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# PET – Oncology

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## **PET-Oncology**

J Nucl Med. 2011 Sep 8. [Epub ahead of print]

### **Molecular Imaging with <sup>11</sup>C-PD153035 PET/CT Predicts Survival in Non-Small Cell Lung Cancer Treated with EGFR-TKI: A Pilot Study.**

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Outcomes are suboptimal when molecularly targeted therapies are used in patient populations unselected for the molecular target. This pilot study examines the correlation of PET using (<sup>11</sup>C)-labeled 4-N-(3-bromoanilino)-6,7-dimethoxyquinazoline ((<sup>11</sup>C)-PD153035), an imaging biomarker of epidermal growth factor receptor (EGFR), with outcomes in patients with non-small cell lung cancer (NSCLC) treated with the EGFR tyrosine kinase inhibitor erlotinib. Patients with advanced chemotherapy-refractory NSCLC were prospectively enrolled on a trial of erlotinib at a dose of 150 mg daily and imaged by (<sup>11</sup>C)-PD153035 PET/CT at baseline, after 1-2 wk, and after 6 wk from the start of treatment. Overall survival and progression-free survival (OS and PFS, respectively) times were correlated with the (<sup>11</sup>C)-PD153035 standardized uptake value (SUV) at each of the imaging times. Twenty-one patients were enrolled. Follow-up to progression was complete in all patients and to death in 18 of 21. By Cox regression analysis, baseline maximum SUV correlated strongly with OS and PFS (hazard ratio = 0.40, P = 0.002, and hazard ratio = 0.044, P < 0.001, respectively) independent of histology. Patients with higher maximum SUV ( $\geq$ median) survived more than twice as long as patients with lower maximum SUV (median OS = 11.4 vs. 4.6 mo, P = 0.002; PFS = 4.4 vs. 1.8 mo, P < 0.001). However, (<sup>11</sup>C)-PD153035 uptake on follow-up scans was less well correlated with survival. Our preliminary results suggest (<sup>11</sup>C)-PD153035 PET/CT may be a noninvasive and rapid method for identifying patients with refractory advanced NSCLC of adenocarcinoma or squamous histology likely to respond to the EGFR tyrosine kinase inhibitor but not for monitoring treatment response.

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Eur J Nucl Med Mol Imaging. 2011 Sep 6. [Epub ahead of print]

### **Early interim (<sup>18</sup>F)-FDG PET in Hodgkin's lymphoma: evaluation on 304 patients.**

Zinzani PL, Rigacci L, Stefoni V, Broccoli A, Puccini B, Castagnoli A, Vaggelli L, Zanoni L, Argnani L, Bacarani M, Fanti S.

Institute of Hematology and Medical Oncology "L. e A. Seragnoli", Policlinico "Sant'Orsola-Malpighi", University of Bologna, Bologna, Italy.

The use of early (interim) PET restaging during first-line therapy of Hodgkin's lymphoma (HL) in clinical practice has considerably increased because of its ability to provide early recognition of treatment failure allowing patients to be transferred to more intensive treatment regimens. Between June 1997 and June 2009, 304 patients with newly diagnosed HL (147 early stage and 157 advanced stage) were treated with the ABVD regimen at two Italian institutions. Patients underwent PET staging and restaging at baseline, after two cycles of therapy and at the end of the treatment. Of the 304 patients, 53 showed a positive interim PET scan and of these only 13 (24.5%) achieved continuous complete remission (CCR), whereas 251 patients showed a negative PET scan and of these 231 (92%) achieved CCR. Comparison between interim PET-positive and interim PET-negative patients indicated a significant association between PET findings and 9-year progression-free survival and 9-year overall survival, with a median follow-up of 31 months. Among the early-stage patients, 19 had a positive interim PET scan and only 4 (21%) achieved CCR; among the 128 patients with a negative interim PET scan, 122 (97.6%) achieved CCR. Among the advanced-stage patients, 34 showed a persistently positive PET scan with only 9 (26.4%) achieving CCR, whereas 123 showed a negative interim PET scan with 109 (88.6%) achieving CCR. Our results demonstrate the role of an early PET scan as a significant step forward in the management of patients with early-stage or advanced-stage HL.

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Eur J Nucl Med Mol Imaging. 2011 Sep 3. [Epub ahead of print]

### **Quantification of receptor-ligand binding with [<sup>18</sup>F]fluciclatide in metastatic breast cancer patients.**

Tomasi G, Kenny L, Mauri F, Turkheimer F, Aboagye EO.

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The purpose of the study was to estimate the receptor-ligand binding of an arginine-glycine-aspartic acid (RGD) peptide in somatic tumours. To this aim, we employed dynamic positron emission tomography (PET) data obtained from breast cancer patients with metastases, studied with the  $\alpha(v)\beta(3/5)$  integrin receptor radioligand [<sup>18</sup>F]fluciclatide. First, compartmental modelling and spectral analysis with arterial input function were performed at the region of interest (ROI) level in healthy lung and liver, and in lung and liver metastases; compartmental modelling was also carried out at the pixel level. The selection of the most appropriate indexes for tumour/healthy tissue differentiation and for estimation of specific binding was then assessed. The two-tissue reversible model emerged as the best according to the Akaike Information Criterion. Spectral analysis confirmed the reversibility of tracer kinetics. Values of kinetic parameters, estimated as mean from parametric maps, correlated well with those computed from ROI analysis. The volume of distribution V(T) was on average higher in lung metastases than in the healthy lung, but lower in liver metastases than in the healthy liver. In agreement with the expected higher  $\alpha(v)\beta(3/5)$  expression in pathology, k(3) and k(3)/k(4) were both remarkably higher in metastases, which makes them more suitable than V(T) for tumour/healthy tissue differentiation. The ratio k(3)/k(4), in particular, appeared a reasonable measure of specific binding. Besides establishing the best quantitative approaches for the analysis of [<sup>18</sup>F]fluciclatide data, this study indicated that the k(3)/k(4) ratio is a reasonable measure of specific binding, suggesting that this index can be used to estimate  $\alpha(v)\beta(3/5)$  receptor expression in oncology, although further studies are necessary to validate this hypothesis.

J Thorac Oncol. 2011 Sep 1. [Epub ahead of print]

### **A Randomized Phase II Trial of Two Regimens of Moderate Dose Chemoradiation Therapy for Patients with Non-small Cell Lung Cancer Not Suitable for Curative Therapy: Trans Tasman Radiation Oncology Study TROG 03.07.**

Burmeister BH, Michael M, Burmeister E, Cox S, Lehman M, Wirth A, Horwood K, Sasso G, Forouzesh B, Ball D.

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There are patients with stage I-III non-small cell lung cancer (NSCLC) who are not suitable for curative radical chemoradiation therapy. There are patients with an isolated solitary extracranial metastasis who have improved outcomes compared with those with cranial or multiple metastases. Patients of good performance status receiving moderate dose radiation therapy have improved survival. Two regimens of moderate dose chemoradiation therapy for such patients were compared in a randomized phase II trial. Patients were eligible if they had stage I-III NSCLC, unsuitable for curative therapy, or stage IV with a PET-detected extracranial solitary metastasis. Patients were randomized to the following groups-arm A: 40 Gy/20 fractions/4 weeks with concurrent weekly vinorelbine 25 mg/m + cisplatin 20 mg/m or arm B: 30 Gy/15 fractions/3 weeks with concurrent weekly gemcitabine 200 mg. Primary end points were feasibility, response rates, and toxicity. Secondary end points were progression-free survival, overall survival, and quality of life. Eighty-four patients were randomized. Compliance was above 90% for both arms. The overall response rate was 51% in arm A and 38% in arm B ( $p = 0.147$ ). Grade 3/4 toxicity in both arms was acceptable. There was no difference in median progression-free survival between the two arms (5.5 versus 5.0 months,  $p = 0.19$ ). Patients in arm A had longer median survival but this did not reach statistical significance (13.1 versus 8.3 months,  $p = 0.25$ ). No difference in quality of life was observed. Arm A was chosen for a future phase II comparison with radiation therapy alone as it demonstrated a response rate greater than 50%, and data suggested that arm A had superior survival to arm B.

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Clin Nucl Med. 2011 Oct;36(10):952-4.

### **Fibrodysplasia Ossificans Progressiva Detected on FDG PET/CT.**

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Fibrodysplasia ossificans progressiva (FOP) is a genetic disorder of the skeletal system which, due to its rarity, is frequently misdiagnosed for a malignancy (Kitterman et al. *Pediatrics*. 2005;116:e654-e661). Consequently, these patients are subjected to multiple invasive diagnostic and therapeutic procedures which instead can aggravate the disease (Kitterman et al. *Pediatrics*. 2005;116:e654-e661). Recognition of the computed tomography appearance of FOP is thus vital, as these patients are likely to be referred for a positron emission tomography/computed tomography (PET/CT) to stage a misdiagnosed cancer. In this study, the PET/CT features of FOP are demonstrated in a child who was referred for staging of an erroneously diagnosed lymphoma.

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Clin Nucl Med. 2011 Oct;36(10):889-93.

### **Noninvasive and invasive staging of ovarian cancer: review of the literature.**

Fuccio C, Castellucci P, Marzola MC, Al-Nahhas A, Fanti S, Rubello D.

From the \*Service of Nuclear Medicine, Hematology-Oncology and Laboratory Medicine Department, Azienda Ospedaliero-Universitaria di Bologna Policlinico Sant'Orsola-Malpighi, University of Bologna, Bologna, Italy; †Department of Nuclear Medicine, Medical Physics and Radiology, Santa Maria della Misericordia Hospital, Rovigo, Italy; and ‡Department of Nuclear Medicine, Hammersmith Hospital, London, United Kingdom.

The use of F-18 FDG PET/CT in the characterization of doubtful adnexal findings and in the staging of ovarian cancer is being extensively evaluated. The purpose of our article is to review the literature and to add our experience to the published works. We concluded that F-18 FDG PET/CT could represent an important method in addition to other imaging modalities (transvaginal ultrasound-, and contrast-enhanced computed tomography) in the characterization of adnexal masses and in the staging of ovarian cancer patients, particularly in assessing the presence of extra-abdominal metastatic spread.

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Clin Nucl Med. 2011 Oct;36(10):867-71.

### **Underperformance of Gallium-67 Scan is Greater in Relapse Than in Initial Staging, Compared With FDG PET.**

Huang YY, You DL, Liu MC, Tan TD, Lee PI, Lee MY.

From the \*Department of Nuclear Medicine, Koo Foundation Sun Yat-Sen Cancer Center, Taipei, Taiwan; †Division of Hematology and Medical Oncology, Department of Medicine, Koo Foundation Sun Yat-Sen Cancer Center, Taipei, Taiwan; and ‡Department of Pathology and Laboratory Medicine, Koo Foundation Sun Yat-Sen Cancer Center, Taipei, Taiwan.

The purpose of this study is to evaluate the performance of gallium-67 scan (GS) and F-18 fluorodeoxyglucose (FDG) PET scan in lymphoma staging and recurrence detection by comparing the 2 imaging studies in the same patient. : A total of 42 patients from the period between July 2002 and May 2006 were included in this study. Of the 42 patients, 6 had Hodgkin disease and 36 had non-Hodgkin lymphomas. All of them underwent one or more FDG PET scans and also underwent corresponding GS performed within 7 days of FDG PET, for staging or detection of lymphoma recurrence. Among the non-Hodgkin lymphoma cases, 18 were diffuse large B-cell lymphoma, 10 were follicular center cell lymphoma, and 8 were of other types. Of the total 46 pairs of imaging performed in these 42 patients, 27 were for staging, and 19 for restaging after recurrence.

In all these studies, FDG PET detected 230 lesion sites, whereas GS detected 85 lesion sites. All of the lesions detected by GS were noted on FDG PET, whereas GS detected only 37.0% of the lesions detected by FDG PET. Among the 27 studies for staging, FDG PET detected 120 lesions, whereas GS detected 68 lesions (56.7%). In the 19 images taken for relapse, FDG PET detected 110 lesions, whereas GS detected only 17 (15.5%). FDG PET is superior to GS in staging and detecting all types of lymphoma. The difference is notably more significant in recurrence detection.

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Clin Nucl Med. 2011 Oct;36(10):854-9.

### **F-18 FDG PET/CT Contributes to More Accurate Detection of Lymph Nodal Metastasis From Actively Proliferating Esophageal Squamous Cell Carcinoma.**

Tanabe S, Naomoto Y, Shirakawa Y, Fujiwara Y, Sakurama K, Noma K, Takaoka M, Yamatsuji T, Hiraki T, Okumura Y, Mitani M, Kaji M, Kanazawa S, Fujiwara T.

From the Departments of \*Gastroenterological Surgery, Transplant and Surgical Oncology, and †Radiology, Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences, Okayama University, Okayama, Japan; ‡Department of Radiology, Kawasaki Medical School Kawasaki Hospital, Okayama, Japan; and §Okayama Diagnostic Imaging Center, Okayama, Japan : Evaluating the status of disease progression is critical for planning a therapeutic strategy for esophageal cancer. In this regard, F-18 fluorodeoxyglucose-labeled positron emission tomography (PET) is one of the most useful diagnostic modalities. However, there is room to improve its diagnostic performance, such as distinguishing lymph nodal metastases from false positives. In this study, we examined the diagnostic accuracy of fluorodeoxyglucose PET accompanied by computed tomography imaging (PET/CT) to detect regional lymph nodal metastasis from esophageal squamous cell carcinoma (ESCC). : A total of 102 patients diagnosed as ESCC were subjected to this study. These patients had a preoperative PET/CT examination to evaluate the existence of metastasis. The values of maximum standardized uptake value (SUVmax) in primary tumors and in metastasized lymph nodes were measured to analyze their relationship with various clinicopathologic characteristics including the status of tumor cell proliferation, which was assessed by immunohistochemistry for Ki-67. : The SUVmax of the primary tumor was positively correlated with tumor size and vessel invasion, and was positively related with the SUVmax of lymph nodal metastasis, especially in cases of poorly differentiated ESCC. The SUVmax of metastasized lymph nodes was higher in larger-sized metastasized lymph nodes, whereas the Ki-labeling index of lymph nodal metastasis was positively related with the SUVmax per unit area (SUVmax/mm). The diagnostic accuracy of PET/CT (87.3%) was higher than that of conventional CT scans (78.4%) . : The improved diagnostic accuracy of PET/CT can be explained by its ability to detect actively progressive metastasis at an early phase regardless of size.

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Clin Nucl Med. 2011 Oct;36(10):848-53.

### **Incidence and Intensity of F-18 FDG Uptake After Vaccination With H1N1 Vaccine.**

Burger IA, Husmann L, Hany TF, Schmid DT, Schaefer NG.

From the \*Division of Nuclear Medicine, Department Medical Radiology, University Hospital of Zurich, Zurich, Switzerland; and †Division of Medical Oncology, Department of Internal Medicine, University Hospital of Zurich, Zurich, Switzerland.

To analyze the effect of H1N1 influenza A virus vaccination in patients referred for staging or follow-up F-18 fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) for different malignant tumors.: Medical history of all patients scheduled for FDG PET/CT during the national vaccination campaign against H1N1 was evaluated for recent vaccination. Site of injection and time between PET/CT and the date of vaccination (dTime) was determined. A difference in the maximum SUV between ipsi- and contralateral deltoid muscle or axillary lymph node of more than 0.5 was determined as positive reaction. The best cut-off dTime for still visible reaction was calculated. All patients with positive ipsilateral lymph node were clinically followed. Institutional Review Board approval was waived. : Of 269 patients, 58 (21.5%) were vaccinated for the H1N1 within 4 weeks prior to PET/CT (mean, 14.5 ± 8.7 days). Of them, 17 (29.3%) patients had FDG-positive

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lymph nodes (mean SUV,  $1.43 \pm 1.06$ ), with a dTime range from 1 to 14 days. Only 2 of them had no increased FDG uptake in the ipsilateral deltoid muscle. The area under the receiver operator characteristic curve revealed a strong relation between time delay (dTime) and axillary activity (AUC, 0.9; 95% confidence interval, 0.816-0.983) with a cutoff at 8 days (Youden Index). At follow-up (mean, 183 days; range, 173-196 days), no patient was found to have required treatment or signs of axillary lymphadenopathy.: H1N1 vaccination can cause false-positive FDG PET/CT findings, when administered less than 14 days before the test, with the highest probability if the vaccination was administered less than 8 days ago. Increased FDG activity in the ipsilateral deltoid muscle is a key finding for accurate interpretation of increased FDG activity in axillary lymph nodes.

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Radiol Clin North Am. 2011 Sep;49(5):1025-51.

### **Nuclear medicine and molecular imaging of the pediatric chest: current practical imaging assessment.**

Grant FD, Treves ST.

Division of Nuclear Medicine and Molecular Imaging, Department of Radiology, Children's Hospital Boston, Pavilion 2, 300 Longwood Avenue, Boston, MA 02115, USA; Joint Program in Nuclear Medicine, Harvard Medical School, Boston, MA, USA. In the chest, the indications for nuclear medicine studies are broader and more varied in children than in adults. In children, nuclear medicine studies are used to evaluate congenital and developmental disorders of the chest, as well as diseases more typical of adults. In the chest, pediatric nuclear medicine uses the same radiopharmaceuticals and imaging techniques as used in adults to evaluate cardiac and pulmonary disease, aerodigestive disorders, and pediatric malignancies. The introduction of PET (mostly using (18)F-FDG) has transformed pediatric nuclear oncology, particular for imaging malignancies in the chest.

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Radiother Oncol. 2011 Aug 30. [Epub ahead of print]

### **(18)F-FDG-PET imaging in radiotherapy tumor volume delineation in treatment of head and neck cancer.**

Delouya G, Igidbashian L, Houle A, Bélair M, Boucher L, Cohade C, Beaulieu S, Filion EJ, Coulombe G, Hinse M, Martel C, Després P, Nguyen-Tan PF.

Department of Radiation Oncology, Centre Hospitalier de l'Université de Montréal (CHUM), Montréal, Canada.

To determine the impact of (18)F-fluorodeoxyglucose positron emission tomography (PET) in radiotherapy target delineation and patient management for head and neck squamous cell carcinoma (HNSCC) compared to computed tomography (CT) alone. Twenty-nine patients with HNSCC were included. CT and PET/CT obtained for treatment planning purposes were reviewed respectively by a neuroradiologist and a nuclear medicine specialist who were blinded to the findings from each other. The attending radiation oncologist together with the neuroradiologist initially defined all gross tumor volume of the primary (GTVp) and the suspicious lymph nodes (GTVn) on CT. Subsequently, the same radiation oncologist and the nuclear medicine specialist defined the GTVp and GTVn on (18)F-FDG-PET/CT. Upon disagreement between CT and (18)F-FDG-PET on the status of a particular lymph node, an ultrasound-guided fine needle aspiration was performed. Volumes based on CT and (18)F-FDG-PET were compared with a paired Student's t-test. For the primary disease, four patients had previous diagnostic tonsillectomy and therefore, FDG uptake occurred in 25 patients. For these patients, GTVp contoured on (18)F-FDG-PET (GTVp-PET) were smaller than the GTVp contoured on CT (GTVp-CT) in 80% of the cases, leading to a statistically significant volume difference ( $p=0.001$ ). Of the 60 lymph nodes suspicious on PET, 55 were also detected on CT. No volume change was observed ( $p=0.08$ ). Ten biopsies were performed for lymph nodes that were discordant between modalities and all were of benign histology. Distant metastases were found in two patients and one had a newly diagnosed lung adenocarcinoma. GTVp-CT was significantly larger when compared to GTVp-PET. No such change was observed for the lymph nodes. (18)F-FDG-PET modified treatment management in three patients, including two for which no curative radiotherapy was attempted. Larger multicenter studies are needed to ascertain whether combined (18)F-FDG-PET/CT in target delineation can influence the main clinical outcomes.

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Dermatol Res Pract. 2012;2012:941921. Epub 2011 Aug 23.

### **Review of diagnostic imaging modalities for the surveillance of melanoma patients.**

Xing Y, Cromwell KD, Cormier JN.

Department of Surgical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX 77030-4009, USA.

As melanoma survival rates continue to increase, optimal surveillance strategies for recurrences are needed, as are effective imaging modalities. Therefore, we performed a meta-analysis to evaluate the current state of imaging modalities for surveillance of melanoma in the published medical literature to determine the sensitivity, specificity, and positive predictive values of ultrasonography, computed tomography (CT), positron emission tomography (PET), and CT-PET combined. Ultrasonography was found to be the most sensitive and specific for detecting lymph node metastases, and PET-CT was the most sensitive and specific for detecting distant metastases. In addition to identifying appropriate surveillance methods, future studies should focus on the most effective and cost-effective intervals for performing these tests. In addition, the results from the meta-analysis related to sensitivity and specificity of the tests should be made available to doctors in community practice.

Acta Radiol. 2011 Aug 26. [Epub ahead of print]

### **The clinical significance and management of incidental focal FDG uptake in the thyroid gland on positron emission tomography/computed tomography (PET/CT) in patients with non-thyroidal malignancy.**

Wong C, Lin M, Chicco A, Benson R.

University of New South Wales, Australia.

**Background**Incidental focal fluorine-18-2-fluoro-2-deoxy-D-glucose (FDG) uptake in the thyroid is not uncommon. A significant proportion is due to intercurrent thyroid cancer on further evaluation.**Purpose**To investigate and discuss the clinical significance and management of incidental focal FDG uptake in the thyroid gland on positron emission tomography/computed tomography (PET/CT) in patients with non-thyroidal malignancy.**Material and Methods**We investigated 188/7896 (2.4%) patients who had incidental focal thyroid uptake on FDG PET/CT in an oncology population over a 45-month period. Diagnosis was confirmed in 63 patients of whom 59 patients had histopathological verification.**Results**Thirty-two percent of confirmed cases were malignant comprising intercurrent thyroid cancer in three-quarters of these patients. Maximum standardized uptake values of the thyroid lesions and SUV ratios compared with background thyroid and mediastinal uptake were not predictive of a benign or malignant etiology. In patients with incidental thyroid cancers, more than half had non-papillary and intermediate to high-risk pathology.**Conclusion**Focal FDG uptake in the thyroid gland on PET/CT showed a malignancy risk of 32%. The intensity of uptake does not predict histology and underpins the importance of further investigations to exclude intercurrent thyroid cancer in suitable patients.

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Proc Natl Acad Sci U S A. 2011 Aug 30;108(35):14620-5. Epub 2011 Aug 23.

### **Preclinical evaluation and validation of [18F]HX4, a promising hypoxia marker for PET imaging.**

Dubois LJ, Lieuwes NG, Janssen MH, Peeters WJ, Windhorst AD, Walsh JC, Kolb HC, Ollers MC, Bussink J, van Dongen GA, van der Kogel A, Lambin P.

Department of Radiation Oncology (Maastro Lab), GROW-School for Oncology and Developmental Biology, Maastricht University Medical Centre, 6200 MD Maastricht, The Netherlands.

Hypoxia has been shown to be an important microenvironmental parameter influencing tumor progression and treatment efficacy. Patient guidance for hypoxia-targeted therapy requires evaluation of tumor oxygenation, preferably in a noninvasive manner. The aim of this study was to evaluate and validate the uptake of [(18)F]HX4, a novel developed hypoxia marker for PET imaging. A heterogeneous accumulation of [(18)F]HX4 was found within rat rhabdomyosarcoma tumors that was significantly ( $P < 0.0001$ ) higher compared with the surrounding tissues, with temporal increasing tumor-to-blood ratios reaching a plateau of  $7.638 \pm 0.926$  and optimal imaging properties 4 h after injection. [(18)F]HX4 retention in normal tissues was found to be short-lived, homogeneous and characterized by a fast progressive temporal clearance. Heterogeneity in [(18)F]HX4 tumor uptake was analyzed based on 16 regions within the tumor according to the different orthogonal planes at the largest diameter. Validation of heterogeneous [(18)F]HX4 tumor uptake was shown by a strong and significant relationship ( $r = 0.722$ ;  $P < 0.0001$ ) with the hypoxic fraction as calculated by the percentage pimonidazole-positive pixels. Furthermore, a causal relationship with tumor oxygenation was established, because combination treatment of nicotinamide and carbogen resulted in a 40% reduction ( $P < 0.001$ ) in [(18)F]HX4 tumor accumulation whereas treatment with 7% oxygen breathing resulted in a 30% increased uptake ( $P < 0.05$ ). [(18)F]HX4 is therefore a promising candidate for noninvasive detection and evaluation of tumor hypoxia at a macroscopic level.

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Radiother Oncol. 2011 Aug 26. [Epub ahead of print]

### **Hypoxia imaging with [F-18] FMISO-PET in head and neck cancer: Potential for guiding intensity modulated radiation therapy in overcoming hypoxia-induced treatment resistance.**

Hendrickson K, Phillips M, Smith W, Peterson L, Krohn K, Rajendran J.

Department of Radiation Oncology, University of Washington Medical Center, Seattle, WA, USA.

Positron emission tomography (PET) imaging with [F-18] fluoromisonidazole (FMISO) has been validated as a hypoxic tracer [1,2]. Head and neck cancer exhibits hypoxia, inducing aggressive biologic traits that impart resistance to treatment. Delivery of modestly higher radiation doses to tumors with stable areas of chronic hypoxia can improve tumor control [3]. Advanced radiation treatment planning (RTP) and delivery techniques such as intensity modulated radiation therapy (IMRT) can deliver higher doses to a small volume without increasing morbidity. We investigated the utility of co-registered FMISO-PET and CT images to develop clinically feasible RTPs with higher tumor control probabilities (TCP). FMISO-PET images were used to determine hypoxic sub-volumes for boost planning. Example plans were generated for 10 of the patients in the study who exhibited significant hypoxia. We created an IMRT plan for each patient with a simultaneous integrated boost (SIB) to the hypoxic sub-volumes. We also varied the boost for two patients. A significant (mean 17%, median 15%) improvement in TCP is predicted when the modest additional boost dose to the hypoxic sub-volume is included. Combined FMISO-PET imaging and IMRT planning permit delivery of higher doses to hypoxic regions, increasing the predicted TCP (mean 17%) without increasing expected complications.

J Nucl Med. 2011 Aug 24. [Epub ahead of print]

### **Comprehensive Approach to Coregistration of Autoradiography and Microscopy Images Acquired from a Set of Sequential Tissue Sections.**

Axente M, He J, Bass CP, Hirsch JI, Sundaresan G, Zweit J, Pugachev A.

Department of Radiation Oncology, Virginia Commonwealth University Medical Center, Richmond, Virginia; and.

Histopathologic validation of a PET tracer requires assessment of colocalization of the tracer with its intended biologic target. Using thin tissue section autoradiography, it is possible to visualize the spatial distribution of the PET tracer uptake and compare it with the distribution of the intended biologic target (as visualized with immunohistochemistry). The purpose of this study was to develop and evaluate an objective methodology for deformable coregistration of autoradiography and microscopy images acquired from a set of sequential tissue sections. Tumor-bearing animals were injected with 3'-deoxy-3'-(18)F-fluorothymidine ((18)F-FLT), (14)C-FDG, and other markers of tumor microenvironment including Hoechst 33342 (blood-flow surrogate). After sacrifice, tumors were excised, frozen, and sectioned. Multiple stacks of sequential 8  $\mu$ m sections were collected from each tumor. From each stack, the middle (reference) sections were used to obtain images of (18)F-FLT and (14)C-FDG uptake distributions using dual-tracer autoradiography. Sections adjacent to the reference were used to acquire all histopathologic data (e.g., images of cell proliferation, hematoxylin and eosin). Hoechst images were acquired from all sections. To correct for deformations and misalignments induced by tissue processing and image acquisition, the Hoechst image of each nonreference section was deformably registered to the reference Hoechst image. This transformation was then applied to all images acquired from the same tissue section. In this way, all microscopy images were registered to the reference Hoechst image. The Hoechst-to-autoradiography image registration was done using rigid point-set registration based on external markers visible in both images. The mean error of Hoechst to (18)F-FLT autoradiography registration (both images acquired from the same section) was  $30.8 \pm 20.1 \mu\text{m}$ . The error of Hoechst-based deformable registration of histopathologic images (acquired from sequential tissue sections) was  $23.1 \pm 17.9 \mu\text{m}$ . Total error of registration of autoradiography images to the histopathologic images acquired from adjacent sections was evaluated at  $44.9 \mu\text{m}$ . This coregistration precision supersedes current rigid registration methods with reported errors of 100-200  $\mu\text{m}$ . Deformable registration of autoradiography and histopathology images acquired from sequential sections is feasible and accurate when performed using corresponding Hoechst images.

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Rev Recent Clin Trials. 2011 Aug 25. [Epub ahead of print]

### **Positron Emission Tomography for Neck Evaluation Following Definitive Treatment with Chemoradiotherapy for Locoregionally Advanced Head and Neck Squamous Cell Carcinoma.**

Bar Ad V, Mishra M, Ohri N, Intenzo C.

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**Objectives:** The objective of the current review was to assess published data on the role of Positron Emission Tomography (PET) for evaluation of nodal residual disease after definitive chemoradiotherapy for head and neck squamous cell carcinoma (HNSCC). **Methods:** Studies were identified by searching PubMed electronic databases. Only studies using a post-chemoradiotherapy PET for nodal residual disease evaluation were included in the present review. Both prospective and retrospective studies were included. Information regarding sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of PET for detecting nodal residual disease after definitive chemoradiotherapy for HNSCC was extracted and analyzed. **Results:** Twenty published studies were included in the present review. Existing data suggest that a negative post-chemoradiotherapy PET scan is associated with a negative predictive value up to 100%. The sensitivity of PET in detecting nodal residual disease is greater for scans performed > 10 weeks after definitive treatment with chemoradiotherapy for HNSCC. **Conclusions:** Further studies are needed to quantify the reliability of PET in detecting nodal residual disease after chemoradiotherapy for locoregionally advanced HNSCC. The optimal timing of PET imaging after chemoradiotherapy remains to be defined.

