negative histology or no subsequent progression of disease. PET scanning had an overall sensitivity of 78% and specificity of 87%; however,
subset analysis (M. D. Anderson staging system) showed a sensitivity of 50% for stage I disease (34 patients and 35 scans) and 33% for stage II disease (9 patients and 9 scans) with specificities of 87% and 100%, respectively. For stage III disease (16 patients and 17 scans), PET showed a sensitivity of 93% and specificity of 50%. Overall, 35% of patients with true-positive scans had their disease restaged. We can conclude therefore that PET is valuable as a staging procedure in patients with known regional spread but is suboptimal in the prediction of outcome in stage I or stage II disease.


Malignant melanoma can metastasize to almost any organ site. Optimal management requires sensitive radiographic evaluation of the entire body. The optimal management of patients with metastatic melanoma requires accurate assessment of extent of disease (EOD). The objective of this study was to evaluate the accuracy of fluorine-18 deoxyglucose (FDG) whole-body positron emission tomography (PET) in determination of EOD in patients with metastatic melanoma and its impact on surgical and medical management decisions. Forty-nine patients (30 men, 19 women; aged 25-83 years) with known or suspected metastatic melanoma underwent EOD evaluation using computerized tomography (CT) of the chest, abdomen, and pelvis, and magnetic resonance imaging (MRI) of the brain. After formulation of an initial treatment plan, the patients underwent FDG-PET imaging. The EOD determined by PET was compared with physical examination and conventional radiography findings. Fifty-one lesions were pathologically evaluated. The impact of PET on patient management was assessed based on the alterations made in
the initial treatment plan after reevaluation of the patients using the information obtained by PET. The PET scan identified more metastatic sites in 27 of 49 (55%) of the patients who had undergone a complete set of imaging studies, including CT scans of the chest, abdomen, and pelvis, and MRI of the brain. In 6 of those 27 patients, PET detected disease outside the fields of CT and MRI. Fifty-one lesions were resected surgically. Of these, 44 were pathologically confirmed to be melanoma. All lesions larger than 1 cm (29 of 29) were positive on PET, whereas only 2 of 15 (13%) lesions smaller than 1 cm were detected by PET. The results of PET led treatment changes in 24 patients (49%). Eighteen of these changes (75%) were surgical. In 12 cases (67%), the planned operative procedure was cancelled, and in 6 cases (33%), an additional operation(s) was performed. In 6 of 24 (25%) patients, biochemotherapy, radiation therapy, or an experimental immunotherapy protocol was prompted by identification of new foci of disease. Compared with conventional imaging, FDG-PET provides more accurate assessment of EOD in patients with metastatic melanoma. Significant surgical and medical treatment alterations were made based on PET results.


BACKGROUND: Several recent studies have demonstrated the low yield of anatomically based computed tomography scans in evaluating Stage III (American Joint Committee on Cancer) patients with malignant melanoma. The purpose of this study was to investigate the efficacy and clinical utility of functionally based positron emission tomography (PET) scans in the same patient population. METHODS: A prospective evaluation of 106 whole body PET scans obtained after injection of 2-fluorine-18, 2-fluoro-2-deoxy-D-glucose (FDG) was performed in 95 patients with clinically evident Stage III
lymph node and/or in-transit melanoma. Areas of abnormality on FDG PET scanning were identified visually as foci of increased metabolic activity compared with background, and all positive foci were assessed pathologically. RESULTS: In this patient population, there were 234 areas that were evaluated pathologically of which 165 were confirmed histologically to be melanoma. PET scanning identified 144 of the 165 areas of melanoma for a sensitivity of 87.3%. The 21 areas of melanoma that were missed included 10 microscopic foci, 9 foci less than 1 cm, and 2 foci greater than 1 cm. There were 39 areas of increased PET activity that were not associated with malignancy for a 78.6% predictive value of a positive test. Of the 39 false-positive areas (false-positive rate of 56.5%), 13 could be attributed to recent surgery, 3 to arthritis, 3 to infection, 2 to superficial phlebitis, 1 to a benign skin nevus, and 1 to a colonic polyp. Pathologic evaluation of the remaining false-positive areas failed to reveal a definitive etiology for their increased activity on PET scan. With the application of pertinent clinical information, the predictive value of a positive PET scan could be improved to 90.6%. The specificity of PET scanning in this study was only 43.5% because very few prophylactic lymph node dissections were performed. Thirty-six of the total 183 abnormal areas (19.7%) on PET scanning proved to be unsuspected areas of metastatic disease. These findings led to a change in the planned clinical management in patients after 16 of the 106 PET scans (15.1%). CONCLUSIONS: FDG PET scanning can be helpful in managing patients with Stage III melanoma in whom further surgery is contemplated. Although false-positive areas are not uncommon, PET scans did change the management of patients 15% of the time. PET’s inability to identify microscopic disease suggests that it is of limited use in evaluating patients with Stage I-II disease.

To be cost-effective, PET must be diagnostically accurate and effective in improving management without increasing treatment cost. To evaluate diagnostic accuracy, we performed prospective evaluations of whole-body PET imaging in staging of non-small-cell lung cancer (99 patients), detection of recurrent colorectal cancer (57 patients), diagnosis of metastatic melanoma (36 patients), and staging of advanced head and neck cancer (29 patients). In each case, PET was more accurate than anatomic imaging for determination of the presence and extent of tumor and demonstration of nonresectable disease. PET was also more accurate than conventional imaging in staging Hodgkin’s disease (30 patients). We evaluated the management impact of PET retrospectively, by reviewing the treatment records of 72 patients with solitary pulmonary nodules or non-small-cell lung cancer, 68 patients with known or suspected recurrent colorectal cancer, 45 patients with known or suspected metastatic melanoma, and 29 patients with advanced head and neck tumors. PET improved patient management by avoiding surgery for nonresectable tumor and for CT abnormalities that proved to be benign by PET imaging. For determining cost impact, the costs of surgical procedures were determined from Medicare reimbursement rates, and the cost of a PET study was taken to be $1800. The savings from contraindicated surgical procedures exceeded the cost of PET imaging by ratios of 2:1 to 4:1, depending on the indication. PET was decisively more accurate and cost-effective than anatomic imaging by CT, combining improved patient care with reduced cost of management.
Section — VII

Head and Neck Malignancies
FDG PET-CT in Head-Neck Cancer

Introduction
Head and neck squamous cell carcinomas (HNSCC) include cancers involving the nasopharynx, oropharynx, hypopharynx, larynx & the oral cavity. Squamous cell carcinomas of the sinonasal region can also be included in HNSCC. Nearly half of the patients have advanced local disease or lymphnode metastases at the time of diagnosis. Treatment involves a multidisciplinary approach involving head-neck surgery, radiation & medical oncology, prosthodontics and speech therapy. Diagnostic imaging plays an important role in staging, restaging, monitoring treatment response and is essential in not only planning adequate treatment but also in reducing treatment related toxicity and functional impairment.

Conventional Imaging
CECT and MRI are the imaging modalities of choice for evaluation of HNSCC. Both have comparable accuracies in evaluating local tumor extent and loco-regional lymphadenopathy. MRI however can be more useful in assessing perineural tumor extension whereas CT scan has been found to be more effective in tumors of the oral cavity.
Ultrasonography is routinely used to assess cervical lymphadenopathy and when coupled with a guided FNAC has a good accuracy.

Summary of evidence for PET-CT
As regards initial staging in untreated head-neck cancer, there are a limited number of prospective studies which examine the impact of PET on management decisions and patient outcomes. Numerous reports have shown that PET is at least as sensitive as MRI & CT in detecting the head-neck primary tumor. But since a non-contrast PET-CT lacks the anatomical detail which an MRI or CT provide, it has a limited role in defining the initial T stage of the disease. For evaluating metastatic disease in regional cervical lymphnodes at initial staging FDG PET is comparable to conventional modalities. In a recent review PET had a sensitivity in the range of 87-90% and specificity of 80-93 % for cervical nodal metastasis at initial staging. Owing to its full body coverage, PET can detect nodal metastases in unexpected locations (mediastinum and axilla) and can unmask unsuspected distant metastatic sites. Several studies have shown that PET may detect occult metastatic disease at initial staging in 10% cases of locally advanced disease. A recent prospective study in patients with clinically N0 neck has shown that FDG PET is of limited value due to its inability to detect disease in nodes < 5 mm. In the evaluation of patients with unknown primary tumor presenting with neck node metastases the data has been variable so far, with results at par if not better than with anatomical imaging modalities. The detection rate for primary tumor was 27% according a meta analysis of studies that addressed patients with negative initial physical examination and MRI. A recent multicentre study shows that PET changes management and improves prognostic stratification in head and neck cancer patients. PET resulted in management change
in about 34% patients and an inferior disease free survival was demonstrated in patients with higher FDG uptake values.

In the context of monitoring treatment response number of studies have shown that PET can detect residual tumor after chemoradiation more accurately than conventional imaging. The negative predictive value of PET to exclude residual disease according to 2 large studies is > 97% when it is performed about 8-12 weeks after completion of treatment. In patients with residual lymphadenopathy a normal PET scan excludes disease with high certainty, but confirmation of this will be required with larger prospective trials. No residual lymphadenopathy with a normal PET scan, neck dissection can be deferred.

For surveillance and detection of recurrence, several studies have shown that FDG PET has a high sensitivity for detecting recurrence at the primary site and regional lymphnodes. In such a setting when a potentially curable salvage option is planned, PET helps in unmasking foci of distant metastases which would change the treatment offered from radical to a palliative one.

For radiation therapy planning several publications have shown that target volumes can be altered in as much as 20% cases when FDG PET-CT is used over CT alone. Hence PET-CT is used as an adjunct to CT and MRI for target definition. Long term outcome data identifying patterns of treatment failure related to PET-CT based target volumes are needed to define a standardized approach, before it can be included in routine clinical practice.
Selected Abstracts


18F-FDG PET has a high accuracy in staging head and neck cancer, but its role in patients with clinically and radiographically negative necks (N0) is less clear. In particular, the value of combined PET/CT has not been determined in this group of patients. Methods: In a prospective study, 31 patients with oral cancer and no evidence of lymphnode metastases by clinical examination or CT/MRI underwent 18F-FDG PET/CT before elective neck dissection. PET/CT findings were recorded by neck side (left or right) and lymph
node level. PET/CT findings were compared with histopathology of dissected nodes, which was the standard of reference. Results: Elective neck dissections (26 unilateral, 5 bilateral; a total of 36 neck sides), involving 142 nodal levels, were performed. Only 13 of 765 dissected lymph nodes harbored metastases. Histopathology revealed nodal metastases in 9 of 36 neck sides and 9 of 142 nodal levels. PET was TP in 6 nodal levels (6 neck sides), false-negative in 3 levels (3 neck sides), true-negative in 127 levels (23 neck sides), and false-positive in 6 levels (4 neck sides). The 3 false-negative findings occurred in metastases smaller than 3 mm or because of inability to distinguish between primary tumor and adjacent metastasis.

TP and false-positive nodes exhibited similar standardized uptakes (4.8 ± 1.1 vs. 4.2 ± 1.0; P 5 not significant). Sensitivity and specificity were 67% and 85% on the basis of neck sides and 67% and 95% on the basis of number of nodal levels, respectively. If a decision regarding the need for neck dissection had been based solely on PET/CT, 3 false-negative necks would have been undertreated, and 4 false-positive necks would have been overtreated.

Conclusion: 18F-FDGPET/CT can identify lymph nodemetastases in a segment of patients with oral cancer and N0 neck. A negative test can exclude metastatic deposits with high specificity. Despite reasonably high overall accuracy, however, the clinical application of PET/CT in the N0 neck may be limited by the combination of limited sensitivity for small metastatic deposits and a relatively high number of false-positive findings. The surgical management of the N0 neck should therefore not be based on PET/CT findings alone.

For patients with locoregional advanced head and neck squamous cell carcinoma (HNSCC), concurrent chemoradiotherapy is a widely accepted treatment, but the need for subsequent neck dissection remains controversial. We investigated the clinical utility of 18F-FDG PET/CT in this setting.

Methods: In this Institutional Review Board (IRB)–approved and Health Insurance Portability and Accountability Act (HIPPA)–compliant retrospective study, we reviewed the records of patients with HNSCC who were treated by concurrent chemoradiation therapy between March 2002 and December 2004. Patients with lymph node metastases who underwent 18F-FDG PET/CT 8 wk after the end of therapy were included. 18F-FDG PET/CT findings were validated by biopsy, histopathology of neck dissection specimens (n 5 18), or clinical and imaging follow-up (median, 37 mo). Results: Sixty-five patients with a total of 84 heminecks could be evaluated. 18F-FDG PET/CT (visual analysis) detected residual nodal disease with a sensitivity of 71%, a specificity of 89%, a positive predictive value (PPV) of 38%, a negative predictive value (NPV) of 97%, and an accuracy of 88%. Twenty-nine heminecks contained residual enlarged lymph nodes (diameter, $1.0 cm), but viable tumor was found in only 5 of them. 18FFDG PET/CT was true-positive in 4 and false-positive in 6 heminecks, but the NPV was high at 94%. Fifty-five heminecks contained no residual enlarged nodes, and PET/CT was truenegative in 50 of these, yielding a specificity of
Lack of residual lymphadenopathy on CT had an NPV of 96%. Finally, normal 18F-FDG PET/CT excluded residual disease at the primary site with a specificity of 95%, an NPV of 97%, and an accuracy of 92%. Conclusion: In patients with HNSCC, normal 18F-FDG PET/CT after chemoradiotherapy has a high NPV and specificity for excluding residual locoregional disease. In patients without residual lymphadenopathy, neck dissection may be withheld safely. In patients with residual lymphadenopathy, a lack of abnormal 18F-FDG uptake in these nodes also excludes viable tumor with high certainty, but confirmation of these data in a prospective study may be necessary before negative 18F-FDG PET/CT may become the only, or at least most-decisive, criterion in the management of the neck after chemoradiotherapy.


OBJECTIVES: This review examines the effectiveness of positron emission tomography (PET) in the detection of recurrent or persistent head and neck squamous cell carcinoma after radiotherapy or chemoradiotherapy. DESIGN: A systematic review and meta-analysis of trials of PET for detecting residual/recurrent head and neck squamous cell carcinoma treated by radiotherapy or chemoradiotherapy. Trials were quality assessed using the Quality Assessment of Diagnostic Accuracy Studies tool for assessing diagnostic accuracy studies. Quantitative data were extracted and a bivariate random effects model used to calculate pooled sensitivity and specificity. SETTING: Tertiary referral head and neck centre. PARTICIPANTS: Prospective and retrospective studies, excluding reviews, which included
patients with head and neck squamous cell carcinoma who had fluorodeoxyglucose PET in the post-treatment phase following primary treatment by radiotherapy or chemoradiotherapy. **MAIN OUTCOMES MEASURES:** Quality assessment, sensitivity, specificity, false positive rates, false negative rates, positive and negative predictive values. **RESULTS:** Twenty-seven of 1871 identified studies were eligible for inclusion. The pooled sensitivity and specificity of PET for detecting residual or recurrent head and neck squamous cell carcinoma were 94% [95% confidence interval (CI), 87-97%] and 82% (95% CI, 76-86%) respectively. Positive and negative predictive values were 75% (95% CI, 68-82%), and 95% (95% CI, 92-97%) respectively. Sensitivity was greater for scans performed 10 weeks or more after treatment. **CONCLUSIONS:** Positron emission tomography is highly accurate in this role. However it is less sensitive early after treatment and has poor anatomical detail. PET may reduce the requirement for check endoscopies and planned neck dissections. A protocol for its use in post-treatment surveillance is proposed.


**PURPOSE:** To determine the accuracy and prognostic significance of post-treatment [(18)F]-fluorodeoxyglucose positron emission tomography (FDG-PET) in head-and-neck squamous cell carcinoma after radiotherapy (RT). **METHODS AND MATERIALS:** This was a retrospective study of 188 patients with head-and-neck squamous cell carcinoma who
had undergone FDG-PET within 12 months after completing RT. All living patients had $\geq 1$ year of follow-up after FDG-PET. All patients had undergone intensity-modulated RT, 128 with definitive and 60 with postoperative intensity-modulated RT. RESULTS: For all patients, the median follow-up after RT completion was 32.6 months and after FDG-PET was 29.2 months. For the neck, 171 patients had negative FDG-PET findings. Of these results, two were falsely negative. Seventeen patients had positive FDG-PET findings, of which 12 were true-positive findings. The sensitivity, specificity, positive predictive value, and negative predictive value for FDG-PET in the assessment of the treatment response in the neck was 86%, 97%, 71%, and 99%, respectively. For the primary site, 151 patients had negative FDG-PET findings, of which two were falsely negative. Thirty-seven patients had positive FDG-PET findings, of which 12 were true-positive findings. The sensitivity, specificity, positive predictive value, and negative predictive value for FDG-PET in the assessment of the treatment response in the primary site was 86%, 86%, 32.4%, and 98.7%, respectively. Patients with positive post-RT PET findings had significantly worse 3-year overall survival and disease-free survival. CONCLUSION: The results of our study have shown that the findings of post-RT FDG-PET have a high negative predictive value and are a significant prognostic factor. It can provide guidance for the management of head-and-neck cancer after definitive treatment.


PURPOSE: Survival in oral cavity squamous cell carcinoma (OSCC) depends heavily on locoregional control. In this prospective study, we sought to investigate whether preoperative maximum standardized uptake value of the neck lymph nodes (SUVnodal-max) may predict prognosis in OSCC patients. METHODS AND MATERIALS: A total of 120 OSCC patients with pathologically positive lymph nodes were investigated. All subjects underwent a [18F]fluorodeoxyglucose (FDG) positron emission tomography (PET) scan within 2 weeks before radical surgery and neck dissection. All patients were followed up for at least 24 months after surgery or until death. Postoperative adjuvant therapy was performed in the presence of pathologic risk factors. Optimal cutoff values of SUVnodal-max were chosen based on 5-year disease-free survival (DFS), disease-specific survival (DSS), and overall survival (OS). Independent prognosticators were identified by Cox regression analysis. RESULTS: The median follow-up for surviving patients was 41 months. The optimal cutoff value for SUVnodal-max was 5.7. Multivariate analyses identified the following independent predictors of poor outcome: SUVnodal-max >/=5.7 for the 5-year neck cancer control rate, distant metastatic rate, DFS, DSS, and extracapsular spread (ECS) for the 5-year DSS and OS. Among ECS patients, the presence of a SUVnodal-max >/=5.7 identified patients with the worst prognosis. CONCLUSION: A SUVnodal-max of 5.7, either alone or in combination with ECS, is an independent prognosticator for 5-year neck cancer control.

(18)F-fluorodeoxyglucose (FDG)-positron emission tomography (PET) has been reported to identify primary tumors in patients with cervical metastases from cancer
Utility of 18F-fluorodeoxyglucose positron emission tomography in the preoperative staging of squamous cell carcinoma of the oropharynx. Kim MR, Roh JL, Kim JS, Lee JH, Cho KJ, Choi SH, Nam SY, Kim SY. However, few reports have assessed the use of combined FDG-PET/computed tomography (CT) in this setting. We therefore examined the utility of combined FDG-PET/CT in the detection of primary tumors and unrecognized metastases in these patients. Patients with previously untreated CUPs underwent head and neck CT and whole-body FDG-PET/CT before panendoscopy and guided biopsy. The diagnostic accuracy of CT and FDG-PET/CT in detecting primary tumors and cervical metastases was compared with that of histopathology. The ability of FDG-PET/CT to detect distant metastases was also tested. Of the 44 eligible patients, 16 had occult primary tumors in the head and neck. FDG-PET/CT was significantly more sensitive than CT for detecting primary tumors (87.5% vs. 43.7%, P=.016), but their specificity did not differ (82.1% vs. 89.3%, P=.500). Thirty-four of 44 patients underwent neck dissection; 67 of 182 dissected cervical levels had metastatic nodal diseases. On a level-by-level basis, FDG-PET/CT was significantly more sensitive than CT (94.0% vs. 71.6%, P<.001), but the two methods were equally specific (94.8% vs. 96.5%). FDG-PET/CT correctly detected distant metastases in 6 of 6 patients. Combined FDG-PET/CT is a useful screening method for primary tumor detection, accurate nodal staging, and distant metastases in patients with CUPs.

Combined (18)F-FDG-PET/CT Imaging in Radiotherapy Target Delineation for Head-and-Neck Cancer. Guido A, Fuccio L, Rombi B, Castellucci P, Cecconi A, Bunkheila F,

PURPOSE: To evaluate the effect of the use of (18)F-fluorodeoxyglucose (FDG)-positron emission tomography (PET)/computed tomography (CT) in radiotherapy target delineation for head-and-neck cancer compared with CT alone.

METHODS AND MATERIALS: A total of 38 consecutive patients with head-and-neck cancer were included in this study. The primary tumor sites were as follow: 20 oropharyngeal tumors, 4 laryngeal tumors, 2 hypopharyngeal tumors, 2 paranasal sinuses tumors, 9 nasopharyngeal tumors, and 1 parotid gland tumor. The FDG-PET and CT scans were performed with a dedicated PET/CT scanner in one session and then fused. Subsequently, patients underwent treatment planning CT with intravenous contrast enhancement. The radiation oncologist defined all gross tumor volumes (GTVs) using both the PET/CT and CT scans. RESULTS: In 35 (92%) of 38 cases, the CT-based GTVs were larger than the PET/CT-based GTVs. The average total GTV from the CT and PET/CT scans was 34.54 cm(3) (range, 3.56-109) and 29.38 cm(3) (range, 2.87-95.02), respectively (p < 0.05). Separate analyses of the difference between the CT- and PET/CT-based GTVs of the primary tumor compared with the GTVs of nodal disease were not statistically significant. The comparison between the PET/CT-based and CT-based boost planning target volumes did not show a statistically significant difference. All patients were alive at the end of the follow-up period (range, 3-38 months). CONCLUSION: GTVs, but not planning target volumes, were significantly changed by the implementation of combined PET/CT. Large multicenter studies are needed to ascertain whether combined PET/CT in target delineation can influence the main clinical outcomes.
Section — VIII

Breast
Breast Cancer

Introduction
Breast cancer is one of the most common cancers seen in women. It presents as a painless lump in most of the case, however with availability of screening methods, there has been a rise in the detection of very small non palpable lesions. Breast-conserving surgery (BCS) and sentinel lymph node biopsy (SLNB) have successfully replaced the more aggressive radical mastectomy (RM) and axillary lymph node dissection (ALND). Multi modality approach is practiced world wide. Neo - adjuvant chemotherapy has been considered to improve the survival in patients with locally advanced breast carcinoma. Adjuvant chemotherapy after surgery has been a long practiced approach. Radiotherapy, local RT to the chest wall and axilla after completion of chemotherapy is routine procedure. If clinical imaging has shown internal mammary nodal involvement then this region is also included. Supraclavicular region is included in cases which has revealed superior group of axillary nodal metastases.

Conventional Imaging /Staging
Mammography for suspicious malignant lesions (Irregular speculated mass, Clustered calcifications, Calcifications,
Smaller than 0.5 mm in diameter, Architectural distortion and Focal asymmetric density). CT scan of the brain, chest, abdomen, and pelvis and Isotope bone scan is performed if any of the following conditions are present - Advanced local disease, Lymph node metastases, Distant metastases, Bony symptoms.

**Evidence of PET or PET/CT in breast carcinoma.**

Diagnosis: There are no large studies which evaluate the role in diagnosing breast carcinoma.

A prospective comparative study evaluating 45 patients with 55 lesions suggests a MRI scan to have a higher sensitivity of 98% as compared to the FDG PET scan with a 80 % sensitivity when a dual point study is done and 62% when a single point study is done. This study reveals that there is an increase in the tracer uptake over time in malignant lesions while benign lesions do not show change or show decrease in uptake.

**Staging**

Multitude studies are available which propose the evidence of FDG PET having superiority in staging the disease, especially in advanced disease.

A large prospective trial evaluating 117 patients suggests a sensitivity of 93% and specificity of 75% for primary lesions. There is 20% false negative results seen in detection of axillary nodes. With respect to location of multifocal lesions PET has higher sensitivity and shows no false positives or negative for distant metastases.

Another prospective study of 48 patients suggests that FDG locates unexpected distant metastases and has an impact in treatment management due to upgrading of disease.
Retrospective analysis of 50 patients showed a sensitivity of 86% and 90% specificity for identifying distant metastases as compared to conventional imaging with higher sensitivity for detection of pulmonary metastases and mediastinal nodal disease. A recent retrospective analysis of 119 patients comparing CI to FDG PET showed a sensitivity and specificity of 87% and 83% respectively for identifying distant metastases.

**Axillary nodal staging:**
A Multi – centric prospective trial has shown FDG PET/CT to be 61% sensitive and 80% specific. False negative nodal staging was due to few and small nodes. The positive predictive value was 90% if SUV was greater than 1.8 and in conditions where there were multiple positive foci but the sensitivity was only 32%. This study suggests FDG PET study not suitable for new patients.

A Case series which evaluated 32 axillae showed that an SUV greater than 2.3 was predictive of axillary metastases.

183 patients evaluated prospectively and a comparison of FDG PET/CT with ultrasonography showed an equal sensitivity and specificity.

**Prediction/prognostication of tumor biology:**
A study evaluating 37 patients had a histological and immunohistochemistry correlation with the SUV uptake and suggested a correlation between the tumor aggressiveness i.e. Ki 67 and mitotic rate; and SUV with p- 0.0098 and 0.0018 respectively.

Another study which compared the histology of the operated specimen of mastectomy with the pre operative FDG PET scan SUV revealed that the triple negative receptor tumors with an aggressive tumor biology had a higher SUV values; early and
also the % difference SUV (early and delayed) was higher; as compared to the receptor positive tumors.

A prospective study of 152 patients showed a strong correlation of increased SUV i.e tracer uptake in tumors with higher tumor invasiveness, size, nuclear grade and estrogen receptor negativity.(p value 0.0001, 0.0001 and 0.012 respectively. If SUV of 4 was used as cut off then the high SUV was also predictive of increased risk of tumor recurrence.

**Treatment response:**
One prospective study evaluating 52 lesions in 11 patients shows a significant difference on between the fall in the SUV values in the pre and post therapy scans in responders as compared to the non responders (p value 0.003) with a longer survival in responders.

**Restaging/recurrence**
An early retrospective analysis of 62 patients comparing CI with FDG PET scan shows a better sensitivity and specificity PPV and NPV with FDG PET, and a change in treatment management in 21% of the patient population. The sensitivity and NPV was 100% in cases with normal tumor markers as compared to 80% with CI.

A study evaluating 73 patients suggested FDG PET of having a sensitivity of 80.6 and a specificity of 97.6 in diagnosing recurrence with a NPV of 98.3% in the clinical suspicious or elevated tumor marker or absent disease status.

60 patients evaluated prospectively with a clinical or radiological suspicion and compared with either histology or a follow up showed a sensitivity specificity and accuracy > 84% for local recurrence and > 97% for distant metastases.

To summarize FDG PET has shown evidence as a probably appropriate tool for staging and in restaging or recurrence as
compared to conventional investigation. Axillary nodal staging with FDG PET scan does not have a higher specificity. There is work which highlights the potential of this modality in prognosticating the disease with regards to tumor biology using FDG PET scans.

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**Dual-time-point 18F-FDG PET/CT versus dynamic breast MRI of suspicious breast lesions. Imbriaco M, Caprio MG, Limite G. AJR Nov 2008; 191 (5) 1323 - 30**

OBJECTIVE: The purpose of our study was to compare dual-time-point (18)F-FDG PET/CT, performed with the patient in the prone position, and contrast-enhanced MRI in patients with suspected breast malignancy. SUBJECTS AND METHODS: Forty-four patients with 55 breast lesions underwent two PET/CT scans (dual-time-point imaging) in the prone position and breast MRI. Sensitivity, specificity, and overall accuracy were calculated. In addition, the average percentage of change in standard uptake values (Delta%SUV(max)) between time point 1 and time point 2 was calculated for PET/CT. A final
histopathologic diagnosis was available for all patients.

RESULTS: MRI showed an overall accuracy of 95%, with sensitivity and specificity of 98% and 80%. Conversely, dual-time-point PET/CT showed an accuracy of 84% for lesions with an SUV(max) \( > \) or \( = \) 2.5 or with a positive Delta%SUV(max), with sensitivity and specificity of 80% and 100% versus 69% accuracy, 62% sensitivity (both, \( p < 0.001 \)), and 100% specificity (\( p \) not significant) for single-time-point PET/CT. On PET/CT, malignant lesions showed an increase in FDG between time points 1 and 2, with a Delta%SUV(max) of 11 +/- 24. Benign lesions showed either no change or a decrease in SUV(max) between time points 1 and 2, with a Delta%SUV(max) of -21 +/- 7. CONCLUSION: A dual time point improves PET/CT accuracy in patients with a suspected breast malignancy over single-time-point PET/CT. On PET/CT, FDG is increasingly taken up over time in breast tumors; conversely, benign lesions show a decrease in FDG uptake over time. These changes in SUV might represent a reliable parameter that can be used to differentiate benign from malignant lesions of the breast on PET/CT examination.


The present study compared the diagnostic accuracy of fluorine-18 2-deoxy-2-fluoro-D-glucose positron emission tomography (FDG-PET) with conventional staging techniques. The differentiation between malignant and benign lesions and the detection of multifocal disease, axillary and internal lymph node involvement, and distant metastases were evaluated. One hundred and seventeen female patients were prospectively examined using FDG-PET and conventional staging methods.
such as chest X-ray, ultrasonography of the breast and liver, mammography and bone scintigraphy. All patients were examined on a modern full-ring PET scanner. Histopathological analysis of resected specimens was employed as the reference method. The readers of FDG-PET were blinded to the results of the other imaging methods and to the site of the breast tumour. The sensitivity and specificity of FDG-PET in detecting malignant breast lesions were 93% and 75% respectively. FDG-PET was twofold more sensitive (sensitivity 63%, specificity 95%) in detecting multifocal lesions than the combination of mammography and ultrasonography (sensitivity 32%, specificity 93%). Sensitivity and specificity of FDG-PET in detecting axillary lymph node metastases were 79% and 92% (41% and 96% for clinical evaluation). FDG-PET correctly indicated distant metastases in seven patients. False-positive or false-negative findings were not encountered with FDG-PET. Chest X-ray was false-negative in three of five patients with lung metastases. Bone scintigraphy was false-positive in four patients. Three patients were upstaged since FDG-PET detected distant metastases missed with the standard staging procedure. It is concluded that, compared with the imaging methods currently employed for initial staging, FDG-PET is as accurate in interpreting the primary tumour and more accurate in screening for lymph node metastases and distant metastases. Due to a false-negative rate of 20% in detecting axillary lymph node metastases, FDG-PET cannot replace histological evaluation of axillary status.


Positron emission tomography combined with computed tomography (PET/CT) has been receiving increasing attention during the recent years for making the diagnosis, for
determining the staging and for the follow-up of various malignancies.

The PET/CT findings of 58 breast cancer patients (age range: 34-79 years old, mean age: 50 years) were retrospectively compared with the PET or CT scans alone. PET/CT was found to be better than PET or CT alone for detecting small tumors or multiple metastases, for accurately localizing lymph node metastasis and for monitoring the response to chemotherapy in breast cancer patients.


Purpose

To prospectively evaluate the effect of adding whole-body 18F-2-fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET) to conventional screening for distant metastases in patients with locally advanced breast cancer (LABC).

Patients and Methods

All women with LABC referred for participation in the LABC Spinoza trial were considered eligible for this study. Patients were included if chest x-ray, bone scan, liver ultrasound, or computed tomography scan performed by the referring physician failed to reveal distant metastases. They underwent whole-body FDG PET scanning before therapy. Patients with subsequently proven distant metastases were switched to alternative forms of chemotherapy, hormonal therapy, or both.

Results

Among the 48 patients evaluated with PET, 14 had abnormal FDG uptake, and metastases were suspected in 12. After simple
clinical evaluation (plain x-ray, history), 10 sites that were suggestive of abnormality remained. Further work-up revealed that four sites were metastases. Proven false positivity occurred in one patient with sarcoidosis. In the other five patients, the reason for abnormal FDG uptake (liver, lung, bone) remained unclear, and patients were treated as planned. Eleven months later, distant metastases were found in one patient at sites unrelated to the previous FDG uptake.

Conclusion

The addition of FDG PET to the standard work-up of patients with LABC may lead to the detection of unexpected distant metastases. This may contribute to a more realistic stratification between patients with true stage III breast cancer and those who are in fact suffering from stage IV disease. Abnormal PET findings should be confirmed to prevent patients from being denied appropriate treatment.


Distant metastases at primary diagnosis are a prognostic key factor in breast cancer patients and play a central role in therapeutic decisions. To detect them, chest X-ray, abdominal ultrasound, and bone scintigraphy are performed as standard of care in Germany and many centers world-wide. Although FDG PET detects metastatic disease with high accuracy, its diagnostic value in breast cancer still needs to be defined. The aim of this study was to compare the diagnostic performance of FDG PET with conventional imaging.

PATIENTS, METHODS: A retrospective analysis of 119 breast cancer patients who presented for staging was
performed. Whole-body FDG-PET (n = 119) was compared with chest X-ray (n = 106) and bone scintigraphy (n = 95). Each imaging modality was independently assessed and classified for metastasis (negative, equivocal and positive. The results of abdominal ultrasound (n = 100) were classified as negative and positive according to written reports. Imaging results were compared with clinical follow-up including follow-up imaging procedures and histopathology.

RESULTS: FDG-PET detected distant metastases with a sensitivity of 87.3% and a specificity of 83.3%. In contrast, the sensitivity and specificity of combined conventional imaging procedures was 43.1% and 98.5%, respectively. Regarding so-called equivocal and positive results as positive, the sensitivity and specificity of FDG-PET was 93.1% and 76.6%, respectively, compared to 61.2% and 86.6% for conventional imaging. Regarding different locations of metastases the sensitivity of FDG PET was superior in the detection of pulmonary metastases and lymph node metastases of the mediastinum in comparison to chest x-ray, whereas the sensitivity of FDG PET in the detection of bone and liver metastases was comparable with bone scintigraphy and ultrasound of the abdomen.

CONCLUSIONS: FDG-PET is more sensitive than conventional imaging procedures for detection of distant breast cancer metastases and should be considered for additional staging especially in patients with high risk primary breast cancer.

Purpose

To determine the accuracy of positron emission tomography with fluorine-18–labeled 2-fluoro-2-deoxy-D-glucose (FDG-PET) in detecting axillary nodal metastases in women with primary breast cancer.

Patients and Methods

In this prospective multicenter study, 360 women with newly diagnosed invasive breast cancer underwent FDG-PET. Images were blindly interpreted by three experienced readers for abnormally increased axillary FDG uptake. Imaging results from 308 assessable axillae were compared with axillary node pathology.

Results

For detecting axillary nodal metastasis, the mean estimated area under the receiver operator curve for the three readers was 0.74 (range, 0.70 to 0.76). If at least one probably or definitely abnormal axillary focus was considered positive, the mean (and range) sensitivity, specificity, and positive and negative predictive values for PET were 61% (54% to 67%), 80% (79% to 81%), 62% (60% to 64%), and 79% (76% to 81%), respectively. False-negative axillae on PET had significantly smaller and fewer tumorpositive lymph nodes (2.7) than true-positive axillae (5.1; P < .005). Semiquantitative analysis of axillary FDG uptake showed that a nodal standardized uptake value (lean body mass) more than 1.8 had a positive predictive value of 90%, but a sensitivity of only 32%. Finding two or more intense foci of tracer uptake in the axilla was highly predictive of axillary metastasis (78% to 83% positive predictive value), albeit insensitive (27%).
Conclusion

FDG-PET has moderate accuracy for detecting axillary metastasis but often fails to detect axilla with small and few nodal metastases. Although highly predictive for nodal tumor involvement when multiple intense foci of tracer uptake are identified, FDG-PET is not routinely recommended for axillary staging of patients with newly diagnosed breast cancer.

Utility of 18F-fluoro-deoxyglucose emission tomography/computed tomography fusion imaging (18F-FDG PET/CT) in combination with ultrasonography for axillary staging in primary breast cancer. Shigeto Ueda, Hitoshi Tsuda, Hideki Asakawa et al. BMC Cancer 2008, 8:165

Background: Accurate evaluation of axillary lymph node (ALN) involvement is mandatory before treatment of primary breast cancer. The aim of this study is to compare preoperative diagnostic accuracy between positron emission tomography/computed tomography with 18F-fluorodeoxyglucose (18F-FDG PET/CT) and axillary ultrasonography (AUS) for detecting ALN metastasis in patients having operable breast cancer, and to assess the clinical management of axillary 18F-FDG PET/CT for therapeutic indication of sentinel node biopsy (SNB) and preoperative systemic chemotherapy (PSC).

Methods: One hundred eighty-three patients with primary operable breast cancer were recruited. All patients underwent 18F-FDG PET/CT and AUS followed by SNB and/or ALN dissection (ALND). Using 18F-FDG PET/CT, we studied both a visual assessment of 18F-FDG uptake and standardized uptake value (SUV) for axillary staging.

Results: In a visual assessment of 18F-FDG PET/CT, the diagnostic accuracy of ALN metastasis was 83% with 58% in sensitivity and 95% in specificity, and when cut-off point of SUV was set at 1.8, sensitivity, specificity, and accuracy were 36, 100, and 79%, respectively. On the other hand, the
diagnostic accuracy of AUS was 85% with 54% in sensitivity and 99% in specificity. By the combination of 18F-FDG PET/CT and AUS to the axilla, the sensitivity, specificity, and accuracy were 64, 94, and 85%, respectively. If either 18F-FDG PET uptake or AUS was positive in allixa, the probability of axillary metastasis was high; 50% (6 of 12) in 18F-FDG PET uptake only, 80% (4 of 5) in AUS positive only, and 100% (28 of 28) in dual positive. By the combination of AUS and 18F-FDG PET/CT, candidates of SNB were more appropriately selected. The axillary 18F-FDG uptake was correlated with the maximum size and nuclear grade of metastatic foci (p = 0.006 and p = 0.03).

Conclusion: The diagnostic accuracy of 18F-FDG PET/CT was shown to be nearly equal to ultrasound, and considering their limited sensitivities, the high radiation exposure by 18F-FDG PET/CT and also costs of the examination, it is likely that AUS will be more cost-effective in detecting massive axillary tumor burden. However, when we cannot judge the axillary staging using AUS alone, metabolic approach of 18F-FDG PET/CT for axillary staging would enable us a much more confident diagnosis.


Background: Positron emission tomography (PET) is a non-invasive imaging modality used in the diagnosis and staging of breast cancer. However, several factors can affect fluorodeoxyglucose (FDG) uptake by a tumor. To clarify the parameters that most affect FDG accumulation in tumors, the relationship between standardized uptake values (SUVs) and clinicopathological factors and immunohistopathological analysis was investigated in breast cancer.

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Material and Methods: PET studies were performed preoperatively on 37 patients with breast carcinoma. SUVs were counted at one hour (early phase) and at two hours (delayed phase) after FDG injection. The relationships between SUVs and 13 clinical, pathological and immunohistochimical factors were studied.

Results: A significant association was found between FDG accumulation and early and delayed phase mitotic counts (p<0.0018 and 0.0010, respectively), Ki67 positive cell percentage (p<0.0098 and 0.0062, respectively), and nuclear grade (p<0.0232 and 0.0195, respectively). On the other hand, nodal status weakly correlated with the delayed phase (p<0.0907). However, other clinicopathological parameters and immunohistopathological status, which included tumor size, age, histology, estrogen receptor, progesterone receptor and Her2/neu overexpression, did not correlate significantly with FDG uptake.

Conclusion: Mitotic count and Ki67 reflect cellular aggressiveness. These parameters were strongly correlated with tracer uptake. Thus our data suggested that the biological behavior of breast cancer is reflected in the variation of FDG uptake by the tumor. However, whether FDG uptake is a true prognostic and predictive factor remains to be confirmed in larger studies over an extended period of time.

Comparison of Triple-negative and Estrogen Receptor positive/ Progesterone Receptor-positive/HER2-negative Breast Carcinoma Using Quantitative Fluorine-18 Fluorodeoxyglucose/Positron Emission Tomography Imaging Parameters


BACKGROUND. This study was designed to investigate the fluorine-18 fluorodeoxyglucose (FDG)-positron emission
tomography (PET) imaging characteristics of triple-negative (estrogen receptor-negative [ER2]/progesterone receptor-negative [PR2]/HER2-negative [HER22]) breast carcinoma and compare the results with characteristics of ER1/PR1/HER22 breast carcinomas, which usually carry a favorable prognosis.

METHODS. Patients with newly diagnosed breast carcinoma who had undergone dual-time-point FDG-PET before any therapeutic intervention and were identified as either ER2/PR2/HER22 or ER1/PR1/HER22 (the control group) on histopathology of the surgical specimen, were considered candidates for inclusion in this analysis. These patients underwent FDG-PET as a component of a prospective study that evaluated the role of multimodality imaging for characterizing primary breast lesions and locoregional staging. Breast cancer lesions were imaged twice at approximately 63 minutes and 101 minutes after the administration of FDG. Maximum standardized uptake values (SUVmax) were measured at both time points (SUVmax1 and SUVmax2) to analyze the data generated. After FDG-PET imaging, the patients underwent either breast-conserving surgery or mastectomy, and histopathology reports were used to provide the definitive diagnosis against which the PET study results were compared.

RESULTS. In total, 88 patients with breast cancer (29 patients with ‘triple-negative’ breast cancer and 59 patients with ER1/PR1/HER22 breast malignancies) were selected among 206 individuals who were enrolled in the study protocol.

The ‘triple-negative’ group comprised 14.08% of the total study population. The age of the patients with this subtype of tumor ranged from 33 years to 75 years (mean age_standard deviation, 51.6 _ 10.1 years), and tumors in this subgroup ranged in size from 0.9 cm to 6 cm (mean size, 1.99 cm). Among the histopathologic subtypes, 25 tumors were
infiltrating ductal carcinoma (86%), and 1 tumor each (3.5% each subtype) was lobular, mixed ductal-lobular, medullary, and tubular.

For the calculation of FDG-PET parameters in this group, only patients who had undergone FDG-PET studies before any intervention were considered, and 18 patients in the triple-negative group met this criterion. According to same criterion, a control group of 59 patients with ER1/PR1/HER22 cancer who had focal FDG uptake were selected for comparison with the triple-negative population.

The breast cancer lesions were observed as areas with focally enhanced uptake of FDG in all patients (sensitivity, 100%) in the triple-negative group. The mean (standard deviation) SUVmax1 of the primary lesion for the triple-negative group was 7.27 ± 5.6, the mean SUVmax2 was 8.29 ± 6.4, and the percentage change in SUVmax (%DSUVmax) was 14.3 ± 15.8%. In the control group of 59 patients with ER1/PR1/HER22 breast carcinoma, the mean values for SUVmax1, SUVmax2, and %DSUVmax were 2.68 ± 1.9, 2.84 ± 2.2, and 3.7 ± 13.0%, respectively. The mean values for SUVmax1, SUVmax2, and %DSUVmax in the triple-negative group were significantly higher compared with the values in the nontriple-negative control group (P < 0.0032, P < 0.002, and P < 0.017, respectively). When the 2 subgroups were compared according to tumor size, grade, and stage, the SUVmax1 was significantly higher in the triple-negative group for both size categories (5.4 vs 1.9, P = 0.006; and 9.2 vs 3.5, P = 0.04) and for grade 3 tumors (9.1 vs 3.9, P = 0.022). The %DSUVmax values for patients in the triple-negative group who had tumors that measured < 2 cm and > 2 cm were 14.8 and 13.8, respectively; and the corresponding values for patients in the control group were 0.6 and 6.7, respectively. Although the mean %DSUVmax clearly was higher in the triple-negative group for both tumor size categories, comparison between the
2 groups demonstrated a statistically significant difference in tumors that measured _2 cm (P 5.016). The authors also observed that, in the triple-negative group, tumor grades were correlated significantly with the magnitude of SUVmax1 and SUVmax2 (P 5.012 and P 5.01, respectively). Stage for stage, tumors from the triple-negative group appeared to have a higher mean SUVmax1 compared with tumors from nontriple-negative control group. However, the trend reached statistical significance in patients with stage II disease.