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Nucl Med Commun. 2011 Aug 22. [Epub ahead of print]

### **Clinical utility of 18F-FDG PET parameters in patients with advanced nasopharyngeal carcinoma: predictive role for different survival endpoints and impact on prognostic stratification.**

Chan SC, Chang JT, Lin CY, Ng SH, Wang HM, Liao CT, Chang CJ, Lin SY, Yen TC.

aDepartment of Nuclear Medicine and Molecular Imaging Center bRadiation Oncology cDiagnostic Radiology dOtorhinolaryngology eDivision of Hematology/Oncology, Department of Internal Medicine, Chang Gung Memorial Hospital, Chang Gung University College of Medicine fClinical Informatics and Medical Statistics Research Center gGraduate Institute of Clinical Medical Science, Chang Gung University hBiostatistical Center for Clinical Research, Chang Gung Memorial Hospital, Taoyuan, Taiwan. To investigate the prognostic impact of different 2-[fluorine-18]fluoro-2-deoxy-D-glucose positron emission tomography (F-FDG PET) parameters in patients with advanced nasopharyngeal carcinoma (NPC). A total of 196 patients with primary stage III-IVb NPC were included in the study. The following parameters derived from pretreatment F-FDG PET were determined: metabolic tumor volume and total lesion glycolysis (TLG) of the primary tumor, maximal

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standardized uptake value of the primary tumor and the neck lymph nodes. Multivariable Cox proportional hazards models were used to identify independent predictors of survival. Multivariable analysis demonstrated that TLG values greater than 330 independently predicted overall survival ( $P=0.0014$ ) and disease-free survival ( $P=0.0005$ ). We identified IVa-b stage and TLG values greater than 330 as independent predictors of local failure-free survival. In addition, a high maximal standardized uptake value of the neck lymph nodes ( $P=0.005$ ), male sex ( $P=0.041$ ), and stage IVa-b ( $P=0.009$ ) independently predicted distant failure-free survival. A TLG cutoff value of 330 allowed a better stratification of overall survival and disease-free survival rates. A scoring system combining significant PET parameters and traditional prognostic factors was formulated to define distinct prognostic groups for local failure-free survival and distant failure-free survival. There was a stepwise decrease in the 5-year local (97.7, 90.4, and 47.3%,  $P<0.0001$ ) and distant control rates (96.8, 88.5, 73.9, and 36.4%,  $P<0.0001$ ) according to the distinct prognostic scores. In patients with advanced NPC, the prognostic significance of F-FDG PET parameters seems to depend on the specific endpoint. The combination of PET metabolic parameters with traditional risk factors may significantly improve prognostic stratification for this group of patients.

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Nucl Med Commun. 2011 Aug 22. [Epub ahead of print]

### **Biological basis of [11C]choline-positron emission tomography in patients with breast cancer: comparison with [18F]fluorothymidine positron emission tomography.**

Contractor KB, Kenny LM, Stebbing J, Challapalli A, Al-Nahhas A, Palmieri C, Shousha S, Lewis JS, Hogben K, De Nguyen Q, Coombes RC, Aboagye EO.

aDepartment of Oncology bDepartments of Nuclear Medicine and Radiology cDepartment of Cellular Pathology dDepartment of Breast Surgery, Imperial College London eImperial College Healthcare NHS Trust, Hammersmith and Charing Cross Hospitals, London, UK.

The biological significance of [C]choline (CHO) uptake in human tumours is unclear and probably linked to choline kinase- $\alpha$  (CHK $\alpha$ ) expression and cell proliferation. We directly compared CHO with [F]fluorothymidine (FLT), an imaging biomarker of proliferation, by positron emission tomography (PET) in patients with breast cancer to investigate whether cell proliferation is an important determinant of CHO uptake. Furthermore, we evaluated CHK $\alpha$  and the Ki67-labelling index (LIKi67) in tumour biopsies. Sequential CHO-PET and FLT-PET within the same imaging session were performed in 21 patients with oestrogen receptor (ER)-positive breast cancer (28 lesions). Average and maximum CHO standardized uptake values (SUV) at 60 min: SUV60,av, and SUV60,max, and the rate constant of net irreversible uptake, Ki, were compared with FLT uptake at 60 min: SUV60,av and SUV60,max. Biopsies were stained for CHK $\alpha$  and LIKi67 in eight cases. Tumours were equally visible on CHO-PET and FLT-PET imaging. Tumour CHO-PET strongly correlated with FLT imaging variables (Pearson's  $r=0.83$ ;  $P<0.0001$  for CHO-SUV60,max vs. FLT-SUV60,max). A statistically significant association was found between CHO-PET variables and categorical scores of cytoplasmic CHK $\alpha$  intensity and between FLT-PET and LIKi67 ( $P<0.05$ , one-way analysis of variance). Choline metabolism and proliferation as assessed by PET were correlated in ER-positive breast cancer, indicating that high CHO uptake is a measure of cellular proliferation in this setting. CHO uptake was also found to be related to cytoplasmic CHK $\alpha$  expression.

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Ann Surg Oncol. 2011 Aug 23. [Epub ahead of print]

### **Use of S-100B to Evaluate Therapy Effects during Bevacizumab Induction Treatment in AJCC Stage III Melanoma.**

Kruijff S, Bastiaannet E, Brouwers AH, Nagengast WB, Speijers MJ, Suurmeijer AJ, Hospers GA, Hoekstra HJ.

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To investigate the feasibility of using bevacizumab to improve the survival of American Joint Committee on Cancer (AJCC) stage III melanoma patients, we investigated how a single bevacizumab treatment affected nodal disease and a panel of biomarkers in clinically fluorodeoxyglucose positron emission tomography (FDG-PET)/computed tomography (CT)-staged, stage III melanoma patients, prior to therapeutic lymph node dissection (TLND). Four weeks before TLND, nine patients (median age 50, range 28.8-62.1 years; two male, seven female) with palpable lymph node metastases received 7.5 mg/kg bevacizumab. Before and after this treatment, all patients were assessed by measurements of the maximum standardized uptake value (SUV<sub>max</sub>) by FDG-PET scan, and serum S-100B and lactate dehydrogenase (LDH). After TLND, the dissection specimen was analyzed for number of removed lymph nodes, number of metastatic lymph nodes, and tumor necrosis. Median follow-up was 15.5 (2.2-32.9) months. Histopathological analysis revealed tumor necrosis in six patients, of whom five had an S-100B decline and one had an unchanged S-100B level after bevacizumab. The other three patients showed an S-100B increase and no necrosis. Tumor necrosis was correlated with S-100B decrease ( $P=0.048$ ). No association was found between necrosis and the markers SUV<sub>max</sub> and LDH. No wound healing disturbances were encountered. Tumor necrosis in dissection specimens was associated with declining S-100B levels, while elevated S-100B was only found in cases with no necrosis. Bevacizumab might be useful in treating AJCC stage III melanoma patients prior to TLND, and S100-B appears to be a useful marker for assessment of treatment effects.

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Head Neck. 2011 Aug 18. doi: 10.1002/hed.21745. [Epub ahead of print]

### **Matched cohort analysis of the effect of pretreatment positron emission tomography on clinical outcomes of patients with head and neck cancer treated with definitive chemoradiotherapy.**

Fried D, Khandani A, Shores C, Weissler M, Hayes N, Hackman T, Rosenman J, Chera BS.

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Pretreatment positron emission tomography (PET) has been shown to be useful for patients with head and neck squamous cell carcinoma (HNSCC) after definitive chemoradiotherapy (CRT). We conducted a retrospective analysis of a matched cohort of 116 patients with HNSCC that underwent CRT treatment at our institution. Pretreatment PET was performed in 58 patients and omitted in the other 58 patients. The 2 cohorts were matched for T classification, N classification, primary site, and smoking history. Kaplan-Meier 2-year estimates of local control (LC), regional control (RC), freedom from distant metastasis (FFDM), cause-specific survival (CSS), and overall survival (OS) were compared with log-rank tests. There were no differences between the 2 cohorts for 2-year endpoints of LC, RC, FFDM, CSS, and OS. On multivariate analysis pretreatment PET imaging did not influence any endpoint. PET imaging before definitive CRT may not significantly improve outcomes in patients with HNSCC.

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Eur J Nucl Med Mol Imaging. 2011 Aug 19. [Epub ahead of print]

### **Diagnostic performance of post-treatment FDG PET or FDG PET/CT imaging in head and neck cancer: a systematic review and meta-analysis.**

Gupta T, Master Z, Kannan S, Agarwal JP, Ghosh-Laskar S, Rangarajan V, Murthy V, Budrukkar A.

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Our objective was to conduct a systematic review and meta-analysis of studies assessing the diagnostic performance of (18)F-fluorodeoxyglucose positron emission tomography (FDG PET) with or without computed tomography (CT) in post-treatment response assessment and/or surveillance imaging of head and neck squamous cell carcinoma (HNSCC).

A systematic search of the indexed medical literature was done using appropriate keywords to identify relevant studies. Metrics of diagnostic test accuracy, viz. sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were extracted from individual studies and combined using a random effects model to yield weighted mean pooled estimates with 95% confidence intervals (95% CI). The impact of timing of post-treatment scan, study quality and advancements in PET technology was explored through meta-regression. A total of 51 studies involving 2,335 patients were included in the meta-analysis. The weighted mean (95% CI) pooled sensitivity, specificity, PPV and NPV of post-treatment FDG PET(CT) for the primary site was 79.9% (73.7-85.2%), 87.5% (85.2-89.5%), 58.6% (52.6-64.5%) and 95.1% (93.5-96.5%), respectively. Similar estimates for the neck were 72.7% (66.6-78.2%), 87.6% (85.7-89.3%), 52.1% (46.6-57.6%) and 94.5% (93.1-95.7%), respectively. Scans done  $\geq 12$  weeks after completion of definitive therapy had moderately higher diagnostic accuracy on meta-regression analysis using time as a covariate. The overall diagnostic performance of post-treatment FDG PET(CT) for response assessment and surveillance imaging of HNSCC is good, but its PPV is somewhat suboptimal. Its NPV remains exceptionally high and a negative post-treatment scan is highly suggestive of absence of viable disease that can guide therapeutic decision-making. Timing of post-treatment imaging has a significant, though moderate impact on diagnostic accuracy.

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Acta Radiol. 2011 Sep 1;52(7):788.

### **Using DWIBS MRI technique as an alternative to bone scan or PET scan for whole-body imaging in oncology patients.**

Kachewar SG.

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Acta Oncol. 2011 Aug 18. [Epub ahead of print]

### **FDG PET/CT differentiating two malignant tumors in the same patient.**

Shai A, Leitzin L, Steiner M, Peer A, Srour S, Shalom RB.

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Department of Oncology, Lin and Lady Davis Carmel Medical Centers , Haifa , Israel.

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Head Neck. 2011 Aug 17. doi: 10.1002/hed.21791. [Epub ahead of print]

### **Relationship between serum thyroglobulin and (18) FDG-PET/CT in (131) I-negative differentiated thyroid carcinomas.**

Giovanella L, Ceriani L, De Palma D, Suriano S, Castellani M, Verburg FA.

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The purpose of this study was to assess the relationship between [(18) F]-fluorodeoxyglucose ((18) FDG)-positron emission tomography/CT ((18) FDG-PET/CT) and serum thyroglobulin (Tg) in patients with recurrent differentiated thyroid carcinoma (DTC). Forty-two patients with recurrent DTC and negative Tg antibodies were included in the study. All patients underwent (131) I therapy due to an increasing serum Tg with a corresponding negative (131) I posttreatment whole body scan. The (18) FDG-PET/CT scans were then performed on all patients, serum Tg was measured concurrently, and respective results were compared. Sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV), and accuracy of the (18) FDG-PET/CT examination were 93%, 84%, 93%, 84%, and 90%, respectively. The sensitivity of (18) FDG-PET/CT significantly increased in patients with serum Tg levels  $\geq 4.6$  ng/mL (96%) in comparison with patients having lower levels (25%;  $p < .001$ ). Nonetheless, 3 of 27 patients (11%) with a true-positive (18) FDG-PET/CT still had a Tg  $< 4.6$  ng/mL. Although (18) FDG-PET/CT scans are more likely to be positive with pretest Tg levels  $\geq 4.6$  ng/mL, 11% of patients with DTC with a lower serum Tg level will still have a positive scan. Our findings are in contrast with the American Thyroid Association (ATA) guidelines, which only recommend to perform (18) FDG-PET/CT in patients with Tg levels  $> 10$  ng/mL.

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J Nucl Med. 2011 Sep;52(9):1333-6. Epub 2011 Aug 17.

### **Hyperpolarized <sup>13</sup>C MRI and PET: In Vivo Tumor Biochemistry.**

Gallagher FA, Bohndiek SE, Kettunen MI, Lewis DY, Soloviev D, Brindle KM.

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Dynamic nuclear polarization (DNP) is an emerging technique for dramatically increasing the sensitivity of magnetic resonance spectroscopy (MRS). This review evaluates the potential strengths and weaknesses of DNP-enhanced (<sup>13</sup>C) magnetic resonance spectroscopic imaging (DNP-MRSI) as a clinical imaging technique in comparison to PET. The major advantage of MRS is chemical shift, which enables the injected molecule to be observed separately from its metabolites, whereas the major advantage of PET is its high sensitivity. Factors such as spatial and temporal resolution and potential risks and costs of the two techniques will be discussed. PET tracers and (<sup>13</sup>C)-labeled molecules that can be used in oncology will be reviewed with reference to the biologic processes they detect. Because DNP-MRSI and PET are, in principle, similar techniques for assessing tumor metabolism, the experiences gained during the development of PET may help to accelerate translation of DNP-MRSI into routine patient imaging.

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Vet Comp Oncol. 2011 Sep;9(3):225-31. doi: 10.1111/j.1476-5829.2010.00259.x. Epub 2011 Jan 21.

### **Comparison of two questionnaires to assess gastrointestinal toxicity in dogs and cats treated with chemotherapy(\*).**

Malone EK, Rassnick KM, Bailey DB, Kiselow MA, Erb HN.

Department of Clinical Sciences, Cornell University College of Veterinary Medicine, Ithaca, NY, USA Oradell Animal Hospital, Oradell, NJ, USA Veterinary Medical Specialists, Campbell, CA, USA Department of Population Medicine and Diagnostic Sciences, Cornell University, Ithaca, NY, USA.

Questionnaires completed by pet owners are widely used instruments to monitor adverse gastrointestinal (GI) effects in the owners' animals undergoing chemotherapy and for reporting toxicoses in clinical trials; however, no questionnaires have been formally evaluated. This study compares two questionnaire-based evaluations of adverse GI events: a basic, open-ended questionnaire and a detailed questionnaire modelled after the grading in the Veterinary Co-operative Oncology Group-Common Terminology Criteria for Adverse Events (VCOG-CTCAE). Owners completed both questionnaires after their dog or cat received moderately emetogenic chemotherapy. Results were used to derive toxicity grades for anorexia, vomiting and diarrhoea. We evaluated 123 pairs of questionnaires. Disagreement in grade of anorexia, vomiting and diarrhoea was found in 24, 7 and 13% of paired questionnaires, respectively ( $\kappa = 0.63, 0.83$  and  $0.71$ , respectively). Although 'good' to 'very good' agreement was found, the potential for only 'fair' agreement between questionnaire methods is of concern and suggests a need to adopt a standardized form.

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Prostate Cancer Prostatic Dis. 2011 Aug 16. doi: 10.1038/pcan.2011.35. [Epub ahead of print]

### **(18)F-fluorocholine for prostate cancer imaging: a systematic review of the literature.**

Bauman G, Belhocine T, Kovacs M, Ward A, Beheshti M, Rachinsky I.

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Positron emission tomography (PET or combined PET-computed tomography (PET/CT)) allows the non-invasive interrogation of metabolic processes using radiolabeled probes. Altered choline metabolism has been noted as a characteristic of prostate cancer (PCa), and radiolabeled choline and choline analogs have been investigated as PET/CT imaging agents for prostate cancer; [(18)F]fluoromethyl-dimethyl-2-hydroxyethyl-ammonium ((18)F-FCH) shows particular promise as a PCa imaging agent given its favorable physical and pharmacokinetic properties. We conducted a systematic review of results to date with (18)F-FCH. As the tracer was first described by DeGrado in 2001, we limited our search from January 2001 to August 2011. In all, 37 studies including 1244 patients met the inclusion criteria. Studies included those detailing the radiosynthesis of (18)F-FCH, preclinical and early clinical dosimetry, and biodistribution (n=7); evaluation of local disease (n=6), nodal disease (n=5), bone metastases and castrate-resistant disease (n=7), biochemical recurrence (n=11), radiotherapy planning (n=7) and sources of false-positive studies (n=2); and some studies reported on multiple indications. Potential sources of variations in the studies affecting reported performance included case series size, variation in extent of disease at imaging (including Gleason grade, and PSA), selection of gold standards for comparison and variations in scan technique. On the basis of the review, we suggest potential scenarios where this metabolic imaging might be considered for further evaluation in clinical trials for guiding PCa management.

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Mol Imaging Biol. 2011 Aug 13. [Epub ahead of print]

### **Importance of Quantification for the Analysis of PET Data in Oncology: Review of Current Methods and Trends for the Future.**

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In oncology, positron emission tomography (PET) is an important tool for tumour diagnosis and staging, assessment of response to treatment and evaluation of the pharmacokinetic properties and efficacy of new drugs. Despite its quantitative potential, however, in daily clinical practice PET is used almost exclusively with 2-deoxy-2-[(18)F]fluoro-D: -glucose ([18)F]FDG and, in addition, [(18)F]FDG data are normally assessed visually or using simple indices as the standardised uptake value (SUV). After explaining why more sophisticated quantification methods can be useful in oncology, the paper reviews the approaches that are commonly used and those available but not routinely employed. Particular emphasis is addressed to the SUV, for its importance in clinical practice. Issues specific to PET quantification in oncology and related examples are then discussed. Finally, some ideas for the development of new quantitative methods for analysing PET data in oncology and for the application of approaches already existing but not commonly employed are presented.

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J Biol Chem. 2011 Aug 8. [Epub ahead of print]

### **A novel positron emission tomography tracer distinguishes normal from cancerous cells.**

Saeed M, Sheff D, Kohen A.

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Development of tumor specific probes for imaging by positron emission tomography (PET) has broad implications in clinical oncology such as diagnosis, staging, and monitoring therapeutic responses in patients, as well as in bio-medical research. Thymidylate synthase (TSase)-based de novo biosynthesis of DNA is an important target for drug development. Increased DNA replication in proliferating cancer cells requires TSase activity, which catalyzes the reductive methylation of 2'-deoxyuridine 5-monophosphate (dUMP) to 2'-deoxythymidine 5-monophosphate (dTMP) by using (R)-N<sup>5</sup>,N<sup>10</sup>-methylene-5,6,7,8-tetrahydrofolate (MTHF) as a co-factor. In principle, radiolabeled-MTHF can be used as a substrate for this reaction to identify rapidly dividing cells. In this proof-of-principle study, actively growing (log phase) breast cancer (MCF7, MDA-MB-231, hTERT-HME1), normal breast cells (HMEC, MCF10A), colon cancer (HT29), and normal colon (FHC) cells were incubated with (14)C-MTHF in culture medium from 30 min to 2h and uptake of radiotracer was measured. Cancerous cell lines incorporated significantly more radioactivity than their normal counterparts. The uptake of radioactively labeled MTHF depended upon a combination of cell doubling time, folate receptor status, S-phase percentage as well as TSase and folate receptors expression in the cells. These findings suggest that the recently synthesized (11)C-MTHF may serve as a new PET tracer for cancer imaging.

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Colorectal Dis. 2011 Aug 11. doi: 10.1111/j.1463-1318.2011.02727.x. [Epub ahead of print]

### **The detection of incidental colorectal tumors with (18) F-FDG PET/CT scans: results of a prospective study.**

Peng J, He Y, Xu J, Sheng J, Cai S, Zhang Z.

Department of Colorectal Surgery, Fudan University Shanghai Cancer Center, Shanghai, China Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, China Department of Endoscopy, Fudan University Shanghai Cancer Center, Shanghai, China Department of Nuclear Medicine, Fudan University Shanghai Cancer Center, Shanghai, China. Purpose: This study assessed the clinical significance of incidental colorectal FDG uptake with (18) F-FDG PET/CT scans and evaluated the importance of colonoscopy when incidental colorectal FDG uptake was observed. Methods: A prospective study was designed conducted in a single institution in a two-year period. In patients undergoing PET/CT scan, all the cases of FDG uptake in colorectum were assigned to have colonoscopy and biopsy. The value of PET/CT was studied by comparing with the colonoscopy and biopsy results. Results: Among 10,978 PET/CT scans, one or more focal FDG uptakes in colorectum was observed in 148 pts (1.35%). In 136 valid patients, malignant colorectal tumors and polyps were found in 23.5% and 20.5% of patients, while the other 56% of cases were found normal. A higher false positive rate was found in right colon compared with distal colorectum (66.2% vs 36.7%,  $P=0.004$ ). A significant increase of the maximum standardized uptake value (SUVmax) was found among normal, polyps and cancer groups. Multivariate analysis revealed that SUVmax was the risk factor for predicting colorectal cancer or polyps and FDG uptake in right colon was a negative predicting factor for finding cancers or polyps. Conclusions: Our study proves the necessity of colonoscopy when incidental FDG uptake is found on PET/CT imaging. The false-positive FDG uptake is more commonly observed in right colon. Although SUVmax is higher in cancer patients, a high SUVmax value is not necessarily resulted in malignancies.

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Hepatogastroenterology. 2011 May-Jun;58(107-108):1029-31.

### **Distal pancreatectomy and portal vein resection without vascular reconstruction for endocrine tumors with massive intraportal growth: report of a case.**

Tsuchikawa T, Kondo S, Hirano S, Tanaka E, Kawasaki R, Kato K, Matsumoto J, Shichinohe T.

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Pancreatic endocrine tumors (PETs) are relatively rare. Owing to their slow growing characteristics, an aggressive surgical approach has been considered to improve patients' survival. A case of PET with portal vein (PV) thrombus, successfully treated by distal pancreatectomy with concomitant PV resection and removal of PV tumor thrombus, preserving collateral pathways, is reported.

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Pediatr Blood Cancer. 2011 Aug 8. doi: 10.1002/pbc.23273. [Epub ahead of print]

### **Impact of PET-CT on involved field radiotherapy design for pediatric Hodgkin lymphoma.**

Paulino AC, Margolin J, Dreyer Z, Teh BS, Chiang S.

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To determine how the incorporation of PET-CT changes radiotherapy treatment in pediatric Hodgkin lymphoma. Fifty-three Hodgkin lymphoma patients with a median age of 14 years (6-21 years) underwent multiagent chemotherapy followed by involved field radiotherapy (IFRT) to initial sites of disease. All patients had conventional staging which included CT scan of the neck, chest, abdomen and pelvis, bone marrow biopsy  $\pm$  MRI, Gallium scan and bone scan. All had an initial 18-F-fluoro-deoxy-D-glucose (FDG) PET-CT. When there was discordance between conventional staging and PET-CT staging, true sites of disease were determined either by biopsy or response to multiagent chemotherapy. In 19 of 53 (35.8%) patients, there was discordance between conventional staging and PET-CT findings. The most common location for the 23 sites of discordance were the spleen in 6 (26.1%), neck in 3 (13%), inguinal nodes in 3 (13%) and mediastinum in 3 (13%). A change in stage occurred in 5 (9.4%) as a result of PET-CT imaging. A change in IFRT fields occurred in 9 (17%); eight were more extensive while one was less extensive. For PET-CT, the specificity, sensitivity, positive predictive value and accuracy were 99.5%, 96.3%, 97.9%, and 98.9%. Incorporation of PET-CT information was found to influence IFRT design in 17% of patients, with most having more extensive radiotherapy fields.

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Curr Opin Oncol. 2011 Aug 5. [Epub ahead of print]

### **Advances in PET imaging of brain tumors: a referring physician's perspective.**

Petirena GJ, Goldman S, Delattre JY.

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To highlight the most recent advances in PET imaging of brain tumors, aiming at expanding the referring physician's knowledge in the field, the sine qua non for translating PET into the practice of neuro-oncology. The role of PET with amino acid tracers in the setting of brain lesions of unknown significance has been better defined, reducing the need for invasive procedures. The impact of PET-guided resection of high-grade glioma using C-methionine (C-MET) has been strongly documented. [F]Fluoroethyl-L-tyrosine is currently available for glioma management; advances in targeting glial tumor biopsy and monitoring response to standard chemoradiation of malignant glioma have been remarkable. 2-(2-nitro-1H-imidazol-1-yl)-N-(2,2,3,3,3-penta-fluoropropyl)-acetamide is a rationally designed radiotracer with potential for imaging hypoxia in glioblastoma. New insights regarding the predictive value of 3-deoxy-3-[F]fluorothymidine in outcome of recurrent malignant glioma treated with bevacizumab/irinotecan have been provided. First steps are being made toward apoptosis PET imaging for early assessment of radiotherapy response in brain metastases. The use of C-MET and F-labeled PET tracers is getting a more precise position in the management of brain tumors. Advances hold promises in routine decision-making and in the design and conduct of clinical trials.

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Clin Nucl Med. 2011 Sep;36(9):781-5.

### **Thyroid Remnant Estimation by Tc-99m-Sestamibi Scanning Predicts the Effectiveness of rhTSH-Stimulated I-131 Ablation in Patients With Differentiated Thyroid Carcinoma.**

Giovanella L, Suriano S, Castellani M, Ceriani L, Verburg FA.

From the \*Department of Nuclear Medicine, PET-CT Center and Thyroid Unit, Oncology Institute of Southern Switzerland, Bellinzona, Switzerland; †Department of Radiology and Nuclear Medicine, IRCCS Ospedale Maggiore e Policlinico, Milano, Italy; and ‡Department of Nuclear Medicine, University of Würzburg, Würzburg, Germany.

: To evaluate the relationship between postsurgical cervical Tc-99m-sestamibi scan uptake and the rate of successful remnant ablation after recombinant human-thyrotropin (rhTSH)-aided-I-131 ablation in patients with differentiated thyroid carcinoma (DTC). : In all, 154 DTC patients who underwent total thyroidectomy and rhTSH-aided remnant ablation with I-131 (3.7 GBq) were enrolled. Tc-99m-sestamibi scans were performed during continuing thyroid hormone administration in all cases. Thyroid ablation was assessed after 6 to 12 months by rhTSH-stimulated I-131-whole-body scan and thyroglobulin measurement. The rate of successful ablation, occurrence of radioiodine-induced thyroiditis, and length of hospitalization were correlated with the Tc-99m-sestamibi scintigraphy results. : Tc-99m-sestamibi uptake was significantly lower in ablated versus nonablated patients ( $P < 0.0001$ ). A visually positive scan and a Tc-99m-sestamibi uptake greater than 0.9% predicted a high-risk of unsuccessful ablation, prolonged hospitalization, and the occurrence of radioiodine-induced thyroiditis. : Tc-99m-sestamibi scintigraphy is a simple and feasible tool to evaluate thyroid remnants and to predict radioiodine ablation results in patients with DTC.

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Eur Radiol. 2011 Aug 7. [Epub ahead of print]

### **Functional imaging of lung cancer using dual energy CT: how does iodine related attenuation correlate with standardized uptake value of 18FDG-PET-CT?**

Schmid-Bindert G, Henzler T, Chu TQ, Meyer M, Nance JW Jr, Schoepf UJ, Dinter DJ, Apfaltrer P, Krissak R, Manegold C, Schoenberg SO, Fink C.

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To investigate the correlation between maximum standardized uptake value (SUV(max)) of (18)FDG PET-CT and iodine-related attenuation (IRA) of dual energy CT (DECT) of primary tumours and (18)FDG PET-CT positive thoracic lymph nodes (LN) in patients with lung cancer. 37 patients with lung cancer (27 NSCLC, 10 SCLC, 86 (18)FDG PET-CT positive thoracic LN) who underwent both (18)FDG PET-CT and DECT were analyzed. The mean study interval between (18)FDG PET-CT and DECT was  $\leq 21$  days in 17 patients. The mean and maximum IRA of DECT as well as of virtual enhanced and virtual 120 kV images of DECT was analyzed and correlated to the SUV(max) of (18)FDG PET-CT in all tumours and (18)FDG PET-CT positive thoracic lymph nodes. Further subgroup analysis was performed for histological subtypes in all groups. A moderate correlation was found between SUV(max) and maximum IRA in all tumours ( $n = 37$ ;  $r = 0.507$ ;  $p = 0.025$ ) whereas only weak or no correlation was found between SUV(max) and all other DECT measurements. A strong correlation was found in patients with study intervals  $\leq 21$  days ( $n = 17$ ;  $r = 0.768$ ;  $p = 0.017$ ). Analysis of histological subtypes of lung cancer showed a strong correlation between SUV(max) and maximum IRA in the analysis of all patients with NSCLC ( $r = 0.785$ ;  $p = 0.001$ ) and in patients with NSCLC and study intervals  $\leq 21$  days ( $r = 0.876$ ;  $p = 0.024$ ). Thoracic LN showed moderate correlation between SUV(max) and maximum IRA in patients with study intervals  $\leq 21$  days ( $r = 0.654$ ;  $p = 0.010$ ) whereas a weak correlation was found between SUV(max) and maximum IRA

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in patients with study intervals >21 days ( $r=0.299$ ;  $p=0.035$ ). DECT could serve as a valuable functional imaging test for patients with NSCLC as the IRA of DECT correlates with SUV(max) of (18)FDG PET-CT.

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Eur J Haematol. 2011 Aug;87(2):123-9. doi: 10.1111/j.1600-0609.2011.01645.x.

### **The utility of positron emission tomography/computed tomography in the staging of extranodal natural killer/T-cell lymphoma.**

Fujiwara H, Maeda Y, Nawa Y, Yamakura M, Ennishi D, Miyazaki Y, Shinagawa K, Hara M, Matsue K, Tanimoto M.

Division of Hematology/Oncology, Department of Medicine, Kameda General Hospital, Chiba, Japan.

Natural killer (NK)/T-cell lymphoma cases are rarely discovered using positron emission tomography/computed tomography (PET/CT). We compared the utility of PET/CT and that of conventional methods (CMs; CT with IV contrast, biopsies from primary sites, and bone marrow examinations) in the staging of extranodal NK/T-cell lymphoma. Nineteen untreated patients with extranodal NK/T-cell lymphoma at three institutions were analyzed. PET/CT and CMs were applied for initial workups following diagnosis. PET/CT and CMs were compared and evaluated for their ability to detect tumor lesions and their influence on the staging and treatment strategies. In total, 116 lesions were detected by CM and PET/CT. Using PET/CT, 108 lesions (93%) were discovered. The number of nodal lesions was 28: all were positive by PET/CT and 26 (93%) by CMs. The number of extranodal lesions was 89: 84 (94%) and 54 (61%) lesions were positive by PET/CT and CMs, respectively. PET/CT was superior to CMs in detecting cutaneous lesions [31/31 lesions (100%) vs. 20/31 lesions (65%), respectively;  $P=0.042$ ]. Bone marrow involvement was confirmed pathologically in only seven patients; four cases (57%) were positive by PET/CT. Using CMs, ten patients (53%) were stages I-II and nine (47%) were stages III-IV. Using PET/CT, eight patients (42%) were in stages I-II and 11 (58%) were in stages III-IV. PET/CT findings altered the stage and treatment strategy in two cases (11%). Our study demonstrated that PET/CT is a useful tool for detecting extranodal lesions in NK/T-cell lymphoma, particularly cutaneous lesions. PET/CT may therefore influence future staging and treatment strategies.