CONCLUSIONS. Triple-negative breast tumors were associated with enhanced FDG uptake commensurate with their aggressive biology and were detected with very high sensitivity by using FDG-PET imaging.


Objective: Using integrated 18F-fluorodeoxyglucose positron emission tomography/computed tomography fusion imaging (18F-FDG PET/CT), the clinical significance of 18F-FDG uptake was evaluated in patients with primary breast cancer.

Methods: Clinicopathological correlation with the level of maximum standardized uptake values (SUV) 60 min obtained from preoperative 18F-FDG PET/CT were examined in 152 patients with primary breast cancer. The prognostic impact of the level of SUV was explored using simulated prognosis derived from computed program Adjuvant! in 136 (89%) patients with invasive ductal carcinoma (IDC).
Results: High SUV level was significantly correlated with tumor invasive size (\( \leq 2 \) cm) (\( P \leq 0.0001 \)), higher score of nuclear grade (\( P \leq 0.0001 \)), nuclear atypia (\( P \leq 0.0001 \)) and mitosis counts (\( P \leq 0.0001 \)), negative hormone receptor status (\( P = 0.001 \)), high score of cerbB-2 expression (\( P = 0.006 \)), lymph node metastasis (\( P = 0.002 \)), and IDC in comparison with invasive lobular carcinoma (\( P = 0.004 \)). Multivariate analyses showed tumor invasive, size, nuclear grade and estrogen receptor negativity were significantly correlated with SUV in primary breast cancer (\( P \leq 0.0001, \leq 0.0001, \text{ and } \leq 0.012 \), respectively), and nuclear grade was significantly correlated with SUV in tumors of invasive size \( 2 \) cm or less (\( P \leq 0.0001 \)). Tumors with high SUV (cutoff value 4.0) showed higher relapse and mortality rate compared to those with low SUV (\( P \leq 0.0001 \)).

Conclusions: High uptake of 18F-FDG would be predictive of poor prognosis in patients with primary breast cancer, and aggressive features of cancer cells in patients with early breast cancer. 18F-FDG PET/CT could be a useful tool to pretherapeutically predict biological characteristics and baseline risk of breast cancer.


Chemotherapy is currently the treatment of choice for patients with high-risk metastatic breast cancer. Clinical response is determined after several cycles of chemotherapy by changes in tumor size as assessed by conventional imaging procedures including CT, MRI, plain film radiography, or ultrasound. The aim of this study was to evaluate the use of sequential 18F-FDG PET to predict response after the first and second cycles of standardized chemotherapy for metastatic breast cancer.
Methods: Eleven patients with 26 metastatic lesions underwent 31 18FFDG PET examinations (240–400 MBq of 18F-FDG; 10-min 2-dimensional emission and transmission scans). Clinical response, as assessed by conventional imaging after completion of chemotherapy, served as the reference. 18F-FDG PET images after the first and second cycles of chemotherapy were analyzed semiquantitatively for each metastatic lesion using standardized uptake values (SUVs) normalized to patients’ blood glucose levels. In addition, whole-body 18F-FDG PET images were viewed for overall changes in the 18F-FDG uptake pattern of metastatic lesions within individual patients and compared with conventional imaging results after the third and sixth cycles of chemotherapy.

Results: After completion of chemotherapy, 17 metastatic lesions responded, as assessed by conventional imaging procedures. In those lesions, SUV decreased to 72% _21% after the first cycle and 54% _ 16% after the second cycle, when compared with the baseline PET scan. In contrast, 18F-FDG uptake in lesions not responding to chemotherapy (n _9) declined only to 94% _ 19% after the first cycle and 79% _9% after the second cycle. The differences between responding and nonresponding lesions were statistically significant after the first (P _ 0.02) and second (P _ 0.003) cycles. Visual analysis of 18F-FDG PET images correctly predicted the response in all patients as early as after the first cycle of chemotherapy. As assessed by 18F-FDG PET, the overall survival in nonresponders (n _5) was 8.8 mo, compared with 19.2 mo in responders (n _6).

Conclusion: In patients with metastatic breast cancer, sequential 18F-FDG PET allowed prediction of response to treatment after the first cycle of chemotherapy. The use of 18F-FDG PET as a surrogate endpoint for monitoring therapy response offers improved patient care by individualizing treatment and avoiding ineffective chemotherapy.

Aim. To evaluate the role of F-18-fluorodeoxyglucose positron-emission tomography (F-18 FDG PET) in the follow-up of breast carcinoma in case of clinical suspicion of local recurrence or distant metastases and/or tumor marker increase in correlation to conventional imaging.

Material and Methods. Retrospective analysis of the results of F-18 FDG PET (ECAT ART®, Siemens CTI MS) of 62 patients (age 58.5 ± 12.8) with surgically resected breast carcinoma (time interval after surgery, 86 ± 82 months, mean follow-up 24 ± 12.6 months). Patient- and lesion-based comparison with conventional imaging (CI) including mammography (MG), ultrasonography (US), computerized tomography (CT), magnetic resonance imaging (MRI), radiography (XR) and bone scintigraphy (BS). Furthermore, we evaluated the influence on tumor stage and therapeutic strategy. A visual qualitative evaluation of lesions was performed.

Results. On a patient base, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy for detecting local recurrence or distant metastases were calculated to be 97%, 82%, 87%, 96% and 90%) compared with 84%, 60%, 73%, 75% and 74% with CI. On a lesion base, significantly more lymph node (84 vs. 23, P < 0.05) and fewer bone metastases (61 vs. 97, P < 0.05) could be detected by using F-18 FDG PFT compared with CI. Sclerotic bone lesions were predominantly detected by BS.
On the other hand, there were several patients with more FDG positive bone lesions and also mixed FDG positive/Tc-99m methylene-diphosphonate (MDP) negative and FDG negative/Tc-99m MDP positive metastases. In case of normal tumor markers, sensitivity, specificity, PPV, NPV and accuracy for detecting local recurrence or distant metastases were calculated to be 100%. 85.0%, 78.6%, 100% and 90.3% for FDG PET and 80%. 50%, 50%, 80% and 61.5% for CI. An upstaging could be observed in 9.7% (6/62) and downstaging in 12.9% (8/62), leading to a change in therapeutic regimen in 13 patients (21%).

Conclusions. F-18 FDG PET demonstrates apparent advantages in the diagnosis of metastases in patients with breast carcinoma, compared with conventional imaging on a patient base. On a lesion base, significantly more lymph node and less bone metastases can be detected by using F-18 FDG PET compared with conventional imaging, including bone scintigraphy. In patients with clinical suspicion but negative tumor marker profile, too, F-18 FDG PET seems to be a reliable imaging tool for detection of tumor recurrence or metastases. Considering the high predictive value of F-18 FDG PET, tumor stage and therapeutic strategy will be reconsidered in several patients.


BACKGROUND:

The aim of this study was to investigate the diagnostic value of FDG PET in the follow-up for breast cancer in disease-free patients and patients suspected of having recurrent or metastatic disease. As a single imaging tool, PET can be
compared with the conventional diagnostic means used for different examination sites.

PATIENTS AND METHODS: A total of 73 PET studies were carried out on 57 patients who had been diagnosed as having breast cancer. Sixteen patients had two PET scans. Thirty-eight scans (52.%) were performed in a follow-up setting. Thirty-five PET scans were performed in patients suspected of having recurrent disease or elevated tumor marker. Depending on the region of suspicion, conventional imaging included computed tomography, magnetic resonance imaging, chest X-ray, ultrasound and X-ray. All the patients in our study were followed-up for a period of 12 months.

RESULTS: PET correctly identified metastatic or recurrent disease in 25 out 27 cases of clinical suspicion. In patients examined because of elevated tumour marker CA 15-3, PET was able to detect recurrence or metastatic disease in six of the eight patients. The absence of disease was correctly diagnosed by PET in 35 out of 38 scans in 24 patients in the follow-up for breast cancer. The overall sensitivity and specificity for PET was 80.6% and 97.6%, respectively. On the basis of a yearly rate of disease progression of 5-8%, the mean positive predictive value was 74.5% and the mean negative predictive value 98.3%.

CONCLUSION: PET has been shown to have impact on the staging and management of recurrent or metastatic breast cancer in cases of suspicion and in a follow-up setting. The current Oncological situation can be clarified with a single basic imaging modality.
Section — IX

Endocrines
Thyroid Cancer

Introduction
Thyroid Cancer is the commonest endocrine malignancy. The differentiated malignancies are a spectrum- with well differentiated on one end and the poorly differentiated on the other end. High risk group of tall cell variant, squamous type have a complex behavior. Medullary carcinoma arising from the C Cells may present also as a part of familial or Multiple Endocrine Neoplasia. Adequate Thyroid surgery followed by radiation either through isotopes or external radiation is the treatment plan in most situations.

Current staging/imaging
Ultrasound, Fine needle Aspiration cytology, isotope scanning is the main stay for imaging most thyroid disorders. Computerized Tomography is useful in the assessment of retrosternal extension and mediastinal disease. Plain x-ray, CECT are useful in imaging suspected metastases from thyroid carcinoma. Isotope scan done after ablative therapy (post therapy scan) picks up occult metastases not seen in earlier scans. Medullary carcinoma thyroid are evaluated with CECT of the neck and thorax. In the post operative period tumor
markers are used in follow-up. With rising markers, USG, CECT are used to detect occult nodes, liver, lung and bone metastases.

**Summary of Evidence for PET**

Evaluation of indeterminate thyroid nodules with FDG has produced conflicting results with SUV and focality of uptake being high predictors of malignancy in one study and the same being labeled as non specific in another. Diffuse uniform uptake of FDG in the thyroid gland in FDG PET studies done for other indications has been labeled to be due to thyroiditis and hypothyroid state. Restaging with FDG PET in patients of differentiated thyroid cancer after surgery & radio iodine therapy with high thyroglobulin and absent 131Iodine uptake has been supported by several studies. The clinical impact has been in identifying lesions that could be surgically removed leading to a fall in Tg levels. At the preoperative staging level, FDG PET scan does not add to the accuracy of USG and CECT.

Medullary carcinoma of thyroid in post operative period with rising Calcitonin (above 500pg/ml), is evaluated with FDG PET. The FDG PET has highest accuracy for liver metastases, followed by lung, skeletal metastases and followed by node metastases. PET/CT done with F DOPA and 68 Ga DOTA TOC appears more fruitful and has highest accuracy for node, lung, skeletal and parenchymal lesions. 124 I PET/CT studios have shown marginally higher accuracy in detection of lesions in rising Tg, non iodine concentrating metastases workup.
### Timing of the PET/CT

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### Selected Abstracts:


PURPOSE: To investigate clinical implications of FDG uptake in the thyroid glands in patients with advanced breast carcinoma by comparing metabolic and morphologic patterns on positron emission tomography (PET)/computed tomography (CT). METHODS: The institutional review board
waived the requirement for informed consent. A retrospective analysis was performed in 146 women (mean age 54 years) with advanced breast carcinoma who received systemic treatment. All patients underwent PET-CT before and after treatment. All PET-CT studies were reviewed in consensus by two reviewers. Morphologic changes including volume and mean parenchymal density of the thyroid glands were evaluated. Maximum standardized uptake value (SUVmax) and total lesion glycolysis (TLG) were determined to evaluate metabolic changes. These parameters were compared between patients with chronic thyroiditis who received thyroid hormone replacement therapy and those who did not. RESULTS: Of the 146 patients, 29 (20%) showed bilaterally diffuse uptake in the thyroid glands on the baseline PET-CT scan. The SUVmax showed a linear relationship with volume (r = 0.428, p = 0.021) and the mean parenchymal density (r = -0.385, p = 0.039) of the thyroid glands. In 21 of the 29 patients (72%) with hypothyroidism who received thyroid hormone replacement therapy, the volume, mean parenchymal density, SUVmax, and TLG of the thyroid glands showed no significant changes. In contrast, 8 of the 29 patients (28%) who did not receive thyroid hormone replacement therapy showed marked decreases in SUVmax and TLG. CONCLUSION: Diffuse thyroid uptake on PET-CT represents active inflammation caused by chronic thyroiditis in patients with advanced breast carcinoma. Diffuse thyroid uptake may also address the concern about subclinical hypothyroidism which develops into overt disease during follow-up.

PMID: 19156410

Is there a role for fluorodeoxyglucose positron emission tomography/computed tomography in cytologically indeterminate thyroid nodules? Hales NW, Krempl GA,

OBJECTIVE: The aim of this study was to determine the accuracy of the fluorine 18 ((18)F)-labeled fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) scan in the evaluation of thyroid nodules in which the cytopathology of fine-needle aspiration (FNA) biopsies are classified as “indeterminate,” ie, either follicular or Hürthle cell lesion. METHODS: At an academic medical center, we conducted a prospective pilot study of 15 patients with thyroid nodules in whom adequate FNA was diagnosed as indeterminate. All patients underwent a whole-body FDG-PET/CT scan followed by thyroidectomy. Preoperative FDG-PET/CT results and the histopathology of the surgical specimen were compared and statistically analyzed. RESULTS: The FNA demonstrated follicular cells in 11 (73%) patients, Hürthle cells in 3 (20%) patients, and both types of cells in 1 (7%) patient. The histopathology of the surgical specimen revealed thyroid cancer in 7 (47%) patients. The FDG-PET/CT scan was positive in 8 patients; 4 (50%) patients were found to have cancer. The FDG-PET/CT scan was negative in 7 patients. Four of these patients had benign lesions and 3 had thyroid carcinoma. Thus, 4 (27%) patients had false-positive FDG-PET/CT scans and 3 (20%) patients had false-negative studies. The sensitivity of FDG-PET/CT to detect a malignant focus was 57% with a specificity of 50%. The positive predictive value was 50% and the negative predictive value was 57%. CONCLUSIONS: In this pilot study of patients with cytologically indeterminate thyroid nodules, FDG-PET/CT was not a predictable indicator of benign or malignant disease. Although a larger series may elucidate a role for FDG-PET/CT, the relatively low predictability shown in this study should caution clinicians about using FDG-PET/CT to consider foregoing thyroidectomy for cytologically indeterminate nodules.

PMID: 18314022

OBJECTIVE: To determine if quantification of [18F]fluorodeoxyglucose (18F-FDG) uptake in a thyroid nodule found incidentally on whole-body 18F-FDG positron emission tomography-computed tomography (PET-CT) can be used to discriminate between malignant and benign aetiology. METHODS: A retrospective review of all patients with focally high uptake in the thyroid as an incidental finding on 18F-FDG PET-CT from May 2003 through May 2006. The uptake in the nodules was quantified using the maximum standardized uptake value (SUVmax). The aetiology was determined by cytology and/or ultrasound, or on histopathology. RESULTS: Incidental focally high uptake was found in 79/7347 patients (1.1%). In 31/48 patients with adequate follow-up, a benign aetiology was determined. Median SUVmax for the benign group was 5.6, range 2.5-53. Malignancy was confirmed in 15/48 patients. The malignancies were papillary thyroid carcinoma in 12, metastasis from squamous cell carcinoma in one, and lymphoma in two. Median SUVmax for the malignant lesions was 6.4, range 3.5-16. Cytology suspicious for follicular carcinoma was found in 2/48 patients. No statistical difference (P=0.12) was found among the SUVmax between the benign and malignant groups. CONCLUSION: Focally high uptake of 18F-FDG in the thyroid as an incidental finding occurred in 1.1% of the patients. Malignancy was confirmed or was suspicious in 17/48 (35%) of the patients that had adequate follow-up. There was no significant difference in the SUVmax between benign and malignant nodules.

PMID: 17414887

In this retrospective study, we investigated whether the (18)F-FDG uptake pattern and CT findings improved the accuracy over the standardized uptake value (SUV) for differentiating benign from malignant focal thyroid lesions incidentally found on (18)F-FDG PET/CT. We also defined the prevalence of these lesions and their risk for cancer. METHODS: (18)F-FDG PET/CT was performed on 1,763 subjects without a previous history of thyroid cancer from May 2003 to June 2004. Two nuclear medicine physicians and 1 radiologist interpreted PET/CT images, concentrating on the presence of focal thyroid lesions, the maximum SUV of the thyroid lesion, the pattern of background thyroid (18)F-FDG uptake, and the CT attenuation pattern of the thyroid lesion. RESULTS: The prevalence of focal thyroid lesions on PET/CT was 4.0% (70/1,763). Diagnostic confirmation was done on 44 subjects by ultrasonography (US)-guided fine-needle aspiration (n = 29) or US with clinical follow-up (n = 15). Among 49 focal thyroid lesions in these 44 subjects, 18 focal thyroid lesions of 17 subjects were histologically proven to be malignant (papillary cancer in 16, metastasis from esophageal cancer in 1, non-Hodgkin’s lymphoma in 1). Therefore, the cancer risk of focal thyroid lesions was 36.7% on a lesion-by-lesion basis or 38.6% on a subject-by-subject basis. The maximum SUV of malignant thyroid lesions was significantly higher than that of benign lesions (6.7 +/- 5.5 vs. 10.7 +/- 7.8; P < 0.05). When only the maximum SUV was applied to differentiate benign from malignant focal thyroid lesions for the receiver-operating-characteristic curve analysis, the area under the curve (AUC) of PET was 0.701. All 16 focal thyroid lesions with very low attenuation or nonlocalization on CT images, or with accompanying diffusely increased thyroid
(18)F-FDG uptake, were benign. When those lesions were regarded as benign lesions, irrespective of the maximum SUV, the AUC of PET/CT was significantly improved to 0.878 (P < 0.01). CONCLUSION: Focal thyroid lesions incidentally found on (18)F-FDG PET/CT have a high risk of thyroid malignancy. Image interpretation that includes (18)F-FDG uptake and the CT attenuation pattern, along with the SUV, significantly improves the accuracy of PET/CT for differentiating benign from malignant focal thyroid lesions.

PMID: 16595494

BACKGROUND: Fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography ((18)FDG-PET/CT) has become an important tool in the postoperative management of de-differentiated thyroid cancer. The utility of this imaging modality in the preoperative assessment of thyroid nodules is unclear. This study was designed to determine whether (18)FDG-PET/CT improves the preoperative diagnosis of thyroid nodules. METHODS: A total of 31 patients with 48 lesions underwent fine-needle aspiration and (18)FDG-PET/CT before surgical resection of thyroid nodules. PET/CT images were obtained 1 hour after intravenous administration of (18)FDG. Standard uptake values were calculated for regions of increased (18)FDG uptake. CT scans were evaluated to identify thyroid pathology. Final pathologic diagnoses were compared with PET/CT findings. RESULTS: Fifteen of 48 lesions were malignant and 33 were benign. Nine of 15 malignant lesions were (18)FDG-avid (sensitivity 60%). Thirty of 33 benign lesions were (18)FDG-cold (specificity 91%). Positive and negative predictive values were 75% and 83%, respectively. CONCLUSIONS: (18)FDG-
PET/CT provides a high negative predictive value for malignancy, making this a potentially useful tool in the evaluation of thyroid nodules with indeterminate fine-needle aspiration. However further studies with larger sample sizes are needed to determine the true efficacy of this test.

PMID: 16360405 [PubMed - indexed for MEDLINE]


Hürthle cell carcinoma is an uncommon and occasionally aggressive differentiated thyroid cancer associated with increased mortality compared with other differentiated thyroid malignancies. Because it generally has lower iodine avidity, 18F-FDG PET has been suggested as a more accurate imaging modality. However, there is limited information with regard to the true diagnostic accuracy and prognostic value of 18F-FDG PET in this disease. METHODS: All patients with Hürthle cell thyroid cancer who underwent their first 18F-FDG PET scan between May 1996 and February 2003 were identified retrospectively. 18F-FDG PET scans were reviewed and compared with all available imaging studies, including CT, ultrasound, and radioiodine scintigraphy (RIS). Abnormal 18F-FDG uptake was assessed visually and by measuring the maximum standardized uptake value (SUVmax) of the most intense lesion. Clinical follow-up for at least 1 y or until death was required for inclusion. RESULTS: Forty-four patients met inclusion criteria. The median follow-up was 2.9 y. There were 24 positive and 20 negative 18F-FDG PET scans with 1 false-positive and 1 false-negative study, resulting in a diagnostic sensitivity of 95.8% and a specificity of 95%. In 5 of 11 patients who had both positive CT and 18F-FDG PET findings, 18F-FDG PET revealed additional sites of disease. Furthermore, 18F-FDG PET correctly classified as negative 3 patients with false-positive CT findings. In 3 of 6 patients with positive
RIS, 18F-FDG PET revealed additional sites of metastatic disease. Ten patients with positive 18F-FDG PET had negative RIS. Only 1 patient with negative 18F-FDG PET had positive RIS. The SUVmax also provided prognostic information: In a stepwise fashion, each increase in intensity by SUVmax unit was associated with a 6% increase in mortality (P < 0.001). The 5-y overall survival in patients with SUVmax < 10 was 92%; it declined to 64% in those with SUVmax > 10 (P < 0.01). CONCLUSION: 18F-FDG PET has excellent diagnostic accuracy in Hürthle cell thyroid cancer patients, improving on CT and RIS. Intense 18F-FDG uptake in lesions is an indicator of a poor prognosis. Our data suggest that all patients with Hürthle cell thyroid cancer should undergo 18F-FDG PET as part of their initial postoperative staging and periodically to screen for occult recurrence, particularly in patients with elevated serum thyroglobulin.

PMID: 16883003 [PubMed - indexed for MEDLINE]

**Integrated PET/CT in differentiated thyroid cancer: diagnostic accuracy and impact on patient management.**


The aim of this study was to investigate the diagnostic accuracy and impact on patient management of the new integrated PET/CT modality in patients with suspected iodine-negative, differentiated thyroid carcinoma (DTC). METHODS: Forty patients with DTC and a suggestion of iodine-negative tumor tissue underwent PET/CT examination (370 MBq (18)F-FDG, coregistered PET/CT whole-body images). As the first step of analysis, PET and CT images were scored blindly and independently by 2 nuclear medicine physicians and 2 radiologists. A 5-point scale was used. The second step consisted of a consensus reading, during which a virtual side-by-side fusion of PET and CT images was initially evaluated and afterward the “real” fusion (i.e., coregistered) PET/CT
images were also scored with the same 5-point scale. The imaging results were compared with histopathologic findings and the course of disease during further follow-up examinations. RESULTS: One hundred twenty-seven lesions in 40 patients were evaluated. Diagnostic accuracy was 93% and 78% for PET/CT and PET, respectively (P = 0.049, per-patient analysis). In 17 (74%) of 23 patients with suspicious (18)F-FDG foci, integrated PET/CT added relevant information to the side-by-side interpretation of PET and CT images by precisely localizing the lesion(s). In tumor-positive PET patients, PET/CT fusion by coregistration led to a change of therapy in 10 (48%) patients. Futile surgery was prevented in an additional 3 patients. CONCLUSION: Integrated PET/CT is able to improve diagnostic accuracy in a therapeutically relevant way in patients with iodine-negative DTC. By precisely localizing tumor tissue, image fusion by integrated PET/CT is clearly superior to side-by-side interpretation of PET and CT images.

PMID: 16595495


The purpose of this prospective study was to compare the value of DOPA PET-CT with FDG PET-CT in the detection of malignant lesions in patients with medullary thyroid carcinoma (MTC). Twenty-six consecutive patients (10 men, 16 women, mean age 59 +/- 14 years) with elevated calcitonin levels were evaluated in this prospective study. DOPA and FDG PET-CT modalities were performed within a maximum of 4 weeks (median 7 days) in all patients. The data were evaluated on a patient- and lesion-based analysis. The final diagnosis of positive PET lesions was based on histopathological findings.
and/or imaging follow-up studies (i.e., DOPA and/or FDG PET-CT) for at least 6 months (range 6-24 months). In 21 (21/26) patients at least one malignant lesion was detected by DOPA PET, while only 15 (15/26) patients showed abnormal FDG uptake. DOPA PET provided important additional information in the follow-up assessment in seven (27%) patients which changed the therapeutic management. The patient-based analysis of our data demonstrated a sensitivity of 81% for DOPA PET versus 58% for FDG PET, respectively. In four (4/26) postoperative patients DOPA and FDG PET-CT studies were negative in spite of elevated serum calcitonin and CEA levels as well as abnormal pentagastrin tests. Overall 59 pathological lesions with abnormal tracer uptake were seen on DOPA and/or FDG PET studies. In the final diagnosis 53 lesions proved to be malignant. DOPA PET correctly detected 94% (50/53) of malignant lesions, whereas only 62% (33/53) of malignant lesions were detected with FDG PET. DOPA PET-CT showed superior results to FDG PET-CT in the preoperative and follow-up assessment of MTC patients. Therefore, we recommend DOPA PET-CT as a one-stop diagnostic procedure to provide both functional and morphological data in order to select those patients who may benefit from (re-)operation with curative intent as well as guiding further surgical procedures.

PMID: 19156423


(18)F-FDG PET value for the assessment of neuroendocrine tumours (NET) is limited. Preliminary studies indicate that somatostatin receptor PET using (68)Ga-DOTA-peptides is more accurate for disease assessment and provide additional data on receptor status, that are crucial for targeted radionuclide
therapy. At present, however, few papers investigated the role of \(^{68}\)Ga-DOTA-NOC PET in NET, especially in unusual situations. The purpose of the present study was to evaluate \(^{68}\)Ga-DOTA-NOC for the evaluation of NET of uncommon presentation. Patients with biopsy-proven NET were scheduled for \(^{68}\)Ga-DOTA-NOC PET; we excluded from further evaluation cases with most common NET tumours (gastro-entero-pancreatic and pulmonary localization of primary lesion, MEN syndromes, medullary thyroid carcinoma, pheochromocytomas). PET results were compared with findings of conventional imaging, including CT, ultrasonography, MR and somatostatin receptor scintigraphy; finally PET results were compared with follow-up data with respect to the impact on patient management. Fourteen patients were finally enrolled; primary tumours were located at uterine level (3 cases), prostate (3 cases), ovary (1 case), kidney (1 case), breast (1 case), ear (1 case); also 3 cases of paraganglioma (at neck, abdominal and mediastinum level) and 1 case of lymphoma were included. \(^{68}\)Ga-DOTA-NOC PET was positive, showing at least 1 lesion, in 6/14 cases while 5 cases turned out negative and 2 inconclusive. On a clinical basis, \(^{68}\)Ga-DOTA-NOC provided additional information in comparison to conventional imaging procedures in 7/14 cases, and was considered useful in 12/14 patients, with 8 patients in which \(^{68}\)Ga-DOTA-NOC PET was determinant for patient’s management. Although the number of patients studied is limited, our data show that \(^{68}\)Ga-DOTA-NOC can be usefully applied for the evaluation of NET of uncommon presentation; in particular very promising results were obtained in paraganglioma. On the other hand, care has to be paid when studying lesions localized at sites of physiological concentration of the tracer, and in presence of inflammation.

PMID: 18358680

PURPOSE: This study sought to compare iodine-124 positron emission tomography/computed tomography (124I-PET/CT) and 2-[18F]fluoro-2-deoxy-D-glucose- (FDG-) PET in the detection of recurrent differentiated thyroid carcinoma (DTC) lesions in patients with increasing serum thyroglobulin (Tg), Tg-antibodies, or both, but without pathological cervical ultrasonography. We assessed the lesion detection accuracy of 124I-PET alone, CT alone, (124)I-PET/CT, FDG-PET, and all these modalities combined. MATERIAL AND METHODS: The study included 21 patients (9 follicular, 12 papillary DTC) who had been rendered disease-free by thyroidectomy and radiiodine treatment (RIT) and followed up for 21-275 months after the last RIT. In all patients, FDG-PET was performed first. Within 1 week, 124I-PET/CT was performed 24 h after oral administration of 43 +/- 11 MBq 124I. Imaging results were correlated with further clinical follow-up with (n = 12) or without (n = 9) post-study histology as the reference standard. RESULTS: The sensitivities for DTC lesion detection were: 124I-PET, 49%; CT, 67%; 124I-PET/CT, 80%; FDG-PET, 70%; and all modalities combined, 91%. For local recurrences (distant metastases), the sensitivities were: 124I-PET, 60% (45%); CT, 20% (84%); and FDG-PET, 65% (71%). One-third of lesions demonstrated pathological tracer uptake with both 124I- and FDG-PET, while two-thirds were positive with only one of these modalities. CONCLUSION: Used together, 124I-PET and CT allow localization of foci of highly specific 124I uptake as well as non-iodine-avid lesions. The combination of 124I-PET/CT and FDG-PET improves restaging in recurrent DTC by enabling detection on whole-body scans of local recurrence or metastases that are often not
found if only one of the methods or other imaging modalities are applied.

PMID: 18193222


BACKGROUND: 18-F-fluoro-2-deoxyglucose positron emission tomography ((18)FDG-PET) is useful in the detection of iodine-negative differentiated thyroid carcinoma (DTC). The aim of this prospective study was to assess therapeutic impact of (18)FDG-PET imaging using a PET/computed tomography (CT) system in patients with iodine-negative recurrence of DTC. METHODS: From 2002 to 2006, patients with recurrence of DTC diagnosed by elevated thyroglobulin level and negative 131-I whole-body scan were included. RESULTS: Forty-five patients (31 women, 14 men), with a mean age of 55 years, with 36 papillary, 5 follicular, and 4 Hürthle carcinomas, were studied. All patients had previously undergone total thyroidectomy and postoperative thyroid remnant ablation with 131-I. The findings of (18)FDG-PET/CT were positive in 31 patients (68.8%) and negative in 14 (32.2%). Results were true positive in 24 of 31 patients. The sensitivity, positive predictive value, and accuracy of (18)FDG-PET/CT were 63%, 77%, and 53%, respectively. Twenty patients were operated on, 19 had neck surgery with mediastinal lymph node dissection (1 case) and lung resection (1 case), and 1 underwent lung resection. Seven patients had a stimulated thyroglobulin level <1 ng/mL. CONCLUSION: (18)FDG-PET/CT is able to select patients who can benefit from surgery. Normalization of thyroglobulin is observed in one third of operated patients.

PMID: 18063081

BACKGROUND: Whole-body (131)I scintigraphy (WBS) and serial thyroglobulin measurement (Tg) are standard methods for detecting thyroid cancer recurrence after total/near total thyroidectomy and (131)I ablation. Some patients develop elevated Tg (Tg-positive) or there is clinical suspicion of recurrence, but WBS are negative (WBS-negative). This may reflect non-iodine-avid recurrence or metastasis. In 2002, the Centers for Medicare and Medicaid Services (CMS) approved positron emission tomography with [(18)F]fluorodeoxyglucose (FDG-PET) for Tg-positive/WBS-negative patients with follicular-cell-origin thyroid cancer. Limited data are available regarding the performance of combined FDG-PET/computed tomography (FDG-PET/CT) for detecting recurrent thyroid cancer in WBS-neg patients.

METHODS: This retrospective review of prospectively collected data analyzed 65 patients who had FDG-PET/CT for suspected thyroid cancer recurrence (April 1998-August 2006). Patients were WBS-negative but were suspected to have recurrence based on Tg levels or clinical grounds. Suspected FDG-PET/CT abnormalities were reported as benign or malignant. Lesions were ultimately declared benign or malignant by surgical pathology or clinical outcome (disease progression).

RESULTS: Of 65 patients who underwent FDG-PET/CT, 47 had positive FDG-PET/CT. Of the positive FDG-PET/CT, 43 studies were true positives, with 21 (49%) confirmed pathologically by surgical resection. The four false positives (3/4 confirmed pathologically) included an infundibular cyst, an inflamed supraclavicular cyst, pneumonitis, and degenerative disc disease. Of the 18 FDG-PET/CT studies that were negative, 17 were true negatives.
and one was a false negative (metastatic papillary carcinoma). Thus, FDG-PET/CT demonstrated a patient-based sensitivity of 98%, specificity of 81%, positive predictive value of 91%, and negative predictive value of 94%. CONCLUSIONS: FDG-PET/CT is useful for detecting thyroid cancer recurrence in WBS-negative patients, and can assist decision making.

PMID: 17882493

18F-FDG PET/CT in patients with suspected recurrent or metastatic well-differentiated thyroid cancer. Shammas A, Degirmenci B, Mountz JM. J Nucl Med. 2007 Feb;48(2):221-6

PET using 18F-FDG has been shown to effectively detect various types of cancer by their increased glucose metabolism. The aim of this study was to evaluate the use of coregistered PET and CT (PET/CT) in patients with suspected thyroid cancer recurrence. METHODS: After total thyroidectomy followed by radioiodine ablation, 61 consecutive patients with elevated thyroglobulin levels or a clinical suspicion of recurrent disease underwent 18F-FDG PET/CT. Of these, 59 patients had negative findings on radioiodine (131I) whole-body scintigraphy (WBS). Fifty-three of the 61 patients had both negative 131I WBS findings and elevated thyroglobulin levels. PET/CT images were acquired 60 min after intravenous injection of 400-610 MBq of 18F-FDG using a combined PET/CT scanner. Any increased 18F-FDG uptake was compared with the coregistered CT image to differentiate physiologic from pathologic tracer uptake. 18F-FDG PET/CT findings were correlated with the findings of histology, postradioiodine WBS, ultrasound, or clinical follow-up serving as a reference. The diagnostic accuracy of 18F-FDG PET/CT was evaluated for the entire patient group and for those patients with serum thyroglobulin levels of less than 5, 5-10, and more than 10 ng/mL. RESULTS: Thirty patients had positive findings on 18F-FDG PET/CT; 26 were true-positive and
4 were false-positive. In 2 patients, increased 18F-FDG uptake identified a second primary malignancy. 18F-FDG PET/CT results were true-negative in 19 patients and false-negative in 12 patients. The overall sensitivity, specificity, and accuracy of 18F-FDG PET/CT were 68.4%, 82.4%, and 73.8%, respectively. The sensitivities of 18F-FDG PET/CT at serum thyroglobulin levels of less than 5, 5-10, and more than 10 ng/mL were 60%, 63%, and 72%, respectively. Clinical management changed for 27 (44%) of 61 patients, including surgery, radiation therapy, or chemotherapy. CONCLUSION: Coregistered 18F-FDG PET/CT can provide precise anatomic localization of recurrent or metastatic thyroid carcinoma, leading to improved diagnostic accuracy, and can guide therapeutic management. In addition, the findings of this study suggest that further assessment of 131I WBS-negative, thyroglobulin-positive patients by 18F-FDG PET/CT may aid in the clinical management of selected cases regardless of the thyroglobulin level.

PMID: 17268018 [PubMed - indexed for MEDLINE]
Neuroendocrine Tumor/ Carcinoid

Introduction
Carcinoid tumors are rare, often insidious neoplasms arising from neuroendocrine cells. The majority arise in the gastrointestinal system, and are often incidentally found during investigations, although some may present as an emergency bleed or perforation. The prosaic symptoms of flushing, diarrhea, and sweating are often overlooked; thus, the diagnosis is usually much delayed and the tumor is advanced at presentation. This diagnostic delay renders effective management difficult and adversely affects outcome.

Conventional Staging
Laboratory estimation of biochemical 5-hydroxyindole-3-acetic acid and chromogranin A. Imaging includes ultrasound, contrast enhanced computerized tomography, magnetic resonance imaging, positron emission tomography, endoscopic ultrasound, capsule endoscopy, enteroscopy and angiography are all used to diagnose, stage, and evaluate treatment response.

Topographic diagnosis (octreoscan, radio-labeled metaiodobenzylguanidine, computerized tomography, magnetic resonance imaging, positron emission tomography,
enteroclysis, endoscopy ultrasound, enteroscopy, capsule endoscopy, and angiography) of carcinoid tumors. The utility and shortcomings exist for the respective modalities. Although considerable advances have been made in establishing the diagnosis of carcinoid tumors and in defining the topography of metastatic disease, the major limitation is the inability to establish an early and timely diagnosis before the advent of metastatic disease.

**Summary of Evidence**

FDG PET has been used and found to be concentrating primary carcinoid lesions especially of the thorax and the metastatic lesions recorded by several cases recorded through several case reports. A retrospective evaluation of FDG PET study in carcinoid showed a sensitivity of 75%. In another diagnostic study it was seen that 50% of the lesions had a SUV of less than 2.5. The absence of FDG uptake does not rule out active disease.

18 F DOPA showed a sensitivity of 93% sensitivity and 89% accuracy for gastro intestinal carcinoid. This was far superior to 111In –pentetreotide that showed only 25% sensitivity and 35% accuracy. In a prospective study of 53 patients sensitivity of (18)F-DOPA PET was 95% (90-98) versus 66% (57-74) for SRS, 57% (48-66) for CT, and 79% (70-86) for combined SRS and CT (p=0.0001, PET vs combined SRS and CT). In individual-lesion analysis, corresponding sensitivities were 96% (95-98), 46% (43-50), 54% (51-58), and 65% (62-69; p<0.0001 for PET vs combined SRS and CT). The study suggested that F DOPA could be a one stop test for diagnosis, staging, prognosis and evaluate treatment response. Whole-body (11)C-5-hydroxytryptophan positron emission tomography has been evaluated as a universal imaging technique for neuroendocrine tumors. It was found to be superior to somatostatin receptor scintigraphy and computed tomography in detecting more lesions. 99mTc HYNIC
Octreotide SPECT study is a convenient one day protocol. It showed a sensitivity of 80%, specificity of 94.4% and accuracy of 82.9%.

Somatostatin Receptor Scintigraphy proved to be more sensitive than Chromograffin Assay in NeuroEndocrine Tumor patients. Tumor differentiation, disease extent and presence of liver metastases impact both SRS and CgA results, whereas non secretory activity is a negative predictor of only CgA increase. Poorly Differentiated Neuro Endocrine tumors and hindgut origin of tumors predispose to discrepancies with negative SRS but increased CgA levels study.

68Ga DOTA TOC PET has shown a sensitivity of 97%, a specificity of 92%, and an accuracy of 96%. It is superior to all the other SRS imaging modalities and when combined with contrast CT as PET/CT would yield the best possible results. It has shown best results for staging, restaging, treatment response and followup evaluation.

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Selected Abstracts


BACKGROUND: Fluorodeoxyglucose positron emission tomography (FDG-PET) is sensitive for detection of neoplastic solitary pulmonary nodules but may have decreased sensitivity for detection of carcinoid tumors. Our purpose was to determine the sensitivity of FDG-PET to detect pulmonary carcinoid tumors. METHODS: We performed a retrospective review of our institutional results regarding FDG-PET in the setting of thoracic carcinoid neoplasms. We identified 16 patients with a pathologic diagnosis of bronchial carcinoid who had an antecedent FDG-PET (from 2000 to 2004). All patients but one presented with pulmonary nodule(s). RESULTS: Sixteen patients had a diagnosis of carcinoid tumor, typical in 11 patients and atypical in 5 patients. The mean greatest pathologic dimension was 2.08 cm (range, 1.0 to 8.3 cm). Overall positron emission tomography (PET) sensitivity was 75% (12 true-positive and 4 false-negative results). The mean (+/- SD) size of carcinoids with false-negative PET results was not significantly different from carcinoids with true-positive results (1.6 +/- 0.81 cm and 2.35 +/- 1.87 cm, p = 0.54). Fifteen of 16 patients were staged pathologically, and positive nodes were found in 2 of these patients. PET lymph node staging agreed with pathologic staging in one stage 4 patient with positive lymph nodes and distant metastasis, but PET results were false negative in the other patient who had N2 with micrometastatic disease; stage IIIB. CONCLUSIONS: FDG-PET imaging is useful for evaluation of typical and atypical thoracic carcinoid tumors. Although overall PET sensitivity for detection of carcinoid
tumors is somewhat reduced as compared to non-small cell lung cancer, it is much higher than prior reports suggest.

PMID: 17218584

**Use of integrated FDG PET/CT imaging in pulmonary carcinoid tumours.** Krüger S, Buck AK, Blumstein NM et al. J Intern Med. 2006 Dec;260(6):545-50

BACKGROUND: Integrated positron emission tomography (PET)/computed tomography (CT) scanners have been recently introduced in the diagnostic work-up of suspected pulmonary malignancy and demonstrate encouraging results in the staging of nonsmall-cell lung cancer. OBJECTIVE: To evaluate the usefulness of integrated FDG PET/CT in pulmonary carcinoid tumours. SETTING: University hospital. METHODS: We studied 13 patients (mean age +/- 1 SD, 57 +/- 11 years) with pulmonary carcinoid tumours. All patients demonstrated a single pulmonary lesion. Integrated PET/CT scan and surgical resection were performed in all patients. RESULTS: The pulmonary lesion size ranged from 1.1 to 5.0 cm. Final histological diagnosis confirmed 12 typical and one atypical pulmonary carcinoid. Mean proliferation rate of the typical carcinoids was 1.7 +/- 1.4%. None of the patients had recurrent carcinoid disease or died during follow-up (864 +/- 218 days). Mean standardized uptake value (SUV) of (18)F-fluorodeoxyglucose (FDG) in typical carcinoids was 3.0 +/- 1.5 (range 1.2 - 6.6); SUV in the atypical carcinoid was remarkably high with a value of 8.5. The SUV was lower than 2.5 in 6 of 12 patients (50%). Mediastinal lymph node metastases or extrathoracic metastases were not detected in any patient. CONCLUSIONS: (18)F-fluorodeoxyglucose PET/CT imaging improves accurate localization of metabolic activity and thus the interpretation of pulmonary lesions on CT. FDG uptake in pulmonary carcinoid tumours is often lower than expected for malignant tumours. Therefore, surgical
resection or biopsy of lesions suspected to be carcinoids should be mandatory, even if they show no hypermetabolism on FDG PET images.

PMID: 17116005


**BACKGROUND:** To assess individual treatment options for patients with carcinoid tumours, accurate knowledge of tumour localisation is essential. We aimed to test the diagnostic sensitivity of 6-[fluoride-18]fluoro-levodopa ((18)F-DOPA PET), compared with conventional imaging methods, in patients with carcinoid tumours. **METHODS:** In a prospective, single-centre, diagnostic accuracy study, (18)F-DOPA PET with carbidopa pretreatment was compared with somatostatin-receptor scintigraphy (SRS), CT, and combined SRS and CT in 53 patients with a metastatic carcinoid tumour. The performance of all imaging methods was analysed for individual patients, for eight body regions, and for the detection of individual lesions. PET and CT images were fused to improve localisation. To produce a composite reference standard, we used cytological and histological findings; all imaging tests, including secondary assessments for newly found lesions; follow-up; and biochemical data. Sensitivities were calculated and compared. **FINDINGS:** In patient-based analysis, we recorded sensitivities of 100% (95% CI 93-100) for (18)F-DOPA-PET, 92% (82-98) for SRS, 87% (75-95) for CT, and 96% (87-100) for combined SRS and CT (p=0.45 for (18)F-DOPA PET vs combined SRS and CT). However, (18)F-DOPA PET detected more lesions, more positive regions, and more lesions per region than combined SRS and CT. In region-based analysis, sensitivity of (18)F-DOPA PET
was 95% (90-98) versus 66% (57-74) for SRS, 57% (48-66) for CT, and 79% (70-86) for combined SRS and CT (p=0.0001, PET vs combined SRS and CT). In individual-lesion analysis, corresponding sensitivities were 96% (95-98), 46% (43-50), 54% (51-58), and 65% (62-69; p<0.0001 for PET vs combined SRS and CT). INTERPRETATION: If the improved tumour localisation seen with (18)F-DOPA-PET compared with conventional imaging is confirmed in future studies, this imaging method could replace use of SRS, help improve prediction of prognosis, and be used to assess patients’ response to treatment for carcinoid tumours.