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Clin Nucl Med. 2011 Jun;36(6):468-9.

### **PET/CT in a patient with adenoma malignum of the uterine cervix.**

Sharp HJ, Pinnix CC, Jhingran A, Euscher ED, Rohren EM, Ramirez PT.

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The findings of positron emission tomography combined with computed tomography (PET/CT) in a patient with FIGO stage IIA adenoma malignum of the uterine cervix are described in this article. PET/CT showed that the cervical tumor was intensely hypermetabolic with no evidence of disease spread. However, lymphadenectomy revealed metastatic spread to paraaortic lymph nodes. PET/CT may be useful in identifying primary site of disease in patients with adenoma malignum; however, the utility in detecting metastatic nodal disease remains to be determined.

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Clin Nucl Med. 2011 Jun;36(6):429-33.

### **Value of dual-time-point FDG PET/CT for mediastinal nodal staging in non-small-cell lung cancer patients with lung comorbidity.**

Hu M, Han A, Xing L, Yang W, Fu Z, Huang C, Zhang P, Kong L, Yu J.

Department of Radiation Oncology and Shandong Province Key Laboratory of Radiation Oncology, Shandong Cancer Hospital, Shandong Academy of Medical Sciences, Jinan, People's Republic of China.

To evaluate the efficacy of dual-time-point F-18 fluorodeoxyglucose positron emission tomography (FDG PET)/ computed tomography (CT) for mediastinal nodal staging in non-small-cell lung cancer patients with lung comorbidity. Fifty-three pathologically proven non-small-cell lung cancer patients with pulmonary comorbidity and 49 patients as controlled group without comorbidity were enrolled. PET/CT was performed at 1-hour (whole body) post-FDG injection and repeated 2 hours (thoracic) after injection. All patients received radical surgery with system mediastinal lymph node (LN) dissection. The results of LN detection by single-time-point and dual-time-point scan were compared with the histopathologic findings. On a per-patient basis, in patients with pulmonary comorbidity, the sensitivity, specificity, accuracy, and positive predictive values (PPV), and negative predictive values of single-time-point scan were 87.5%, 59.5%, 67.9%, 48.3%, and 91.7%, respectively. Those values of dual-time-point scan were 93.8%, 67.6%, 75.5%, 55.6%, and 96.2%, respectively. In patients without comorbidity, dual-time-point scan was similar in those values to single-time-point. On a per-nodal station basis, the specificity, accuracy, and PPV of dual-time-point scan were better than those of single-time-point with statistically significant differences ( $P = 0.017, 0.002, \text{ and } 0.027$ , respectively) in patients with pulmonary comorbidity, but the difference was not statistically significant in patients with no pulmonary comorbidity. Dual-time-point FDG PET/CT is more effective for mediastinal nodal staging than single-time-point in patients with pulmonary comorbidity. Dual-time-point scan was useful for diagnosis of mediastinal LN metastases in reducing the false-positive results in all patients, but improved specificity, accuracy, and PPV only in patients with pulmonary comorbidity.

Ann Surg Oncol. 2011 May 6. [Epub ahead of print]

### **Value of EUS in Determining Curative Resectability in Reference to CT and FDG-PET: The Optimal Sequence in Preoperative Staging of Esophageal Cancer?**

Schreurs LM, Janssens AC, Groen H, Fockens P, van Dullemen HM, van Berge Henegouwen MI, Sloof GW, Pruijm J, van Lanschot JJ, Steyerberg EW, Plukker JT.

Department of Surgery/Surgical Oncology, University Medical Center Groningen, Groningen, The Netherlands.

The separate value of endoscopic ultrasonography (EUS), multidetector computed tomography (CT), and (18)F-fluorodeoxyglucose positron emission tomography (FDG-PET) in the optimal sequence in staging esophageal cancer has not been investigated adequately. The staging records of 216 consecutive operable patients with esophageal cancer were reviewed blindly. Different staging strategies were analyzed, and the likelihood ratio (LR) of each module was calculated conditionally on individual patient characteristics. A logistic regression approach was used to determine the most favorable staging strategy. Initial EUS results were not significantly related to the LRs of initial CT and FDG-PET results. The positive LR (LR+) of EUS-fine-needle aspiration (FNA) was 4, irrespective of CT and FDG-PET outcomes. The LR+ of FDG-PET varied from 13 (negative CT) to 6 (positive CT). The LR+ of CT ranged from 3-4 (negative FDG-PET) to 2-3 (positive FDG-PET). Age, histology, and tumor length had no significant impact on the LRs of the three diagnostic tests. This study argues in favor of PET/CT rather than EUS as a predictor of curative resectability in esophageal cancer. EUS does not correspond with either CT or FDG-PET. LRs of FDG-PET were substantially different between subgroups of negative and positive CT results and vice versa.

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Int J Gynecol Cancer. 2011 May;21(4):699-705.

### **Metabolic response of pelvic and para-aortic lymph nodes during radiotherapy for carcinoma of the uterine cervix: using positron emission tomography/computed tomography.**

Yoon MS, Nam TK, Chung WK, Jeong SY, Ahn SJ, Nah BS, Song JY, Jeong JU.

Source

Department of Radiation Oncology, Chonnam National University Medical School, Gwangju, South Korea.

We evaluated the metabolic response of lymph nodes (LNs) using consecutive F-fluorodeoxyglucose-positron emission tomography/computed tomography (PET/CT) and correlated the metabolic response with the volumetric response measured by consecutive CT. Twenty-two patients with cervical cancer that had positive LNs underwent preradiotherapy (pre-RT) and inter-RT PET/CT. The metabolic response of the LNs was assessed quantitatively and semiquantitatively by measurement of the maximal standardized uptake value. All patients underwent inter-RT CT simulation after 45 Gy to the whole pelvis and inter-RT PET/CT scans after median 63 Gy to the gross LNs. A total of 48 pelvic and para-aortic LNs were found on the pre-RT PET/CT. The mean maximal standardized uptake value of nodal disease decreased from the pre-RT of 5.2 (SD, 3.1; range, 1.8-15.6) to the inter-RT of 1.1 (SD, 2.1; range, 0-11.1). Classifying the metabolic response of all 48 nodal lesions on the inter-RT PET/CT, 38 had a complete metabolic response. The initial volume of LNs had no correlation with the metabolic response ( $r = 0.194$ ,  $P = 0.186$ ). The metabolic response between the pre-RT PET/CT and inter-RT PET/CT was significantly associated with the volume response between the pre-RT CT and inter-RT CT ( $r = 0.314$ ,  $P < 0.05$ ). However, 18 (38%) LNs showed discrepancy between metabolic response and residual LN volume. Six (27%) patients had modified RT during treatment based on inter-RT PET/CT. We suggest that the PET/CT can be a useful tool for the evaluation of the interim response of the LNs and aid in selecting patients that need further treatment. The results showed a significant correlation between the metabolic and volumetric responses during RT, although the anatomical changes of LNs would not always represent the metabolic status.

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Eur J Radiol. 2011 May 3. [Epub ahead of print]

### **Prognostic value of preoperative FDG-PET in stage IA lung adenocarcinoma.**

Murakami S, Saito H, Sakuma Y, Kondo T, Oshita F, Ito H, Tsuboi M, Hasegawa C, Yokose T, Kameda Y, Nakayama H, Yamada K.

Department of Thoracic Oncology, Kanagawa Cancer Center Hospital, Yokohama, Kanagawa, Japan.

Maximum standardized uptake value (SUVmax) of 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) has been found to have prognostic value. We previously reported the correlation between SUVmax and pathological invasive area, and determined an SUVmax cut-off value of 2.15 for predicting the recurrence potential of an invasive area of diameter 5mm. Here, we evaluate the validity of FDG-PET for prediction of recurrence in pathological stage IA lung adenocarcinoma. From February 2006 to May 2008, 100 patients with pathological stage IA lung adenocarcinoma underwent complete resection at our hospital. Tumors were classified as air-type or solid-type based on thin-section computed tomography (TS-CT) findings and the influence of TS-CT classification, SUVmax, and clinicopathologic features were evaluated in terms of the incidence of recurrence. Unlike air-type adenocarcinomas, recurrent disease was detected in 8 of 62 solid-type adenocarcinomas.

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SUVmax and diameter of invasive area were significantly correlated with recurrence and a shorter time to recurrence. All 8 recurrent cases had pathological invasive area >5mm. All except one case of recurrence were solid-type adenocarcinomas with SUVmax $\geq$ 2.15. Three-year disease-free survival rates were 100% in air-type adenocarcinomas, 97.1% in solid-type adenocarcinomas with SUVmax<2.15, and 74.1% in solid-type adenocarcinoma with SUVmax $\geq$ 2.15. Combined evaluation of TS-CT classification and SUVmax had significant value in predicting recurrence in stage IA lung adenocarcinoma, reflecting the aggressiveness of primary lung adenocarcinoma. Prediction of tumor aggressiveness could contribute to decision-making regarding the choice of surgical procedure and treatment after surgery.

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Acta Oncol. 2011 May 5. [Epub ahead of print]

**Feasibility of FDG-PET/CT imaging during concurrent chemo-radiotherapy in patients with locally advanced pancreatic cancer.**

Bjerregaard JK, Fischer BM, Vilstrup MH, Petersen H, Mortensen MB, Hansen CR, Asmussen JT, Pfeiffer P, Højlund-Carlson PF.

Source

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Chin Med J (Engl). 2011 Apr;124(7):1010-4.

**Clinical applications of 18F-fluorodeoxyglucose positron emission tomography/computed tomography in carcinoma of unknown primary.**

Hu M, Zhao W, Zhang PL, Ju GF, Fu Z, Zhang GL, Kong L, Yang YQ, Ma YD, Yu JM.

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Carcinoma of unknown primary (CUP) encompasses a heterogeneous group of tumors with varying clinical features. The management of patients of CUP remains a clinical challenge. The purpose of this study was to evaluate the clinical applications of integrated (18)F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) information in patients with CUP, including detecting the occult primary tumor and effecting on disease therapy. One hundred and forty-nine patients with histologically-proven metastases of CUP were included. For all patients, the conventional diagnostic work-up was unsuccessful in localizing the primary site. Whole-body PET/CT images were obtained approximately 60 minutes after intravenous injection of 350 - 425 MBq of (18)F-FDG. In 24.8% of patients, FDG PET/CT detected primary tumors that were not apparent after conventional workup. In this group of patients, the overall sensitivity, specificity, and accuracy rates of FDG PET/CT in detecting unknown primary tumors were 86.0%, 87.7%, and 87.2%, respectively. FDG PET/CT imaging also led to the detection of previously unrecognized metastases in 29.5% of patients. Forty-seven (31.5%, 47 of 149) patients underwent a change in therapeutic management. FDG PET/CT is a valuable tool in patients with CUP, because it assisted in detecting unknown primary tumors and previously unrecognized distant metastases, and optimized the management of these patients.

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Pediatr Radiol. 2011 May;41 Suppl 1:S186-94. Epub 2011 Apr 27.

**Regional and whole-body imaging in pediatric oncology.**

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The goals of tumor imaging include tumor detection, tumor characterization and differential diagnosis, imaging-guided biopsy, evaluation of tumor extent and staging, assessment of treatment responses, and surveillance for residual tumor or tumor recurrence. In clinical practice, various combinations of imaging modalities are used to achieve these goals. Recently introduced tumor imaging methods, such as diffusion MRI, perfusion MRI, whole-body MRI, and positron emission tomography (PET-CT), have shown promising results. Depending on tumor type and management plan, imaging protocols for children should be individually optimized to achieve the shortest examination time, the highest image quality, the lowest risk, and maximum clinical benefits. In this article, the roles of regional and whole-body tumor imaging will be reviewed, and several important issues related to recent technical developments will be discussed.

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Pediatr Radiol. 2011 May;41 Suppl 1:S172-85. Epub 2011 Apr 27.

Pediatric oncology and the future of oncological imaging.

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## **PET-Oncology**

The future of pediatric oncology will be influenced by changes in drug design and treatment strategy, with genomic medicine and molecular-based diagnostics and therapeutics playing increasingly important roles. The role of imaging as a means of measuring response to therapy has also evolved, with the development of new technologies and higher sensitivity means of detecting tumors. Conventional anatomical imaging techniques are being increasingly supplemented with functional techniques, including FDG-PET imaging and diffusion-weighted MR imaging. The risk-adapted treatment regimens of the past, which led to improved event-free and overall survival in many pediatric cancers, have paved the way for new response-based treatment paradigms. Response-based approaches seek to identify patients with a high likelihood of cure, treating them less aggressively, while those not responding to therapy are identified early and redirected into more aggressive therapeutic regimens. These advances will require concurrent development of imaging biomarkers as surrogates of early response to therapy. Incorporating these techniques into new response-directed treatment algorithms will be crucial as personalized medicine and molecular-targeted, tumor-specific therapies gain acceptance for the treatment of children with cancer.

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Nucl Med Biol. 2011 May;38(4):485-91. Epub 2011 Mar 3.

### **Noninvasive assessment of cell proliferation in ovarian cancer using [18F] 3'deoxy-3-fluorothymidine positron emission tomography/computed tomography imaging.**

Richard SD, Bencherif B, Edwards RP, Elishaev E, Krivak TC, Mountz JM, DeLoia JA.

Department of Obstetrics, Gynecology and Reproductive Services, Division of Gynecologic Oncology, University of Pittsburgh, Pittsburgh, PA 15213, USA.

Positron emission tomography (PET)/computed tomography (CT) imaging of suspected new and recurrent ovarian carcinoma was performed to assess the relationship between [(18)F] 3'deoxy-3-fluorothymidine ((18)FLT) uptake and histopathological tissue markers of cellular proliferation (Ki67) and thymidine kinase-1 (TK-1) expression. Six subjects were included in this pilot study. Subjects were injected with 5 mCi of (18)FLT prior to a planned surgery and then scanned on a GE Discovery-ST PET/CT scanner within an hour of injection. Regions of interest in tumor and control tissue were identified on the diagnostic CT scans and marked for later surgical biopsy. Surgery was performed within 2 days after the scan. At the time of surgery, the regions of interest identified on PET/CT were available to guide the surgeon to the tumor biopsy sites. Tissue from normal ovarian tissue control regions was also sampled. (18)FLT uptake in tumor and control tissue regions was calculated by measuring the maximum standardized uptake values (SUV(max)). The excised tumor and normal ovarian tissue control tissues were analyzed by immunohistochemical staining for Ki67 and CD34. TK-1 messenger RNA expression was measured by real-time polymerase chain reaction. (18)FLT uptake (SUV(max)) was higher in malignant (mean 4.85/range 1.7-8.8) compared to benign (1.65/range 1.4-1.9) and normal ovarian control tissue (1.12/range 0.6-1.5). Mitotic index, as determined by Ki67 staining, was higher in malignant (18.89/range 11.97-27.19) compared to benign (0.59/range 0.23-0.95) and control tissue (0.45/range 0.06-1.20). TK-1 expression was also higher in malignant (35.52/range 5.21-106.62) compared to benign (8.71/range 4.74-12.67) and control tissue (9.79/range 0.85-39.46). An increasing trend between (18)FLT uptake and Ki67 mitotic index is seen in malignant tissue. CD 34 staining between malignant, benign and control tissues was not qualitatively different. An increasing trend between (18)FLT uptake and Ki67 mitotic index is seen in malignant tissue. Additional studies will determine whether (18)FLT PET/CT is specific enough to distinguish between cancerous and noncancerous cells and to assess its role in ovarian carcinoma patient management.

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Nucl Med Biol. 2011 May;38(4):461-75. Epub 2011 Feb 4.

### **Radiopharmacological evaluation of 6-deoxy-6-[18F]fluoro-D-fructose as a radiotracer for PET imaging of GLUT5 in breast cancer.**

Wuest M, Trayner BJ, Grant TN, Jans HS, Mercer JR, Murray D, West FG, McEwan AJ, Wuest F, Cheeseman CI.

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Several clinical studies have shown low or no expression of GLUT1 in breast cancer patients, which may account for the low clinical specificity and sensitivity of 2-deoxy-2-[(18)F]fluoro-D-glucose ([18]F)FDG used in positron emission tomography (PET). Therefore, it has been proposed that other tumor characteristics such as the high expression of GLUT2 and GLUT5 in many breast tumors could be used to develop alternative strategies to detect breast cancer. Here we have studied the in vitro and in vivo radiopharmacological profile of 6-deoxy-6-[(18)F]fluoro-D-fructose (6-[(18)F]FDF) as a potential PET radiotracer to image GLUT5 expression in breast cancers. Uptake of 6-[(18)F]FDF was studied in murine EMT-6 and human MCF-7 breast cancer cells over 60 min and compared to [(18)F]FDG. Biodistribution of 6-[(18)F]FDF was determined in BALB/c mice. Tumor uptake was studied with dynamic small animal PET in EMT-6 tumor-bearing BALB/c mice and human xenograft MCF-7 tumor-bearing NIH-III mice in comparison to [(18)F]FDG. 6-[(18)F]FDF metabolism was investigated in EMT-6 tumors reaching 3.65±0.30% ID/g (n=3) at 5 min post injection and decreasing to 1.75±0.03% ID/g (n=3) at 120 min post injection. Dynamic small animal PET showed significantly lower radioactivity uptake after 15 min post injection in MCF-7 tumors [standard uptake value (SUV)=0.76±0.05; n=3] compared to EMT-6 tumors (SUV=1.23±0.09; n=3). Interestingly, [(18)F]FDG uptake was significantly different in MCF-7 tumors (SUV(15 min) 0.74±0.12 to SUV(120 min) 0.80±0.15; n=3) versus EMT-6 tumors (SUV(15 min) 1.01±0.33 to SUV(120 min) 1.80±0.25; n=3). 6-[(18)F]FDF was shown to be a substrate for recombinant human ketohexokinase, and it was metabolized rapidly in vivo. Based on the GLUT5 specific transport and phosphorylation by ketohexokinase, 6-[(18)F]FDF may represent a novel radiotracer for PET imaging of GLUT5 and ketohexokinase-expressing tumors.

Int J Radiat Oncol Biol Phys. 2011 Apr 28. [Epub ahead of print]

### **What Is the Best Way to Contour Lung Tumors on PET Scans? Multiobserver Validation of a Gradient-Based Method Using a NSCLC Digital PET Phantom.**

Werner-Wasik M, Nelson AD, Choi W, Arai Y, Faulhaber PF, Kang P, Almeida FD, Xiao Y, Ohri N, Brockway KD, Piper JW, Nelson AS.

Department of Radiation Oncology, Thomas Jefferson University Hospital, Philadelphia, PA.

To evaluate the accuracy and consistency of a gradient-based positron emission tomography (PET) segmentation method, GRADIENT, compared with manual (MANUAL) and constant threshold (THRESHOLD) methods. Contouring accuracy was evaluated with sphere phantoms and clinically realistic Monte Carlo PET phantoms of the thorax. The sphere phantoms were 10-37 mm in diameter and were acquired at five institutions emulating clinical conditions. One institution also acquired a sphere phantom with multiple source-to-background ratios of 2:1, 5:1, 10:1, 20:1, and 70:1. One observer segmented (contoured) each sphere with GRADIENT and THRESHOLD from 25% to 50% at 5% increments. Subsequently, seven physicians segmented 31 lesions (7-264 mL) from 25 digital thorax phantoms using GRADIENT, THRESHOLD, and MANUAL. For spheres <20 mm in diameter, GRADIENT was the most accurate with a mean absolute % error in diameter of 8.15% (10.2% SD) compared with 49.2% (51.1% SD) for 45% THRESHOLD ( $p < 0.005$ ). For larger spheres, the methods were statistically equivalent. For varying source-to-background ratios, GRADIENT was the most accurate for spheres >20 mm ( $p < 0.065$ ) and <20 mm ( $p < 0.015$ ). For digital thorax phantoms, GRADIENT was the most accurate ( $p < 0.01$ ), with a mean absolute % error in volume of 10.99% (11.9% SD), followed by 25% THRESHOLD at 17.5% (29.4% SD), and MANUAL at 19.5% (17.2% SD). GRADIENT had the least systematic bias, with a mean % error in volume of -0.05% (16.2% SD) compared with 25% THRESHOLD at -2.1% (34.2% SD) and MANUAL at -16.3% (20.2% SD;  $p$  value <0.01). Interobserver variability was reduced using GRADIENT compared with both 25% THRESHOLD and MANUAL ( $p$  value <0.01, Levene's test). GRADIENT was the most accurate and consistent technique for target volume contouring. GRADIENT was also the most robust for varying imaging conditions. GRADIENT has the potential to play an important role for tumor delineation in radiation therapy planning and response assessment.

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Clin Oncol (R Coll Radiol). 2011 Apr 28. [Epub ahead of print]

### **Bone Metastases: Assessment of Therapeutic Response through Radiological and Nuclear Medicine Imaging Modalities.**

Vassiliou V, Andreopoulos D, Frangos S, Tselis N, Giannopoulou E, Lutz S.

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Radiological and nuclear medicine imaging modalities used for assessing bone metastases treatment response include plain and digitalised radiography (XR), skeletal scintigraphy (SS), dual-energy X-ray absorptiometry (DEXA), computed tomography (CT), magnetic resonance imaging (MRI), [(18)F] fluorodeoxyglucose positron emission tomography (FDG-PET) and PET/CT. Here we discuss the advantages and disadvantages of these assessment modalities as evident through different clinical trials. Additionally, we present the more established response criteria of the International Union Against Cancer and the World Health Organization and compare them with newer MD Anderson criteria. Even though serial XR and SS have been used to assess the therapeutic response for decades, several months are required before changes are evident. Newer techniques, such as MRI or PET, may allow an earlier evaluation of response that may be quantified through monitoring changes in signal intensity and standard uptake value, respectively. Moreover, the application of PET/CT, which can follow both morphological and metabolic changes, has yielded interesting and promising results that give a new insight into the natural history of metastatic bone disease. However, only a few studies have investigated the application of these newer techniques and further clinical trials are needed to corroborate their promising results and establish the most suitable imaging parameters and evaluation time points. Last, but not least, there is an absolute need to adopt uniform response criteria for bone metastases through an international consensus in order to better assess treatment response in terms of accuracy and objectivity.

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Lung Cancer. 2011 Aug;73(2):121-6. Epub 2011 Apr 27.

The role of positron emission tomography in management of small cell lung cancer.

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Accurate radiological staging of small-cell lung cancer (SCLC) is of paramount importance in selection of individual patients with limited stage disease for potentially curative treatment while avoiding toxic treatment in those with distant metastatic disease. [(18)F] fluorodeoxy-D-glucose (FDG) positron emission tomography (PET) is an attractive tool for this purpose but there is limited evidence to support its use in the routine staging of SCLC. Whether therapeutic decisions based on FDG-PET imaging should be made remains uncertain. There is only preliminary evidence for use of FDG-PET as a prognostic biomarker, in the assessment of response to treatment and delineation of disease in conformal radiation planning.

Neoplasma. 2011;58(4):291-7.

### **Determining the extent and stage of disease in patients with newly diagnosed non-Hodgkin's lymphoma using 18F-FDG-PET/CT.**

Papajik T, Myslivecek M, Skopalova M, Malan A, Buriankova E, Koza V, Hnatkova M, Trneny M, Sedova Z, Kubova Z, Koranda P, Flodr P, Jarkovsky J, Dusek L, Indrak K.

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Positron emission tomography (PET) using 2-[fluorine-18]-fluoro-2-deoxy-D-glucose (18F-FDG) combined with computed tomography (CT) represents a three-dimensional imaging method suitable for staging in patients with non-Hodgkin's lymphomas (NHLs). The aim of our prospective multicenter study was to assess the value of initial PET/CT as compared with CT and PET alone for determining the stage and extent of the disease. A total of 122 patients with newly diagnosed NHL were examined using PET/CT. Four patients with resected lymphoma lesion and negative PET/CT were therefore excluded from the study. Of the remaining 118 cases, a total of 117 (99%) were described as 18F-FDG-avid. When compared with PET/CT, CT and PET showed very good sensitivity of lymph node imaging (97% and 100%, respectively); the specificity, however, was significantly lower (66.7% and 94.4%, respectively;  $p=0.0001$ ). When detecting organ lesions, the sensitivity of CT and PET was lower than that of PET/CT (92.5% and 96.3%, respectively;  $p=0.0001$ ); specificity was significantly decreased in CT and a little lower in PET (59.5% and 91.9%;  $p=0.0001$ ). When compared with CT alone, PET/CT changed staging of the disease in 11 patients (9%) and was able to detect a total of 82 discrepancies in 67 of the 117 patients (57%). In conclusion, PET/CT is a new standard in imaging the involvement of lymph nodes and extranodal organs in NHL patients regardless of their histopathological types. Both sensitivity and specificity of the examination are higher than those of CT as well as PET alone.

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J Surg Oncol. 2011 Aug 1;104(2):155-61. doi: 10.1002/jso.21954. Epub 2011 Apr 25.

### **Neoadjuvant GTX chemotherapy and IMRT-based chemoradiation for borderline resectable pancreatic cancer.**

Patel M, Hoffe S, Malafa M, Hodul P, Klapman J, Centeno B, Kim J, Helm J, Valone T, Springett G.

Division of Gastrointestinal Oncology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, Florida 33612, USA.

To improve the likelihood of achieving a margin-free resection, neoadjuvant induction chemotherapy with GTX (gemcitabine, docetaxel, and capecitabine) followed by 5-FU-IMRT was administered to patients with borderline resectable pancreatic cancer. The utility of computed tomography (CT), endoscopic ultrasound (EUS), positron emission tomography (PET), and CA 19-9 during diagnostic workup and assessment of response was also examined. Seventeen patients with borderline resectable pancreatic cancer received a median of three cycles of neoadjuvant GTX induction chemotherapy followed by 5-FU-IMRT with dose painting. CA 19-9, CT mass size, and PET SUV were examined before and after neoadjuvant treatment. Diagnostic EUS and CT scans displayed similar mean mass sizes and extent of vascular involvement. Eight of the 17 patients achieved an R0 resection. Median CA 19-9 levels, CT mass size, and PET SUV all significantly decreased after neoadjuvant therapy. The median progression-free survival and overall survival were 10.48 and 15.64 months, respectively. Six patients are still alive. Neoadjuvant GTX induction chemotherapy followed by 5-FU-IMRT shows promise in improving the likelihood of resectability with negative margins in borderline resectable pancreatic cancer. CT and EUS play complimentary roles during diagnostic workup. CT scans, CA 19-9, and PET scans are useful in judging response to neoadjuvant therapy.

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Clin Imaging. 2011 May-Jun;35(3):228-31.

### **Siliconomas mimicking cancer.**

Grubstein A, Cohen M, Steinmetz A, Cohen D.

Source

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Silicone breast implants are widely used for breast augmentation and breast reconstruction following mastectomy. Implant rupture has specific radiological signs. With the advent use of new imaging technique such as positron emission tomography (PET) computed tomography (CT) and magnetic resonance imaging (MRI) of the breast, these signs may simulate malignancy. We retrospectively reviewed four cases of patients with silicon breast implants who arrive to the mammography clinic for further evaluation of a suspected malignant process demonstrated on either PET CT or breast MRI. Two cases were of PET CT performed for routine oncology follow-up of breast cancer. On both, the PET CT demonstrated multiple-spread benign silicone granulomas manifesting as multiple masses having an increase fluorodeoxyglucose (FDG) uptake. One case of a new mass was demonstrated as a suspicious mass on the dynamic sequences on MRI of the breast. Ultrasound-guided biopsy demonstrated benign tissue response to silicone. One case demonstrated bilateral ruptured breast implants on breast MRI, as well as bilateral axillary and mediastinal lymphadenopathy. Eventually, the patient underwent bronchoscopy for pulmonary workup of dry cough, revealing

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sarcoidosis. Silicone granulomas can manifest as masses with suspicious morphology and enhancement dynamics on breast MRI or with increased FDG uptake on PET CT. The presence of silicone implants and awareness of the possibility of a rupture and formation of silicone granulomas may help in facilitating a correct diagnosis.

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Cancer. 2011 May 1;117(9):1928-34. doi: 10.1002/cncr.25739. Epub 2010 Nov 16.

### **Laparoscopic extraperitoneal para-aortic lymphadenectomy in locally advanced cervical cancer: a prospective correlation of surgical findings with positron emission tomography/computed tomography findings.**

Ramirez PT, Jhingran A, Macapinlac HA, Euscher ED, Munsell MF, Coleman RL, Soliman PT, Schmeler KM, Frumovitz M, Ramondetta LM.

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Failure to detect metastasis to para-aortic nodes in patients with locally advanced cervical cancer leads to suboptimal treatment. No previous studies have prospectively compared positron emission tomography (PET)/computed tomography (CT) with laparoscopic extraperitoneal staging in the evaluation of para-aortic lymph nodes. Sixty-five patients were enrolled; 60 were available for analysis. Patients with stage IB2-IVA cervical cancer without evidence of para-aortic lymphadenopathy on preoperative CT or magnetic resonance imaging (MRI) were prospectively enrolled. All patients underwent preoperative PET/CT. Laparoscopic extraperitoneal lymphadenectomy was performed from the common iliac vessels to the left renal vein. The median age at diagnosis was 48 years (range, 23-84). The median operative time was 140 minutes (range, 89-252). The median blood loss was 22.5 mL (range, 5-150). The median length of hospital stay was 1 day (range, 0-4). The median number of lymph nodes retrieved was 11 (range, 1-39). Fourteen (23%) patients had histopathologically positive para-aortic nodes. Of the 26 patients with negative pelvic and para-aortic nodes on PET/CT, 3 (12%) had histopathologically positive para-aortic nodes. Of the 27 patients with positive pelvic but negative para-aortic nodes on PET/CT, 6 (22%) had histopathologically positive para-aortic nodes. The sensitivity and specificity of PET/CT in detecting positive para-aortic nodes when nodes were negative on CT or MRI were 36% and 96%, respectively. Eleven (18.3%) patients had a treatment modification based on surgical findings. Laparoscopic extraperitoneal para-aortic lymphadenectomy is safe and feasible. Surgical staging of patients with locally advanced cervical cancer should be considered before planned radiation and chemotherapy.

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Acta Radiol. 2011 Jul 1;52(6):646-50. Epub 2011 Apr 20.

### **Measurement of tumor volume by PET to evaluate prognosis in patients with advanced non-small cell lung cancer treated by non-surgical therapy.**

Yan H, Wang R, Zhao F, Zhu K, Jiang S, Zhao W, Feng R.

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Patients with advanced non-small cell lung cancer (NSCLC) seem to have disparity in prognosis. Accurate prediction of prognosis could be useful in the future to predict individual risk and to develop more aggressive or alternative treatment strategies. To evaluate the prognostic value of metabolic tumor volume (MTV) measured by 18F-fluorodeoxyglucose positron emission tomography (18F-FDG PET) in patients with NSCLC. We retrospectively reviewed 120 patients with pathologically proven NSCLC (61 squamous cell carcinomas and 59 adenocarcinomas) who underwent pretreatment 18F-FDG PET. MTV and maximum standardized uptake value (SUVmax) for the primary tumors were measured by 18F-FDG PET. Pretreatment variables (age, sex, American Joint Committee on Cancer [AJCC] stage, histological type, SUVmax, and MTV) were analyzed to identify their correlation with two-year survival. To further evaluate and compare the predictive value of PET parameters, MTV, and SUVmax, time-dependent receiver-operating characteristic curve (ROC) analysis was used. In the univariate analysis, AJCC stage, histological type, MTV, and SUVmax of primary tumor were significant predictors of survival. On multivariate analysis, independent prognostic factors associated with decreased two-year survival were AJCC stage (hazard ratio [HR] 2.236, P = 0.003), histological type (HR 2.038, P = 0.004), and MTV (HR 1.016, P = 0.001). SUVmax was not a significant factor (HR 0.96, P = 0.490). On time-dependent ROC analysis, MTV showed good predictive performance for two-year survival consistently better than SUVmax. MTV, a volumetric parameter of 18F-FDG PET, is an important independent prognostic factor for survival and a better predictor of survival than SUVmax for the primary tumor in patients with advanced NSCLC.

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Expert Rev Anticancer Ther. 2011 Apr;11(4):613-20.

### **Imaging changes after stereotactic body radiation therapy for lung and liver tumors.**

Lo SS, Teh BS, Wang JZ, Huang Z, Zook J, Price T, Mayr NA, Grecula JC, Timmerman RD, Cardenas HR.

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## **PET-Oncology**

Stereotactic body radiation therapy (SBRT) is gaining wide acceptance as a treatment modality for lung and liver tumors, and it is crucial to make an accurate evaluation of the local effects of ablative doses of radiation in terms of local tumor control and normal tissue reaction or damage. The very complex radiation dose distribution of SBRT, the use of a large number of non-opposing and noncoplanar beams, and the delivery of individual ablative doses of radiation may cause substantially different radiographic appearance on diagnostic imaging compared with conventional radiation therapy. Different patterns of radiographic changes have been observed in the lung and liver after SBRT. This article reviews the post-SBRT imaging changes in the lung and liver. Since computed tomography and PET are the most commonly used diagnostic imaging tools for monitoring lung tumor and computed tomography for liver tumors, this article will focus on the changes observed on those imaging modalities.

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Clin Oncol (R Coll Radiol). 2011 Oct;23(8):512-7. Epub 2011 Apr 17.

### **Neck Dissection can be avoided after Sequential Chemoradiotherapy and Negative Post-treatment Positron Emission Tomography-Computed Tomography in N2 Head and Neck Squamous Cell Carcinoma.**

Loo SW, Geropantass K, Beadsmoore C, Montgomery PQ, Martin WM, Roques TW.

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This study assessed neck control in patients with N2 head and neck squamous cell carcinoma (HNSCC) treated with sequential chemoradiotherapy (SCRT) and the incidence of neck recurrence when neck dissection was withheld in those with negative post-treatment fluorine-18 fluorodeoxyglucose positron emission tomography (FDG PET). Thirty-four consecutive patients with N2 HNSCC who were treated with radical intent using SCRT were included. Twenty-seven patients received concomitant platinum-based chemotherapy with their radiotherapy. Nineteen patients were treated with intensity-modulated radiotherapy. PET-computed tomography (PET-CT) was obtained 3 months after the completion of radical radiotherapy. Neck dissection was carried out only in those with increased FDG uptake in the neck. The median follow-up was 39.1 months. One patient had increased FDG uptake in the neck post-treatment, which was false positive for malignancy. The remaining 33 patients were observed without neck dissection. No regional recurrence occurred. The negative predictive value (NPV) of post-treatment PET-CT was 100%. Good disease control in the neck can be achieved in patients with N2 HNSCC with SCRT. Post-treatment PET-CT has a high NPV. Neck dissection can be avoided if post-treatment PET-CT is negative.

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Semin Respir Crit Care Med. 2011 Feb;32(1):94-101. Epub 2011 Apr 15.

### **Advances in the treatment of small-cell lung cancer.**

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Small-cell lung cancer (SCLC) is an aggressive malignancy characterized by early metastatic dissemination and responsiveness to initial therapy. The incidence of SCLC has been declining over the past decade, mainly due to a decreased incidence in men. Positron-emission tomographic (PET) scans appear to improve the accuracy of staging and treatment planning in patients with SCLC. Limited-stage (LS) SCLC is a potentially curable disease, with long-term survival of ~20% when treated with platinum-based chemotherapy plus concurrent thoracic radiation. Hyperfractionated thoracic radiation and prophylactic cranial irradiation (PCI) may significantly improve overall survival in selected patients with LS-SCLC. For patients with extensive-stage (ES) SCLC, survival can be increased with combination chemotherapy, but the disease remains incurable, and long-term survival is rare. The use of PCI has recently been reported to further improve overall survival in ES-SCLC. Several newer cytotoxic agents, such as amrubicin, have promising activity in early clinical trials. Although many potential molecular targets have been identified in preclinical studies of SCLC, molecularly targeted therapy has yet to demonstrate any substantial activity in clinical trials. Nonetheless, future advances in this disease will undoubtedly depend on improvements in our understanding of the molecular mechanisms that drive the proliferation and survival of SCLC cells.

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J Nucl Med. 2011 May;52(5):705-11. Epub 2011 Apr 15.

### **Correlation between 18F-FDG uptake on PET and molecular biology in metastatic pulmonary tumors.**

Kaira K, Okumura T, Ohde Y, Takahashi T, Murakami H, Oriuchi N, Endo M, Kondo H, Nakajima T, Yamamoto N.

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(18)F-FDG PET can help in predicting therapeutic response and outcome in patients with metastatic pulmonary tumors. However, no satisfactory biologic explanation exists for this phenomenon. The aim of this study was to investigate the underlying biologic mechanisms of (18)F-FDG uptake in metastatic pulmonary tumors. One hundred forty-six patients with metastatic pulmonary tumors who underwent (18)F-FDG PET before treatment were included in this study. Tumor sections were stained by immunohistochemistry for glucose transporter 1 (Glut1), glucose transporter 3 (Glut3), hexokinase I, hypoxia-inducible factor-1 $\alpha$  (HIF-1 $\alpha$ ), vascular endothelial growth factor (VEGF), and microvessel

## **PET-Oncology**

density determined by CD34. (18)F-FDG uptake and the expression of these biomarkers were correlated in primary lung cancer and benign pulmonary lesions. (18)F-FDG uptake in metastatic pulmonary tumors correlated significantly with the expression of Glut1 ( $\gamma = 0.4579$ ,  $P < 0.0001$ ), HIF-1 $\alpha$  ( $\gamma = 0.3654$ ,  $P < 0.0001$ ), hexokinase I ( $\gamma = 0.3921$ ,  $P < 0.0001$ ), VEGF ( $\gamma = 0.5528$ ,  $P < 0.0001$ ), and CD34 ( $\gamma = 0.2342$ ,  $P = 0.0044$ ). (18)F-FDG uptake in metastatic pulmonary tumors was significantly lower than in primary lung cancer but higher than in benign pulmonary lesions. High uptake of (18)F-FDG was significantly associated with poor outcome after pulmonary metastasectomy. In patients with metastatic pulmonary tumors, (18)F-FDG uptake and the expression of Glut1, HIF-1 $\alpha$ , and VEGF were significantly higher in adenocarcinoma and squamous cell carcinoma than in sarcoma. (18)F-FDG uptake was significantly correlated with tumor size ( $P < 0.0001$ ), but there was no significant relationship between tumor size and the expression of these biomarkers. The amount of (18)F-FDG uptake in metastatic pulmonary tumors is determined by the presence of glucose metabolism (Glut1), phosphorylation of glucose (hexokinase I), hypoxia (HIF-1 $\alpha$ ), and angiogenesis (VEGF and microvessel density).

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J Nucl Med. 2011 May;52(5):784-91. Epub 2011 Apr 15.

### **In vivo imaging of intraprostatic-specific gene transcription by PET.**

Pouliot F, Karanikolas BD, Johnson M, Sato M, Priceman SJ, Stout D, Sohn J, Satyamurthy N, deKernion JB, Wu L.

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Better intraprostatic cancer imaging techniques are needed to guide clinicians in prostate cancer treatment decisions. Because many genes are specifically overexpressed in cancer cells, one strategy to improve prostate cancer detection is to image intraprostatic cancer-specific transcriptional activity. Because of the obstacles of weak cancer- or tissue-specific promoter activity and bladder clearance of many PET tracers, intraprostatic PET of gene transcriptional activity has not been previously reported. The two-step transcriptional amplification (TSTA) system that amplifies the prostate-specific antigen promoter activity was used for PET imaging of the reporter gene herpes simplex virus type-1 sr39 thymidine kinase (HSV1-sr39tk). The TSTA-sr39tk system was injected directly into prostates or prostatic tumors as a replication-incompetent adenovirus (AdTSTA-sr39tk) and imaged using PET. AdTSTA-sr39tk was able to image prostate-specific antigen promoter transcriptional activity by 9-(4-(18)F-fluoro-3-[hydroxymethyl]butyl)guanine PET, in both mouse and canine prostates in vivo. Ex vivo small-animal PET images, scintigraphic counts, and sr39tk expression analysis confirmed the specificity of the observed signal. Here, by combining the TSTA-amplified signal with a protocol for tracer administration, we show that in vivo PET detection of transcriptional activity is possible in both mouse and immunocompetent canine prostates. These results suggest that imaging applications using transcription-based tumor-specific promoters should be pursued to better visualize cancer foci that escape detection by conventional biopsies.

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J Nucl Med. 2011 May;52(5):712-9. Epub 2011 Apr 15.

### **Impact of time-of-flight PET on whole-body oncologic studies: a human observer lesion detection and localization study.**

Surti S, Scheuermann J, El Fakhri G, Daube-Witherspoon ME, Lim R, Abi-Hatem N, Moussallem E, Benard F, Mankoff D, Karp JS.

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Phantom studies have shown improved lesion detection performance with time-of-flight (TOF) PET. In this study, we evaluate the benefit of fully 3-dimensional, TOF PET in clinical whole-body oncology using human observers to localize and detect lesions in realistic patient anatomic backgrounds. Our hypothesis is that with TOF imaging we achieve improved lesion detection and localization for clinically challenging tasks, with a bigger impact in large patients. One hundred patient studies with normal (18)F-FDG uptake were chosen. Spheres (diameter, 10 mm) were imaged in air at variable locations in the scanner field of view corresponding to lung and liver locations within each patient. Sphere data were corrected for attenuation and merged with patient data to produce fused list-mode data files with lesions added to normal-uptake scans. All list files were reconstructed with full corrections and with or without the TOF kernel using a list-mode iterative algorithm. The images were presented to readers to localize and report the presence or absence of a lesion and their confidence level. The interpretation results were then analyzed to calculate the probability of correct localization and detection, and the area under the localized receiver operating characteristic (LROC) curve. The results were analyzed as a function of scan time per bed position, patient body mass index ( $BMI < 26$  and  $BMI \geq 26$ ), and type of imaging (TOF and non-TOF). Our results showed that longer scan times led to an improved area under the LROC curve for all patient sizes. With TOF imaging, there was a bigger increase in the area under the LROC curve for larger patients ( $BMI \geq 26$ ). Finally, we saw smaller differences in the area under the LROC curve for large and small patients when longer scan times were combined with TOF imaging. A combination of longer scan time (3 min in this study) and TOF imaging provides the best performance for imaging large patients or a low-uptake lesion in small or large patients. This imaging protocol also provides similar performance for all patient sizes for lesions in the same organ type with similar relative uptake, indicating an ability to provide a uniform clinical diagnosis in most oncologic lesion detection tasks.

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Radiother Oncol. 2011 May;99(2):218-24. Epub 2011 Apr 16.

### **Prognostic impact of postoperative, pre-irradiation (18)F-fluoroethyl-L-tyrosine uptake in glioblastoma patients treated with radiochemotherapy.**

Pirotth MD, Holy R, Pinkawa M, Stoffels G, Kaiser HJ, Galldiks N, Herzog H, Coenen HH, Eble MJ, Langen KJ.

## **PET-Oncology**

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Resection is considered as essential for the efficacy of modern adjuvant treatment of glioblastoma multiforme (GBM). Previous studies have indicated that amino acid PET is more specific than contrast enhancement on MRI for detecting residual tumor tissue after surgery. In a prospective study we investigated the prognostic impact of postoperative tumor volume and tumor/brain ratios (TBR) in PET using O-(2-[(18)F]fluoroethyl)-l-tyrosine (FET) in comparison with MRI. Forty-four patients with GBM were investigated by FET PET and MRI after surgery. Tumor volume in FET PET with a tumor/brain ratio (TBR) $>1.6$  and a TBR $>2$ , mean and maximum TBR and gadolinium contrast-enhancement on MRI (Gd-volume) were determined. Thereafter patients received a fractionated radiotherapy with concomitant temozolomide (RCX). The median follow-up was 15.4 (3-35) months. The prognostic value of postoperative residual tumor volume in FET PET, TBR(mean,) TBR(max) and Gd-volume was evaluated using Kaplan-Maier estimates for disease-free survival (DFS) and overall survival (OS). Postoperative tumor volume in FET PET had a significant independent influence on OS and DFS (OS 20.0 vs. 6.9 months; DFS 9.6 vs. 5.1 months,  $p<0.001$ ; cut-off 25 ml). Similar results were observed when a TBR  $\geq 2$  (cut-off 10 ml) was used to define the tumor volume in (18)F-FET PET. The TBR(mean) and TBR(max) of FET uptake had a significant influence on DFS ( $p<0.05$ ). Gd-volume in MRI had significant effect on OS and DFS in the univariate analysis. No independent significant influence in OS or DFS could be observed for Gd-volume in MRI. Our data indicate that the tumor volume in FET PET after surgery of GBM has a strong prognostic impact for these patients. FET PET appears to be helpful to determine the residual tumor volume after surgery of GBM and may serve as a valuable tool for optimal planning of radiation treatment.

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Int J Radiat Oncol Biol Phys. 2011 Jul 1;80(3):885-92. Epub 2011 Apr 12.

### **MicroPET/CT imaging of an orthotopic model of human glioblastoma multiforme and evaluation of pulsed low-dose irradiation.**

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Glioblastoma multiforme (GBM) is an aggressive tumor that typically causes death due to local progression. To assess a novel low-dose radiotherapy regimen for treating GBM, we developed an orthotopic murine model of human GBM and evaluated in vivo treatment efficacy using micro-positron-emission tomography/computed tomography (microPET/CT) tumor imaging. Orthotopic GBM xenografts were established in nude mice and treated with standard 2-Gy fractionation or 10 0.2-Gy pulses with 3-min interpulse intervals, for 7 consecutive days, for a total dose of 14 Gy. Tumor growth was quantified weekly using the Flex Triumph (GE Healthcare/Gamma Medica-Ideas, Waukesha, WI) combined PET-single-photon emission CT (SPECT)-CT imaging system and necropsy histopathology. Normal tissue damage was assessed by counting dead neural cells in tissue sections from irradiated fields. Tumor engraftment efficiency for U87MG cells was 86%. Implanting  $0.5 \times 10^6$  cells produced a 50- to 70-mm<sup>3</sup> tumor in 10 to 14 days. A significant correlation was seen between CT-derived tumor volume and histopathology-measured volume ( $p = 0.018$ ). The low-dose 0.2-Gy pulsed regimen produced a significantly longer tumor growth delay than standard 2-Gy fractionation ( $p = 0.045$ ). Less normal neuronal cell death was observed after the pulsed delivery method ( $p = 0.004$ ). This study successfully demonstrated the feasibility of in vivo brain tumor imaging and longitudinal assessment of tumor growth and treatment response with microPET/CT. Pulsed radiation treatment was more efficacious than the standard fractionated treatment and was associated with less normal tissue damage.

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J Gastrointest Surg. 2011 May;15(5):719-29.

### **Update on staging and surgical treatment options for esophageal cancer.**

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Esophageal cancer remains a challenging clinical problem, with overall long-term survivorship consistently at a level of approximately 30%. The incidence of esophageal cancer is increasing worldwide, with the most dramatic increase being seen with respect to esophageal adenocarcinoma. Pretreatment staging accuracy has improved with the utilization of CT and PET scans, as well as endoscopic ultrasound and endoscopic mucosal resection. In an increasing percentage of patients, endoscopic techniques are being utilized in selected patients for the treatment of high-grade dysplasia in Barrett's and intramucosal cancer. Surgery remains the treatment of choice in all appropriate patients with invasive and locoregional esophageal cancer, although multimodality therapy is now used in most patients with stage II or stage III disease. Outcomes for esophagectomy have been dominated by concerns regarding high mortality and morbidity; however, mortality rates associated with esophageal resection have dramatically decreased, especially in high-volume specialty centers. This manuscript highlights some of the evolutionary issues associated with staging and endoscopic and surgical treatments of Barrett's and esophageal cancer.

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J Clin Oncol. 2011 May 10;29(14):1844-54. Epub 2011 Apr 11.

### **Role of functional imaging in the management of lymphoma.**

Cheson BD.

## **PET-Oncology**

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18-F-fluorodeoxyglucose (FDG) -positron emission tomography (PET), and more recently PET/computed tomography (CT), is the most sensitive and specific imaging technique currently available for patients with lymphoma. Nevertheless, despite being increasingly used in pretreatment assessment, midtreatment evaluation of response, post-treatment restaging, and surveillance during follow-up of patients with lymphoma, its impact on clinical outcome in most clinical situations remains to be confirmed. PET/CT provides its greatest clinical benefit in the post-treatment evaluation of Hodgkin's lymphoma and diffuse large B-cell lymphoma; however, the role of metabolic imaging in other indications and in other histologies remains to be demonstrated. Ongoing risk-adapted studies will hopefully provide evidence for clinical improvement on the basis of altering treatment as a result of interim PET results. Efforts are ongoing to better standardize the conduct and interpretation of FDG-PET scans. FDG-PET has the potential to improve lymphoma patient management; however, its usefulness will likely vary by histology, stage, therapy, and clinical setting.

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Oncologist. 2011;16(6):783-7. Epub 2011 Apr 11.

### **Everolimus induces rapid plasma glucose normalization in insulinoma patients by effects on tumor as well as normal tissues.**

Fiebrich HB, Siemerink EJ, Brouwers AH, Links TP, Remkes WS, Hospers GA, de Vries EG.

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Mammalian target of rapamycin inhibitor everolimus administered to four insulinoma patients rapidly controlled hypoglycemia (Kulke et al., N Engl J Med 2009;360:195-197). We wanted to identify the kinetics of everolimus effects on controlling hypoglycemia and understand underlying mechanisms. Three consecutive patients with a metastasized symptomatic insulinoma were started on 100 µg of octreotide subcutaneously three times daily. Because of persisting hypoglycemias, treatment with daily 10 mg of oral everolimus was initiated. Serial plasma glucose levels and serum insulin levels were measured. Computer tomography (CT) scans were performed before and after 2 and 5 months of treatment. [<sup>18</sup>F]fluoro-2-deoxy-d-glucose positron emission tomography (<sup>18</sup>F-FDG-PET) scans, to visualize glucose metabolism, were made before and after 2 weeks, 5 weeks, and 5 months of treatment. The <sup>18</sup>F-FDG uptake was quantified as the maximum standardized uptake value. All patients achieved control of hypoglycemia on everolimus within 14 days. Insulin levels were 2.5- to 6.3-fold elevated before start of treatment and declined 14%-64% after 4 weeks of treatment. CT scans showed stable disease at 2 months in all patients, with progressive disease after 5 months in one. Before treatment, both the tumor lesions and the muscles and myocardium showed high <sup>18</sup>F-FDG uptake. Everolimus reduced tumor and muscle <sup>18</sup>F-FDG uptake after 2 weeks by 26% ± 14% and 19% ± 41%, and after 5 months by 31% ± 13% and 27% ± 41%. Everolimus normalizes plasma glucose levels in metastatic insulinoma within 14 days, coinciding with a lower glucose uptake in tumor and muscles and declining (pro)insulin levels. This effect on tumor as well as normal tissues explains the rapid controlling of hypoglycemia.

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J Surg Oncol. 2011 May 1;103(6):602-6. doi: 10.1002/jso.21695.

### **Single photon emission tomography/computed tomography (SPET/CT) and positron emission tomography/computed tomography (PET/CT) to image cancer.**

Alberini JL, Edeline V, Giraudet AL, Champion L, Paulmier B, Madar O, Poinignon A, Bellet D, Pecking AP.

Service de Médecine nucléaire, Institut Curie, Hôpital René Huguenin, 35 rue Dailly, F 92210 Saint-Cloud,

France. alberini@crh1.org Hybrid systems associating the sharpness of anatomic images coming from computed tomography (CT) and radionuclide functional imaging (SPET or PET) are opening a new era in oncology. This multimodal imaging method is now routinely used for the diagnosis, extent, follow up, treatment response and detection of occult disease in different types of malignancies with a significant impact on the treatment strategy leading for a change for more than 68% of all investigated patients.

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Mol Imaging Biol. 2011 Apr 9. [Epub ahead of print]

### **Prospective Evaluation of (99m)Tc MDP Scintigraphy, (18)F NaF PET/CT, and (18)F FDG PET/CT for Detection of Skeletal Metastases.**

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Technetium (Tc) methylene diphosphonate (MDP) has been the standard method for bone scintigraphy for three decades. (18)F sodium fluoride ((18)F NaF) positron emission tomography (PET)/computed tomography (CT) has better resolution and is considered superior. The role of 2-deoxy-2-[(18)F]fluoro-D-glucose ((18)F FDG) PET/CT is proven in a variety of cancers, for which it has changed the practice of oncology. There are few prospective studies comparing these three methods of detection of skeletal metastases. Thus, we were prompted to initiate this

## **PET-Oncology**

prospective pilot trial. This is a prospective study (Sep 2007-Dec 2010) of 52 patients with proven malignancy referred for evaluation of skeletal metastases. There were 37 men and 15 women, 19-84 years old (average, 55.6±15.9). Technetium-99m ((99m)Tc) MDP bone scintigraphy, (18)F NaF PET/CT, and (18)F FDG PET/CT were subsequently performed within 1 month. Skeletal lesions were detected by (99m)Tc MDP bone scintigraphy in 22 of 52 patients, by (18)F NaF PET/CT in 24 of 52 patients, and by (18)F FDG PET/CT in 16 of 52 patients. The image quality and evaluation of extent of disease were superior by (18)F NaF PET/CT over (99m)Tc MDP scintigraphy in all 22 patients with skeletal lesions on both scans and over (18)F FDG PET/CT in 11 of 16 patients with skeletal metastases on (18)F FDG PET/CT. In two patients, (18)F NaF PET/CT showed skeletal metastases not seen on either of the other two scans. Extraskelatal lesions were identified by (18)F FDG PET/CT in 28 of 52 subjects. Our prospective pilot-phase trial demonstrates superior image quality and evaluation of skeletal disease extent with (18)F NaF PET/CT over (99m)Tc MDP scintigraphy and (18)F FDG PET/CT. At the same time, (18)F FDG PET detects extraskelatal disease that can significantly change disease management. As such, a combination of (18)F FDG PET/CT and (18)F NaF PET/CT may be necessary for cancer detection. Additional evaluation with larger cohorts is required to confirm these preliminary findings.

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Case Rep Oncol. 2011 Feb 25;4(1):106-14.

### **Hodgkin's Lymphoma and Paraneoplastic Phenomena in the Central Nervous System: A Case Report and Review of the Literature.**

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A 25-year-old male patient presented to our Ear, Nose and Throat clinic with a history of nausea, vomiting, headache, vertigo and weight loss of 5 kg over the preceding 3 months. An enlarged cervical lymph node was detected at clinical examination. Lymph node biopsy showed nodular lymphocyte-predominant Hodgkin's lymphoma (NLPHL, nodular paragranuloma). Because of the neurological symptoms a cerebral MRI scan was performed and revealed an intense perivascular, bilateral, contrast-medium enhancing lesion of the temporal lobes suggestive of cerebral vasculitis. Cerebrospinal fluid analysis showed an increased number of mononuclear cells, but there was no indication for neurotropic viral or bacterial infections. EEG revealed a left temporal epileptic focus, and anti-epileptic therapy was initiated. NLPHL was treated with 2 cycles of ABVD chemotherapy and 20 Gy involved-field radiotherapy. Steroid therapy (prednisone 100 mg q.d.) for the presumed paraneoplastic neurological manifestation was started 1 week before chemotherapy and led to the rapid disappearance of complaints. Because of renewed onset of nausea and vertigo after 3 weeks of treatment with ABVD chemotherapy and 4 weeks of treatment with steroids, a follow-up brain MRI and EEG were performed and demonstrated complete disappearance of the 'vasculitic' changes without additional pathologic findings. Five months after therapy, the patient is without neurological symptoms and a PET-CT showed a complete remission. This case is a unique example of paraneoplastic central nervous system (CNS) involvement in a patient with newly diagnosed NLPHL. We present a review of the literature on paraneoplastic CNS symptoms in Hodgkin's lymphoma.

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Dis Colon Rectum. 2011 May;54(5):518-25.

### **Metabolic response of rectal cancer assessed by 18-FDG PET following chemoradiotherapy is prognostic for patient outcome.**

Yeung JM, Kalff V, Hicks RJ, Drummond E, Link E, Taouk Y, Michael M, Ngan S, Lynch AC, Heriot AG.

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Complete pathological response has proven prognostic benefits in patients with locally advanced rectal cancer treated with neoadjuvant chemoradiotherapy. Sequential 18-FDG PET may be an early surrogate for pathological response to chemoradiotherapy. The aim of this study was to identify whether metabolic response measured by FDG PET following chemoradiotherapy is prognostic for tumor recurrence and survival following neoadjuvant therapy and surgical treatment for primary rectal cancer. Patients with primary rectal cancer treated by long-course neoadjuvant chemoradiotherapy followed by surgery had FDG PET performed before and 4 weeks after treatment, before surgical resection was performed. Retrospective chart review was undertaken for patient demographics, tumor staging, recurrence rates, and survival. : Between 2000 and 2007, 78 patients were identified (53 male, 25 female; median age, 64 y). After chemoradiotherapy, 37 patients (47%) had a complete metabolic response, 26 (33%) had a partial metabolic response, and 14 (18%) had no metabolic response as assessed by FDG PET (1 patient had missing data). However, only 4 patients (5%) had a complete pathological response. The median postoperative follow-up period was 3.1 years during which 14 patients (19%) had a recurrence: 2 local, 9 distant, and 3 with both local and distant. The estimated percentage without recurrence was 77% at 5 years (95% CI 66%-89%). There was an inverse relationship between FDG PET metabolic response and the incidence of recurrence within 3 years (P = .04). Kaplan-Meier analysis of FDG PET metabolic response and overall survival demonstrated a significant difference in survival among patients in the 3 arms: complete, partial, and no metabolic response (P = .04); the patients with complete metabolic response had the best prognosis. Complete or partial metabolic response on PET following neoadjuvant chemoradiotherapy and surgery predicts a lower local recurrence rate and improved survival compared with patients with no metabolic response. Metabolic response may be used to stratify prognosis in patients with rectal cancer.

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## **PET-Oncology**

Int J Radiat Oncol Biol Phys. 2011 Apr 4. [Epub ahead of print]

### **A Prospective Evaluation of Staging and Target Volume Definition of Lymph Nodes by (18)FDG PET/CT in Patients with Squamous Cell Carcinoma of Thoracic Esophagus.**

Yu W, Fu XL, Zhang YJ, Xiang JQ, Shen L, Chang JY.

Department of Radiation Oncology, Cancer Hospital, Fudan University, Shanghai, China.

To determine an optimal standardized uptake value (SUV) threshold for detecting lymph node (LN) metastases in esophageal cancer using (18)F-Fluorodeoxyglucose positron emission tomography/computer tomography ((18)FDG PET/CT) and to define the resulting nodal target volume, using histopathology as a "gold standard." Sixteen patients with esophageal squamous cell carcinoma who underwent radical esophagectomy and three-field LN dissection after (18)FDG PET/CT and CT scans were enrolled into this study. Locations of LN groups were recorded according to a uniform LN map. Diagnostic performance of different SUV thresholds was assessed by receiver operating characteristic analysis. The optimal cutoff SUV was determined by plotting the false-negative rate (FNR) and false-positive rate (FPR), the sum of both error rates (FNR+FPR), and accuracy against a hypothetical SUV threshold. For each patient, nodal gross tumor volumes (GTVNs) were generated with CT alone (GTVNCT), PET/CT (GTVNPET), and pathologic data (GTVNpath). GTVNCT or GTVNPET was compared with GTVNpath by means of a conformity index (CI), which is the intersection of the two GTVNs divided by the sum of them minus the intersection, e.g.,  $CI(CT\&path) = \frac{GTVN(CT\&path)}{GTVN(CT) + GTVN(path) - GTVN(CT\&path)}$ . LN metastases occurred in 21 LN groups among the 144 specimens taken from the 16 patients. The area under the receiver operating characteristic curve was  $0.9017 \pm 0.0410$ . The plot of error rates showed a minimum of FNR+FPR for an SUV of 2.36, at which the sensitivity, specificity, and accuracy were 76.19%, 95.93%, and 93.06%, respectively, whereas those of CT were 33.33%, 94.31%, and 85.42% (p values: 0.0117, 0.7539, and 0.0266). Mean GTVN(CT), GTVN(PET), and GTVN(path) were  $1.52 \pm 2.38$ ,  $2.82 \pm 4.51$ , and  $2.68 \pm 4.16\text{cm}^3$ , respectively. Mean  $CI(CT\&path)$  and  $CI(PET\&path)$  were 0.31 and 0.65 (p value = 0.0352). Diagnostic superiority of PET/CT at an SUV threshold of 2.36 over CT has potential value in nodal target volume definition, but whether this can contribute to better treatment outcomes needs prospective analyses of recurrences in a larger cohort of patients.