PMID: 16945767


Neuroendocrine tumors (NETs) can be small and situated almost anywhere throughout the body. Our objective was to investigate whether whole-body (WB) positron emission tomography (PET) with (11)C-5-hydroxytryptophan (5-HTP) can be used as a universal imaging technique for NETs and to compare this technique with established imaging methods. Forty-two consecutive patients with evidence of NET and a detected lesion on any conventional imaging (six bronchial, two foregut, 16 midgut, and two thymic carcinoids; one ectopic Cushing’s syndrome; four gastrinomas; one insulinoma; six nonfunctioning endocrine pancreatic tumors; one gastric carcinoid, one paraganglioma; and two endocrine-differentiated pancreatic carcinomas) were studied. The WB-(11)C-5-HTP-PET examinations were compared with WB-computed tomography (CT) and somatostatin receptor
scintigraphy (SRS). Tumor lesions were imaged with PET in 95% of the patients. In 58% of the patients, PET could detect more lesions than SRS and CT and equal numbers in 34%, whereas in three cases, SRS or CT showed more lesions. In 84% (16 of 19 patients), PET could visualize the primary tumor compared with 47 and 42% for SRS and CT, respectively. The surgically removed PET-positive primary tumor sizes were 6-30 mm. To conclude, this study indicates that WB-(11)C-5-HTP-PET can be used as a universal imaging method for detection of NETs. This study also shows that WB-(11)C-HTP-PET is sensitive in imaging small NET lesions, such as primary tumors, and can in a majority of cases image significantly more tumor lesions than SRS and CT.

PMID: 15755858


AIM: To evaluate the use of 99mTc-EDDA-hydrazinonicotinyl-Tyr3-octreotide (Tc-TOC) for staging and follow-up of neuroendocrine gastro-entero-pancreatic (GEP) tumors with special focus on the acquisition protocol including single photon emission computed tomography (SPECT).

METHODS: Eighty-eight patients (37 female, 51 male; age range: 16 to 81 years; mean age: 56.3 years) were studied: 42 patients for staging after initial histological confirmation and 46 patients during post-therapy follow-up. An average activity of 400 MBq of the radiopharmaceutical was injected. All tumors originated from neuroendocrine tissue of the gastroenteropancreatic tract. Whole body scintigrams at 4 h postinjection and SPECT of the abdomen were obtained in all patients. Additional planar images of the abdomen were
acquired at 2 h after injection in 68 patients. RESULTS: The Tc-TOC scan result was true-positive in 56 patients, true-negative in 17, false-negative in 14, and false-positive in 1 patient. The false-positive finding was caused by a colonic adenoma. Overall, a scan sensitivity of 80% (56/70 patients), specificity of 94.4% (17/18 patients) and accuracy of 82.9% (73/88 patients) were calculated on patient basis. In total, Tc-TOC detected 357 foci in 69 patients. In 7 patients equivocal findings were observed in the bowel at 4 h postinjection without corresponding tracer uptake in the scan 2 h earlier, meaning that these abnormal findings were correctly classified as non-malignant. In addition to planar views, SPECT revealed further 62 lesions. CONCLUSIONS: Tc-TOC with one-day, dual-time acquisition protocol is an accurate staging procedure in patients with neuroendocrine GEP tumors. SPECT shows high sensitivity for detection of abdominal lesions, while earlier images improve the reliability of abnormal abdominal findings.

PMID: 16172569


PURPOSE: Somatostatin receptor scintigraphy (SRS) and chromogranin A (CgA) assay have successfully been implemented in the clinical work-up and management of neuroendocrine tumour (NET) patients. However, there is still a lack of studies comparing results in these patients. Our aim was to compare directly in NET patients SRS and CgA assay results with special regard to tumour features such as grade of malignancy, primary origin, disease extent and function.
METHODS: One hundred twenty consecutive patients with histological confirmed NETs were investigated with (111)In-DOTA-DPhe(1)-Tyr(3)-octreotide (([111]In-DOTA-TOC) SRS and CgA immunoradiometric assay. Tumours were classified by cell characteristics [well-differentiated NETs, well-differentiated neuroendocrine carcinomas, poorly differentiated neuroendocrine carcinomas (PDNECs)], primary origin (foregut, midgut, hindgut, undetermined), disease extent (limited disease, metastases, primary tumour and metastases) and functionality (secretory, nonsecretory).

RESULTS: SRS was positive in 107 (89%) patients; CgA levels were increased in 95 (79%) patients. Overall, concordance between SRS and CgA results was found in 84 patients. Positive SRS but normal CgA level were found in 24 patients, with higher prevalence (p<0.05) in patients with nonsecretory tumours. Conversely, negative SRS but CgA level increased were seen in 12 patients, with higher proportion (p<0.05) in patients with PDNECs and tumours of hindgut origin. CONCLUSIONS: Overall, (111)In-DOTA-TOC SRS proved to be more sensitive than CgA in NETs patients. Tumour differentiation, disease extent and presence of liver metastases impact both SRS and CgA results, whereas nonsecretory activity is a negative predictor of only CgA increase. PDNECs and hindgut origin of tumours predispose to discrepancies with negative SRS but increased CgA levels.

PMID: 18425512 [PubMed - indexed for MEDLINE]


The aim of this study was to evaluate the diagnostic value of a new somatostatin analog, (68)Ga-labeled 1,4,7,10-tetraazacyclododecane-N,N’,N’’,N’’’-tetraacetic acid-d-Phe(1)-Tyr(3)-octreotide (([68]Ga-DOTA-TOC), for PET in
patients with known or suspected neuroendocrine tumors. PET was compared with conventional scintigraphy and dedicated CT. METHODS: Eighty-four patients (48 men, 36 women; age range, 28-79 y; mean age +/- SD, 58.2 +/- 12.2 y) were prospectively studied. For analysis, patients were divided into 3 groups: detection of unknown primary tumor in the presence of clinical or biochemical suspicion of neuroendocrine malignancy (n = 13 patients), initial tumor staging (n = 36 patients), and follow-up after therapy (n = 35 patients). Each patient received 100-150 MBq (68)Ga-DOTA-TOC. Imaging results of PET were compared with (99m)Tc-labeled hydrazinonicotinyl-Tyr(3)-octreotide ((99m)Tc-HYNIC-TOC) and (111)In-DOTA-TOC. CT was also performed on every patient using a multidetector scanner. Each imaging modality was interpreted separately by observers who were unaware of imaging findings before comparison with PET. The gold standard for defining true-positive (TP), true-negative (TN), false-positive (FP), and false-negative (FN) results was based on all available histologic, imaging, and follow-up findings. RESULTS: PET was TP in 69 patients, TN in 12 patients, FP in 1 patient, and FN in 2 patients, indicating a sensitivity of 97%, a specificity of 92%, and an accuracy of 96%. The FP finding was caused by enhanced tracer accumulation in the pancreatic head, and the FN results were obtained in patients with a tumor of the gastrointestinal tract displaying liver metastases. (68)Ga-DOTA-TOC showed higher diagnostic efficacy compared with SPECT (TP in 37 patients, TN in 12 patients, FP in 1 patient, and FN in 34 patients) and diagnostic CT (TP in 41 patients, TN in 12 patients, FP in 5 patients, and FN in 26 patients). This difference was of statistical significance (P < 0.001). However, the combined use of PET and CT showed the highest overall accuracy. CONCLUSION: (68)Ga-DOTA-TOC PET shows a significantly higher

PURPOSE: (18)F-FDG positron emission tomography (PET) value for the assessment of neuro-endocrine tumours (NET) is limited. Preliminary studies indicate that (18)F-DOPA and (68)Ga-DOTA-NOC are more accurate for disease assessment and (68)Ga-DOTA peptides provide additional data on receptor status that are crucial for targeted radionuclide therapy. At present, there are no comparative studies investigating their role in NET. AIM: The aim of this study was to compare (68)Ga-DOTA-NOC and (18)F-DOPA for the evaluation of gastro-entero-pancreatic and lung neuro-endocrine tumours. MATERIALS AND METHODS: Thirteen patients with biopsy-proven NET (gastro-entero-pancreatic or pulmonary) were prospectively enrolled and scheduled for (18)F-DOPA and (68)Ga-DOTA-NOC PET. PET results obtained with both tracers were compared with each other, with other conventional diagnostic procedures (CT, ultrasound) and with follow-up (clinical, imaging). RESULTS: The most common primary tumour site was the pancreas (8/13) followed by the ileum (2/13), the lung (2/13) and the duodenum (1/13). The carcinoma was well differentiated in 10/13 and poorly differentiated in 3/13 cases. (68)Ga-DOTA-NOC PET was positive, showing at least one lesion, in 13/13 cases while (18)F-DOPA PET was positive in 9/13. On a lesions basis, (68)Ga-DOTA-NOC identified more lesions than (18)F-DOPA.
(71 vs 45), especially at liver, lung and lymph node level. (68)Ga-DOTA-NOC correctly identified the primary site in six of eight non-operated cases (in five cases, the primary was surgically removed before PET), while (18)F-DOPA identified the primary only in two of eight cases. CONCLUSIONS: Although the patients studied are few and heterogeneous, our data show that (68)Ga-DOTA-NOC is accurate for the detection of gastro-entero-pancreatic and lung neuro-endocrine tumours in either the primary or metastatic site and that it offers several advantages over (18)F-DOPA.

PMID: 18418596
Section — X

Thoracic Malignancies
Lung Cancer and Solitary Pulmonary Nodule

Introduction
Lung cancer is the commonest type of cancer with over a million cases diagnosed annually and is the leading cause of cancer mortality, accounting for over 900,000 deaths every year. About 80% of lung cancers are non-small cell lung cancers and the remaining 20% small cell lung cancer. Accurate staging of lung cancer is extremely important and directly guides treatment decisions. Early localized lung cancer is treated with surgery with or without adjuvant chemotherapy, patients with positive ipsilateral mediastinal lymphadenopathy are treated with neoadjuvant chemotherapy followed by surgery, while more advanced cases are treated with palliative chemotherapy with or without radiotherapy.

Conventional Staging
Conventional staging of lung cancer includes contrast enhanced computed tomography (CECT) scan of the thorax and upper abdomen, a radionuclide bone scan, and a magnetic resonance imaging (MRI) scan of the brain.
PET and PET-CT scanning: summary of evidence

Diagnosis

Solitary pulmonary nodule (SPN): PET and PET-CT are important tools in the diagnostic workup of pulmonary nodules 5 to 6 mm or greater. PET scanning has a sensitivity of 91 to 97% and a specificity of 78 to 88% for predicting the pathologic nature of SPN. (LOE 2)

An indeterminate SPN has a 24% chance of being malignant even with an SUV of less than 2.5. SPNs with an SUV of 2.6 to 4.0 have an 80% chance of being malignant while it is 96% when the SUV is 4.1 and above (LOE 3)

However, it is important to be aware of the limitations of using SUVs to guide clinical decisions. SUV can be affected by several factors not directly related to the intrinsic metabolic activity of the tumor.

Staging: PET-CT scans have been shown in two randomized trials to be superior to PET alone in the staging of patients with NSCLC. (LOE 1)

PET scans give superior molecular information but has limited spatial resolution and anatomic data. Integrated PET-CT permits anatomic definition to be added to help resolve metabolic ambiguity. The improved localization with PET-CT also allows radiologists and nuclear physicians to differentiate areas of normal physiological uptake from abnormal areas of increased uptake.

Mediastinal lymph node staging:

PET scan was found to be significantly (p<0.001) superior to CT scans in mediastinal nodal staging of NSCLC in a recent meta analysis of non-randomized studies. (LOE 2)
Mean sensitivity and specificity for PET were 79% and 91% respectively while that for CT scan was 60% and 77% respectively. The diagnostic accuracy was 92% for FDG-PET (vs 75% for CT), positive predictive value was 90% for PET (vs 50% for CT) and the negative predictive value was 93% for PET (vs 85% for CT).

PET-CT has a higher accuracy for mediastinal nodal involvement compared to PET scan. (LOE 2)

**Distant metastases**

PET scan is superior to conventional staging and improves staging accuracy from 13% to 59%. PET scan shows more metastatic bone lesions than bone scan. It has also been well established in a large randomized trial that PET scan is superior to conventional staging both with mediastinal nodal (N2) and distant metastases detection (M1). (LOE 1)

**Response to chemotherapy and/or radiation**

Patients who have a baseline PET scan prior to starting neoadjuvant chemotherapy or chemoradiation will benefit from a post treatment PET scan. Several studies have shown that a high accuracy ranging from 73 to 85 percent. (LOE 3)

The optimum time to repeat a PET scan after radiation is one month (LOE 3)
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**Selected Abstracts:**


PURPOSE: To meta-analytically compare 2-[fluorine 18]fluoro-2-deoxy-D-glucose positron emission tomography (PET) and computed tomography (CT) for the demonstration of mediastinal nodal metastases in patients with non-small cell lung cancer. MATERIALS AND METHODS: English-language reports on the diagnostic performance of PET (14 studies, 514 patients) and/or CT (29 studies, 2,226 patients) for demonstration of mediastinal nodal metastases from NSCLC were selected by using the MEDLINE database. In eligible studies, an objective diagnostic standard was used, data were presented to allow recalculation of contingency tables, and established diagnostic criteria were used for
abnormal test results. Summary receiver operating characteristic (ROC) curves were calculated. RESULTS: Pooled point estimates of diagnostic performance and summary ROC curves indicated that PET was significantly more accurate than CT for demonstration of nodal metastases (P < .001). Mean sensitivity and specificity (+/- 95% CI) were 0.79 +/- 0.03 and 0.91 +/- 0.02, respectively, for PET and 0.60 +/- 0.02 and 0.77 +/- 0.02, respectively, for CT. The log odds ratios were 1.79 (95% CI: 1.49, 2.09) for CT and 3.77 (95% CI: 2.77, 4.77) for PET (P < .001). Subgroup analyses did not alter findings. CONCLUSION: PET is superior to CT for mediastinal staging of non-small cell lung cancer, independent of performance index or clinical context of PET imaging.


The stage of non-small cell lung cancer (NSCLC) determines that the treatment strategy and proper staging lead to improved survival. Integrated positron emission tomography/computerized tomography (CT) scan provides more accurate staging and better targets for biopsy than traditional methods such as CT scans of the chest and upper abdomen, bone scans, and magnetic resonance imaging scans. Integrated positron emission tomography/ CT is the best initial test for an indeterminate pulmonary nodule that is 8 mm or greater; for the noninvasive staging of patients with NSCLC, it is the only test that produces a quantitative assessment of an NSCLC’s virulence or biologic aggressiveness in a particular patient and is the best tool for restaging patients after radiation and and/or chemotherapy. Finally, its use as a tool for postoperative surveillance is under study.

OBJECTIVES: The American College of Surgeons Oncology Group undertook a trial to ascertain whether positron emission tomography with 18F-fluorodeoxyglucose could detect lesions that would preclude pulmonary resection in a group of patients with documented or suspected non-small cell lung cancer found to be surgical candidates by routine staging procedures. METHODS: A total of 303 eligible patients registered from 22 institutions underwent positron emission tomography after routine staging (computed tomography of chest and upper abdomen, bone scintigraphy, and brain imaging) had deemed their tumors resectable. Positive findings required confirmatory procedures. RESULTS: Positron emission tomography was significantly better than computed tomography for the detection of N1 and N2/N3 disease (42% vs 13%, P =.0177, and 58% vs 32%, P =.0041, respectively). The negative predictive value of positron emission tomography for mediastinal node disease was 87%. Unsuspected metastatic disease or second primary malignancy was identified in 18 of 287 patients (6.3%). Distant metastatic disease indicated in 19 of 287 patients (6.6%) was subsequently shown to be benign. By correctly identifying advanced disease (stages IIIA, IIIB, and IV) or benign lesions, positron emission tomography potentially avoided unnecessary thoracotomy in 1 of 5 patients. CONCLUSIONS: In patients with suspected or proven non-small cell lung cancer considered resectable by standard staging procedures, positron emission tomography can prevent nontherapeutic thoracotomy in a significant number of cases. Use of positron emission tomography for mediastinal staging should not be relied on as a sole staging modality, and positive findings should be confirmed by mediastinoscopy. Metastatic
disease, especially a single site, identified by positron emission tomography requires further confirmatory evaluation.


**PURPOSE:** To prospectively study the impact of \(^{18}\text{F}\) fluorodeoxyglucose (FDG) positron emission tomography (PET) on clinical management of patients with non–small-cell lung cancer (NSCLC).

**PATIENTS AND METHODS:** One hundred five consecutive patients with NSCLC undergoing \(^{18}\text{F}\) FDG PET were analyzed. Before PET, referring physicians recorded scan indication, conventional clinical stage, and proposed treatment plan. PET scan results were reported in conjunction with available clinical and imaging data, including results of computed tomography (CT). Subsequent management and appropriateness of PET-induced changes were assessed by follow-up for at least 6 months or until the patient’s death.

**RESULTS:** Indications for PET were primary staging (n = 59), restaging (n = 34), and suspected malignancy subsequently proven to be NSCLC (n = 12). In 27 (26%) of 105 of cases, PET results led to a change from curative to palliative therapy by upstaging disease extent. Validity of the PET result was established in all but one case. PET appropriately downstaged 10 of 16 patients initially planned for palliative therapy, allowing either potentially curative treatment (four patients) or no treatment (six patients). PET influenced the radiation delivery in 22 (65%) of 34 patients who subsequently received radical radiotherapy. Twelve patients considered probably inoperable on conventional imaging studies were downstaged by PET and underwent potentially curative surgery. PET missed only one primary tumor (5-mm scar carcinoma). CT
and PET understaged three of 20 surgical patients (two with N1 lesions < 5 mm and one with unrecognized atrial involvement), and PET missed one small intrapulmonary metastasis apparent on CT. No pathological N2 disease was missed on PET.

CONCLUSION: FDG PET scanning changed or influenced management decisions in 70 patients (67%) with NSCLC. Patients were frequently spared unnecessary treatment, and management was more appropriately targeted.


Background Determining the stage of non–small cell lung cancer often requires multiple preoperative tests and invasive procedures. Whole-body positron emission tomography (PET) may simplify and improve the evaluation of patients with this tumor. Methods We prospectively compared the ability of a standard approach to staging (computed tomography [CT], ultrasonography, bone scanning, and, when indicated, needle biopsies) and one involving PET to detect metastases in mediastinal lymph nodes and at distant sites in 102 patients with resectable non– small-cell lung cancer. The presence of mediastinal metastatic disease was confirmed histopathologically. Distant metastases that were detected by PET were further evaluated by standard imaging tests and biopsies.

Patients were followed postoperatively for six months by standard methods to detect occult metastases. Logistic-regression analysis was used to evaluate the ability of PET and CT to identify malignant mediastinal lymph nodes. Results The sensitivity and specificity of PET for the detection of mediastinal metastases were 91 percent (95 percent confidence
interval, 81 to 100 percent) and 86 percent (95 percent confidence interval, 78 to 94 percent), respectively. The corresponding values for CT were 75 percent (95 percent confidence interval, 60 to 90 percent) and 66 percent (95 percent confidence interval, 55 to 77 percent). When the results of PET and CT were adjusted for each other, only PET results were positively correlated with the histopathological findings in mediastinal lymph nodes (P<0.001). PET identified distant metastases that had not been found by standard methods in 11 of 102 patients. The sensitivity and specificity of PET for the detection of both mediastinal and distant metastatic disease were 95 percent (95 percent confidence interval, 88 to 100 percent) and 83 percent (95 percent confidence interval, 74 to 92 percent), respectively. The use of PET for clinical staging resulted in a different stage from the one determined by standard methods in 62 patients: the stage was lowered in 20 and raised in 42. Conclusions PET improves the rate of detection of local and distant metastases in patients with non–small-cell lung cancer. (N Engl J Med 2000; 343:254-61.)


Background: We compared the diagnostic accuracy of integrated positron-emission tomography (PET) and computed tomography (CT) with that of CT alone, that of PET alone, and that of conventional visual correlation of PET and CT in determining the stage of disease in non–small-cell lung cancer.

Methods: In a prospective study, integrated PET–CT was performed in 50 patients with proven or suspected non–small-cell lung cancer. CT and PET alone, visually correlated PET and CT, and integrated PET–CT were evaluated separately, and a tumor–node–metastasis (TNM) stage was assigned on
the basis of image analysis. Nodal stations were identified according to the mapping system of the American Thoracic Society. The standard of reference was histopathological assessment of tumor stage and node stage. Extrathoracic metastases were confirmed histopathologically or by at least one other imaging method. A paired sign test was used to compare integrated PET–CT with the other imaging methods.

Results: Integrated PET–CT provided additional information in 20 of 49 patients (41 percent), beyond that provided by conventional visual correlation of PET and CT. Integrated PET–CT had better diagnostic accuracy than the other imaging methods. Tumor staging was significantly more accurate with integrated PET–CT than with CT alone (P=0.001), PET alone (P<0.001), or visual correlation of PET and CT (P=0.013); node staging was also significantly more accurate with integrated PET–CT than with PET alone (P=0.013). In metastasis staging, integrated PET–CT increased the diagnostic certainty in two of eight patients.

Conclusions: Integrated PET–CT improves the diagnostic accuracy of the staging of non–small-cell lung cancer.
Esophageal Cancer

Introduction
Esophageal cancer is subdivided into the following four groups: epithelial tumors, metastatic tumors, lymphomas, and sarcomas. Cancers of epithelial origin, predominantly squamous cell carcinomas and adenocarcinomas, are the most common; other histological types are rare. Internationally there is steady increase in the incidence of Adenocarcinoma.

Conventional Staging:
Endoscopy with biopsy is the centrestage. Endoultrasoundography (EUS) may be performed alongside and it helps in T and N staging with scope of Biopsy of some of the nodes. CECT of the thorax and abdomen is the first imaging study of choice. The overall accuracy of CT depends on the size of the lesion. A bone scan is done when bone pain is encountered to rule out bone involvement. FDG PET has been used since a long time and is now considered standard, if not mandatory for the staging of the disease. Laparoscopy appears to be most useful for evaluating intra-abdominal spread of disease in patients with a bulky distal third or GE junction primary and/or celiac adenopathy.
Summary of Evidence:

Diagnosis:
As a diagnostic tool PET has been evaluated on patients with precancerous esophagus disease. It was seen that focality and eccentricity of FDG uptake prove to be valuable PET/CT characteristics for the differentiation of nonspecific FDG uptake in the esophagus. FDG PET study with delayed imaging and uptake characteristics have helped detect malignant transformation in precancerous condition in animal models. 18F- FDG accumulation was a sensitive marker in reflux esophageal injury carcinogenic progression from intestinal metaplasia to Esophageal adeonocarcinoma.

Staging:
HTA documents from several countries till 2004 have recorded level 2 evidence of PET in staging. The sensitivity and specificity of FDG PET was founds to be persistently significantly higher than that of CECT. It also showed survival data based on PET demonstrated Disease state in local and distant lesions. In 2006 Peter Macallum group showed that FDG PET/CT information in primary staging of esophagus carcinoma hanged the clinical management of more than one-third of patients and provided superior prognostic stratification compared with conventional investigations. When PET-CT was assessed for staging patients for minimally invasive oesophagectomy (MIO) with potentially resectable disease from the perspective of a multidisciplinary team (MDT) deciding on operability with conventional staging investigations; it was seen that the highest impact was made by impacting M stage. A preoperative evaluation of FDG PET in 41 superficial squamous cell ca of the esophagus identified FDG uptake as the single factor correlating to the depth of the tumor and inversely proportional to the disease free survival. Westerterp et al from Amsterdam investigated biological
parameters involved in 18FDG uptake in esophageal adenocarcinoma for selection of patients with increased 18FDG uptake and prediction of prognostic value. There was a significant correlation between 18FDG uptake and tumor size and between 18FDG uptake and tumor recurrence. A prospective study to evaluate the preoperative efficacy of FDG PET /CT compared to CECT. It was seen that PET was more accurate than CT in defining N and M status and could result in a reduction of unnecessary surgery in a significant number of patients (49%). From Cleveland there is another conflicting report of FDG PET in superficial oesophagus tumor. Following their prospective study they concluded that because positron emission tomography can neither differentiate pTis from T1 nor classify T, N, and M, it is not indicated in staging superficial esophageal cancer. Finding a synchronous primary tumor in approximately every 20th patient is its only benefit. However this statement could have been different had PET/CT been used rather than stand alone PET. The American College of Surgeons Oncology Group trial Z0060, completed a prospective multi-institutional trial with a primary objective to evaluate whether FDG PET detects evidence of metastatic disease that precludes esophagectomy in patients with esophageal cancer who are surgical candidates after routine staging. 189 patients were evaluated. They concluded that although 22% of eligible patients did not undergo esophagectomy, FDG-PET after standard clinical staging for esophageal carcinoma identified confirmed M1b disease in at least 4.8% (95% confidence interval: 2.2%-8.9%) of patients before resection. Unconfirmed PET evidence of M1 disease and regional adenopathy (N1 disease) led to definitive nonsurgical or induction therapy in additional patients. A prospective study of preop evaluation of esophagus ca in Dublin reported that FDG PET alters M stage in 23% patients. As a prognostic indicator the number of PET lesions was identified as the best indicator of overall survival.
Response Evaluation

FDG PET and SUV analysis has been found to be the best choice in the evaluation of chemo radiation treatment response in Esophagus carcinoma. The use of post-treatment FDG-PET for assessment of tumor response after Chemo radiation hanged the clinical management of more than one-third of Esophagus carcinoma patients. Complete Metabolic Response status as assessed by PET powerfully stratified prognosis. Even in the absence of a baseline study, normalisation of uptake at all sites of known unmoral involvement carries a good medium-term prognosis. The MUNICON phase II trial used FDG PET as a tool of evaluating treatment response. This study confirmed prospectively the usefulness of early metabolic response evaluation, and shows the feasibility of a PET-guided treatment algorithm. When EUS and PET were evaluated to predict disease free survival, EUS T stage, EUS N stage, location and SUV of the primary tumor are pretreatment factors that are associated with disease-specific survival. However, only EUS T stage was found to be an independent prognostic factor.

There is excellent evidence of the utility of FDG PET/CT in staging and evaluation of chemo-radiation treatment response. FDG PET findings could provide prognostic information. The role of FDG PET/CT is inconclusive in the evaluation of superficial tumors. AS a diagnostic tool to pick up a lesion in a high risk patient, the evidence is inadequate.
Timing of the PET/CT | Hierarchy of Diagnostic Efficacy | Relevance of Test | Level of Evidence
--- | --- | --- | ---
Diagnosis | 2 | Potentially Appropriate | 1 level 1
Staging | 3 | Appropriate | 9 level 1, 4 level 2
Response evaluation | 3 | Appropriate | 7 level 1
Restaging | 4 | Appropriate | 2 level 1
Suspected recurrence | 2 | Appropriate | 2 level 2
Followup | 1 | Potentially appropriate | 1 level 1
RT planning | 2 | Probably appropriate | 1 level 1

Selected Abstracts:

BACKGROUND: In this study, we investigate the use of PET scanning in the carcinogenic progression of reflux esophagitis to Barrett’s esophagus to high grade dysplasia to esophageal adenocarcinoma, and correlate the uptake levels of 18F-FDG related to histological changes, and the rates of proliferation and apoptosis. METHODS: An established esophagoduodenal anastomosis rat model in conjunction with micro-PET scanning at 1 week, 1 month, 3 month, and 6 month after procedure was performed. RESULTS: Increased uptake levels of 18F-FDG were observed in the esophagi after EDA procedure. The higher level of 18F-FDG uptake within esophageal
epithelium was identified in intestinal metaplastic transformation and esophagoduodenal adenocarcinoma by histological examination. CONCLUSIONS: Dynamic PET scanning represents a powerful tool in analyzing morphological carcinogenic transformation non-invasively in the esophagus. 18F- FDG accumulation was a sensitive marker in reflux esophageal injury carcinogenic progression from intestinal metaplasia to EAC.


PURPOSE: To evaluate the clinical impact of FDG-PET in staging oesophageal cancer and whether this information improves prognostic stratification. METHODS: Impact was based on comparison of a prospectively recorded pre-PET plan with post-PET treatment in 68 consecutive patients undergoing primary staging. Survival was analysed using the Kaplan-Meier product limit method and the Cox proportional hazards regression model. RESULTS: FDG-PET findings impacted on the management of 27/68 patients (40%): in 12 therapy was changed from curative to palliative and in three from palliative to curative, while in 12 other patients there was a change in the treatment modality or delivery but not in the treatment intent. The median survival was 21 months, with post-PET stage and treatment intent both strongly associated with survival (p<0.001). Conventional stage was not able to clearly stratify this population. CONCLUSION: The use of FDG-PET for primary staging of oesophageal cancer changed the clinical management of more than one-third of patients and provided superior prognostic stratification compared with conventional investigations.

OBJECTIVE: Our objective was to assess the role of fusion positron emission tomography-computed tomography (PET-CT) in staging patients for minimally invasive oesophagectomy (MIO) with potentially resectable disease from the perspective of a multidisciplinary team (MDT) deciding on operability with conventional staging investigations. METHODS: Fifty consecutive patients presenting with potentially operable oesophageal or oesophagogastric junctional tumours were staged with computed tomography (CT) and endoluminal ultrasound (EUS). The MDT categorised patients as group A (n=33; CT N0M0) or group B (n=17; CT N1/possible M1). All patients underwent FDG PET-CT. Patients with localised disease (at T3), including single level N1 disease on PET-CT, were deemed suitable for induction chemotherapy followed by surgery. RESULTS: PET-CT re-categorised 12% of patients as inoperable on grounds of distant metastases (four in group A, two in group B). Five patients did not proceed to resection for other reasons. Two had metastatic disease at thoracoscopy. Resection specimens (n=37) contained 24 nodes (median). Compared with pN status, positive predictive value of PET-CT was 40% and negative predictive value was 43%. The expected PET-CT N1 group had the highest mean number of involved nodes. Median survival for all patients (n=50) was 31.9 months for group A compared with 17.3 months for group B (not statistically significant). There was no significant difference between patients who were PET-CT N0 or N1 in survival or disease-free survival in patients undergoing surgery (n=37). CONCLUSIONS: PET-CT informs the MDT decision
to operate in avoiding futile surgery in stage IV disease or widespread nodal disease. In this study, overall PET-CT N1 status has low positive and negative predictive value for overall pN status.

PMID: 18328726


(18)F-fluorodeoxyglucose (FDG) positron emission tomography (PET) is used for pre-treatment staging and evaluation of response to pre-operative therapy in advanced thoracic esophageal cancers. To evaluate the clinical significance of PET diagnosis of superficial thoracic esophageal cancers, FDG-PET was conducted preoperatively in 41 patients with such cancers without pre-operative therapy. We compared the PET diagnosis with clinicopathological findings with respect to both the primary tumor and lymph node (LN) metastasis. Of the 41 superficial thoracic esophageal cancers, 21 (51.2%) were PET positive for primary tumors. Although tumor length and histological type did not correlate with FDG uptake by primary tumors, non-flat (elevated or depressed) tumors showed significantly stronger FDG uptake than flat ones. Of 28 tumors infiltrating the deep submucosal layer, 19 (67.9%) were PET positive, while only two (15.4%) of 13 tumors infiltrating only the mucosa or shallow submucosal layer were PET positive. Manova identified FDG uptake as the only independent risk factor for deep submucosal invasion (odds ratio, 7.407; P = 0.0279). In 13 patients with pathological LN metastasis, although no LN metastasis was detected by FDG-PET, FDG uptake by the primary tumors was the only risk factor for LN metastasis (P = 0.0318).
PET-negative tumors tended to reflect longer disease-free survival than PET-positive tumors, although this was not significant. FDG-PET is useful for detecting tumors infiltrating the middle or deep submucosal layer (sm2/sm3), and for predicting LN metastasis in patients with superficial thoracic esophageal cancers. FDG-PET is helpful for decision-making regarding treatment of such patients.

PMID: 18269650


PURPOSE: Variable uptake of 18FDG has been noticed in positron emission tomography (PET) studies of patients with oesophageal adenocarcinoma. The aim of the present study was to investigate biological parameters involved in 18FDG uptake in oesophageal adenocarcinoma for selection of patients with increased 18FDG uptake and prediction of prognostic value of 18FDG PET. PATIENTS AND METHODS: Preoperative PET scans were performed in 26 patients with histologically proven oesophageal adenocarcinoma. 18FDG uptake was semiquantitatively measured by SUV (BSAg. )Tumour sections were stained by immunohistochemistry for angiogenic markers (VEGF, CD31), glucose transporter-1 (Glut-1), hexokinase (HK) isoforms, for proliferation marker (Ki67), for macrophage marker (CD68) and for apoptosis marker (cleaved caspase-3). Cell densities, differentiation grade, degree of necrosis and mucus, T-stage and tumour size were assessed. In addition follow-up was analysed. RESULTS: No association was found between 18FDG uptake and angiogenic markers. In contrast, a significant correlation was found between 18FDG uptake and Glut-1 expression. No correlations were found between 18FDG uptake and HK isoforms, Ki67 or cleaved caspase-3. Also, no correlations
were found between 18FDG uptake and cell density, differentiation grade, CD68, mucus and necrosis. However, there was a significant correlation between 18FDG uptake and tumour size and between 18FDG uptake and tumour recurrence. CONCLUSIONS: Glut-1 expression and tumour size seem parameters associated with 18FDG uptake in patients with biopsy proven oesophageal adenocarcinoma, and may be used to select oesophageal cancer patients in whom 18FDG-PET is of diagnostic value and may predict disease outcome.

PMID: 17653575


OBJECTIVES: The American College of Surgeons Oncology Group trial Z0060 is a prospective multi-institutional trial with a primary objective to evaluate whether positron emission tomography (PET) with F-18 fluorodeoxyglucose (FDG) detects evidence of metastastic disease that precludes esophagectomy in patients with esophageal cancer who are surgical candidates after routine staging. METHODS: Patients with resectable, biopsy-proven carcinoma were enrolled after computed tomography of chest and abdomen demonstrated no evidence of metastasis. FDG-PET was performed according to specified standards. FDG-PET findings suggesting metastases required confirmation and patients without metastases on PET were expected to proceed to surgery. RESULTS: A total of 262 patients were registered. Of these, 199 were deemed eligible and of these, 189 patients were evaluable. Seventy-three patients were ineligible or unevaluable. Reasons for ineligibility included nonresectable disease by routine staging (39), missing or outdated staging procedures (12), PET technical protocol violations (10), no
cancer (4), pre-PET induction therapy (3), claustrophobia (1), and other causes (4). There were 145 (78%) patients who went on to have surgery, 42 (22%) who did not, and 2 patients for whom the surgical status was not determined. The reasons for no resection included the following: M1 disease found by PET and confirmed (9), M1 disease found by PET and not confirmed (2), M1 disease at exploration not found by PET (7), decline or death before surgery (10), patient refusal of surgery (7), unresectable local tumor at exploration (5), and extensive N1 disease precluding operation (2). Eight (4.2%) patients undergoing resection had a recurrence in the first 6 months. CONCLUSIONS: Although 22% of eligible patients did not undergo esophagectomy, FDG-PET after standard clinical staging for esophageal carcinoma identified confirmed M1b disease in at least 4.8% (95% confidence interval: 2.2%-8.9%) of patients before resection. Unconfirmed PET evidence of M1 disease and regional adenopathy (N1 disease) led to definitive nonsurgical or induction therapy in additional patients.

PMID: 17320575


BACKGROUND: Various studies have demonstrated that 18F-Fluorodeoxyglucose-positron emission tomography (FDG-PET), measuring altered tissue glucose metabolism, is a promising non-invasive method for detecting both distant nodal and haematogenous metastases in patients with oesophageal carcinoma (OC) and might thus prevent futile esophagectomy. Moreover, FDG-PET is a promising tool in assessing response to non-surgical treatment, and might therefore be used for an early decision on whether treatment should be stopped or continued. MATERIAL AND
METHODS: Review of the recent literature regarding the diagnostic performance of FDG-PET in the preoperative staging of patients with OC and regarding diagnostic accuracy of FDG-PET in assessing response to neoadjuvant therapy in patients with OC compared to conventional techniques (especially computed tomography (CT) and endoscopic ultrasonography (EUS)). RESULTS: A search of the literature resulted in the inclusion of 16 studies on the diagnostic value of FDG-PET. Sensitivity and specificity for the detection of locoregional metastases were moderate. Sensitivity and specificity were reasonable for distant metastases. The diagnostic accuracy of FDG-PET in assessing response to treatment was similar to the accuracy of EUS, but significantly higher than that of CT. CONCLUSIONS: The staging value of FDG-PET in OC patients is limited in the detection of locoregional metastases; however; its value is higher in the detection of distant lymphatic and haematogenous metastases. Moreover, FDG-PET is a valuable tool for the non-invasive assessment of histopathologic tumour response after neoadjuvant therapy.

PMID: 16782630


**BACKGROUND:** In patients with locally advanced adenocarcinoma of the oesophagogastric junction (AEG), early metabolic response defined by 18-fluorodeoxyglucose-PET ([18F]FDG-PET) during neoadjuvant chemotherapy is predictive of histopathological response and survival. We aimed to assess the feasibility of a PET-response-guided treatment algorithm and its potential effect on prognosis.

**METHODS:** Between May 27, 2002, and Aug 4, 2005, 119
patients with locally advanced adenocarcinoma of AEG type 1 (distal oesophageal adenocarcinoma) or type 2 (gastric cardia adenocarcinoma) were recruited into this prospective, single-centre study. All patients were assigned to 2 weeks of platinum and fluorouracil-based induction chemotherapy (evaluation period). Those with decreases in tumour glucose standard uptake values (SUVs), predefined as decreases of 35% or more at the end of the evaluation period and measured by PET, were defined as metabolic responders. Responders continued to receive neoadjuvant chemotherapy of folinic acid and fluorouracil plus cisplatin, or folinic acid and fluorouracil plus cisplatin and paclitaxel, or folinic acid and fluorouracil plus oxaliplatin for 12 weeks and then proceeded to surgery. Metabolic non-responders discontinued chemotherapy after the 2-week evaluation period and proceeded to surgery. The primary endpoint was median overall survival of metabolic responders and non-responders. Secondary endpoints were median event-free survival, postoperative complications and mortality, number of residual tumour-free (R0) resections, and histopathological responses. This study has been registered in the European Clinical Trials Database (EudraCT) as trial 2007-003356-11. FINDINGS: 110 patients were evaluable for metabolic responses. 54 of these patients had metabolic responses (ie, decrease of 35% or more in tumour glucose SUV) after 2 weeks of induction chemotherapy, corresponding to a response of 49% (95% CI 39-59). 104 patients had tumour resection (50 in the responder group and 54 in the non-responder group). After a median follow-up of 2.3 years (IQR 1.7-3.0), median overall survival was not reached in metabolic responders, whereas median overall survival was 25.8 months (19.4-32.2) in non-responders (HR 2.13 [1.14-3.99, p=0.015]). Median event-free survival was 29.7 months (95% CI 23.6-35.7) in metabolic responders and 14.1 months (7.5-20.6) in non-responders (hazard ratio [HR] 2.18 [1.32-3.62], p=0.002). Major histological remissions (<10% residual
tumour) were noted in 29 of 50 metabolic responders (58% [95% CI 48-67]), but no histological response was noted in metabolic non-responders. **INTERPRETATION:** This study confirmed prospectively the usefulness of early metabolic response evaluation, and shows the feasibility of a PET-guided treatment algorithm. These findings might enable tailoring of multimodal treatment in accordance with individual tumour biology in future randomised trials.

PMID: 17693134

**Metabolic Tumor Width Parameters as Determined on PET/CT Predict Disease-free Survival and Treatment Response in Squamous Cell Carcinoma of the Esophagus.**

Roedl JB, Halpern EF, Colen RR et al. Mol Imaging Biol. 2008 Sep 4

**MATERIALS AND METHODS:** We investigated the utility of metabolic tumor width parameters in predicting response to chemoradiotherapy and in predicting disease-free survival in patients with esophageal cancer. Furthermore, we evaluated the possible confounding effect of therapy-induced esophagitis on the evaluation of treatment response. Forty-nine patients with squamous cell carcinoma, who had undergone positron emission tomography/computed tomography (PET/CT) exams before and after neoadjuvant chemoradiotherapy, were included in the study. In the slice with the maximum 2-deoxy-2-[F-18]fluoro-D-glucose (FDG) uptake of the tumor, the following metabolic tumor width parameters were measured: Area of the tumor, maximum diameter of the tumor, maximum and mean standardized uptake value (SUV). Furthermore, the “diameter-SUV index” was calculated by multiplying the tumor diameter by the mean SUV. **RESULTS:** The decrease of the metabolic tumor diameter between pre- and post-treatment PET/CT scans was the single best predictor of treatment response and tumor-free survival. However, the
accuracy of predicting response and survival was even higher when using the decrease of the “diameter-SUV index” as the metabolic criterion for treatment response. A decrease by more than 55% of the diameter-SUV index identified pathologic responders (n = 22) with a sensitivity of 91% and a specificity of 93%. Radiation esophagitis was found to have a significant impact on the assessment of treatment response when evaluating therapy response based on the maximum SUV, whereas no confounding effect of radiation esophagitis was seen when evaluating therapy response based on the tumor diameter or the diameter-SUV index. CONCLUSION: The present study shows that tumor width parameters, especially the tumor diameter or the combination of diameter and SUV in the “diameter-SUV index”, are valuable for predicting tumor-free survival and treatment response independent from the presence of radiation esophagitis.

PMID: 18769974

Adenocarcinomas of the esophagus: Response to chemoradiotherapy is associated with decrease of metabolic tumor volume as measured on PET-CT Comparison to histopathologic and clinical response evaluation. Roedl JB, Colen RR, Holalkere NS et al. Radiother Oncol. 2008 Dec;89(3):278-86. Epub 2008 Aug 11

PURPOSE: We determined whether evaluation of treatment response is feasible by measuring metabolic tumor volume parameters on 18F-FDG (Fluorodeoxyglucose) PET-CT (Positron emission tomography-Computed tomography). We compared the response evaluation based on metabolic tumor volume parameters to a histopathologic and clinical response evaluation (clinical response criteria: RECIST criteria=Response evaluation criteria in solid tumors, and WHO criteria=World health organization). PATIENTS AND
METHODS: A total of 51 study subjects with adenocarcinomas (Type I due to Siewert classification) of the esophagus underwent PET-CT scans before and after neoadjuvant chemoradiotherapy. Tumor volume, maximum and mean standardized uptake values (SUV) were assessed before and after chemoradiotherapy. Furthermore, the total lesion glycolysis (TLG) was calculated by multiplying the tumor volume by the mean SUV of the volume. Clinical response evaluation was performed with endoscopic ultrasound and CT using RECIST and WHO criteria. The reference standard for treatment response was the postsurgical histopathology. RESULTS: The decrease of tumor volume between the pre- and post-treatment PET-CT scans was a better predictor of histopathologic response and survival than the decrease of the SUV and of the clinical response evaluation based on RECIST and WHO criteria. The highest accuracy, however, was achieved when using the TLG for the identification of treatment responders. A decrease of the TLG by >78% between pre- and post-therapy scans predicted histopathologic response with a sensitivity and specificity of 91% and 93%, respectively. CONCLUSIONS: Tumor volume and TLG can be used to assess treatment response and survival in patients with esophageal adenocarcinoma.