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Int J Radiat Oncol Biol Phys. 2011 Apr 4. [Epub ahead of print]

### **F-18-FDG-PET Confined Radiotherapy of Locally Advanced NSCLC With Concomitant Chemotherapy: Results of the PET-PLAN Pilot Trial.**

Fleckenstein J, Hellwig D, Kremp S, Grgic A, Gröschel A, Kirsch CM, Nestle U, Rube C.

**Department of Radiotherapy and Radiation Oncology, Saarland University Medical School, Homburg, Germany.**

The integration of fluoro-deoxy-D-glucose positron emission tomography (FDG-PET) in the process of radiotherapy (RT) planning of locally advanced non-small-cell lung cancer (NSCLC) may improve diagnostic accuracy and minimize interobserver variability compared with target volume definition solely based on computed tomography. Furthermore, irradiating only FDG-PET-positive findings and omitting elective nodal regions may allow dose escalation by treating smaller volumes. The aim of this prospective pilot trial was to evaluate the therapeutic safety of FDG-PET-based RT treatment planning with an autocontour-derived delineation of the primary tumor. Eligible patients had Stages II-III inoperable NSCLC, and simultaneous, platinum-based radiochemotherapy was indicated. FDG-PET and computed tomography acquisitions in RT treatment planning position were coregistered. The clinical target volume (CTV) included the FDG-PET-defined primary tumor, which was autodelineated with a source-to-background algorithm, plus FDG-PET-positive lymph node stations. Limited by dose restrictions for normal tissues, prescribed total doses were in the range of 66.6 to 73.8 Gy. The primary endpoint was the rate of out-of-field isolated nodal recurrences (INR). As per intent to treat, 32 patients received radiochemotherapy. In 15 of these patients, dose escalation above 66.6 Gy was achieved. No Grade 4 toxicities occurred. After a median follow-up time of 27.2 months, the estimated median survival time was 19.3 months. During the observation period, one INR was observed in 23 evaluable patients. FDG-PET-confined target volume definition in radiochemotherapy of NSCLC, based on a contrast-oriented source-to-background algorithm, was associated with a low risk of INR. It might provide improved tumor control because of dose escalation.

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**Clin Endocrinol (Oxf). 2011 May;74(5):644-8. doi: 10.1111/j.1365-2265.2011.04005.x.**

18FDG-positron emission tomography/computed tomography (PET/CT) scanning in thyroid nodules with nondiagnostic cytology.

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To assess the role of positron emission tomography/computed tomography (PET/CT) scans with (18) FDG ((18)FDG-PET/CT) in the evaluation of thyroid nodules with nondiagnostic cytology. Eighty-eight patients with a single euthyroid nodule and repeatedly nondiagnostic ultrasound-guided fine-needle cytology (US-FNC) were enrolled in the present study. Nodules concentrating (18)FDG were considered positive (i.e. suspicious for malignancy). Histological findings were obtained after surgery in all patients. None of 41 patients with negative (18)FDG-PET/CT scan had a final histological diagnosis of malignancy (i.e. no false-negative results). Twenty-nine patients with final histological diagnosis of thyroid cancer had positive (18)FDG-PET/CT scan. Eighteen patients with final histological diagnosis of benign lesions (including four with follicular adenomas) also had positive (18)FDG-PET/CT scans. The sensitivity, specificity, accuracy, positive predictive value (PPV) and

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negative predictive value (NPV) were 100%, 69%, 79%, 62% and 100%, respectively. A negative (18)FDG-PET/CT scan accurately excludes malignancy in thyroid nodules with non-diagnostic US-FNC procedures. Histology is still necessary to distinguish benign from malignant disease in (18)FDG-PET/CT-positive nodules, but unnecessary surgery could have been reduced from 88 to 41 cases (46%) in our series.

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J Korean Med Sci. 2011 Apr;26(4):574-6. Epub 2011 Mar 28.

### **Pulmonary BALT lymphoma successfully treated with eight cycles weekly rituximab: report of first case and F-18 FDG PET/CT images.**

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Extra marginal-zone lymphomas of the lung is a very rare tumor and it originates from bronchial-associated lymphoid tissue. A 68-yr-old woman presented with productive cough and dyspnea. A thorax computed tomography scan showed a 9 × 10 cm in size mass in the left lung and pleural effusion in the lower lobe of left lung. Positron emission tomography/computed tomography (PET/CT) revealed intense uptake foci at the upper and middle sites of left lung and slight uptake foci at the mediastinal lymph nodes which showed malignant involvement. After bronchoscopic biopsy, the diagnosis of pulmonary bronchial-associated lymphoid tissue (BALT) lymphoma was confirmed. At the end of the eight cycles weekly rituximab treatment, complete response was obtained by PET/CT findings. It is concluded that extended rituximab schedule is more effective and it would be beneficial to investigate the use of PET/CT in the diagnosis and evaluating of the treatment response of pulmonary BALT lymphoma.

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PLoS One. 2011 Mar 25;6(3):e18198.

### **HER1-targeted 86Y-panitumumab possesses superior targeting characteristics than 86Y-cetuximab for PET imaging of human malignant mesothelioma tumors xenografts.**

Nayak TK, Garmestani K, Milenic DE, Baidoo KE, Brechbiel MW.

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Malignant mesothelioma (MM), a rare form of cancer is often associated with previous exposure to fibrous minerals, such as asbestos. Asbestos exposure increases HER1-activity and expression in pre-clinical models. Additionally, HER1 over-expression is observed in the majority of MM cases. In this study, the utility of HER1-targeted chimeric IgG(1), cetuximab, and a human IgG(2), panitumumab, radiolabeled with (86)Y, were evaluated for PET imaging to detect MM non-invasively in vivo, and to select an antibody candidate for radioimmunotherapy (RIT). Radioimmunoconjugates (RICs) of cetuximab and panitumumab were prepared by conjugation with CHX-A"-DTPA followed by radiolabeling with (86)Y. The HER1 expression of NCI-H226, NCI-H2052, NCI-H2452 and MSTO-211H human mesothelioma cells was characterized by flow cytometry. In vivo biodistribution, pharmacokinetic analysis, and PET imaging were performed in tumor bearing athymic mice. In vivo studies demonstrated high HER1 tumor uptake of both RICs. Significant reduction in tumor uptake was observed in mice co-injected with excess mAb (0.1 mg), demonstrating that uptake in the tumor was receptor specific. Significant differences were observed in the in vivo characteristics of the RICs. The blood clearance  $T_{1/2\alpha}$  of (86)Y-cetuximab (0.9-1.1 h) was faster than (86)Y-panitumumab (2.6-3.1 h). Also, the tumor area under the curve (AUC) to liver AUC ratios of (86)Y-panitumumab were 1.5 to 2.5 times greater than (86)Y-cetuximab as observed by the differences in PET tumor to background ratios, which could be critical when imaging orthotopic tumors and concerns regarding radiation doses to normal organs such as the liver. This study demonstrates the more favorable HER1-targeting characteristics of (86)Y-panitumumab than (86)Y-cetuximab for non-invasive assessment of the HER1 status of MM by PET imaging. Due to lower liver uptake, panitumumab based immunoconjugates may fare better in therapy than corresponding cetuximab based immunoconjugates.

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Phys Med Biol. 2011 May 7;56(9):2687-98. Epub 2011 Apr 5.

### **The reliability of proton-nuclear interaction cross-section data to predict proton-induced PET images in proton therapy.**

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In vivo PET range verification relies on the comparison of measured and simulated activity distributions. The accuracy of the simulated distribution depends on the accuracy of the Monte Carlo code, which is in turn dependent on the accuracy of the available cross-section data for  $\beta(+)$  isotope production. We have explored different cross-section data available in the literature for the main reaction channels ((16)O(p,pn)(15)O, (12)C(p,pn)(11)C and (16)O(p,3p3n)(11)C) contributing to the production of  $\beta(+)$  isotopes by proton beams in patients. Available experimental and theoretical values were implemented in the simulation and compared with measured PET images obtained with a high-resolution PET scanner. Each reaction channel was studied independently. A phantom with three different materials was built, two of them with high carbon or oxygen concentration and a third one with average soft tissue composition. Monoenergetic and SOBP field irradiations of the

## **PET-Oncology**

phantom were accomplished and measured PET images were compared with simulation results. Different cross-section values for the tissue-equivalent material lead to range differences below 1 mm when a 5 min scan time was employed and close to 5 mm differences for a 30 min scan time with 15 min delay between irradiation and scan (a typical off-line protocol). The results presented here emphasize the need of more accurate measurement of the cross-section values of the reaction channels contributing to the production of PET isotopes by proton beams before this in vivo range verification method can achieve mm accuracy.

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**Eur J Nucl Med Mol Imaging. 2011 Aug;38(8):1449-58. Epub 2011 Apr 2.**

Can FDG PET predict radiation treatment outcome in head and neck cancer? Results of a prospective study.

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In head and neck cancer (HNC) various treatment strategies have been developed to improve outcome, but selecting patients for these intensified treatments remains difficult. Therefore, identification of novel pretreatment assays to predict outcome is of interest. In HNC there are indications that pretreatment tumour (18)F-fluorodeoxyglucose (FDG) uptake may be an independent prognostic factor. The aim of this study was to assess the prognostic value of FDG uptake and CT-based and FDG PET-based primary tumour volume measurements in patients with HNC treated with (chemo)radiotherapy. A total of 77 patients with stage II-IV HNC who were eligible for definitive (chemo)radiotherapy underwent coregistered pretreatment CT and FDG PET. The gross tumour volume of the primary tumour was determined on the CT (GTV(CT)) and FDG PET scans. Five PET segmentation methods were applied: interpreting FDG PET visually (PET(VIS)), applying an isocontour at a standardized uptake value (SUV) of 2.5 (PET(2.5)), using fixed thresholds of 40% and 50% (PET(40%), PET(50%)) of the maximum intratumoral FDG activity (SUV(MAX)) and applying an adaptive threshold based on the signal-to-background (PET(SBR)). Mean FDG uptake for each PET-based volume was recorded (SUV(mean)). Subsequently, to determine the metabolic volume, the integrated SUV was calculated as the product of PET-based volume and SUV(mean). All these variables were analysed as potential predictors of local control (LC), regional recurrence-free survival (RRFS), distant metastasis-free survival (DMFS), disease-free survival (DFS) and overall survival (OS) in oral cavity/oropharynx tumours. PET(VIS) was the only volume-based method able to predict LC. Both PET(VIS) and GTV(CT) were able to predict DMFS, DFS and OS in these subsites. Integrated SUVs were associated with LC, DMFS, DFS and OS, while SUV(mean) and SUV(MAX) were not. In hypopharyngeal/laryngeal tumours none of the variables was associated with outcome. There is no role yet for pretreatment FDG PET as a predictor of (chemo)radiotherapy outcome in HNC in daily routine. However, this potential application needs further exploration, focusing both on FDG PET-based primary tumour volume, integrated SUV and SUV(MAX) of the primary tumour.

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Eur J Radiol. 2011 Mar 31. [Epub ahead of print]

**Clinical usefulness of dual-time FDG PET-CT in assessment of esophageal squamous cell carcinoma.**

Shum WY, Hsieh TC, Yeh JJ, Chen JH, Su CC, Liang JA, Kao CH.

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We conducted this study to investigate the value of the dual-time 2-[(18)F]fluoro-2-deoxy-d-glucose (FDG) positron emission tomography-computed tomography (PET-CT) in assessment of the primary tumor, loco-regional lymph node and distant metastasis in patients with esophageal squamous cell carcinoma. Twenty-six patients with histologically proved esophageal squamous cell carcinoma underwent dual-time FDG PET-CT before radical surgery. The standardized uptake values (SUV(max)) were obtained including early SUV(max) and delayed SUV(max), respectively. The retention index (RI) was also calculated. The results were evaluated retrospectively according to the final pathologic findings. Four diagnostic criteria including (1) early SUV(max)  $\geq$  2.5 alone, (2) RI  $\geq$  10% alone, (3) a combination of early SUV(max)  $\geq$  2.5 and RI  $\geq$  10%, and (4) a combination of early SUV(max)  $\geq$  2.5 or RI  $\geq$  10% were used for differentiating malignancy from a benign lesion, respectively. The sensitivity of FDG PET-CT in detecting the primary tumor with combination of early SUV(max)  $\geq$  2.5 or RI  $\geq$  10% was 96.2%. It was statistically significantly higher than the results using the other three criteria ( $p < 0.0001$ ). For loco-regional lymph node detection, there was no significant difference among the 4 criteria. For distal metastases, the significantly higher specificity (100%) was found when using combination of early SUV(max)  $\geq$  2.5 and RI  $\geq$  10% or using early SUV(max)  $\geq$  2.5 alone than using the other two criteria ( $p = 0.0058$ ). With regard to accuracy, no significant correlations were observed among primary tumor, loco-regional lymph nodes and distant metastasis ( $p > 0.05$ ). The preliminary result of this study demonstrated that dual-time point FDG PET-CT had limited value in detection of primary tumor and loco-regional lymph nodes metastasis. For the distant metastasis, the sensitivity and specificity would be improved if RI  $\geq$  10% is used as a supplemental criterion. Efforts should be made to improve the ability of the dual-time FDG PET-CT technique to assess primary tumor and loco-regional lymph nodes metastasis.

## **PET-Oncology**

Radiother Oncol. 2011 Apr;99(1):44-8. Epub 2011 Mar 30.

### **FET-PET for malignant glioma treatment planning.**

Niyazi M, Geisler J, Siefert A, Schwarz SB, Ganswindt U, Garry S, Schnell O, Suchorska B, Kreth FW, Tonn JC, Bartenstein P, la Fougère C, Belka C.

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The aim of this study was to compare MRI-based morphological gross tumour volumes (GTVs) to biological tumour volumes (BTVs), defined by the pathological radiotracer uptake in positron emission tomography (PET) imaging with (18)F-fluoroethyltyrosine (FET), subsequently clinical target volumes (CTVs) and finally planning target volumes (PTVs) for radiotherapy planning of glioblastoma. Seventeen patients with glioblastoma were included into a retrospective protocol. Treatment-planning was performed using clinical target volume (CTV=BTV+20mm or CTV=GTV+20mm+inclusion of the edema) and planning target volume (PTV=CTV+5mm). Image fusion and target volume delineation were performed with OTP-Masterplan®. Initial gross tumour volume (GTV) definition was based on MRI data only or FET-PET data only (BTV), secondarily both data sets were used to define a common CTV. FET based BTVs (median 43.9 cm(3)) were larger than corresponding GTVs (median 34.1cm(3), p=0.028), in 11 of 17 cases there were major differences between GTV/BTV. To evaluate the conformity of both planning methods, the index  $(CTV(MRT) \cap CTV(FET)) / (CTV(MRT) \cup CTV(FET))$  was quantified which was significantly different from 1 ( $0.73 \pm 0.03$ ,  $p < 0.001$ ). With FET-PET-CT planning, the size and geometrical location of GTVs/BTVs differed in a majority of patients. It remains open whether FET-PET-based target definition has a relevant clinical impact for treatment planning.

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Radiother Oncol. 2011 Apr;99(1):18-22. Epub 2011 Mar 30.

### **Radiographic and metabolic response rates following image-guided stereotactic radiotherapy for lung tumors.**

Mohammed N, Grills IS, Wong CY, Galerani AP, Chao K, Welsh R, Chmielewski G, Yan D, Kestin LL.

Department of Radiation Oncology, William Beaumont Hospital, Royal Oak, MI 48073, USA.

To evaluate radiographic and metabolic response after stereotactic body radiotherapy (SBRT) for early lung tumors.

Thirty-nine tumors were treated prospectively with SBRT (dose=48-60 Gy, 4-5 Fx). Thirty-six cases were primary NSCLC (T1N0=67%; T2N0=25%); three cases were solitary metastases. Patients were followed using CT and PET at 6, 16, and 52 weeks post-SBRT, with CT follow-up thereafter. RECIST and EORTC criteria were used to evaluate CT and PET responses. At median follow-up of 9 months (0.4-26), RECIST complete response (CR), partial response (PR), and stable disease (SD) rates were 3%, 43%, 54% at 6 weeks; 15%, 38%, 46% at 16 weeks; 27%, 64%, 9% at 52 weeks. Mean baseline tumor volume was reduced by 46%, 70%, 87%, and 96%, respectively at 6, 16, 52, and 72 weeks. Mean baseline maximum standardized uptake value (SUV) was 8.3 (1.1-20.3) and reduced to 3.4, 3.0, and 3.7 at 6, 16, and 52 weeks after SBRT. EORTC metabolic CR/PR, SD, and progressive disease rates were 67%, 22%, 11% at 6 weeks; 86%, 10%, 3% at 16 weeks; 95%, 5%, 0% at 52 weeks. SBRT yields excellent RECIST and EORTC based response. Metabolic response is rapid however radiographic response occurs even after 1-year post treatment.

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Cancer. 2011 Mar 31. doi: 10.1002/cncr.26122. [Epub ahead of print]

### **Prognostic significance of baseline positron emission tomography and importance of clinical complete response in patients with esophageal or gastroesophageal junction cancer treated with definitive chemoradiotherapy.**

Suzuki A, Xiao L, Hayashi Y, Macapinlac HA, Welsh J, Lin SH, Lee JH, Bhutani MS, Maru DM, Hofstetter WL, Swisher SG, Ajani JA.

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Metabolic imaging is of interest in esophageal cancer; however, the usefulness of initial standardized uptake value (SUV) in positron emission tomography (PET) is unknown in patients with esophageal or gastroesophageal carcinoma treated with definitive chemoradiotherapy. The authors hypothesized that initial SUV would correlate with patient outcome. The authors retrospectively analyzed esophageal or gastroesophageal carcinoma patients who had baseline PET and endoscopic ultrasonography in addition to other routine staging. All patients received definitive chemoradiotherapy. Multiple statistical methods were used. The authors analyzed 209 consecutive esophageal or gastroesophageal carcinoma patients treated with definitive chemoradiation for outcome; of these, 180 had baseline PET for additional analyses. The median overall survival (OS) for all patients was 20.7 months (95% confidence interval, 18.8-26.3). Patients with clinical complete response (CR) lived longer than those with less than clinical CR ( $P < .0001$ ). The median initial SUV was 12.7 (range, 0-51). Higher initial SUV was associated with longer tumors ( $P = .0001$ ), higher T-stage status ( $P < .0001$ ), positive N-stage status ( $P = .0001$ ), higher overall stage ( $P < .0001$ ), lack of clinical CR ( $P = .0002$ ), and squamous cell histology ( $P < .0001$ ). In the univariate analysis, initial SUV was associated with OS (Cox model,  $P = .016$ ; log-rank test,  $P = .002$ ). In the multivariate analysis, initial SUV dichotomized by the median value ( $P = .024$ ) and tumor grade ( $P = .016$ ) proved to be independent OS prognosticators. Median initial SUV for clinical CR patients was 10.2, compared with 15.3 for less than clinical CR patients ( $P = .0058$ ). The data indicate that a higher initial SUV is associated with poorer OS in patients with esophageal or gastroesophageal carcinoma receiving definitive chemoradiation. Upon validation, baseline PET may become a useful stratification factor in randomized trials and for individualizing therapy.

Med Phys. 2011 Feb;38(2):598-611.

### **Endocervical ultrasound applicator for integrated hyperthermia and HDR brachytherapy in the treatment of locally advanced cervical carcinoma.**

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The clinical success of hyperthermia adjunct to radiotherapy depends on adequate temperature elevation in the tumor with minimal temperature rise in organs at risk. Existing technologies for thermal treatment of the cervix have limited spatial control or rapid energy falloff. The objective of this work is to develop an endocervical applicator using a linear array of multisector tubular ultrasound transducers to provide 3-D conformal, locally targeted hyperthermia concomitant to radiotherapy in the uterine cervix. The catheter-based device is integrated within a HDR brachytherapy applicator to facilitate sequential and potentially simultaneous heat and radiation delivery. Treatment planning images from 35 patients who underwent HDR brachytherapy for locally advanced cervical cancer were inspected to assess the dimensions of radiation clinical target volumes (CTVs) and gross tumor volumes (GTVs) surrounding the cervix and the proximity of organs at risk. Biothermal simulation was used to identify applicator and catheter material parameters to adequately heat the cervix with minimal thermal dose accumulation in nontargeted structures. A family of ultrasound applicators was fabricated with two to three tubular transducers operating at 6.6-7.4 MHz that are unsectored (360 degrees), bisected (2 x 180 degrees), or trisected (3 x 120 degrees) for control of energy deposition in angle and along the device length in order to satisfy anatomical constraints. The device is housed in a 6 mm diameter PET catheter with cooling water flow for endocervical implantation. Devices were characterized by measuring acoustic efficiencies, rotational acoustic intensity distributions, and rotational temperature distributions in phantom. The CTV in HDR brachytherapy plans extends 20.5 +/- 5.0 mm from the endocervical tandem with the rectum and bladder typically <8 mm from the target boundary. The GTV extends 19.4 +/- 7.3 mm from the tandem. Simulations indicate that for 60 min treatments the applicator can heat to 41 degrees C and deliver > 5EM(43 degrees C) over 4-5 cm diameter with T<sub>max</sub> < 45 degrees C and 1 kg m<sup>-3</sup> s<sup>-1</sup> blood perfusion. The 41 degrees C contour diameter is reduced to 3-4 cm at 3 kg m<sup>-3</sup> s<sup>-1</sup> perfusion. Differential power control to transducer elements and sectors demonstrates tailoring of heating along the device length and in angle. Sector cuts are associated with a 14-47 degrees acoustic dead zone, depending on cut width, resulting in a approximately 2-4 degrees C temperature reduction within the dead zone below T<sub>max</sub>. Dead zones can be oriented for thermal protection of the rectum and bladder. Fabricated devices have acoustic efficiencies of 33.4%-51.8% with acoustic output that is well collimated in length, reflects the sectoring strategy, and is strongly correlated with temperature distributions. A catheter-based ultrasound applicator was developed for endocervical implantation with locally targeted, 3-D conformal thermal delivery to the uterine cervix. Feasibility of heating clinically relevant target volumes was demonstrated with power control along the device length and in angle to treat the cervix with minimal thermal dose delivery to the rectum and bladder.

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Cancer. 2011 Mar 29. doi: 10.1002/cncr.26090. [Epub ahead of print]

### **High frequency of neurolymphomatosis as a relapse Disease of intravascular large B-cell lymphoma.**

Matsue K, Hayama BY, Iwama KI, Koyama T, Fujiwara H, Yamakura M, Takeuchi M, O'uchi T.

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Intravascular large B-cell lymphoma (IVL) is characterized by lymphoma cell proliferation in the lumina of small vessels in various organs. A high incidence of neurologic symptoms associated with the central nervous system has been reported, but peripheral nerve involvement (neurolymphomatosis [NL]) rarely has been described. The medical records from patients who were diagnosed with IVL over the past 4 years were reviewed. A diagnosis of NL was made based on the combination of neurologic symptoms and their correspondence with imaging studies, such as magnetic resonance imaging (MRI), (18) F-fluoro-2-deoxy-D-glucose (FDG)-positron emission tomography/computed tomography (PET/CT), and/or the histologic confirmation of lymphoma cells within the peripheral nerves, nerve root/plexuses, or cranial nerves. Four patients with NL were identified among 11 patients who had IVL. All cases of NL occurred as relapsed disease during or shortly after the completion of chemotherapy. Although MRI studies of the brains and whole spines revealed nerve infiltration by gadolinium enhancement in 2 patients, the technology was not sensitive enough to detect such infiltration in the remaining 2 patients. In contrast, FDG-PET/CT studies successfully revealed cranial or peripheral nerve lesions in all 4 patients and was useful for evaluating therapeutic response. Patients received treatment with high-dose methotrexate with or without other systemic chemotherapy, which achieved varied success. Further studies will be needed to determine the optimal treatment. Considering the rarity of IVL and NL, the current observations suggested that IVL may have a predilection not only for the vessels but also for both the central and peripheral nervous systems.

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Int J Radiat Oncol Biol Phys. 2011 Mar 25. [Epub ahead of print]

### **Noninvasive Evaluation of Microscopic Tumor Extensions Using Standardized Uptake Value and Metabolic Tumor Volume in Non-Small-Cell Lung Cancer.**

Meng X, Sun X, Mu D, Xing L, Ma L, Zhang B, Zhao S, Yang G, Kong FM, Yu J.

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## **PET-Oncology**

To prospectively evaluate whether maximal microscopic extensions (ME<sub>max</sub>) correlate with maximal standardized uptake value (SUV<sub>max</sub>) and metabolic tumor volume (MTV) at 18F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) images in non-small-cell lung cancer (NSCLC). Thirty-nine patients with Stage I-IIIa NSCLC underwent surgery after FDG-PET/CT scanning. SUV<sub>max</sub> and MTV were calculated on the PET/CT images. The maximum linear distance from the tumor margin to the farthest extent of the tumor in every dimension was measured at the tumor section. The correlations among ME<sub>max</sub>, SUV<sub>max</sub>, MTV and other clinical pathologic parameters were analyzed. ME<sub>max</sub> for all patients had a significant correlation with SUV<sub>max</sub> ( $r = 0.777$ ,  $p = 0.008$ ) and MTV ( $r = 0.724$ ,  $p < 0.001$ ). When expressed in terms of the probability of covering ME with respect to a given margin, we suggested that margins of 1.93 mm, 3.90 mm, and 9.60 mm for SUV<sub>max</sub>  $\leq 5$ , 5-10, and  $>10$  added to the gross tumor volume would be adequate to cover 95% of ME. This study demonstrated that tumors with high SUV<sub>max</sub> and MTV have more ME<sub>max</sub> and would therefore require more margin expansion from gross tumor volume to clinical target volume. FDG-PET/CT, especially for SUV<sub>max</sub>, is promising and effective and merits additional study in noninvasive delimiting of the clinical target volume margin for NSCLC.

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Rev Esp Med Nucl. 2011 Jul-Aug;30(4):248-50. Epub 2011 Mar 26.

**[Lung hot spot as pitfall in PET-CT interpretation: focal lung uptake of 18F-fluorodeoxyglucose].**

[Article in Spanish]

Redal Peña MC, Pena Pardo FJ, Muñoz Iglesias J, Crespo-Jara A, Rebollo J, Brugarolas Masllorens A.

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(18)F-FDG PET-CT has become an essential tool in oncology patient management. The normal distribution of the FDG and the possible artifacts (pitfalls), including those from CT-based attenuation correction, have already been described in several reviews. However, only a few cases of FDG focal lung uptake have been reported recently. We present two cases of oncology patients during a routine follow-up with this type of pitfall, without morphological correlation in the CT scan. We repeated the study in one of them, which made it possible to verify normalization of the hyperuptake, orienting us towards a possible pitfall.

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J Med Phys. 2011 Jan;36(1):35-9.

**To study tumor motion and planning target volume margins using four dimensional computed tomography for cancer of the thorax and abdomen regions.**

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In this study, four dimensional computed tomography (4DCT) scanning was performed during free breathing on a 16-slice Positron emission tomography PET /computed tomography (CT) for abdomen and thoracic patients. Images were sorted into 10 phases based on the temporal correlation between surface motion and data acquisition with an Advantage Workstation. Gross tumor volume gross tumor volume (GTV) s were manually contoured on all 10 phases of the 4DCT scan. GTVs in the multiple CT phases were called GTV4D. GTV4D plus an isotropic margin of 1.0 cm was called CTV4D. Two sets of planning target volume (PTV) 4D (PTV4D) were derived from the CTV4D, i.e. PTV4D(2cm) = CTV4D plus 1 cm setup margin (SM) and 1 cm internal margin (IM) and PTV4D(1.5cm) = CTV4D plus 1 cm SM and 0.5cm IM. PTV3D was derived from a CTV3D of the helical CT scan plus conventional margins of 2 cm. PTV(gated) was generated only selecting three CT phases, with a total margin of 1.5 cm. All four volumes were compared. To quantify the extent of the motion, we selected the two phases where the tumor exhibited the greatest range of motion. We also studied the effect of different PTV volumes on dose to the surrounding critical structures. Volume of CTV4D was greater than that of CTV3D. We found, on an average, a reduction of 14% volume of PTV4D(1.5cm) as compared with PTV3D and reduction of 10% volume of PTV(gated) as compared with PTV4D(1.5cm). We found that 2 cm of margin was inadequate if true motion of tumor was not known. We observed greater sparing of critical structures for PTVs drawn taking into account the tumor motion.

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Eur J Cancer. 2011 Jul;47(10):1595-602. Epub 2011 Mar 21.

**VEGF-SPECT with <sup>111</sup>In-bevacizumab in stage III/IV melanoma patients.**

Nagengast WB, Hooge MN, van Straten EM, Kruijff S, Brouwers AH, den Dunnen WF, de Jong JR, Hollema H, Dierckx RA, Mulder NH, de Vries EG, Hoekstra HJ, Hospers GA.

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A feasibility study was performed to investigate the presence of VEGF in melanoma lesions by VEGF-SPECT with (111)In-bevacizumab. In addition the effect of a single therapeutic bevacizumab dose on (111)In-bevacizumab uptake was compared with VEGF levels in resected

## **PET-Oncology**

melanoma lesions. Eligible were patients with stage III/IV melanoma who presented with nodal recurrent disease. VEGF-SPECT was performed after administration of 100 Mbq (111)In-bevacizumab (8 mg) at days 0, 2, 4 and 7 post injection. Tumour visualisation and quantification were compared with CT and FDG-PET. On day 7 a single dose of 7.5mg/kg bevacizumab was administered intravenously. On day 21, a second tracer dose (111)In-bevacizumab was administered and scans were obtained on days 21, 25 and 28. Metastases were surgically resected within 2 weeks after the last VEGF-SPECT scan and immunohistological (IHC) VEGF tumour expression was compared with (111)In-bevacizumab tumour uptake. Nine patients were included. FDG-PET and CT detected both in total 12 nodal lesions which were all visualised by VEGF-SPECT. At baseline, (111)In-bevacizumab tumour uptake varied 3-fold between and  $1.6 \pm 0.1$ -fold within patients. After a therapeutic dose of bevacizumab there was a  $21 \pm 4\%$  reduction in (111)In-bevacizumab uptake. The (111)In-bevacizumab tumour uptake in the second series positively correlated with the VEGF-A expression in the resected tumour lesions. VEGF-SPECT could visualise all known melanoma lesions. A single dose of bevacizumab slightly lowered (111)In-bevacizumab uptake. Future studies should elucidate the role of VEGF-SPECT in the selection of patients and the individual dosing of bevacizumab treatment.