PMID: 18701180


BACKGROUND: Positron emission tomography (PET) with [18F]fluorodeoxyglucose (FDG) might be useful for staging oesophageal squamous cell carcinoma (SCC). FDG-PET may be more accurate than computed tomography (CT) in diagnosing lymph node metastasis. This retrospective study compared the ability of FDG-PET and CT to diagnose recurrent oesophageal carcinoma. METHODS: Fifty-five
patients with thoracic oesophageal SCC who had undergone radical oesophagectomy were studied. The accuracy of FDG-PET and CT in detecting recurrence during follow-up was calculated using data from the first images generated by either modality that suggested the presence of recurrent disease. Lesions deemed to be equivocal on these scans were considered as positive for recurrence. RESULTS: Twenty-seven of the 55 patients had recurrent disease in a total of 37 organs. Locoregional recurrence was observed in 19 patients (35 per cent). Distant recurrent disease occurred in 15 patients (27 per cent) in 18 organs. Six patients had recurrence in the liver, four in the lung, six in bone and two in distant lymph nodes. FDG-PET showed 96 per cent sensitivity, 68 per cent specificity and 82 per cent accuracy in demonstrating recurrent disease. The corresponding values for CT were 89, 79 and 84 per cent. The sensitivity of FDG-PET was higher than that of CT in detecting locoregional recurrence, but its specificity was lower because of FDG uptake in the gastric tube and thoracic lymph nodes. In distant organs the sensitivity of PET in detecting lung metastasis was lower than that of CT, but its sensitivity for bone metastasis was higher. CONCLUSION: FDG-PET has a larger field than CT. Combined PET-CT would appear to be an appropriate modality for the detection of recurrent oesophageal cancer.

PMID: 15286962


PURPOSE: To determine the optimal method of using (18)F-fluorodeoxyglucose positron emission tomography (FDG-PET) to estimate gross tumor length in esophageal carcinoma.
METHODS AND MATERIALS: Thirty-six patients with esophageal squamous cell carcinoma treated with radical surgery were enrolled. Gross tumor volumes (GTVs) were delineated using three different methods: visual interpretation, standardized uptake value (SUV) 2.5, and 40% of maximum standard uptake value (SUV(max)) on FDG-PET imaging. The length of tumors on PET scan were measured and recorded as Length(vis), Length(2.5), and Length(40), respectively, and compared with the length of gross tumor in the resected specimen (Length(gross)). All PET data were reviewed again postoperatively, and the GTV was delineated using various percentages of SUV(max). The optimal-threshold SUV was generated when the length of PET matched the Length(gross).

RESULTS: The mean (+/-SD) Length(gross) was 5.48 +/- 1.98 cm. The mean Length(vis), Length(2.5), and Length(40) were 5.18 +/- 1.93 cm, 5.49 +/- 1.79 cm, and 4.34 +/- 1.54 cm, respectively. The mean Length(vis) (p = 0.123) and Length(2.5) (p = 0.957) were not significantly different from Length(gross), and Length(2.5) seems more approximate to Length(gross.) The mean Length(40) was significantly shorter than Length(gross) (p < 0.001). The mean optimal threshold was 23.81% +/- 11.29% for all tumors, and it was 19.78% +/- 8.59%, 30.92% +/- 12.28% for tumors >=5 cm, and <5 cm, respectively (p = 0.009). The correlation coefficients of the optimal threshold were -0.802 and -0.561 with SUV(max) and Length(gross), respectively. CONCLUSIONS: The optimal PET method to estimate the length of gross tumor varies with tumor length and SUV(max); an SUV cutoff of 2.5 provided the closest estimation in this study.

PMID: 18538492
Section — XI

Brain Tumors
FDG PET/CT in Brain Tumors

Introduction
Malignant gliomas and metastatic tumors are the most common brain tumors. According to the classification of the World Health Organization (WHO), gliomas are of 3 main types—astrocytomas, oligodendrogliomas, and mixed oligo-astrocytomas. These tumors are typically heterogeneous in that different levels of malignant degeneration can occur in different regions within the same tumor. Analysis of the most malignant region of the tumors establishes grading: low-grade, or WHO grades I and II, and high-grade, or WHO grades III and IV. There are 3 subtypes of low-grade gliomas: pilocytic astrocytoma (grade I), astrocytoma (grade II), and oligodendroglioma (grade II). High-grade gliomas include anaplastic tumors (astrocytoma and oligodendroglioma, grade III) and glioblastoma (grade IV). Glioblastoma is the most malignant and most common glioma, accounting for 45%–50% of all gliomas. The mean age at onset is 61 y for glioblastoma and 40 y for anaplastic astrocytoma. Men are more frequently affected than women, with a sex ratio of 3:2. Low-grade tumors typically affect younger patients than do high-grade glioma.
Current Imaging

The clinical gold standard, MRI, provides excellent anatomic details. Standard T1- and T2-weighted MRI is highly sensitive in determining the size and location of brain tumors, as well as mass effect, edema, hemorrhage, necrosis, and signs of increased intracranial pressure. But at times, it is difficult to differentiate neoplastic lesion from vascular lesion and inflammatory process in brain on MRI. It is also clinically challenging to evaluate disease status with MRI in treated subgroup. Treatment induced changes such as radiation necrosis is difficult to be distinguished from recurrent tumor. This issue is becoming clinically more critical now that concurrent chemoradiation and stereotactic radiosurgery are being used.

Summary of Evidence

Imaging of brain tumors with 18F-FDG was the first oncologic application of PET. Various studies have demonstrated diagnostic limitations of 18F-FDG PET. It is difficult to appreciate modest FDG uptake (equivalent to white matter) in low grade gliomas and some recurrent high grade glioma in the background of intense physiological FDG uptake in normal brain tissue (Grey matter). FDG uptake in high grade tumors have been reported to be either less than or similar to normal grey matter (Cortex), there by making detection of these tumors also difficult. There is overlap in FDG uptake pattern between garde I & II and grade II & III gliomas. 18F-FDG uptake is generally high in high-grade tumors. But anaplastic glioma may show low or modest FDG uptake similar to a low grade glioma. However, FDG uptake within low grade gliomas is statistically different from high grade glioma (Glioblastoma).

Mankoff DA, et al have shown that excretion/washout of FDG from normal brain tissue is comparatively faster than from tumor. Therefore delayed imaging (3-8 hours post injection)
can improve tumor delineation due to enhanced FDG uptake within tumor.

Co-registration of 18F-FDG PET images with MR images greatly improves the performance of 18F-FDG PET. Any 18F-FDG uptake higher than the adjacent background should be considered recurrent tumor if that uptake corresponds to abnormalities on MRI. A series of 117 post-radiotherapy patients demonstrated a sensitivity of 96% and specificity of 77% in distinguishing recurrent tumor from radiation necrosis when such criteria were used. The optimal time for performing 18FFFDG PET after radiation is not known. The general recommendation is that, for the purpose of evaluating tumor growth, 18F-FDG PET should not be performed less than 6 wks after the completion of radiation treatment.

**Evaluation of Recurrent Tumors**

The prognostic value of 18F-FDG uptake is well established: High uptake in a previously known low-grade tumor establishes the diagnosis of anaplastic transformation. But it is difficult to evaluate recurrence in low grade tumors (grade I/II) with FDG PET scan without any anaplastic transformation. In contrast to 18F-FDG uptake, amino acid uptake has been shown to be increased relative to normal brain tissue in most low- and high-grade tumors, and radiolabeled amino acids might therefore be preferable for evaluating recurrent tumors. However, in radionuclide techniques, Thallium (Tl 201) brain SPECT is probably more appropriate examination for diagnosis of possible brain tumor recurrence, especially for ruling it out.

Amino acid PET tracers and amino acid analog PET tracers (11-C Methionine, MET; O-(2-18F-fluoroethyl)-L-tyrosine, FET; 3,4-dihydroxy- 6-18F-fluoro-L-phenylalanine, FDOPA; and 3’-deoxy-3’-18F-fluorothymidine, FLT; are found to be more sensitive than (18)F-FDG in imaging recurrent tumors.
and in particular recurrent low-grade tumors. They are also promising in differentiating between recurrent tumors and treatment-induced changes. 18-FLT PET is a reflective of proliferative activity and has shown to be useful in monitoring treatment response.

<table>
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<th>Timing of the PET/CT</th>
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<th>Relevance of Test</th>
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**Selected Abstracts**

**Clinical applications of PET in brain tumors. Chen W. J Nucl Med. 2007 Sep;48 (9):1468-81.**

Malignant gliomas and metastatic tumors are the most common brain tumors. Neuroimaging plays a significant role clinically. In low-grade tumors, neuroimaging is needed to evaluate recurrent disease and to monitor anaplastic transformation into high-grade tumors. In high-grade and metastatic tumors, the imaging challenge is to distinguish between recurrent tumor and treatment-induced changes such as radiation necrosis. The current clinical gold standard, MRI, provides superior structural detail but poor specificity in identifying viable tumors in brain treated with surgery, radiation, or chemotherapy. (18)F-FDG PET identifies anaplastic
transformation and has prognostic value. The sensitivity and specificity of (18)F-FDG in evaluating recurrent tumor and treatment-induced changes can be improved significantly by co-registration with MRI and potentially by delayed imaging 3-8 h after injection. Amino acid PET tracers are more sensitive than (18)F-FDG in imaging recurrent tumors and in particular recurrent low-grade tumors. They are also promising in differentiating between recurrent tumors and treatment-induced changes.


The evaluation of primary brain tumor is challenging. Neuroimaging plays a significant role. At diagnosis, imaging is needed to establish a differential diagnosis, provide prognostic information, as well as direct biopsy. After the initial treatment, imaging is needed to distinguish recurrent disease from treatment-related changes such as radiation necrosis. In low-grade gliomas, this also includes monitoring anaplastic transformation into high-grade tumors. Recently, targeted treatments have been an extremely active area of research. Evaluation in clinical trials of such targeted treatments demands advanced roles of imaging such as treatment planning, monitoring response, and predicting treatment outcomes. Current clinical gold standard magnetic resonance imaging provides superior structural detail but poor specificity in identifying viable tumors in treated brain with surgery/radiation/chemotherapy. (18)F-fluorodeoxyglucose positron emission tomography (FDG-PET) is capable of identifying anaplastic transformation and has prognostic value. The sensitivity and specificity of FDG in evaluating recurrent tumor and treatment-induced changes can be significantly improved by coregistration with magnetic resonance imaging and potentially by delayed imaging 3 to 8 hours after injection.
Amino acid PET tracers can be more sensitive than FDG in imaging some recurrent tumors, in particular recurrent low-grade tumors. They are also promising for differentiating between recurrent tumors and treatment-induced changes. Newer PET tracers to image important aspects of tumor biology have been actively studied. Tracers for imaging membrane transport such as (18)F-choline have shown promise in differential diagnosis. (18)F-labeled nucleotide analogs such as 3'-deoxy-3'-(18)F]-fluorothymidine (FLT) and (18)F-FMAU have been developed to image proliferation. The use of FLT has demonstrated prognostic power in predicting treatment response in patients treated with an antiangiogenic agent. Tracers for imaging hypoxia such as (18)F-FMISO have been studied and appear promising in providing prognostic information as well as planning treatment.

**FDG-PET on irradiated brain tumor: ten years’ summary.**

PURPOSE: To evaluate FDG-PET in post-radiotherapy differentiation of tumor recurrence/malignant degeneration and radiation reaction, and to assess the role of PET in terms of survival. MATERIAL AND METHODS: 117 consecutive patients with a total of 156 FDG-PET examinations with positive but non-diagnostic MRI and/or CT were included. Final diagnosis was based on histopathology or correlated with radiologic and clinical follow-up. Brain metastases from lung carcinomas were further studied separately. Survival time was analysed using the Kaplan-Meier method. RESULTS: There were 61 true-positive, 2 false-positive, 15 false-negative, and 51 true-negative PET examinations; 5 positive and 22 negative PET examinations were indeterminate. The positive predictive value of a PET examination was 96% in all and 100% in brain metastases from lung carcinoma. The negative predictive value based on the histopathologic results was 55.6%. Survival time
was significantly longer in patients with negative PET.

CONCLUSION: FDG-PET is a valuable tool in the detection of tumor recurrence, especially lung carcinoma metastasis. FDG uptake is a prognostic marker.


The purpose of this prospective study was to clarify the individual and combined role of L-methyl-\textsuperscript{11}C-methionine-positron emission tomography (MET-PET) and 32-deoxy-32-\textsuperscript{18}F-fluorothymidine (FLT)-PET in tumor detection, noninvasive grading, and assessment of the cellular proliferation rate in newly diagnosed histologically verified gliomas of different grades. \textit{Materials and methods:} Forty-one patients with newly diagnosed gliomas were investigated with MET-PET before surgery. Eighteen patients were also examined with FLT-PET. MET and FLT uptakes were assessed by standardized uptake value of the tumor showing the maximum uptake (SUV\textsubscript{max}), and the ratio to uptake in the normal brain parenchyma (T/N ratio). All tumors were graded by the WHO grading system using surgical specimens, and the proliferation activity of the tumors were determined by measuring the Ki-67 index obtained by immunohistochemical staining. \textit{Results:} On semiquantitative analysis, MET exhibited a slightly higher sensitivity (87.8\%) in tumor detection than FLT (83.3\%), and both tracers were 100\% sensitive for malignant gliomas. Low-grade gliomas that were false negative on MET-PET also were false negative on FLT-PET. Although the difference of MET SUV\textsubscript{max} and T/N ratio between grades II and IV gliomas was statistically significant (\(P < 0.001\)), there was a significant overlap of
MET uptake in the tumors. The difference of MET $SUV_{\text{max}}$ and $T/N$ ratio between grades II and III gliomas was not statistically significant. Low-grade gliomas with oligodendroglial components had relatively high MET uptake. The difference of FLT $SUV_{\text{max}}$ and $T/N$ ratio between grades III and IV gliomas was statistically significant ($P < 0.01$). Again, the difference of FLT $SUV_{\text{max}}$ and $T/N$ ratio between grades II and III gliomas was not statistically significant. Grade III gliomas with non-contrast enhancement on MR images had very low FLT uptake. In 18 patients who underwent PET examination with both tracers, a significant but relatively weak correlation was observed between the individual $SUV_{\text{max}}$ of MET and FLT ($r = 0.54$, $P < 0.05$) and $T/N$ ratio of MET and FLT ($r = 0.56$, $P < 0.05$). Total FLT uptake in the tumor had a higher correlation ($r = 0.89$, $P < 0.001$) with Ki-67 proliferation index than MET uptake ($r = 0.49$, $P < 0.01$).
Section — XII

Pediatric Tumors
Paediatric Extracranial Solid Tumors

These include liver tumors, non Hodgkins and Hodgkins lymphoma, neuroblastoma, rhabdomyosarcoma, Wilms tumor, Ewings sarcoma and Osteosarcoma. Staging of almost all tumors includes the assessment of the local spread of the primary tumor, metastatic nodal extent and the location of distant blood borne metastatic sites. Conventional modalities include CT scan and or MRI, bone scan, bone marrow biopsy and tumor markers.

Evidence of utility of FDG PET in pediatric sarcomas.

Staging
A prospective multi centre trial comparing the role of PET in staging of pediatric soft tissue sarcomas. This study depicts the superiority of PET in identifying lymphnode and bone metastases as compared to the conventional imaging modalities but CT being superior for pulmonary metastases. It suggests PET/CT to be a useful adjunct to other conventional imaging modalities (CIM) in planning treatment. The retrospective analysis of 36 patients with pediatric abdominal neoplasams suggests the likely indication of FDG PET, and mentions it as a promising tool. Another retrospective study assesses the sensitivity of PET/CT versus PET and CT alone in all pediatric
sarcomas and conveys that there is no significant change in the sensitivities of PET/CT and CT in identifying either the primary or metastatic sites. The specificity of PET/CT improves in cases with pulmonary metastases > 0.5 cms and lymph node > 1 cms.

**Follow up/restaging:**
A prospective study which analysed 19 patients of paediatric sarcomas with FDG PET/CT has shown a sensitivity of 100% for primary site recurrence with a 77% sensitivity for distant metastases.

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<tr>
<th>Timing of the PET/CT</th>
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<td>Diagnosis</td>
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**Early experience with PET/CT scan in the evaluation of pediatric abdominal neoplasms.** James J. Murphy, Mansour Tawfeeq, Brett Chang, Helen Nadel. *Journal of Pediatric Surgery* (2008) 43, 2186–2192

Purpose: Positron emission tomography/computerized tomography (PET/CT) scan provides both functional and anatomical information in a single diagnostic test. It has the potential to be a valuable tool in the evaluation of pediatric
abdominal tumors. The goal of this study is to report our early experience with this technology.

Methods: Children who underwent PET/CT scan in the workup for abdominal neoplasms between July 2005 and January 2008 were identified. Retrospective review of all radiologic studies, operative notes, and pathologic reports was undertaken.

Results: A total of 36 patients were collected. These included Burkitt’s lymphoma (8), neuroblastoma (7), rhabdomyosarcoma (6), ovarian tumor (3), Wilms’ tumor (2), hepatocellular carcinoma (2), paraganglioma (1), germ cell tumor (1), undifferentiated sarcoma (1), renal primitive neuroectodermal tumor (1), gastrointestinal stromal tumor (1), adrenocortical carcinoma (1), inflammatory pseudotumor (1), and adrenal adenoma (1). All neoplasms were fluorodeoxyglucose (FDG) were avid. Our experience identified several potential uses for PET/CT scan in this group of patients. These include (1) preoperative staging, (2) selection of appropriate site for biopsy, (3) identification of occult metastatic disease, (4) follow-up for residual or recurrent disease, and (5) assessment of response to chemotherapy. It can also be valuable when the standard diagnostic studies are equivocal or conflicting.

Conclusions: Preliminary data indicate that PET/CT is a promising tool in the evaluation of pediatric abdominal malignancies. The delineation of the exact role of this diagnostic modality will require additional experience.


OBJECTIVE: The objective of this retrospective study was to compare the diagnostic value of 2-[(18)F]fluoro-2-deoxy-D:
glucose positron emission tomography ((18)F-FDG PET)/CT versus (18)F-FDG PET and CT alone for staging and restaging of pediatric solid tumors.

METHODS: Forty-three children and adolescents (19 females and 24 males; mean age, 15.2 years; age range, 6-20 years) with osteosarcoma (n = 1), squamous cell carcinoma (n = 1), synovial sarcoma (n = 2), germ cell tumor (n = 2), neuroblastoma (n = 2), desmoid tumor (n = 2), melanoma (n = 3), rhabdomyosarcoma (n = 5), Hodgkin’s lymphoma (n = 7), non-Hodgkin-lymphoma (n = 9), and Ewing’s sarcoma (n = 9) who had undergone (18)F-FDG PET/CT imaging for primary staging or follow-up of metastases were included in this study. The presence, location, and size of primary tumors was determined separately for PET/CT, PET, and CT by two experienced reviewers. The diagnosis of the primary tumor was confirmed by histopathology. The presence or absence of metastases was confirmed by histopathology (n = 62) or clinical and imaging follow-up (n = 238).

RESULTS: The sensitivities for the detection of solid primary tumors using integrated (18)F-FDG PET/CT (95%), (18)F-FDG PET alone (73%), and CT alone (93%) were not significantly different (p > 0.05). Seventeen patients showed a total of 153 distant metastases. Integrated PET/CT had a significantly higher sensitivity for the detection of these metastases (91%) than PET alone (37%; p < 0.05), but not CT alone (83%; p > 0.05). When lesions with a diameter of less than 0.5 cm were excluded, PET/CT (89%) showed a significantly higher specificity compared to PET (45%; p < 0.05) and CT (55%; p < 0.05). In a sub-analysis of pulmonary metastases, the values for sensitivity and specificity were 90%, 14%, 82% and 63%, 78%, 65%, respectively, for integrated PET/CT, stand-alone PET, and stand-alone CT. For the detection of regional lymph node metastases, (18)F-FDG PET/CT, (18)F-FDG PET alone, and CT alone were diagnostically
correct in 83%, 61%, and 42%. A sub-analysis focusing on the ability of PET/CT, PET, and CT to detect osseous metastases showed no statistically significant difference between the three imaging modalities (p > 0.05).

CONCLUSION: Our study showed a significantly increased sensitivity of PET/CT over that of PET for the detection of distant metastases but not over that of CT alone. However, the specificity of PET/CT for the characterization of pulmonary metastases with a diameter > 0.5 cm and lymph node metastases with a diameter of <1 cm was significantly increased over that of CT alone.


Purpose

The objective of this study was to evaluate the impact of positron emission tomography (PET) using fluorine-18-fluorodeoxyglucose (FDG) for initial staging and therapy planning in pediatric sarcoma patients.

Patients and Methods

In this prospective multicenter study, 46 pediatric patients (females, n = 22; males, n = 24; age range, 1 to 18 years) with histologically proven sarcoma (Ewing sarcoma family tumors, n = 23; osteosarcoma, n = 11; rhabdomyosarcoma, n = 12) were examined with conventional imaging modalities (CIMs), including ultrasound, computed tomography (CT), magnetic resonance imaging, and bone scintigraphy according to the standardized algorithms of the international therapy optimization trials, and whole-body FDG-PET. A lesion- and patient-based analysis of PET alone and CIMs alone and a side-by-side (SBS) analysis of FDG-PET and CIMs were
performed. The standard of reference consisted of all imaging material, follow-up data (mean follow-up time, 24 ± 12 months), and histopathology and was determined by an interdisciplinary tumor board.

**Results**

FDG-PET and CIMs were equally effective in the detection of primary tumors (accuracy, 100%). PET was superior to CIMs concerning the correct detection of lymph node involvement (sensitivity, 95% vs. 25%, respectively) and bone manifestations (sensitivity, 90% vs. 57%, respectively), whereas CT was more reliable than FDG-PET in depicting lung metastases (sensitivity, 100% vs. 25%, respectively). The patient-based analysis revealed the best results for SBS, with 91% correct therapy decisions. This was significantly superior to CIMs (59%; \( P < 0.001 \)).

**Conclusion**

In staging pediatric sarcoma, subsidiary FDG-PET scanning depicts important additional information and has a relevant impact on therapy planning when analyzed side-by-side with CIMs.

**Evidence for utility of PET/CT in Rhabdomyosarcoma:**

**Staging**

A retrospective study analyzed 24 patients of RMS and has concluded that PET has similar sensitivity for identifying primary lesions as compared to other CIM but has a higher negative predictive value in situation where the CT and MRI have equivocal findings; the sensitivity was calculated at 77% with a specificity of 99%.

Treatment response and restaging or follow up.
A retrospective analysis of 4 patients was done in evaluating the treatment response of the primary site. This small data shows a reduction in FDG uptake is suggestive of good response to therapy as also seen by a long remission period in these patients.

<table>
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<td>Diagnosis</td>
<td>Level 2</td>
<td>Potentially appropriate</td>
<td>1 level 3 study</td>
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<tr>
<td>Staging</td>
<td>Level 2</td>
<td>Potentially appropriate</td>
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<td>Response evaluation</td>
<td>Level 5</td>
<td>Potentially appropriate</td>
<td>1 level 4 study</td>
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<tr>
<td>Restaging</td>
<td>Level 2</td>
<td>Potentially appropriate</td>
<td>1 level 3 study</td>
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<tr>
<td>Suspected recurrence</td>
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<td>Followup</td>
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<td>RT planning</td>
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Abstracts:


BACKGROUND: Complete staging of rhabdomyosarcoma is critical to deliver appropriate therapy. We evaluated the role of F-fluorodeoxyglucose positron emission tomography (PET) in the staging of patients with rhabdomyosarcoma.

METHODS: Twenty-four patients with rhabdomyosarcoma had a PET scan during staging evaluation, before or within 13 days of initiation of therapy. PET was compared with computed tomography (CT), magnetic resonance imaging (MRI), bone
scan, and pathology. RESULTS: Ninety-six sites were evaluated. All patients had positive PET scans at the primary site. Thirty-one PET positive sites at primary, regional, or distant sites were biopsied. Pathology in all 31 confirmed disease. Standardized uptake value for the primary site at diagnosis ranged from 2.4 to 12.7 (mean 6.4). At 23 sites, CT or MRI was equivocal for the detection of regional or distant spread. In these cases, a negative PET helped to exclude disease in 21 of 23 patients. PET failed to capture sites of disease visualized by CT, MRI, or bone scan at 10 sites. When comparing PET with the final clinical determination of disease extent, PET was 77% sensitive and 95% specific. CONCLUSIONS: These preliminary data indicate that PET is a useful adjunct in staging rhabdomyosarcoma. A prospective study of PET for staging of rhabdomyosarcoma is warranted.


PURPOSE: The purpose of this study was to study the use of 2-deoxy-2-[F-18]-fluoro-D-glucose positron emission tomography (F-18 FDG PET) for monitoring therapeutic response by rhabdomyosarcoma (RMSA) in children. PATIENTS AND METHODS: A retrospective case study was performed by searching a computer database for the patients with RMSA in whom F-18 FDG PET studies were performed pre- and posttreatment. The data of the PET studies from these patients were analyzed in conjunction with clinical treatment and other imaging studies to determine whether interval changes of F-18 FDG uptake by the RMSA reflect response of RMSA to treatment. RESULTS: Four patients with RMSA who received both pretreatment and posttreatment F-18 FDG PET studies were identified from the database and included
in this study. A dramatic decrease of F-18 FDG uptake by the
tumor was evident in the patients who had a favorable response
to the therapy and prolonged remission of the disease. In
contrast, persistent abnormal FDG uptake in one patient was
associated with early relapse of the RMSA. CONCLUSIONS:
F-18 FDG PET may be useful for monitoring therapeutic
response by RMSA in children, which needs to be verified
with a prospective study in a larger patient population.

Positron emission tomography/computed tomography with
18fluoro-deoxyglucose in the detection of local recurrence
and distant metastases of pediatric sarcoma. Arush MW,
Israel O, Postovsky S, Militianu D, Meller I, Zaidman I,
Sapir AE, Bar-Shalom R. Pediatr Blood Cancer
2007;49:901–905

BACKGROUND: Combined positron emission tomography
with (18)fluoro-deoxyglucose and computed tomography
(FDG-PET/CT) has been used in the diagnosis and staging of
various malignancies, but their use in the management of
pediatric sarcomas is less well defined. The potential role of
FDG-PET/CT in the diagnosis of local recurrence and distant
metastases of pediatric sarcomas was investigated.

PROCEDURE: Nineteen children (aged 2-21) with sarcoma
(9 Ewing sarcoma, 3 osteogenic sarcoma, 7
rhabdomyosarcoma) were evaluated between January 2000
and December 2005 by FDG-PET/CT for suspected local
relapse or distant metastases. The results of 21 FDG-PET
studies, 16 CT scans, 9 magnetic resonance imaging (MRI)
studies, and 7 bone scans (BSs) were compared with surgical
pathology or clinical follow-up for at least 3 months.

RESULTS: FDG-PET detected local relapse in all seven
patients and distant metastases in 10/13 (77%). FDG-PET/
CT and CT/MRI/BS results were discordant in eight patients.
FDG-PET/CT was the only modality that detected distant
metastases in two patients. PET/CT was true negative and
excluded disease in three patients with abnormal CT/BSs and was false negative in three patients with distant metastases. CONCLUSION: FDG-PET/CT may be useful and complementary to other imaging modalities for the detection of recurrent pediatric sarcomas, especially at the primary site. Its potential advantages and limitations compared with conventional imaging modalities need to be further investigated in larger homogenous patient groups.
Neuroblastoma

Introduction
Neuroblastoma is the most common extracranial solid tumor in infancy. Tumors can occur in the abdominal cavity (40% adrenal, 25% paraspinal ganglia) or can involve other sites (15% thoracic, 5% pelvic, 3% cervical tumors, 12% miscellaneous). More than 90% of patients have elevated homovanillic acid (HVA) and/or vanillylmandelic acid (VMA) detectable in urine. Serum markers associated with a poor prognosis include (1) elevated ferritin levels, (2) elevated serum lactate dehydrogenase (LDH) levels, and (3) elevated serum neuron-specific enolase (NSE) levels.

Conventional staging
ISerum LDH (useful as biologic marker), Ferritin (useful as biologic marker), CBC count and differential (Anemia or other cytopenias suggest bone marrow involvement.) Urine collection for catecholamines (VMA/HVA)

Chest and abdominal radiographs to evaluate for the presence of a mass or calcifications. A CT scan of the primary site is essential to determine tumor extent. The main body of the tumor is usually indistinguishable from nodal masses. In cases
of paraspinal masses, MRI aids in determining the presence of intraspinal tumor and cord compression. I23/131-methyliodobenzylguanadine (MIBG) accumulates in catecholaminergic cells and provides a specific way of identifying primary and metastatic disease if present. Increasing numbers of institutions have access to MIBG scanning. A technetium-99 bone scan can also be used to evaluate bone metastases. Especially in patients with negative MIBG study findings.

**Evidence in use of FDG PET/CT in neuroblastoma.**

**Staging:**
Literature search has not revealed either a prospective trial or a large retrospective analysis on patients using FDG PET in staging of neuroblastoma patients.

Follow up and re staging:
A prospective study of 51 patients has identified PET to be superior to the CIM in locating local recurrences and either superior or equivocal in tracing metastatic disease. It suggests PET as an adjunct to bone marrow evaluation in restaging of disease.

There is a case report of meningeal metastases identified by FDG PET.

Another case report has shown the ability of this modality to locate MIBG negative disease, caused probable due to receptor changes.

No large or small data analysis is available to validate the use in restaging the disease.
Timing of the PET/CT | Hierarchy of Diagnostic Efficacy | Relevance of Test | Level of Evidence
--- | --- | --- | ---
Diagnosis | – | – | –
Staging | – | – | –
Response evaluation | – | – | –
Restaging | – | – | –
Suspected recurrence | – | – | –
Follow up | Level 2 | Potentially appropriate | 1 Level 3 study1 level 5 study
RT planning | – | – | –

Abstracts


PURPOSE: Although positron emission tomography (PET) with fluorine-18 fluorodeoxyglucose ((18)F-FDG) has a major impact on the treatment of adult cancer, the reported experience with extracranial tumors of childhood is limited. We describe a role for PET in patients with neuroblastoma (NB).

PATIENTS AND METHODS: In 51 patients with high-risk NB, 92 PET scans were part of a staging evaluation that included iodine-123 or iodine-131 metaiodobenzylguanidine (MIBG) scan, bone scan, computed tomography (and/or magnetic resonance imaging), urine catecholamine measurements, and bone marrow (BM) examinations. The minimum number of tests sufficient to detect NB was determined.
RESULTS: Of 40 patients who were not in complete remission, only 1 (2.5%) had NB that would have been missed had a staging evaluation been limited to PET and BM studies, and 13 (32.5%) had NB detected by PET but not by BM and urine tests. PET was equal or superior to MIBG scans for identifying NB in soft tissue and extracranial skeletal structures, for revealing small lesions, and for delineating the extent and localizing sites of disease. In 36 evaluations of 22 patients with NB in soft tissue, PET failed to identify only two long-standing MIBG-negative abdominal masses. PET and MIBG scans showed more skeletal lesions than bone scans, but the normally high physiologic brain uptake of FDG blocked PET visualization of cranial vault lesions. Similar to MIBG, FDG skeletal uptake was diffusely increased with extensive or progressing BM disease but faint or absent with minimal or nonprogressing BM disease.

CONCLUSION: In the absence or after resolution of cranial vault lesions, and once the primary tumor is resected, PET and BM tests suffice for monitoring NB patients at high risk for progressive disease in soft tissue and bone/BM.
Wilms Tumor

Wilms tumor is the commonest renal tumor in children. This arises either sporadically, as a component of genetic disorders or as a familial disease. Conventional imaging includes an Ultrasound, CT scan, chest X ray and a bone scan. These help identify the tumor size, nodal extent, the status of the opposite kidney and the presence of liver, pulmonary or skeletal metastases. A MRI scan is not usually done.

Evidence of use of FDG PET in Wilms tumor

A retrospective study of 12 patients shows no additional value of FDG PET in staging of Wilms tumor but shows additional value in restaging of disease, similarly another small study of 4 patients and an interesting image article reveals concentration of FDG in recurrent disease.

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Abstracts


To evaluate FDG-PET for staging, grading, preoperative response assessment and posttherapeutic evaluation in children with Wilms tumour (WT).

In this study, 23 FDG-PET examinations in 12 paediatric patients (female, n = 5; male, n = 7; age, 1-19 years) with WT (primary, n = 9; relapsed, n = 3) were analysed. All patients were examined with conventional imaging methods (CIM) according to the SIOP2001/GPOH trial protocol. Additionally, FDG-PET/PET-CT was performed for staging (n = 12), preoperative response assessment (n = 6) and posttherapeutic evaluation (n = 5). Imaging results of FDG-PET and CIM were analysed regarding the accuracy in tumour visualisation, impact on therapeutic management and preoperative response assessment, with clinical follow-up and histopathology as the standard of reference.

FDG-PET and CIM showed concordant results for staging of primary WT, whereas FDG-PET was superior in 1/3 cases with recurrent WT. Concerning histological differentiation, one case with anaplastic WT had an standard uptake value (SUV) of 12.3, which was remarkably higher than the average SUV in the eight cases with intermediate risk histology. No parameter analysed for PET or CIM was reliably predictive for histological regression or clinical outcome. After completion of therapy, FDG-PET was superior to CIM in 2/5 cases in detecting residual disease with therapeutic relevance.
FDG-PET does not provide additional information to the traditional imaging work-up for staging WT patients, preoperative response assessment and clinical outcome. FDG-PET was advantageous in ruling out residual disease after completion of first line treatment and in pretherapeutic staging of relapse patients. Furthermore, there seems to be a good correlation of initial SUV and histological differentiation.

PET FDG studies of Wilms tumors.
Section — XIII

Guidelines & Recommendations
The following are the abstracts of recommendations of the use of FDG PET in oncology:

**Recommendations on the use of 18F-FDG PET in oncology.**

The rationale was to develop recommendations on the use of (18)F-FDG PET in breast, colorectal, esophageal, head and neck, lung, pancreatic, and thyroid cancer; lymphoma, melanoma, and sarcoma; and unknown primary tumor. Outcomes of interest included the use of (18)F-FDG PET for diagnosing, staging, and detecting the recurrence or progression of cancer. METHODS: A search was performed to identify all published randomized controlled trials and systematic reviews in the literature. An additional search was performed to identify relevant unpublished systematic reviews. These publications comprised both retrospective and prospective studies of varied methodologic quality. The anticipated consequences of false-positive and false-negative tests when evaluating clinical usefulness, and the impact of (18)F-FDG PET on the management of cancer patients, were also reviewed. Results and CONCLUSION: (18)F-FDG PET
should be used as an imaging tool additional to conventional radiologic methods such as CT or MRI; any positive finding that could lead to a clinically significant change in patient management should be confirmed by subsequent histopathologic examination because of the risk of false-positive results. (18)F-FDG PET should be used in the appropriate clinical setting for the diagnosis of head and neck, lung, or pancreatic cancer and for unknown primary tumor. PET is also indicated for staging of breast, colon, esophageal, head and neck, and lung cancer and of lymphoma and melanoma. In addition, (18)F-FDG PET should be used to detect recurrence of breast, colorectal, head and neck, or thyroid cancer and of lymphoma.

PMID: 18287273 [PubMed - indexed for MEDLINE]


OBJECTIVE: The purpose of these guidelines is to offer to the nuclear medicine team a framework that could prove helpful in daily practice. These guidelines contain information related to the indications, acquisition, processing and interpretation of (18)F-fluorodeoxyglucose positron emission tomography ((18)F-FDG PET) in paediatric oncology. The Oncology Committee of the European Association of Nuclear Medicine (EANM) has published excellent procedure guidelines on tumour imaging with (18)F-FDG PET (Bombardieri et al., Eur J Nucl Med Mol Imaging 30:BP115-24, 2003). These guidelines, published by the EANM Paediatric Committee, do not intend to compete with the existing guidelines, but rather aim at providing additional information on issues particularly relevant to PET imaging of children with
cancer. CONCLUSION: The guidelines summarize the views of the Paediatric Committee of the European Association of Nuclear Medicine. They should be taken in the context of “good practice” of nuclear medicine and of any national rules, which may apply to nuclear medicine examinations. The recommendations of these guidelines cannot be applied to all patients in all practice settings. The guidelines should not be deemed inclusive of all proper procedures or exclusive of other procedures reasonably directed to obtaining the same results.

PMID: 18536914 [PubMed - indexed for MEDLINE]


The use of positron emission tomography (PET) is increasing rapidly in the United States, with the most common use of PET scanning related to oncology. It is especially useful in the staging and management of lymphoma, lung cancer, and colorectal cancer, according to a panel of expert radiologists, surgeons, radiation oncologists, nuclear medicine physicians, medical oncologists, and general internists convened in November 2006 by the National Comprehensive Cancer Network. The Task Force was charged with reviewing existing data and developing clinical recommendations for the use of PET scans in the evaluation and management of breast cancer, colon cancer, non-small cell lung cancer, and lymphoma. This report summarizes the proceedings of this meeting, including discussions of the background of PET, possible future developments, and the role of PET in oncology.

PMID: 17509259

Practical guidelines for the use of FDG PET in the management of lymphoma are given, based on the evidence presented in the previous article. A statement and recommendations are given where appropriate. The recommendations are summarized at the end of the paper.

PMID: 17414884 [PubMed - indexed for MEDLINE]


In the past 10 years, positron emission tomography (PET), usually with F-fluoro-2-deoxy-D-glucose (FDG), has become an important imaging modality in patients with lung cancer. FDG-PET is recommended for the diagnosis of indeterminate pulmonary nodules, for which it is significantly more accurate than computed tomography (CT) in the distinction between benign and malignant lesions. A large body of evidence convincingly demonstrates that loco-regional lymph node staging by FDG-PET (in correlation with CT images) is significantly superior to CT alone, with a negative predictive value equal or even superior to mediastinoscopy. FDG-PET also improves extrathoracic staging through detection of lesions missed at conventional imaging or characterization of lesions that remain equivocal on conventional imaging. Ongoing studies now concentrate on more advanced clinical applications, such as the planning of radiotherapy, the response evaluation after the induction of therapy, the early detection of recurrence, and the use in lung cancer screening. Technical innovations, such as PET cameras with better spatial resolution, or new radiopharmaceutical probes to study
applications of PET in molecular biology hold promise for future refinements in this field.

PMID: 17409830 [PubMed - indexed for MEDLINE]

(NOPR) – National oncological PET registry

The following abstracts summarize the composition of the National Oncologic Pet registry and its interim findings.


The Centers for Medicare and Medicaid Services (CMS) has provided a mechanism for expanded coverage of selected promising technologies under its “coverage with evidence development (CED)” policy. The National Oncologic PET Registry (NOPR) was designed to address the CED requirements for collection of clinical and demographic data to allow for CMS coverage of PET for previously noncovered cancer types and indications. The NOPR opened in May 2006. This report reviews the NOPR’s data collection and analysis plan. METHODS: NOPR is a nationwide prospective internet-based registry. All PET facilities that are participating providers in the Medicare program may enroll in NOPR. The PET facility is responsible for collecting and entering patient data into the NOPR database through a Web application at: (http://www.cancerPETregistry.org/). Data are collected from the requesting physician on Pre-PET and Post-PET forms. The primary research goal is to assess the effect of PET on referring physicians’ plans of intended patient management across the spectrum of expanded cancer indications (diagnosis, staging, restaging, suspected recurrence, and treatment monitoring). The NOPR investigators will have access to data only on cases in which both the patient and the referring physician have
consented to allow their data to be used for research. Data will be analyzed and compared in aggregate for all cancers by category (e.g., staging) and then for specific high-impact types and indications (e.g., staging of pancreatic cancer) when 200 patients have been accrued to a specific combination or after the NOPR has been operational for 1 y. CONCLUSION: The NOPR will allow an accurate assessment of the impact of PET on intended patient management across a wide spectrum of cancer indications.

PMID: 17942807


OBJECTIVE: The purpose of this article is to review the recent expansion of Medicare coverage for 18F-FDG PET for certain cancer indications under the Centers for Medicare & Medicaid Services’ new Coverage with Evidence Development (CED) policy and to describe the specific operational mechanics of the National Oncologic PET Registry (NOPR). CONCLUSION: The NOPR will make possible a more accurate assessment of the actual influence of PET on patient management across a wide spectrum of cancer indications. By linking access to PET for virtually all Medicare beneficiaries to the collection of clinically valuable evidence, the NOPR represents the cutting edge of the CED approach.

PMID: 17377055 [PubMed - indexed for MEDLINE]

Impact of positron emission tomography/computed tomography and positron emission tomography (PET) alone on expected management of patients with cancer: initial results from the National Oncologic PET Registry.

PURPOSE: Under Medicare’s Coverage with Evidence Development policy, positron emission tomography (PET)/computed tomography (CT) and PET became covered services for previously noncovered cancer indications if prospective registry data were collected. The National Oncologic PET Registry (NOPR) was developed to meet these coverage requirements and to assess how PET affects care decisions. METHODS: The NOPR collected questionnaire data from referring physicians on intended patient management before and after PET. After 1 year, the cohort included data from 22,975 studies (83.7% PET/CT) from 1,178 centers. The numbers of scans performed for diagnosis of suspected cancer (or unknown primary cancer), initial cancer staging, restaging, and suspected cancer recurrence were approximately equal. Prostatic, pancreatic and ovarian cancers represented approximately 30% of cases. RESULTS: If PET data were not available, the most common pre-PET plan would have been other imaging. In these patients, the post-PET strategies changed to watching in 37% and treatment in 48%. In patients with planned biopsy before PET, biopsy was avoided in approximately 70%. If the pre-PET strategy was treatment, the post-PET strategy involved a major change in type in 8.7% and goal in 5.6%. When intended management was classified as either treatment or nontreatment, the post-PET plan was three-fold more likely to lead to treatment than nontreatment (28.3% v 8.2%; odds ratio = 3.4; 95% CI, 3.2 to 3.6). Overall, physicians changed their intended management in 36.5% (95% CI, 35.9 to 37.2) of cases after PET. CONCLUSION: This large, prospective, nationally representative registry of elderly cancer patients found that physicians often change their intended management on the basis of PET scan results across the full spectrum of its potential uses.

PMID: 18362365

We previously reported aggregate data showing that PET was associated with a change in intended management for over one third of patients participating in the National Oncologic PET Registry (NOPR). Here, we present results for specific cancer types and indications for testing. METHODS: The NOPR collected questionnaire data from referring physicians on intended management before and after PET. Data were available from 40,863 PET studies done at 1,368 centers. The impact of PET was assessed for 18 cancer types in patients with pathologically confirmed cancer by type and indication for testing (initial staging, restaging, or detection of suspected recurrence), other than treatment monitoring. RESULTS: When intended management was classified as treatment or nontreatment, physicians changed their intended management for 38.0% of cases (95% confidence interval = 37.6%-38.5%). The frequencies of changes in management ranged from 48.7% for myeloma to 31.4% for nonmelanoma skin cancer. Comparisons across testing indications revealed that only in multiple myeloma did PET have a consistently greater impact on intended management. When the intended management plan before PET was treatment, a change in the intent of treatment (curative vs. palliative) or a major change in the modality of treatment occurred at similar frequencies across different cancer types. CONCLUSION: The impact of PET on physicians’ intended management for patients with known cancer was consistent across cancer types.

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