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Oncologist. 2011;16(4):445-51. Epub 2011 Mar 22.

### **18F-FDG PET/CT as a diagnostic tool in patients with extracervical carcinoma of unknown primary site: a literature review.**

Moller AK, Loft A, Berthelsen AK, Damgaard Pedersen K, Graff J, Christensen CB, Perell K, Petersen BL, Daugaard G.

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Carcinoma of unknown primary (CUP) represents a heterogeneous group of metastatic malignancies for which no primary tumor site can be identified after extensive diagnostic workup. Failure to identify the primary site may negatively influence patient management. The aim of this review was to evaluate (18)F-fluorodeoxyglucose positron emission tomography/computed tomography ((18)F-FDG PET/CT) as a diagnostic tool in patients with extracervical CUP. A comprehensive literature search was performed and four publications were identified (involving 152 patients) evaluating (18)F-FDG PET/CT in CUP patients with extracervical metastases. All studies were retrospective and heterogeneous in inclusion criteria, study design, and diagnostic workup prior to (18)F-FDG PET/CT. (18)F-FDG PET/CT detected the primary tumor in 39.5% of patients with extracervical CUP. The lung was the most commonly detected primary tumor site ( $\square 50\%$ ). The pooled estimates of sensitivity, specificity, and accuracy of (18)F-FDG PET/CT in the detection of the primary tumor site were 87%, 88%, and 87.5%, respectively. The present review of currently available data indicates that (18)F-FDG PET/CT might contribute to the identification of the primary tumor site in extracervical CUP. However, prospective studies with more uniform inclusion criteria are required to evaluate the exact value of this diagnostic tool.

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Br J Radiol. 2011 Mar 22. [Epub ahead of print]

### **Positron emission tomography (PET) imaging approaches for external beam radiation therapies: current status and future developments.**

Price PM, Green MM.

Department of Academic Radiation Oncology, The University of Manchester, The Christie Hospital NHS Foundation Trust, Manchester M20 4BX, UK. In an era in which it is possible to deliver radiation with high precision, there is a heightened need for enhanced imaging capabilities to improve tumour localisation for diagnostic, planning and delivery purposes. This is necessary to increase the accuracy and overall efficacy of all types of external beam radiotherapy (RT), including particle therapies. Positron emission tomography (PET) has the potential to fulfil this need by imaging fundamental aspects of tumour biology. The key areas where PET may support the RT process include: improving disease diagnosis and staging; assisting tumour volume delineation; defining tumour phenotype or biological tumour volume; assessment of treatment response; and in-beam monitoring of radiation dosimetry. The role of PET and its current developmental status in these key areas are overviewed here, highlighting its advantages and drawbacks.

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Am J Clin Oncol. 2011 Mar 17. [Epub ahead of print]

### **Positron Emission Tomography for Predicting Pathologic Response After Neoadjuvant Chemoradiotherapy for Locally Advanced Rectal Cancer.**

Chennupati SK, Quon A, Kamaya A, Pai RK, La T, Krakow TE, Graves E, Koong AC, Chang DT.

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To investigate whether before and after chemoradiotherapy (CRT) positron emission tomography (PET) predict for pathologic response after preoperative CRT in patients with locally advanced rectal adenocarcinoma. Thirty-five patients who underwent pre-CRT and post-CRT PET scans before surgery were included. All patients were staged with endoscopic ultrasound or high resolution CT. CRT was given with 50.4 Gy at 1.8 Gy per fraction and concurrent 5-fluorouracil-based chemotherapy. Surgery occurred at a median of 46 days (range, 27 to 112 d) after

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completing CRT. The maximum standardized uptake value (SUVmax) and the metabolic tumor volume (MTV) using various minimum SUV thresholds (2, 2.5, 3) on the PET scans (MTV2.0, MTV2.5, MTV3.0) were determined. Post-CRT PET scans were done 3 to 5 weeks after completion of CRT. Pathologic response was assessed using the tumor regression grade (TRG) scale. Patients with complete or near-complete response (TRG=0 to 1) were considered pathologic responders. The pre-CRT and post-CRT PET scan SUVmax and MTV values were correlated with TRG. The  $\Delta$ SUVmax and  $\Delta$ MTV were correlated with TRG. No correlation was seen with SUVmax (P=0.99), MTV2.0 (P=0.73), MTV2.5 (P=0.73), or MTV3.0 (P=0.31) on the pre-CRT PET between pathologic responders versus nonresponders. No correlation was noted between SUVmax (P=0.49), MTV2.0 (P=0.73), MTV2.5 (P=0.49), or MTV3.0 (P=0.31) on the post-CRT PET scan and pathologic response. Finally, the  $\Delta$ SUVmax (P=0.32),  $\Delta$ MTV2.0 (P=0.99),  $\Delta$ MTV2.5 (P=0.31),  $\Delta$ MTV3.0 (P=0.31) did not correlate with pathologic response. Changes seen on PET have limited value in predicting for pathologic response of rectal cancer after preoperative neoadjuvant therapy.

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J Clin Oncol. 2011 May 1;29(13):1701-8. Epub 2011 Mar 21.

### **Early prediction of nonprogression in advanced non-small-cell lung cancer treated with erlotinib by using [(18)F]fluorodeoxyglucose and [(18)F]fluorothymidine positron emission tomography.**

Zander T, Scheffler M, Nogova L, Kobe C, Engel-Riedel W, Hellmich M, Papachristou I, Toepelt K, Draube A, Heukamp L, Buettner R, Ko YD, Ullrich RT, Smit E, Boellaard R, Lammertsma AA, Hallek M, Jacobs AH, Schlesinger A, Schulte K, Querings S, Stoelben E, Neumaier B, Thomas RK, Dietlein M, Wolf J.

Source

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Positron emission tomography (PET) with both 2'-deoxy-2'-[(18)F]fluoro-D-glucose (FDG) and 3'-[(18)F]fluoro-3'-deoxy-L-thymidine (FLT) was evaluated with respect to the accuracy of early prediction of nonprogression following erlotinib therapy, independent from epidermal growth factor receptor (EGFR) mutational status, in patients with previously untreated advanced non-small-cell lung cancer (NSCLC). Thirty-four patients with untreated stage IV NSCLC were evaluated in this phase II trial. Changes in FDG and FLT uptake after 1 (early) and 6 (late) weeks of erlotinib treatment were compared with nonprogression measured by computed tomography after 6 weeks of treatment, progression-free survival (PFS), and overall survival (OS). Changes in FDG uptake after 1 week of therapy predicted nonprogression after 6 weeks of therapy with an area under the receiver operating characteristic curve of 0.75 (P = .02). Furthermore, patients with an early metabolic FDG response (cutoff value: 30% reduction in the peak standardized uptake value) had significantly longer PFS (hazard ratio [HR], 0.23; 95% CI, 0.09 to 0.59; P = .002) and OS (HR, 0.36; 95% CI, 0.13 to 0.96; P = .04). Early FLT response also predicted significantly longer PFS (HR, 0.31; 95% CI, 0.10 to 0.95; P = .04) but not OS and was not predictive for nonprogression after 6 weeks of therapy. Early FDG-PET predicts PFS, OS, and nonprogression after 6 weeks of therapy with erlotinib in unselected, previously untreated patients with advanced NSCLC independent from EGFR mutational status.

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Obstet Gynecol Clin North Am. 2011 Mar;38(1):1-21, vii.

### **PET/CT in gynecologic cancer: present applications and future prospects--a clinician's perspective.**

Amit A, Schink J, Reiss A, Lowenstein L.

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This article briefly reviews the epidemiology, diagnosis, and treatment of the common gynecologic malignancies, with an emphasis on the shortcomings of current clinical practice. The persistent need to achieve early diagnosis, adjust proper treatment, enhance surveillance, and improve the outcome of these patients has led to the development of new diagnostic modalities. Novel tools such as 18F-fluorodeoxyglucose PET/CT should aim at enhancing the clinician's ability to make critical decisions in treating difficult scenarios.

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Ann Nucl Med. 2011 Jul;25(6):414-8. Epub 2011 Mar 16.

### **Phase I clinical study of NMK36: a new PET tracer with the synthetic amino acid analogue anti-[18F]FACBC.**

Asano Y, Inoue Y, Ikeda Y, Kikuchi K, Hara T, Taguchi C, Tokushige T, Maruo H, Takeda T, Nakamura T, Fujita T, Kumagai Y, Hayakawa K.

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NMK36 is a novel PET tracer containing a synthetic amino acid analogue anti-[(18)F]FACBC as the active ingredient, and is under development for the use of tumor diagnosis. A Phase I clinical study of NMK36 was conducted to evaluate its safety, biodistribution, and radiation dosimetry in healthy volunteers. Six healthy volunteers (Japanese male) received a bolus injection of NMK36 (174.4-201.4 MBq) intravenously. The safety

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of NMK36 was evaluated by monitoring signs/symptoms, electrocardiography, recording vital signs, and laboratory examinations at baseline and several time points in 6 days after injection. A total of 11 whole-body PET-CT scans were acquired up to 4 h post-injection, and venous blood and urine samples were also collected for 6 and 24 h post-injection, respectively. Based on the results of the biodistribution study, absorbed radiation dose was estimated by the MIRD method. Although two adverse events occurred after the injection of NMK36, they were mild and disappeared without any specific treatment. NMK36 preferentially accumulated in the pancreas and liver early after injection, followed by rapid clearance from the pancreas. Persistent uptake was observed in the skeletal muscle. NMK36 showed low uptake in the brain, and its urinary excretion was limited ( $5.40 \pm 1.43\%$  of the injected dose at 24 h post-injection). The liver was the critical organ, with a mean absorbed dose of  $40.6 \mu\text{Gy}/\text{MBq}$ . The estimated effective dose of NMK36 was  $13.8 \mu\text{Sv}/\text{MBq}$ , which was similar to or lower than those of radiotracers approved for clinical use including  $^{18}\text{F}$ FDG. The findings of this study indicate that NMK36 is well tolerated. NMK36 has favorable characteristics for imaging brain and pelvic tumors, such as low brain uptake, slow urinary excretion, and high in vivo stability.

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Exp Oncol. 2010 Sep;32(3):149-52.

### **Imaging of tumor physiology: impacts on clinical radiation oncology.**

Astner ST, Shi K, Vaupel P, Molls M.

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As the metabolic microenvironment markedly influences the therapeutic response of malignant tumors, imaging of the microenvironment is one of the goals researcher have been aiming at for years. Several methods such as positron emission tomography, functional magnetic resonance imaging (MRI) or contrast enhanced MRI/CT are now available. For radiation oncology, tumor oxygenation and perfusion are the most important (patho-) physiological parameters that might be included in radiotherapy regimens and treatment planning. In order to overcome resistance of tumor cells resulting from hypoxia, positron emission tomography (PET) using nitroimidazole tracers is the most advanced technique at this time. Since reproducibility of the PET signal/tracer distribution, thresholding and exact quantification are not thoroughly understood and further investigation is needed before including it into radiotherapy regimens. To image tumor perfusion, dynamic contrast enhanced computed tomography (DCE-CT) or dynamic contrast enhanced magnetic resonance imaging (DCE-MRI) are the most suitable techniques. Co-investigation of tumor oxygenation and perfusion should be performed in order to investigate their interaction and consequences for radiooncology.

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Nucl Med Commun. 2011 Jun;32(6):479-85.

### **Comparison of PET-CT images with the histopathological picture of a resectable primary tumor for delineating GTV in nonsmall cell lung cancer.**

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This study was designed to investigate the feasibility of a method derived from fused positron emission tomography-computed tomography (PET-CT) images for the delineation of gross tumor volume (GTV) in nonsmall cell lung cancer (NSCLC) and to explore the correlation between PET-CT and histopathological findings. Thirty-seven patients were enrolled in this study; all patients were evaluated by PET-CT and underwent surgery within 1 week after the scan. The radiation oncologist, together with the radiologist, first delineated the GTV-based CT and then with an experienced nuclear medicine physician contoured the same GTV using the distinctive visual 'halo' in fused PET-CT images. The characteristics of the halo phenomenon were analyzed, including the standardized uptake value (SUV). The excised surgical specimens were labeled and the maximum diameter of the tumor in the right-left axis of the tissue blocks was measured on consecutive histopathology slides; the histopathological slice images were scanned using a digital pathology scanner after staining with hematoxylin and eosin. The mean SUV of the external margins of the halos was  $2.41 \pm 0.73$  (range 1.4-4.1); the histopathological type and T-stage significantly influenced the SUV of the external margin of the halos ( $P=0.004$  and  $0.027$ ). The correlation coefficients of maximum diameter in the right-left axis and in the anterior-posterior axis between fused PET-CT images and histopathology were 0.935 and 0.943, respectively; the values between CT imaging and histopathological examination were 0.82 and 0.763. There is a correlation between GTV based on the 'halo' of fused PET-CT images and the excised surgical specimen of primary tumor. It may be feasible to use the 'halo' characteristics in fused PET-CT images to delineate GTV in NSCLCs, but its reliability should be further investigated to establish an accurate spatial imaging-pathology correlation for primary tumors delineation in NSCLCs.

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Nucl Med Commun. 2011 Jun;32(6):475-8.

### **Prostate-specific antigen kinetics and choline PET/CT in patients with biochemical relapse after primary treatment for prostate cancer.**

Castellucci P, Fuccio C, Marzola MC, Al-Nahhas A, Rubello D, Fanti S.

## **PET-Oncology**

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Over the past few years, several studies have proved the potential role of diagnostic procedures in patients with treated prostate cancer who develop biochemical relapse. Notably, no precise indications exist regarding the use of emerging modalities such as positron emission tomography/computerized tomography (PET/CT) scanning with radiolabeled choline. However, the literature suggests that the main and most important application of choline PET/CT at present is in disease restaging in cases of biochemical relapse for the detection of local, lymph node-related or distant recurrence. In this setting, it is well known that prostate-specific antigen (PSA) values play a significant role in the follow-up of these patients. This short review aims at summarizing the results of the most relevant published studies with particular interest directed towards a better understanding of the relationship between PSA kinetics and choline PET/CT detection rate and the potential use of PSA kinetics for an optimal selection of patients who may benefit most from this diagnostic procedure particularly at an early stage of biochemical recurrence.

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Int J Radiat Oncol Biol Phys. 2011 Mar 9. [Epub ahead of print]

### **Repeated positron emission tomography-computed tomography and perfusion-computed tomography imaging in rectal cancer: fluorodeoxyglucose uptake corresponds with tumor perfusion.**

Janssen MH, Aerts HJ, Buijsen J, Lambin P, Lammering G, Ollers MC.

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The purpose of this study was to analyze both the intratumoral fluorodeoxyglucose (FDG) uptake and perfusion within rectal tumors before and after hypofractionated radiotherapy. Rectal cancer patients, referred for preoperative hypofractionated radiotherapy (RT), underwent FDG-positron emission tomography (PET)-computed tomography (CT) and perfusion-CT (pCT) imaging before the start of hypofractionated RT and at the day of the last RT fraction. The pCT-images were analyzed using the extended Kety model, quantifying tumor perfusion with the pharmacokinetic parameters  $K(\text{trans})$ ,  $v(e)$ , and  $v(p)$ . The mean and maximum FDG uptake based on the standardized uptake value (SUV) and transfer constant ( $K(\text{trans})$ ) within the tumor were correlated. Also, the tumor was subdivided into eight subregions and for each subregion the mean and maximum SUVs and  $K(\text{trans})$  values were assessed and correlated. Furthermore, the mean FDG uptake in voxels presenting with the lowest 25% of perfusion was compared with the FDG uptake in the voxels with the 25% highest perfusion. The mean and maximum  $K(\text{trans})$  values were positively correlated with the corresponding SUVs ( $\rho = 0.596$ ,  $p = 0.001$  and  $\rho = 0.779$ ,  $p < 0.001$ ). Also, positive correlations were found for  $K(\text{trans})$  values and SUVs within the subregions (mean,  $\rho = 0.413$ ,  $p < 0.001$ ; and max,  $\rho = 0.540$ ,  $p < 0.001$ ). The mean FDG uptake in the 25% highest-perfused tumor regions was significantly higher compared with the 25% lowest-perfused regions ( $10.6\% \pm 5.1\%$ ,  $p = 0.017$ ). During hypofractionated radiotherapy, stable mean ( $p = 0.379$ ) and maximum ( $p = 0.280$ ) FDG uptake levels were found, whereas the mean ( $p = 0.040$ ) and maximum ( $p = 0.003$ )  $K(\text{trans})$  values were found to significantly increase. Highly perfused rectal tumors presented with higher FDG-uptake levels compared with relatively low perfused tumors. Also, intratumor regions with a high FDG uptake demonstrated with higher levels of perfusion than regions with a relatively low FDG-uptake. Early after hypofractionated RT, stable FDG uptake levels were found, whereas tumor perfusion was found to significantly increase.

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NMR Biomed. 2011 Mar 8. doi: 10.1002/nbm.1689. [Epub ahead of print]

### **Diffusion-weighted MRI in early chemotherapy response evaluation of patients with diffuse large B-cell lymphoma - a pilot study: comparison with 2-deoxy-2-fluoro-D-glucose-positron emission tomography/computed tomography.**

Wu X, Kellokumpu-Lehtinen PL, Pertovaara H, Korkola P, Soimakallio S, Eskola H, Dastidar P.

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To determine the feasibility of diffusion-weighted MRI (DWI) in the evaluation of the early chemotherapeutic response in patients with aggressive non-Hodgkin's lymphoma (NHL), eight patients with histologically proven diffuse large B-cell lymphoma were imaged by MRI, including DWI, and positron emission tomography/computed tomography (PET/CT) before treatment (E1), and after 1 week (E2) and two cycles (E3) of chemotherapy. In all patients, whole-body screening using T(1) - and T(2) -weighted images in the coronal plane was performed. To quantitatively evaluate the chemotherapeutic response, axial images including DWI were acquired. Apparent diffusion coefficient (ADC) maps were reconstructed, and the ADC value of the tumor was measured. In addition, the tumor volume was estimated on axial T(2) -weighted images. The maximum standardized uptake value (SUV(max)) and active tumor volume were measured on fused PET/CT images. Lymphomas showed high signal intensity on DW images and low signal intensity on ADC maps, except for necrotic foci. The mean pre-therapy ADC was  $0.71 \times 10^{-3} \text{ mm}^2/\text{s}$ ; it increased by 77% at E2 ( $p < 0.05$ ) and 24% more at E3 (insignificant); the total increase was 106% ( $p < 0.05$ ). The mean tumor volume by MRI was  $276 \text{ mL}$  at baseline; it decreased by 58% at E2 ( $p < 0.05$ ) and 65% more at E3 ( $p < 0.05$ ), giving a total decrease of 84% ( $p < 0.05$ ). All the imaged pre-therapy tumors were strongly positive on PET/CT, with a mean SUV(max) of 20. The SUV(max) decreased by 60% at E2 ( $p < 0.05$ ) and 59% more at E3 ( $p < 0.05$ ), giving a total decrease of 83% ( $p < 0.05$ ). The active tumor burden decreased by 66% at E2 ( $p < 0.05$ ). At baseline, both central and peripheral tumor ADC values correlated inversely with SUV(max) ( $p < 0.05$ ), and also correlated inversely with active tumor burden on PET/CT and with tumor volume on MRI at E2 ( $p < 0.05$ ). In conclusion, the results of DWI in combination with whole-body MRI were comparable with those of integrated PET/CT.

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Phys Med Biol. 2011 Apr 7;56(7):2045-57. Epub 2011 Mar 8.

### **Modelling and simulation of [18F]fluoromisonidazole dynamics based on histology-derived microvessel maps.**

Mönnich D, Troost EG, Kaanders JH, Oyen WJ, Alber M, Thorwarth D.

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Hypoxia can be assessed non-invasively by positron emission tomography (PET) using radiotracers such as [(18)F]fluoromisonidazole (Fmiso) accumulating in poorly oxygenated cells. Typical features of dynamic Fmiso PET data are high signal variability in the first hour after tracer administration and slow formation of a consistent contrast. The purpose of this study is to investigate whether these characteristics can be explained by the current conception of the underlying microscopic processes and to identify fundamental effects. This is achieved by modelling and simulating tissue oxygenation and tracer dynamics on the microscopic scale. In simulations, vessel structures on histology-derived maps act as sources and sinks for oxygen as well as tracer molecules. Molecular distributions in the extravascular space are determined by reaction-diffusion equations, which are solved numerically using a two-dimensional finite element method. Simulated Fmiso time activity curves (TACs), though not directly comparable to PET TACs, reproduce major characteristics of clinical curves, indicating that the microscopic model and the parameter values are adequate. Evidence for dependence of the early PET signal on the vascular fraction is found. Further, possible effects leading to late contrast formation and potential implications on the quantification of Fmiso PET data are discussed.

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J Med Imaging Radiat Oncol. 2011 Feb;55(1):58-64. doi: 10.1111/j.1754-9485.2010.02230.x.

### **Initial clinical test of a breast-PET scanner.**

Raylman RR, Abraham J, Hazard H, Koren C, Filburn S, Schreiman JS, Kurian S, Majewski S, Marano GD.

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The goal of this initial clinical study was to test a new positron emission/tomography imager and biopsy system (PEM/PET) in a small group of selected subjects to assess its clinical imaging capabilities. Specifically, the main task of this study is to determine whether the new system can successfully be used to produce images of known breast cancer and compare them to those acquired by standard techniques. The PEM/PET system consists of two pairs of rotating radiation detectors located beneath a patient table. The scanner has a spatial resolution of  $\approx 2$  mm in all three dimensions. The subjects consisted of five patients diagnosed with locally advanced breast cancer ranging in age from 40 to 55 years old scheduled for pre-treatment, conventional whole body PET imaging with F-18 Fluorodeoxyglucose (FDG). The primary lesions were at least 2 cm in diameter. The images from the PEM/PET system demonstrated that this system is capable of identifying some lesions not visible in standard mammograms. Furthermore, while the relatively large lesions imaged in this study were all visualised by a standard whole body PET/CT scanner, some of the morphology of the tumours (ductal infiltration, for example) was better defined with the PEM/PET system. Significantly, these images were obtained immediately following a standard whole body PET scan. The initial testing of the new PEM/PET system demonstrated that the new system is capable of producing good quality breast-PET images compared standard methods.

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Int J Radiat Oncol Biol Phys. 2011 Mar 5. [Epub ahead of print]

### **PET-based Treatment Response Evaluation in Rectal Cancer: Prediction and Validation.**

Janssen MH, Ollers MC, van Stiphout RG, Riedl RG, van den Bogaard J, Buijsen J, Lambin P, Lammering G.

Department of Radiation Oncology (MAASTRO), GROW Research Institute, University Medical Centre Maastricht, Maastricht, the Netherlands.

To develop a positron emission tomography (PET)-based response prediction model to differentiate pathological responders from nonresponders. The predictive strength of the model was validated in a second patient group, treated and imaged identical to the patients on which the predictive model was based.

Fifty-one rectal cancer patients were prospectively included in this study. All patients underwent fluorodeoxyglucose (FDG) PET-computed tomography (CT) imaging both before the start of chemoradiotherapy (CRT) and after 2 weeks of treatment. Preoperative treatment with CRT was followed by a total mesorectal excision. From the resected specimen, the tumor regression grade (TRG) was scored according to the Mandard criteria. From one patient group (n = 30), the metabolic treatment response was correlated with the pathological treatment response, resulting in a receiver operating characteristic (ROC) curve based cutoff value for the reduction of maximum standardized uptake value (SUV(max)) within the tumor to differentiate pathological responders (TRG 1-2) from nonresponders (TRG 3-5). The applicability of the selected cutoff value for new patients was validated in a second patient group (n = 21). When correlating the metabolic and pathological treatment response for the first patient group using ROC curve analysis (area under the curve = 0.98), a cutoff value of 48% SUV(max) reduction was selected to differentiate pathological responders from nonresponders (specificity of 100%, sensitivity of 64%). Applying this cutoff value to the second patient group resulted in a specificity and sensitivity of, respectively, 93% and 83%, with only one of the pathological nonresponders being false positively predicted as pathological responding. For rectal cancer, an accurate PET-based prediction of the pathological treatment

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response is feasible already after 2 weeks of CRT. The presented predictive model could be used to select patients to be considered for less invasive surgical interventions or even a "wait and see" policy. Also, based on the predicted response, early modifications of the treatment protocol are possible, which might result in an improved clinical outcome.

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Int J Radiat Oncol Biol Phys. 2011 Mar 4. [Epub ahead of print]

### **Clinical Utility of 4D FDG-PET/CT Scans in Radiation Treatment Planning.**

Aristophanous M, Berbeco RI, Killoran JH, Yap JT, Sher DJ, Allen AM, Larson E, Chen AB.

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The potential role of four-dimensional (4D) positron emission tomography (PET)/computed tomography (CT) in radiation treatment planning, relative to standard three-dimensional (3D) PET/CT, was examined. Ten patients with non-small-cell lung cancer had sequential 3D and 4D [(18)F]fluorodeoxyglucose PET/CT scans in the treatment position prior to radiation therapy. The gross tumor volume and involved lymph nodes were contoured on the PET scan by use of three different techniques: manual contouring by an experienced radiation oncologist using a predetermined protocol; a technique with a constant threshold of standardized uptake value (SUV) greater than 2.5; and an automatic segmentation technique. For each technique, the tumor volume was defined on the 3D scan (VOL3D) and on the 4D scan (VOL4D) by combining the volume defined on each of the five breathing phases individually. The range of tumor motion and the location of each lesion were also recorded, and their influence on the differences observed between VOL3D and VOL4D was investigated. We identified and analyzed 22 distinct lesions, including 9 primary tumors and 13 mediastinal lymph nodes. Mean VOL4D was larger than mean VOL3D with all three techniques, and the difference was statistically significant ( $p < 0.01$ ). The range of tumor motion and the location of the tumor affected the magnitude of the difference. For one case, all three tumor definition techniques identified volume of moderate uptake of approximately 1 mL in the hilar region on the 4D scan (SUV maximum, 3.3) but not on the 3D scan (SUV maximum, 2.3). In comparison to 3D PET, 4D PET may better define the full physiologic extent of moving tumors and improve radiation treatment planning for lung tumors. In addition, reduction of blurring from free-breathing images may reveal additional information regarding regional disease.

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Dtsch Med Wochenschr. 2011 Mar;136(10):468-72. Epub 2011 Mar 1.

### **[Positron emission tomography (PET) and PET/CT for guiding therapy in oncology].**

[Article in German]

Haug AR, Bartenstein P.

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Eur J Nucl Med Mol Imaging. 2011 Jul;38(7):1191-202. Epub 2011 Mar 2.

### **Prognostic value of 18F-FDG PET image-based parameters in oesophageal cancer and impact of tumour delineation methodology.**

Hatt M, Visvikis D, Albarghach NM, Tixier F, Pradier O, Cheze-le Rest C.

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(18)F-fluorodeoxyglucose (FDG) positron emission tomography (PET) image-derived parameters, such as standardized uptake value (SUV), functional tumour length (TL) and tumour volume (TV) or total lesion glycolysis (TLG), may be useful for determining prognosis in patients with oesophageal carcinoma. The objectives of this work were to investigate the prognostic value of these indices in oesophageal cancer patients undergoing combined chemoradiotherapy treatment and the impact of TV delineation strategies. A total of 45 patients were retrospectively analysed. Tumours were delineated on pretreatment (18)F-FDG scans using adaptive threshold and automatic (fuzzy locally adaptive Bayesian, FLAB) methodologies. The maximum standardized uptake value (SUV(max)), SUV(peak), SUV(mean), TL, TV and TLG were computed. The prognostic value of each parameter for overall survival was investigated using Kaplan-Meier and Cox regression models for univariate and multivariate analyses, respectively. Large differences were observed between methodologies (from -140 to +50% for TV). SUV measurements were not significant prognostic factors for overall survival, whereas TV, TL and TLG were, irrespective of the segmentation strategy. After multivariate analysis including standard tumour staging, only TV ( $p < 0.002$ ) and TL ( $p = 0.042$ ) determined using FLAB were independent prognostic factors. Whereas no SUV measurement was a significant prognostic factor, TV, TL and TLG were significant prognostic factors for overall survival, irrespective of the delineation methodology. Only functional TV and TL derived using FLAB were independent prognostic factors, highlighting the need for accurate and robust PET tumour delineation tools for oncology applications.

## **PET-Oncology**

Clin Cancer Res. 2011 Apr 15;17(8):2400-9. Epub 2011 Mar 1.

### **PET tumor metabolism in locally advanced breast cancer patients undergoing neoadjuvant chemotherapy: value of static versus kinetic measures of fluorodeoxyglucose uptake.**

Dunnwald LK, Doot RK, Specht JM, Gralow JR, Ellis GK, Livingston RB, Linden HM, Gadi VK, Kurland BF, Schubert EK, Muzi M, Mankoff DA.

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Changes in tumor metabolism from positron emission tomography (PET) in locally advanced breast cancer (LABC) patients treated with neoadjuvant chemotherapy (NC) are predictive of pathologic response. Serial dynamic [(18)F]-FDG (fluorodeoxyglucose) PET scans were used to compare kinetic parameters with the standardized uptake value (SUV) as predictors of pathologic response, disease-free survival (DFS), and overall survival (OS). Seventy-five LABC patients underwent FDG PET prior to and at midpoint of NC. FDG delivery (K(1)), FDG flux (K(i)), and SUV measures were calculated and compared by clinical and pathologic tumor characteristics using regression methods and area under the receiver operating characteristic curve (AUC). Associations between K(1), K(i), and SUV and DFS and OS were evaluated using the Cox proportional hazards model. Tumors that were hormone receptor negative, high grade, highly proliferative, or of ductal histology had higher FDG K(i) and SUV values; on an average, FDG K(1) did not differ systematically by tumor features. Predicting pathologic response in conjunction with estrogen receptor (ER) and axillary lymph node positivity, kinetic measures (AUC = 0.97) were more robust predictors than SUV (AUC = 0.84, P = 0.005). Changes in K(1) and K(i) predicted both DFS and OS, whereas changes in SUV predicted OS only. In multivariate modeling, only changes in K(1) remained an independent prognosticator of DFS and OS. Kinetic measures of FDG PET for LABC patients treated with NC accurately measured treatment response and predicted outcome compared with static SUV measures, suggesting that kinetic analysis may hold advantage of static uptake measures for response assessment.

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Semin Oncol. 2011 Feb;38(1):70-86.

### **Positron emission tomography imaging of cancer biology: current status and future prospects.**

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Positron emission tomography (PET) is one of the most rapidly growing areas of medical imaging, with many applications in the clinical management of patients with cancer. The principal goal of PET imaging is to visualize, characterize, and measure biological processes at the cellular, subcellular, and molecular levels in living subjects using noninvasive procedures. PET imaging takes advantage of the traditional diagnostic imaging techniques and introduces positron-emitting probes to determine the expression of indicative molecular targets at different stages of cancer progression. Although [(18)F]fluorodeoxyglucose ((18)F)FDG)-PET has been widely utilized for staging and restaging of cancer, evaluation of response to treatment, differentiation of post-therapy alterations from residual or recurrent tumor, and assessment of prognosis, [(18)F]FDG is not a target-specific PET tracer. Over the last decade, numerous target-specific PET tracers have been developed and evaluated in preclinical and clinical studies. This review provides an overview of the current status and trends in the development of non-[(18)F]FDG PET probes in oncology and their application in the investigation of cancer biology.

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Semin Radiat Oncol. 2011 Apr;21(2):157-66.

### **Image-based biomarkers in clinical practice.**

Bayouth JE, Casavant TL, Graham MM, Sonka M, Muruganandham M, Buatti JM.

Source

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The growth of functional and metabolically informative imaging is eclipsing anatomic imaging alone in clinical practice. The recognition that magnetic resonance (MR) and positron emission tomography (PET)-based treatment planning and response assessment are essential components of clinical practice and furthermore offer the potential of quantitative analysis being important. Extracting the greatest benefit from these imaging techniques will require refining the best combinations of multimodality imaging through well-designed clinical trials that use robust image-analysis tools and require substantial computer based infrastructure. Through these changes and enhancements, image-based biomarkers will enhance clinical decision making and accelerate the progress that is made through clinical trial research.

## **PET-Oncology**

Expert Rev Anticancer Ther. 2011 Feb;11(2):195-204.

### **Clinical applications of positron emission tomography in sarcoma management.**

Quak E, van de Luijngaarden AC, de Geus-Oei LF, van der Graaf WT, Oyen WJ.

Source

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Positron emission tomography (PET) with the fluorine-18-labeled glucose analog FDG is a technique that noninvasively visualizes glucose metabolism in the human body. In oncology, the addition of FDG-PET to the conventional anatomical imaging techniques provides very useful clinical information in diagnosis, staging, treatment response monitoring and follow-up. In the heterogeneous group of patients with sarcoma, FDG-PET has been shown to be of great value in improving patient care. In this article we will discuss the current role of FDG-PET in the management of patients with sarcoma and its value in assessing tumor grade, guiding biopsy, staging, monitoring treatment response, restaging and prognostication. Our future expectation is that the value of PET will only augment owing to the implementation of FDG-PET in clinical guidelines, the increasing availability worldwide, and the development of new tracers and new hybrid imaging techniques.

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Oncologist. 2011;16(3):319-26. Epub 2011 Feb 21.

### **Role of 18F-fluorodeoxyglucose positron emission tomography in predicting epidermal growth factor receptor mutations in non-small cell lung cancer.**

Mak RH, Digumarthy SR, Muzikansky A, Engelman JA, Shepard JA, Choi NC, Sequist LV.

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To compare (18)F-fluorodeoxyglucose positron emission tomography (FDG-PET) and computed tomography (CT) imaging characteristics in non-small cell lung cancer (NSCLC) with or without epidermal growth factor receptor (EGFR) mutations.

We retrospectively identified NSCLC patients who underwent EGFR mutation testing and pretreatment FDG-PET and CT scans. The maximum standard uptake value (SUV(max)) of the primary tumor and any metastases was measured and normalized to the SUV of blood in the pulmonary artery. We compared normalized SUV(max) values between EGFR-mutant and wild-type patients and modeled radiographic and clinical predictors of EGFR mutation status. Receiver operator characteristic (ROC) curves were used to identify potential SUV cutoffs predictive of genotype. We included 100 patients (24 EGFR-mutant and 76 wild-type). There was a trend for higher normalized SUV(max) in the primary tumors among patients with EGFR-wild-type versus mutant (median, 3.4; range, 0.6-12.8; versus median, 2.9; range, 0.4-5.0;  $p = .09$ ). Normalized SUV(max) of nodal and distant metastases, and CT characteristics were not associated with genotype. On multivariate analysis, low normalized SUV(max) of the primary tumor was predictive for EGFR mutation (odds ratio, 0.72; 95% confidence interval, 0.53-0.98;  $p = .034$ ). ROC curve analyses yielded an area under the curve of 0.62, and identified a potential cutoff of  $\geq 5.0$  to distinguish wild-type from mutant tumors. In this retrospective study, high FDG avidity (normalized SUV(max)  $\geq 5$ ) correlated with EGFR-wild-type genotype. Although genotyping remains the gold standard, further work to validate FDG-PET as a surrogate for tumor genotype may provide useful information in patients without available tumor tissue.

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Phys Med Biol. 2011 Mar 21;56(6):1585-600. Epub 2011 Feb 18.

### **Production of clinically useful positron emitter beams during carbon ion deceleration.**

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In external beam radiation therapy, radioactive beams offer the best clinical solution to simultaneously treat and in vivo monitor the dose delivery and tumor response using PET or PET-CT imaging. However, difficulties mainly linked to the low production efficiency have so far limited their use. This study is devoted to the analysis of the production of high energy (11)C fragments, preferably by projectile fragmentation of a stable monodirectional and monoenergetic primary (12)C beam in different absorbing materials (decelerators) in order to identify the optimal elemental composition. The study was performed using the Monte Carlo code SHIELD-HIT07. The track length and fluence of generated secondary particles were scored in a uniform absorber of 300 cm length and 10 cm radius, divided into slices of 1 cm thickness. The (11)C fluence build-up and mean energy variation with increasing decelerator depth are presented. Furthermore, the fluence of the secondary (11)C beam was studied as a function of its mean energy and the corresponding remaining range in water. It is shown that the maximum (11)C fluence build-up is high in compounds where the fraction by weight of hydrogen is high, being the highest in liquid hydrogen. Furthermore, a cost effective alternative solution to the single medium initially envisaged is presented: a two-media decelerator that comprises a first liquid hydrogen section followed by a second decelerating section made of a hydrogen-rich material, such as polyethylene (C(2)H(4)). The purpose of the first section is to achieve a

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fast initial (11)C fluence build-up, while the second section is primarily designed to modulate the mean energy of the generated (11)C beam in order to reach the tumor depth. Finally, it was demonstrated that, if the intensity of the primary (12)C beam can be increased by an order of magnitude, a sufficient intensity of the secondary (11)C beam is achieved for therapy and subsequent therapeutic PET imaging sessions. Such an increase in the intensity might be easily achieved with a superconducting cyclotron.

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Rev Esp Med Nucl. 2011 Mar-Apr;30(2):88-93. Epub 2011 Feb 19.

### **[Dual time point 18F-FDOPA PET as a tool for characterizing brain tumors].**

[Article in Spanish]

González-Forero M, Prieto E, Domínguez I, Vigil C, Peñuelas I, Arbizu J.

Source

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(18)F-FDOPA is an amino acid analogue used to evaluate presynaptic dopaminergic activity, which has aroused great interest in neuro-oncology. We have evaluated five (18)F-FDOPA PET studies of patients referred for study of parkinsonian syndrome. Two subjects had previously treated high-grade brain tumors, one nonspecific brain injury, and 2 subjects presented unexpected tumoral lesions. For all lesions SUVmax, time to SUVmax and tumor-to-normal grey matter SUVmax rate (T/N) were calculated, and 90 minutes (18)F-FDOPA kinetics were analyzed. Tumor lesions corresponded to three malignant neurocytomas, one meningioma, one pineocytoma and one intrasinusal hemangioma. Both malignant and benign tumors exhibited high uptake of (18)F-FDOPA well above the normal cortex. However, the analysis of the curve uptake displayed characteristic patterns that facilitate the characterization of tumor lesions. A dual phase maximum uptake was observed, with an early 10 minutes uptake in malignant lesions, and a late 60 to 90 minutes uptake in benign or low grade lesions.

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Eur J Cancer. 2011 Jun;47(9):1312-8. Epub 2011 Feb 18.

### **Prognostic significance of interim $^{18}$ F-FDG PET/CT after three or four cycles of R-CHOP chemotherapy in the treatment of diffuse large B-cell lymphoma.**

Yang DH, Min JJ, Song HC, Jeong YY, Chung WK, Bae SY, Ahn JS, Kim YK, Bom HS, Chung IJ, Kim HJ, Lee JJ.

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(18)F-fluoro-2-dexoy-D-glucose-positron emission tomography (FDG-PET)/computerised tomography (CT) has been used for staging and monitoring responses to treatment in patients with diffuse large B cell lymphoma (DLBCL). The sequential interim PET/CT was prospectively investigated to determine whether it provided additional prognostic information and could be a positive predictable value within patients with the same international prognostic index (IPI) after the use of rituximab in DLBCL. One hundred and sixty-one patients with newly diagnosed DLBCL were enrolled; the assessment of the PET/CT was performed at the time of diagnosis and mid-treatment of rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP). Sixty-seven patients (41.6%) presented with advanced stage disease and 27 (16.8%) had bulky lesions. Forty-three patients (26.7%) continued to have positive metabolic uptakes with a significantly high relapse rate (62.8%) compared to the patients with a negative interim PET/CT (12.1%) ( $P < 0.01$ ). After a median follow-up of 30.8 months, the positivity of interim PET/CT was found to be a prognostic factor for both overall survival (OS) and progression-free survival (PFS), with a hazard ratio of 4.07 (2.62-6.32) and 5.46 (3.49-8.52), respectively. In the low-risk IPI group, the 3-year OS and PFS rates were significantly different in the patients with positive (53.3% and 52.5%) and negative (93.8% and 88.3%) interim PET/CT, respectively ( $P < 0.01$ ). These significant prognostic differences of interim PET/CT responses were consistent with the results of the patients with high-risk IPI group ( $P < 0.01$ ). Interim PET/CT scanning had a significant predictive value for disease progression and survival of DLBCL in post-rituximab treatment; it might be the single most important determinant of clinical outcome in patients with the same IPI risk.

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J Appl Clin Med Phys. 2010 Oct 7;12(1):3306.

### **Correction of motion-induced misalignment in co-registered PET/CT and MRI (T1/T2/FLAIR) head images for stereotactic radiosurgery.**

Li G, Xie H, Ning H, Citrin D, Kaushal A, Camphausen K, Miller RW.

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The purpose was to evaluate and correct the co-registration of diagnostic PET/CT and MRI/MRI images for stereotactic radiosurgery (SRS) using 3D volumetric image registration (3DVIR). The 3DVIR utilizes the homogeneity of color distribution over a volumetric anatomical landmark as the registration criterion with submillimeter accuracy. Fifty-three PET/CT and MRI (T1, T2 and FLAIR) image sets of patients with brain lesions

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were acquired sequentially from a hybrid PET/CT or an MRI scanner with common diagnostic head holding devices. Twenty-five sets of head 18F-FDG-PET/CT images were scanned over a 10-minute interval and 14 whole-body sets were scanned over a 30-minute interval. Fourteen sets of MRI images were acquired, and each 3-modal image set (T1, T2 and FLAIR) was scanned in sequence at time 0, ~5 and ~20 minutes. The misalignments in these "co-registered" images were evaluated and corrected using the 3DVIR. Using the head immobilization devices commonly found in diagnostic PET/CT and MRI/MRI imaging, 80%-100% of these "co-registered" images were identified as misaligned. For PET/CT, the magnitude of misalignment was  $0.4^\circ \pm 0.5^\circ$  and  $0.7 \pm 0.4$  mm for 10-minute scans, and  $0.8^\circ \pm 1.2^\circ$  and  $2.7 \pm 1.7$  mm for 30-minute scans. For MRI/MRI, the magnitude was  $0.2^\circ \pm 0.4^\circ$  and  $0.3 \pm 0.2$  mm for 5-minute scan intervals, and  $1.1^\circ \pm 0.7^\circ$  and  $1.2 \pm 1.4$  mm for 20-minute intervals. Small, but significant, misalignment is present in the co-registered diagnostic PET/CT and MRI/MRI images and can be corrected in SRS treatment planning using the volumetric image registration for improved target localization within the clinical error tolerance.

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Radiologe. 2011 Mar;51(3):215-9.

### **[Whole-body diffusion-weighted imaging in oncology: technical aspects and practical relevance].**

[Article in German]

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This review illustrates the relevance of whole-body diffusion-weighted imaging (WB-DWI) in the field of oncological imaging. WB-DWI is an alternative method to positron-emission tomography/computed tomography (PET/CT) due to the lack of radiation and lower examination costs. Technical aspects of WB-DWI and the current role of the method in cancer imaging regarding practical requirements in oncology are presented.

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J Nucl Med. 2011 Mar;52(3):331-4. Epub 2011 Feb 14.

### **Molecular imaging in radiotherapy planning for head and neck tumors.**

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Molecular imaging uses noninvasive techniques to visualize various biologic pathways and physiologic characteristics of tumors and normal tissues. In relation to radiation therapy, PET with the tracer (18)F-FDG offers a unique opportunity to refine the target volume delineation in patients with squamous cell carcinoma of the head and neck, in turn affecting dose distribution and, it is hoped, patient outcome. Even more so, in the framework of adaptive treatment and theragnostics, whereby dose distribution is adapted in space and time over the typical course of radiotherapy, molecular imaging with PET offers an elegant research avenue to further improve the therapeutic ratio. Such implementation could be of particular interest with tracers other than (18)F-FDG, such as tracers of hypoxia and proliferation.

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J Nucl Med. 2011 Mar;52(3):431-6. Epub 2011 Feb 14.

### **Total abdominal 18F-FDG uptake reflects intestinal adenoma burden in Apc mutant mice.**

Heijink DM, Kleibeuker JH, Nagengast WB, Oosterhuis D, Brouwers AH, Koornstra JJ, de Jong S, de Vries EG.

Department of Medical Oncology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands.

Apc mutant (Apc(Min)) mice develop multiple adenomas in their intestines and are widely used to study colorectal carcinogenesis and chemopreventive approaches. Molecular imaging of intestinal adenomas could potentially provide noninvasive longitudinal evaluation of these lesions in living mice. Therefore, the aim of this study was to investigate the role of (18)F-FDG PET in the Apc(Min) mouse model. Apc(Min) mice (n = 8) fed a purified diet were imaged serially after injection of (18)F-FDG at age 9 and 12 wk using a small-animal PET scanner. Abdominal uptake of the tracer was quantified. After dissection, intestines were imaged separately, and intestinal tracer uptake was quantified. Tracer distribution was compared with results from microscopic examination regarding adenoma number and size. Thereafter, findings were validated serially in 20 Apc(Min) mice aged 6, 8, 10, and 12 wk that received standard chow to increase adenoma numbers. In vivo abdominal (18)F-FDG uptake was correlated with microscopy results. Microscopic examination showed that the mice developed 25-35 intestinal adenomas at age 12 wk. Ex vivo (18)F-FDG PET of the dissected intestines visualized all large adenomas and most small adenomas. Ex vivo total intestinal (18)F-FDG uptake correlated with in vivo total abdominal uptake and with the number of large adenomas at age 9 and 12 wk. At 12 wk, there was a clear correlation between in vivo abdominal tracer uptake and the number of large adenomas but not the total number of lesions. Intestinal adenomas in Apc(Min) mice are metabolically active lesions that take up (18)F-FDG. Abdominal (18)F-FDG uptake at age 12 wk serves as a readout modality for large intestinal adenomas.

J Nucl Med. 2011 Mar;52(3):470-7. Epub 2011 Feb 14.

### **In vitro and in vivo evaluation of <sup>64</sup>Cu-labeled SarAr-bombesin analogs in gastrin-releasing peptide receptor-expressing prostate cancer.**

Lears KA, Ferdani R, Liang K, Zheleznyak A, Andrews R, Sherman CD, Achilefu S, Anderson CJ, Rogers BE.

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Bombesin is a 14-amino-acid amphibian peptide that binds with high affinity to the gastrin-releasing peptide receptor (GRPR), which is overexpressed on a variety of solid tumors. It has been demonstrated that bombesin analogs can be radiolabeled with a variety of radiometals for potential diagnosis and treatment of GRPR-positive tumors. In this regard, several studies have used different chelators conjugated to the 8 C-terminal amino acids of bombesin(7-14) for radiolabeling with (<sup>64</sup>Cu). These analogs have demonstrated GRPR-specific small-animal PET of tumors but have various advantages and disadvantages. The objective of this study was to conjugate the previously described (1-N-(4-aminobenzyl)-3,6,10,13,16,19-hexaazabicyclo[6.6.6]-eicosane-1,8-diamine) (SarAr) chelator to bombesin(7-14), radiolabel the conjugate with (<sup>64</sup>Cu), and evaluate in vitro and in vivo. SarAr was synthesized as previously published and conjugated to bombesin(7-14) by solid-phase peptide synthesis using standard Fmoc chemistry. Succinic acid (SA), 8-aminooctanoic acid (Aoc), and Gly-Ser-Gly (GSG) were used as linkers between SarAr and bombesin(7-14) to yield the resulting SarAr-SA-Aoc-bombesin(7-14) and SarAr-SA-Aoc-GSG-bombesin(7-14) peptides. The unlabeled peptides were evaluated in a competitive binding assay using PC-3 prostate cancer cells and (<sup>125</sup>I)-Tyr(4)-bombesin to determine the inhibitory concentration of 50%. The peptides were radiolabeled with (<sup>64</sup>Cu) and evaluated for internalization into PC-3 cells in vitro and for in vivo tumor uptake in mice bearing PC-3 xenografts using biodistribution and small-animal PET/CT studies. The competitive binding assay demonstrated that both SarAr-SA-Aoc-bombesin(7-14) and SarAr-SA-Aoc-GSG-bombesin(7-14) bound with high affinity to GRPR with an inhibitory concentration of 50% of 3.5 and 4.5 nM, respectively. Both peptides were radiolabeled with (<sup>64</sup>Cu) at room temperature without further purification and demonstrated similar internalization into PC-3 cells. In vivo, the radiolabeled peptides demonstrated tumor-specific uptake (13.0 and 8.5 percentage injected dose per gram for (<sup>64</sup>Cu)-SarAr-SA-Aoc-bombesin(7-14) and (<sup>64</sup>Cu)-SarAr-SA-Aoc-GSG-bombesin(7-14), respectively, at 1 h) and imaging that was comparable to, or better than, that of the previously reported (<sup>64</sup>Cu)-labeled bombesin analogs. The (<sup>64</sup>Cu)-SarAr-SA-Aoc-GSG-bombesin(7-14) had more rapid blood clearance and lower tumor and normal-tissue uptake than (<sup>64</sup>Cu)-SarAr-SA-Aoc-bombesin(7-14), resulting in similar tumor-to-blood ratios for each analog (15.1 vs. 11.3 for (<sup>64</sup>Cu)-SarAr-SA-Aoc-bombesin(7-14) and (<sup>64</sup>Cu)-SarAr-SA-Aoc-GSG-bombesin(7-14), respectively, at 1 h). These studies demonstrate that (<sup>64</sup>Cu)-SarAr-SA-Aoc-bombesin(7-14) and (<sup>64</sup>Cu)-SarAr-SA-Aoc-GSG-bombesin(7-14) bound with high affinity to GRPR-expressing cells and that these peptides can be used for PET of GRPR-expressing prostate cancer.

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Cancer Treat Rev. 2011 Aug;37(5):331-43. Epub 2011 Feb 12.

### **Therapeutic implications of molecular imaging with PET in the combined modality treatment of lung cancer.**

van Loon J, van Baardwijk A, Boersma L, Ollers M, Lambin P, De Ruyscher D.

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Molecular imaging with PET, and certainly integrated PET-CT, combining functional and anatomical imaging, has many potential advantages over anatomical imaging alone in the combined modality treatment of lung cancer. The aim of the current article is to review the available evidence regarding PET with FDG and other tracers in the combined modality treatment of locally advanced lung cancer. The following topics are addressed: tumor volume definition, outcome prediction and the added value of PET after therapy, and finally its clinical implications and future perspectives. The additional value of FDG-PET in defining the primary tumor volume has been established, mainly in regions with atelectasis or post-treatment effects. Selective nodal irradiation (SNI) of FDG-PET positive nodal stations is the preferred treatment in NSCLC, being safe and leading to decreased normal tissue exposure, providing opportunities for dose escalation. First results in SCLC show similar results. FDG-uptake on the pre-treatment PET scan is of prognostic value. Data on the value of pre-treatment FDG-uptake to predict response to combined modality treatment are conflicting, but the limited data regarding early metabolic response during treatment do show predictive value. The FDG response after radical treatment is of prognostic significance. FDG-PET in the follow-up has potential benefit in NSCLC, while data in SCLC are lacking. Radiotherapy boosting of radioresistant areas identified with FDG-PET is subject of current research. Tracers other than (<sup>18</sup>F)FDG are promising for treatment response assessment and the visualization of intra-tumor heterogeneity, but more research is needed before they can be clinically implemented.

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Nucl Med Biol. 2011 Feb;38(2):295-300. Epub 2010 Oct 27.

### **PET imaging of blood flow and glucose metabolism in localized musculoskeletal tumors of the extremities.**

Lindholm P, Sutinen E, Oikonen V, Mattila K, Tarkkanen M, Kallajoki M, Aro H, Böhling T, Kivioja A, Elomaa I, Minn H.

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## **PET-Oncology**

Little is known about blood flow in sarcomas. Our purpose was to study glucose metabolism and blood flow in untreated localized musculoskeletal tumors of the extremities using [(18)F]fluorodeoxyglucose (FDG), oxygen-15 labeled water ([15O]H<sub>2</sub>O) and positron emission tomography (PET). Six patients with high-grade osteosarcoma (OS), two with soft-tissue sarcoma (STS) and one with aneurysmal bone cyst had PET studies with [15O]H<sub>2</sub>O and FDG. Arterial blood sampling and autoradiography calculation method were used to define blood flow as milliliters per 100 g times minutes. Tumor FDG uptake was measured as standardized uptake values (SUVs) and regional metabolic rates for FDG (rMRFDG). Two patients also had FDG PET studies during (one patient) and after (two patients) preoperative chemotherapy. All patients underwent dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI). The PET findings were compared with the clinical follow-up data and results of DCE-MRI. Blood flow in bone tumors was 31.7-75.2 ml/(100 g×min) and in STS 9.0-45.9 ml/(100 g×min). [(18)F]-Fluorodeoxyglucose uptake and rMRFDG in untreated bone tumors were 5.4-18.4 and 10.9-57.4 μmol/100 g/min, respectively. [(18)F]-Fluorodeoxyglucose uptake and rMRFDG in STS were 2.6-11.5 and 5.6-32.2 μmol/100 g/min, respectively. Four of five sarcomas with SUV>9.0 have already relapsed. High blood flow in untreated OS was related to long overall survival, while the predictive power of glucose metabolism was less apparent. Good histopathological response to therapy was not associated with long survival. Measurement of blood flow in musculoskeletal tumors appears to be feasible by PET and [(15)O]H<sub>2</sub>O. The influence of tumor blood flow and glucose metabolism on the final outcome in sarcoma is variable and needs further research.

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Int J Radiat Oncol Biol Phys. 2011 Feb 5. [Epub ahead of print]

### **3'-deoxy-3'-[(18)F]fluorothymidine PET Quantification of Bone Marrow Response to Radiation Dose.**

McGuire SM, Menda Y, Boles Ponto LL, Gross B, Buatti J, Bayouth JE.

Department of Radiation Oncology, University of Iowa Hospitals and Clinics, Iowa City, Iowa 52242.

The purpose of this study was to quantify the relationship of bone marrow response to radiation dose, using 3'-deoxy-3'-[(18)F]fluorothymidine ([18F]FLT)-labeled uptake quantified in positron-emission tomography (PET) scans. Pre- and post-Week 1 treatment [(18)F]FLT PET images were registered to the CT images used to create the radiation treatment plan. Changes in [(18)F]FLT uptake values were measured using profile data of standardized uptake values (SUVs) and doses along the vertebral bodies located at a field border where a range of radiation doses were present for 10 patients. Data from the profile measurements were grouped into 1 Gy dose bins from 1 to 9 Gy to compare SUV changes for all patients. Additionally, the maximum pretreatment, the post-Week 1 treatment, and the dose values located within the C6-T7 vertebrae that straddled the field edge were measured for all patients. Both the profile and the individual vertebral data showed a strong correlation between SUV change and radiation dose. Relative differences in SUVs between bins >1 Gy and <7 Gy were statistically significant ( $p < 0.01$ , two-sample t test). The reduction in SUV was approximately linear until it reached a reduction threshold of 75%-80% in SUV for doses greater than 6 Gy/week for both the dose-binned data and the vertebral maximum SUVs. The change in SUV observed in head and neck cancer patients treated with chemoradiation shows the potential for using [(18)F]FLT PET images for identifying active bone marrow and monitoring changes due to radiation dose. Additionally, the change in [(18)F]FLT uptake observed in bone marrow for different weekly doses suggests potential dose thresholds for reducing bone marrow toxicity.

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Int J Radiat Oncol Biol Phys. 2011 Feb 5. [Epub ahead of print]

### **The Role of Pretreatment FDG-PET in Nasopharyngeal Carcinoma Treated with Intensity-Modulated Radiotherapy.**

Liu WS, Wu MF, Tseng HC, Liu JT, Weng JH, Li YC, Lee JK.

School of Medicine, Chung Shan Medical University and Department of Radiation Oncology, Chung Shan Medical University Hospital, Taichung, Taiwan.

Pretreatment with 2- [(18)F] fluorodeoxyglucose positron emission tomography ((18)F-FDG-PET) was evaluated as a predictor of local failure-free survival (LFFS), disease-free survival (DFS), and overall survival (OS) in patients with nonkeratinizing nasopharyngeal carcinoma (NPC) treated with intensity-modulated radiation therapy (IMRT) alone or concurrently with chemotherapy (CCRT). Seventy-five M0 NPC patients who received FDG-PET before treatment were analyzed. The primary tumor FDG uptake was measured as the maximum standardized uptake value (SUV<sub>max</sub>). The LFFS, DFS, and OS were calculated by the Kaplan-Meier method, and the differences were evaluated on log-rank test. The prognostic significance was assessed by univariate and multivariate analyses. Eighteen patients received IMRT alone and 57 received CCRT. The mean SUV<sub>max</sub> was significantly higher in 12 patients with locoregional or distant failure than in those without failure ( $p < 0.001$ ). On multivariate analysis, the SUV<sub>max</sub> was the only significant variable for 5-year LFFS ( $p = 0.017$ ) and DFS ( $p = 0.000$ ) but not for OS ( $p = 0.065$ ). SUV<sub>max</sub> is a potential independent prognostic predictor of clinical outcomes in patients with nasopharyngeal carcinoma treated with IMRT alone or with CCRT. A high (18)F-FDG uptake (SUV<sub>max</sub> >5) indicates poor outcome in patients with NPC.

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BMC Cancer. 2011 Feb 9;11:63.

### **In vivo identification and specificity assessment of mRNA markers of hypoxia in human and mouse tumors.**

Busk M, Toustrup K, Sørensen BS, Alsner J, Horsman MR, Jakobsen S, Overgaard J.

## **PET-Oncology**

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Tumor hypoxia is linked to poor prognosis, but identification and quantification of tissue hypoxia remains a challenge. The hypoxia-specificity of HIF-1 $\alpha$  target genes in vivo has been questioned due to the confounding influence of other microenvironmental abnormalities known to affect gene expression (e.g., low pH). Here we describe a new technique that by exploiting intratumoral oxygenation heterogeneity allows us to identify and objectively rank the most robust mRNA hypoxia biomarkers. Mice carrying human (FaDudd) or murine (SCCVII) tumors were injected with the PET hypoxia tracer FAZA. Four hours post-injection tumors were removed, frozen, and crushed into milligram-sized fragments, which were transferred individually to pre-weighed tubes containing RNAlater and then weighed. For each fragment radioactivity per tissue mass and expression patterns of selected mRNA biomarkers were analyzed and compared. In both tumour models, fragmentation into pieces weighing 10 to 60 mg resulted in tissue fragments with highly variable relative content of hypoxic cells as evidenced by an up to 13-fold variation in FAZA radioactivity per mass of tissue. Linear regression analysis comparing FAZA retention with patterns of gene expression in individual tissue fragments revealed that CA9, GLUT1 and LOX mRNA levels were equally and strongly correlated to hypoxic extent in FaDudd. The same link between hypoxia and gene expression profile was observed for CA9 and GLUT1, but not LOX, in SCCVII tumors. Apparent in vivo hypoxia-specificity for other putative molecular markers of tissue hypoxia was considerably weaker. The portrayed technique allows multiple pairwise measurements of mRNA transcript levels and extent of hypoxia in individual tumors at a smallest possible volumetric scale which (by limiting averaging effects inherent to whole-tumor analysis) strengthen the conclusiveness on true hypoxia-specificity of candidate genes while limiting the required number of tumors. Among tested genes, our study identified CA9, GLUT1 and possibly LOX as highly specific biomarkers of tumor hypoxia in vivo.

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Int J Radiat Oncol Biol Phys. 2011 Sep 1;81(1):277-83. Epub 2011 Feb 6.

### **Simultaneous (68)Ga-DOTATOC-PET/MRI for IMRT Treatment Planning for Meningioma: First Experience.**

Thorwarth D, Henke G, Müller AC, Reimold M, Beyer T, Boss A, Kolb A, Pichler B, Pfannenberg C.

Section of Biomedical Physics, University Hospital for Radiation Oncology, Eberhard-Karls-Universität Tübingen, Tübingen, Germany.

To evaluate intensity-modulated radiotherapy (IMRT) treatment planning based on simultaneous positron-emission tomography and magnetic resonance imaging (PET/MRI) of meningioma. A meningioma patient was examined prior to radiotherapy with dedicated planning computed tomography (CT), MRI, PET/CT with gallium-68-labeled DOTATOC ((68)Ga-DOTATOC), and simultaneous (68)Ga-DOTATOC-PET/MRI. The first gross target volume (GTV) was defined based on a combination of separate MR and (68)Ga-DOTATOC-PET/CT imaging (GTV(PET/CT+MR)). Then, the simultaneous PET/MR images were used to delineate a second GTV (GTV(PET/MR)) by following exactly the same delineation strategy. After an isotropic expansion of those volumes by a 4-mm safety margin, the resulting planning target volumes (PTVs) were compared by calculating the intersection volume and the relative complements. A cross-evaluation of IMRT plans was performed, where the treatment plan created for the PTV(PET/CT+MR) was applied to the PET/MR-based PTV(PET/MR). Generally, target volumes for IMRT treatment planning did not differ between MRI plus (68)Ga-DOTATOC-PET/CT and simultaneous PET/MR imaging. Only in certain regions of the GTV were differences observed. The overall volume of the PET/MR-based PTV was approximately the same as that obtained from PET/CT data. A small region of infiltrative tumor growth next to the main tumor mass was better visualized with combined PET/MR due to smaller PET voxel sizes and improved recovery. An IMRT treatment plan was optimized for the PTV(PET/CT+MR). The evaluation of this plan with respect to the PTV(PET/MR) showed parts of the target volume that would not have received the full radiation dose after delineation of the tumor, based on simultaneous PET/MR. This case showed that differences in target volumes delineated on the basis of separate MR and PET/CT and simultaneous PET/MR may be observed that can have significant consequences for an effectively applied radiotherapy treatment plan.

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Int J Radiat Oncol Biol Phys. 2011 Feb 5. [Epub ahead of print]

### **Comparison of Physical Examination and Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography 4-6 Months After Radiotherapy to Assess Residual Head-and-Neck Cancer.**

Zundel MT, Michel MA, Schultz CJ, Maheshwari M, Wong SJ, Campbell BH, Massey BL, Blumin J, Wilson JF, Wang D.

Department of Radiation Oncology, Medical College of Wisconsin, Milwaukee, WI.

To retrospectively compare fluorodeoxyglucose positron emission tomography/computed tomography (PET/CT) and physical examination 4-6 months after radiotherapy for assessing residual head-and-neck cancer (HNC).

From July 2002 through March 2006, 52 HNC patients underwent definitive radiotherapy or chemoradiotherapy. Categorical assessments of residual tumor by PET/CT and physical examination 4-6 months after therapy were correlated and compared with clinical outcomes. Pretreatment data, including tumor stage and primary site standardized uptake value, were also gathered retrospectively and correlated with clinical outcomes. Median follow-up time was 58 months. Twenty-one patients had either locoregionally "positive" (17 of 21) or "equivocal" (4 of 21) PET/CT scans, whereas 31 patients had locoregionally negative scans. Four patients failed treatment and had biopsy-confirmed residual or recurrent local disease. All patients, including patients with locally suspicious scans or examinations who refused biopsies, were followed clinically for a minimum of 29 months after therapy, with no other cases of treatment failure detected during this time. No patient had residual nodal disease after therapy. Sensitivities of PET/CT vs. physical examination for early detection of treatment failure were 100% vs. 50%, whereas the specificities of the two modalities were 64.6% vs. 89.6%, respectively. Higher initial T stage and American Joint Commission on Cancer stage correlated with increased incidence of positive/equivocal PET/CT results and treatment failure. Maximal standardized uptake value was not predictive of any clinical outcome. A negative result on PET/CT obtained 4-6 months after radiotherapy is highly sensitive and correlates with

## **PET-Oncology**

successful locoregional control. Patients with negative scans may reasonably be spared invasive diagnostic procedures, such as biopsy and neck dissection, unless recurrent disease is suspected on clinical grounds. Close follow-up is prudent for HNC patients with abnormal findings on posttherapy PET/CT scan.

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Radiother Oncol. 2011 Feb;98(2):270-6. Epub 2011 Feb 3.

### **FDG-PET provides the best correlation with the tumor specimen compared to MRI and CT in rectal cancer.**

Buijsen J, van den Bogaard J, Janssen MH, Bakers FC, Engelsman S, Öllers M, Beets-Tan RG, Nap M, Beets GL, Lambin P, Lammering G.

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To compare CT-, MR- and PET-CT based tumor length measurements in rectal cancer with pathology. Twenty-six rectal cancer patients underwent both MR and PET-CT imaging followed by short-course radiotherapy (RT 5×5 Gy) and surgery within 3 days after RT. Tumor length was measured manually and independently by 2 observers on CT, MR and PET. PET-based tumor length measurements were also generated automatically using the signal-to-background-ratio (SBR) method. All measurements were correlated with the tumor length on the pathological specimen. CT-based measurements did not show a valuable correlation with pathology. MR-based measurements correlated only weakly, but still significantly (Pearson correlation=0.55 resp. 0.57;  $p<0.001$ ). Manual PET measurements reached a good correlation with pathology, but less strong (Pearson correlation 0.72 and 0.76 for the two different observers) than automatic PET-CT based measurements, which provided the best correlation with pathology (Pearson correlation of 0.91 ( $p<0.001$ )). Bland-Altman analysis demonstrated in general an overestimation of the tumor diameter using manual measurements, while the agreement of automatic contours and pathology was within acceptable ranges. A direct comparison of the different modalities revealed a significant better precision for PET-based auto-contours as compared to all other measurements. Automatically generated PET-CT based contours show the best correlation with the surgical specimen and thus provide a useful and powerful tool to accurately determine the largest tumor dimension in rectal cancer. This could be used as a quick and reliable tool for target delineation in radiotherapy. However, a 3D volume analysis is needed to confirm these results

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Radiother Oncol. 2011 Mar;98(3):357-9. Epub 2011 Feb 3.

### **18F-FLT-PET for detection of rectal cancer.**

Muijs CT, Beukema JC, Widder J, van den Bergh AC, Havenga K, Pruim J, Langendijk JA.

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This pilot study was undertaken to examine the ability of (18)F-3'-fluoro-3'-deoxy-1-thymidine positron emission tomography ((18)F-FLT-PET) to detect rectal cancer, to identify pathologic lymph nodes and to determine the accuracy of tumour length estimation in comparison with computer tomography (CT). Nine patients with biopsy proven rectal cancer underwent CT and (18)F-FLT-PET scanning prior to short-term pre-operative radiotherapy (5×5Gy). Within 10 days after the start of radiotherapy a surgical resection was performed. Tumour lengths and regional lymph node visualisation on both imaging modalities were compared with pathology findings. 11 tumours were visible on CT. (18)F-FLT-PET visualised 7 out of 9 tumours (78%). The pathology-based tumours lengths correlated better with CT as compared to FLT-PET( $r=0.91$ ,  $p<0.01$ ). (18)F-FLT-PET was not able to visualise pathologic lymph nodes. However, CT identified all patients with pathologic lymph nodes. Primary rectal cancer can be visualised by (18)F-FLT-PET in the majority of cases but not in all. However, (18)F-FLT-PET was not able to identify pathologic lymph nodes. Therefore, we conclude that (18)F-FLT-PET has limited value for the detection of pathologic lymph nodes and tumour delineation in rectal cancer.

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Eur Urol. 2011 Jul;60(1):125-30. Epub 2011 Jan 18.

### **Prospective evaluation of 11C-choline positron emission tomography/computed tomography and diffusion-weighted magnetic resonance imaging for the nodal staging of prostate cancer with a high risk of lymph node metastases.**

Budiharto T, Joniau S, Lerut E, Van den Bergh L, Mottaghy F, Deroose CM, Oyen R, Ameye F, Bogaerts K, Haustermans K, Van Poppel H.

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Contrast-enhanced computed tomography (CT) and magnetic resonance (MR) imaging for lymph node (LN) staging of prostate cancer (PCa) are largely inadequate. Our aim was to assess prospectively the sensitivity, specificity, and positive and negative predictive values for the LN staging by (11)C-choline positron emission tomography (PET)-CT and MR diffusion-weighted imaging (DWI) of the pelvis before retropubic radical prostatectomy (RRP) with extended pelvic LN dissection (PLND). From February 2008 to August 2009, 36 patients with histologically proven PCa and no pelvic LN involvement on contrast-enhanced CT with a risk  $\geq 10\%$  but  $\leq 35\%$  at LN metastasis according to the Partin tables were enrolled in this study. Patients preoperatively underwent (11)C-choline PET-CT and DWI. Subsequently all patients underwent a wide RRP and an extended PLND. Sensitivity, specificity, and positive and negative predictive values (PPV and NPV) for LN status of (11)C-choline PET-CT

## **PET-Oncology**

and DWI were calculated with the final histopathology of the LNs as comparator. Seventeen patients (47%) had a pN1 stage, and 38 positive LNs were identified. On a LN region-based analysis, sensitivity, specificity, PPV, NPV, and the number of correctly recognised cases at (11)C-choline PET-CT were 9.4%, 99.7%, 75.0%, 91.0%, and 7.9%, respectively, and at DWI these numbers were 18.8%, 97.6%, 46.2%, 91.7%, and 15.8%, respectively. Twelve LN regions containing macrometastases, of which 2 had capsular penetration, were not detected by (11)C-choline PET-CT; 11 LNs, of which 2 had capsular penetration, were not detected by DWI. This is a small study with 36 patients, but we intend to recruit more patients. From this prospective histopathology-based evaluation of (11)C-choline PET-CT and DWI for LN staging in high-risk PCa patients, it is concluded that these techniques cannot be recommended at present to detect occult LN metastases before initial treatment.

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Clin Nucl Med. 2011 Mar;36(3):248-51.

### **A rare case of pemphigus vegetans mimicking malignancy on F-18 FDG PET/CT.**

D'souza MM, D'souza PV, Jaimini A, Sharma R, Tripathi M, Singh D, Mondal A.

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A 42-year-old man with a history of chronic smoking and alcoholism was suspected to harbor a malignancy involving the perioral region and the scalp. He underwent an F-18 FDG PET/CT scan which revealed abnormal F-18 FDG accumulation in the oral mucosa and lips, extending to the nose, scalp, and bilateral cervical lymph nodes. Further work-up ultimately revealed the lesions to be secondary to pemphigus vegetans. Pemphigus vegetans is a rare variant of pemphigus vulgaris, an autoimmune bullous cutaneous disorder and involves mainly the flexural regions of the body. Unlike pemphigus vulgaris, lesions of pemphigus vegetans present as heaped up, eroded, and ulcerative plaques in the intertriginous regions of the body. Occasional lesions may be present on scalp and elsewhere in the Hallopeau variant of the disease. The use of F-18 FDG PET in the field of oncology is rapidly evolving; however, it is not tumor specific. The integration of CT into PET has increased the specificity of this modality. Nevertheless, there are many physiologic and benign conditions that may result in high accumulation of FDG, and may mimic malignancy. Familiarity with F-18 FDG-avid nonmalignant lesions may extend the use of F-18 FDG PET imaging beyond the field of oncology. To the best of our knowledge, this is the first description of PET/CT findings in pemphigus vegetans.

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Clin Nucl Med. 2011 Mar;36(3):192-8.

### **C11-acetate and F-18 FDG PET for men with prostate cancer bone metastases: relative findings and response to therapy.**

Yu EY, Muzi M, Hackenbracht JA, Rezvani BB, Link JM, Montgomery RB, Higano CS, Eary JF, Mankoff DA.

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This study tested the feasibility of C11-acetate (acetate) positron emission tomography (PET) imaging to assess response to therapy in men with bone metastatic prostate cancer and compared results for disease detection and response evaluation with F-18 fluorodeoxyglucose (FDG) PET. Men with  $\geq 3$  prostate cancer bone metastases identified by Tc-99m methylene diphosphonate (MDP) bone scintigraphy and/or computed tomography were enrolled in a prospective study of serial acetate and FDG PET imaging. Patients were imaged before and 6 to 12 weeks after initial androgen deprivation therapy for new metastatic prostate cancer or first-line chemotherapy with docetaxel for castration-resistant prostate cancer. Qualitative assessment and changes in the tumor:normal uptake ratio were used to assess response by both acetate and FDG PET. In addition, the detection of bone metastases pretherapy was compared for acetate and FDG PET. A total of 8 patients with documented bone metastases were imaged, of which 6 were imaged both pre- and post-therapy. Acetate PET detected bone metastases in all 8 patients, whereas FDG PET detected lesions in 6 of the 7 imaged patients. Acetate PET generally detected more metastases with a higher tumor:normal uptake ratio. Qualitative and quantitative assessments of post-treatment response correlated with composite clinical designations of response, stable disease, or progression in 6 of 6 and 5 of 6 by acetate and 4 of 5 and 3 of 5 by FDG PET, respectively. In this pilot study, results indicate that acetate PET holds promise for response assessment of prostate cancer bone metastases and is complementary to FDG PET in bone metastasis detection.

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Phys Med Biol. 2011 Mar 7;56(5):1281-98. Epub 2011 Feb 1.

### **Implementation and workflow for PET monitoring of therapeutic ion irradiation: a comparison of in-beam, in-room, and off-line techniques.**

Shakirin G, Braess H, Fiedler F, Kunath D, Laube K, Parodi K, Prieznitz M, Enghardt W.

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An independent assessment of the dose delivery in ion therapy can be performed using positron emission tomography (PET). For that a distribution of positron emitters which appear as the result of interaction between ions of the therapeutic beam and the irradiated tissue is measured during or after the irradiation. Three concepts for PET monitoring implemented in various therapy facilities are considered in this

## **PET-Oncology**

paper. The in-beam PET concept relies on the PET measurement performed simultaneously to the irradiation by means of a PET scanner which is completely integrated into the irradiation site. The in-room PET concept allows measurement immediately after irradiation by a standalone PET scanner which is installed very close to the irradiation site. In the off-line PET scenario the measurement is performed by means of a standalone PET/CT scanner 10-30 min after the irradiation. These three concepts were evaluated according to image quality criteria, integration costs, and their influence onto the workflow of radiotherapy. In-beam PET showed the best performance. However, the integration costs were estimated as very high for this modality. Moreover, the performance of in-beam PET depends heavily on type and duty cycle of the accelerator. The in-room PET is proposed for planned therapy facilities as a good compromise between the quality of measured data and integration efforts. For facilities which are close to the nuclear medicine departments off-line PET can be suggested under several circumstances.

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Rev Med Chil. 2010 Nov;138(11):1441-50. Epub 2011 Jan 27.

[Article in Spanish]

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Metabolic imaging studies are an integral part of oncology practice, particularly with 18 fluorodeoxyglucose PET scanning. Lung cancer is one of the primary indications of a PET/CT study. It is helpful in staging, evaluating treatment response and follow-up of these patients. The recent development of PET/CT, which incorporates a multislice CT scanner to the PET detector, improves results, combining metabolic information from the PET with anatomic data obtained with CT. It reduces false positive results from PET in cases of inflammatory disease such as pneumonia or Drug reactions, which are frequent in this group of patients. These conditions are easily recognized by CT. It also improves the detection of primary tumors, when they are adjacent to atelectasis or desmoplastic reactions. PET-CT studies are able to characterize the metabolism of mediastinal and hilar lymph nodes, thus obviating the need for further related imaging studies or invasive procedures. In the assessment of metastatic disease, it allows a whole body analysis in only one study, with high predictive value and optimal cost-benefit relation. The detection of a second primary tumor is not infrequent in these patients. PET-CT is useful in the evaluation of treatment response after chemotherapy, and for the long term follow-up.

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Eur J Surg Oncol. 2011 Mar;37(3):225-32. Epub 2011 Jan 31.

### **The value of pre operative S-100B and SUV in clinically stage III melanoma patients undergoing therapeutic lymph node dissection.**

Kruijff S, Bastiaannet E, Speijers MJ, Kobold AC, Brouwers AH, Hoekstra HJ.

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High preoperative serum S-100B values and Standardized Uptake Values (SUV) of Fluorodeoxyglucose (FDG) in PET for clinically stage III melanoma patients could be indicators of recurrence after surgical treatment. Aim was to assess the correlation and the prognostic value of these markers. All melanoma patients with palpable nodal metastases, without distant metastases, were included from February 2004 to December 2007. Preoperative SUV and S-100B was determined. The correlation between SUV and S-100B and their relations with DFS and DSS were calculated by Cox Proportional Hazard Analysis. 62 Patients, median age 56.9 years, were included in the study. An elevated S-100B was found in 31 patients (50%) and elevated SUV in 24 patients (38.7%). No relation was found between S-100B and SUV. DFS was reduced (31.1%) for patients with an elevated S-100B (HR = 3.1; p = 0.02) in comparison to a normal S-100B (44.6%). The DFS was 42.0% for patients with a SUV below the cut-off point and 29.0% for patients with an elevated SUV (HR = 1.1; p = 0.8). DSS was 60.7% in a normal S-100B and 44.7% for patients with an elevated S-100B (HR = 2.2; p = 0.07). DSS was 59.1% for patients with a normal SUV and 43.5% for patients with elevated SUV (HR = 1.1; p = 0.8). S-100B and SUV in stage III melanoma are not correlated and each have different associations with various histopathological factors. S-100B, in contrast with SUV, is associated with nodal tumor load, and when elevated, predicts a shorter DFS. Preoperative serum S-100B and Fluorodeoxyglucose (FDG) Standardized Uptake Value (SUV) in clinically stage III melanoma are not correlated. S-100B is a strong predictor for Disease Free Survival (DFS) in stage III melanoma.

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Int J Radiat Oncol Biol Phys. 2011 Jan 27. [Epub ahead of print]

### **Analysis of Pretreatment FDG-PET SUV Parameters in Head-and-Neck Cancer: Tumor SUV(mean) has Superior Prognostic Value.**

Higgins KA, Hoang JK, Roach MC, Chino J, Yoo DS, Turkington TG, Brizel DM.

Department of Radiation Oncology, Duke University Medical Center, Durham, NC.

To evaluate the prognostic significance of different descriptive parameters in head-and-neck cancer patients undergoing pretreatment [<sup>18</sup>F]-fluoro-D-glucose-positron emission tomography (FDG-PET) imaging. Head-and-neck cancer patients who underwent FDG-PET before a course of curative intent radiotherapy were retrospectively analyzed. FDG-PET imaging parameters included maximum (SUV(max)), and mean (SUV(mean)) standard uptake values, and total lesion glycolysis (TLG). Tumors and lymph nodes were defined on co-registered axial computed tomography (CT) slices. SUV(max) and SUV(mean) were measured within these anatomic regions. The relationships between pretreatment SUV(max), SUV(mean), and TLG for the primary site and lymph nodes were assessed using a univariate analysis for disease-free survival (DFS), locoregional control (LRC), and distant metastasis-free survival (DMFS). Kaplan-Meier survival curves were generated and compared via

## **PET-Oncology**

the log-rank method. SUV data were analyzed as continuous variables. A total of 88 patients was assessed. Two-year OS, LRC, DMFS, and DFS for the entire cohort were 85%, 78%, 81%, and 70%, respectively. Median SUV(max) for the primary tumor and lymph nodes was 15.4 and 12.2, respectively. Median SUV(mean) for the primary tumor and lymph nodes was 7 and 5.2, respectively. Median TLG was 770. Increasing pretreatment SUV(mean) of the primary tumor was associated with decreased disease-free survival ( $p = 0.01$ ). Neither SUV(max) in the primary tumor or lymph nodes nor TLG was prognostic for any of the clinical endpoints. Patients with pretreatment tumor SUV(mean) that exceeded the median value (7) of the cohort demonstrated inferior 2-year DFS relative to patients with  $SUV(mean) \leq$  the median value of the cohort, 58% vs. 82%, respectively,  $p = 0.03$ . Increasing SUV(mean) in the primary tumor was associated with inferior DFS. Although not routinely reported, pretreatment SUV(mean) may be a useful prognostic FDG-PET parameter and should be further evaluated prospectively.

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Eur Radiol. 2011 Jun;21(6):1277-85. Epub 2011 Jan 28.

### **PET/CT without capacity limitations: a Danish experience from a European perspective.**

Højilund-Carlsen PF, Gerke O, Vilstrup MH, Nielsen AL, Thomassen A, Hess S, Højilund-Carlsen M, Vach W, Petersen H.

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We report the 3-year clinical experience of a large new Danish PET/CT centre without capacity limitations in relation to national and European developments.

The use of PET/CT in cancer was registered from early 2006 to early 2009 to judge the impact on patient management and to compare it with national and European trends. 6056 PET/CT examinations were performed in 4327 patients. Activity increased by 86 examinations per month compared with the same month the year before. Referrals came primarily from oncology (23.0%), haematology (21.6%), surgery (12.6%), internal medicine (12.7%) and gynaecology (5.5%). Referral indications were diagnosis (31.3%), staging (22.3%), recurrence detection (21.2%), response evaluation (17.0%) and other (8.2%). Response from nearly 60% of users showed that PET/CT caused a change in diagnosis and/or staging and/or treatment plan in 36.0% of cases. During the study period, there was a steep increase in the national use of FDG and in the European use of PET/CT. We recorded a constantly increasing use of PET/CT that caused a change in diagnosis and/or staging and/or treatment plan in 36.0% of cases. In line with national and European trends this may suggest a shift in favour of functional rather than anatomical imaging.

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Nat Rev Clin Oncol. 2011 Jan 25;8(4):233-42.

### **PET-CT for radiotherapy treatment planning and response monitoring in solid tumors.**

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PET imaging has evolved as an indispensable tool for staging in oncology. Multiple quantitative measurements can be performed, enabling the effects of treatment to be monitored before changes are detectable with the use of conventional imaging modalities. PET tracers are available to visualize and quantify the most important mechanisms of resistance to radiotherapy and chemoradiotherapy. Reproducibility of these tracers depends on the particular tracer and the underlying biology of the process that is being investigated. PET enables clinicians to select patients for intensified treatment on the basis of resistance mechanisms taking place at the molecular level. From translational studies and randomized trials, it has become clear that appropriate patient selection can prevent unnecessary rejection of various treatment options through the observation of individual patients rather than only looking at the results of a large study population.

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Phys Med Biol. 2011 Feb 21;56(4):1063-82. Epub 2011 Jan 25.

### **Monte Carlo patient study on the comparison of prompt gamma and PET imaging for range verification in proton therapy.**

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The purpose of this work was to compare the clinical adaptation of prompt gamma (PG) imaging and positron emission tomography (PET) as independent tools for non-invasive proton beam range verification and treatment validation. The PG range correlation and its differences with PET have been modeled for the first time in a highly heterogeneous tissue environment, using different field sizes and configurations. Four patients with different tumor locations (head and neck, prostate, spine and abdomen) were chosen to compare the site-specific behaviors of the PG and PET images, using both passive scattered and pencil beam fields. Accurate reconstruction of dose, PG and PET distributions was achieved by using the planning computed tomography (CT) image in a validated GEANT4-based Monte Carlo code capable of modeling the

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treatment nozzle and patient anatomy in detail. The physical and biological washout phenomenon and decay half-lives for PET activity for the most abundant isotopes such as (11)C, (15)O, (13)N, (30)P and (38)K were taken into account in the data analysis. The attenuation of the gamma signal after traversing the patient geometry and respective detection efficiencies were estimated for both methods to ensure proper comparison. The projected dose, PG and PET profiles along many lines in the beam direction were analyzed to investigate the correlation consistency across the beam width. For all subjects, the PG method showed on average approximately 10 times higher gamma production rates than the PET method before, and 60 to 80 times higher production after including the washout correction and acquisition time delay. This rate strongly depended on tissue density and elemental composition. For broad passive scattered fields, it was demonstrated that large differences exist between PG and PET signal falloff positions and the correlation with the dose distribution for different lines in the beam direction. These variations also depended on the treatment site and the particular subject. Thus, similar to PET, direct range verification with PG in passive scattering is not easily viable. However, upon development of an optimized 3D PG detector, indirect range verification by comparing measured and simulated PG distributions (currently being explored for the PET method) would be more beneficial because it can avoid the inherent biological challenges of the PET imaging. The improved correlation of PG and PET with dose when using pencil beams was evident. PG imaging was found to be potentially advantageous especially for small tumors in the presence of high tissue heterogeneities. Including the effects of detector acceptance and efficiency may hold PET superior in terms of the amplitude of the detected signal (depending on the future development of PG detection technology), but the ability to perform online measurements and avoid signal disintegration (due to washout) with PG are important factors that can outweigh the benefits of higher detection sensitivity.

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Adv Hematol. 2011;2011:271595. Epub 2010 Dec 22.

### **Prognostication and Risk-Adapted Therapy of Hodgkin's Lymphoma Using Positron Emission Tomography.**

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The use of (18)F-fluorodeoxyglucose positron emission tomography (FDG-PET) for response assessment in lymphoma is now widespread. Prognostic information obtained from PET performed after two to three cycles of chemotherapy may guide more individualized, risk-adapted therapeutic strategies. Progress in the risk stratification of Hodgkin's lymphoma through midtreatment PET is reviewed, with a focus on management implications in newly diagnosed and relapsed disease. How to tailor treatment on the basis of the interim PET result is not yet defined but is the subject of ongoing trials.

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Can J Surg. 2011 Apr;54(2):83-8.

### **Incidental thyroid "PETomas": clinical significance and novel description of the self-resolving variant of focal FDG-PET thyroid uptake.**

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Source

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Recent series of incidental thyroid activity on fluorodeoxyglucose positron emission tomography (FDG-PET) in patients evaluated for nonthyroidal malignancy, which we refer to as a "PEToma," have suggested that such lesions are associated with a significant incidence of primary thyroid cancer. We retrospectively reviewed 6457 FDG-PET scans performed on 4726 patients from May 2004 to March 2007. We reviewed the cases of patients whose PET or computed tomography (CT) radiology reports described PET uptake within the thyroid to identify incidence and malignant potential of PETomas and evaluate their clinical and histopathologic features. We found that 160 patients (3.4%) had incidental, abnormal FDG uptake in the thyroid gland, 103 of whom had focal uptake (the PEToma group). Of these patients, 50 (48%) underwent further investigations, including ultrasonography in 48, fine-needle aspiration cytology in 38 and computed tomography in 3. Ten patients underwent surgery, and papillary thyroid cancer was identified in 9. The remaining 53 patients with PETomas underwent no further investigation. Interestingly, 5 patients who had focal uptake within the thyroid showed either spontaneous resolution on repeat FDG-PET (self-resolving) or no focal lesion on subsequent ultrasonography (false-positive). The incidence of papillary thyroid cancer in the present series is similar to that in the literature. Although some patients will show self-resolving or false-positive focal thyroid uptake on FDG-PET, we believe that, if the patient's clinical status permits, the evaluation of patients with incidental thyroid PEToma should include ultrasonographic confirmation and fine-needle aspiration cytology.

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World J Gastroenterol. 2011 Jan 14;17(2):231-5.

### **18F-fluorodeoxyglucose positron emission tomography in the diagnosis of small pancreatic cancer.**

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To investigate the role of (18)F-fluorodeoxyglucose positron emission tomography (FDG-PET) in the diagnosis of small pancreatic cancer. This study involved 31 patients with proven invasive ductal cancer of the pancreas. The patients were divided into 3 groups according to the maximum diameter of the tumor: TS1 (maximum tumor size  $\leq 2.0$  cm), TS2 ( $> 2.0$  cm and  $\leq 4.0$  cm) or TS3-4 ( $> 4.0$  cm). The relationships between the TS and various diagnostic tools, including FDG-PET with dual time point evaluation, were analyzed. The tumors ranged from 1.3 to 11.0 cm in diameter. Thirty of the 31 patients (97%) had a positive FDG-PET study. There were 5 patients classified as TS1, 15 as TS2 and 11 as TS3-4. The sensitivity of FDG-PET, computed tomography (CT) and magnetic resonance imaging (MRI) were 100%, 40%, 0% in TS1, 93%, 93%, 89% in TS2 and 100%, 100%, 100% in TS3-4. The sensitivity of FDG-PET was significantly higher in comparison to CT and MRI in patients with TS1 ( $P < 0.032$ ). The mean standardized uptake values (SUVs) did not show a significant difference in relation to the TS (TS1:  $5.8 \pm 4.5$ , TS2:  $5.7 \pm 2.2$ , TS3-4:  $8.2 \pm 3.9$ ), respectively. All the TS1 tumors (from 13 to 20 mm) showed higher SUVs in FDG-PET with dual time point evaluation in the delayed phase compared with the early phase, which suggested the lesions were malignant. These results indicate that FDG-PET with dual time point evaluation is a useful modality for the detection of small pancreatic cancers with a diameter of less than 20 mm.

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Ann Saudi Med. 2011 Jan-Feb;31(1):3-13.

### **18F-FDG PET/CT imaging in oncology.**

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Accurate diagnosis and staging are essential for the optimal management of cancer patients. Positron emission tomography with 2-deoxy-2-[fluorine-18]fluoro-D-glucose integrated with computed tomography (18F-FDG PET/CT) has emerged as a powerful imaging tool for the detection of various cancers. The combined acquisition of PET and CT has synergistic advantages over PET or CT alone and minimizes their individual limitations. It is a valuable tool for staging and restaging of some tumors and has an important role in the detection of recurrence in asymptomatic patients with rising tumor marker levels and patients with negative or equivocal findings on conventional imaging techniques. It also allows for monitoring response to therapy and permitting timely modification of therapeutic regimens. In about 27% of the patients, the course of management is changed. This review provides guidance for oncologists/radiotherapists and clinical and surgical specialists on the use of 18F-FDG PET/CT in oncology.

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Head Neck. 2011 Jan 14. [Epub ahead of print]

### **Results of a prospective study of positron emission tomography-directed management of residual nodal abnormalities in node-positive head and neck cancer after definitive radiotherapy with or without systemic therapy.**

Porceddu SV, Pryor DI, Burmeister E, Burmeister BH, Poulsen MG, Foote MC, Panizza B, Coman S, McFarlane D, Coman W.

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The purpose of this study was to present our prospectively evaluated positron emission tomography (PET)-directed policy for managing the neck in node-positive head and neck squamous cell carcinoma (N+HNSCC) after definitive radiotherapy (RT) with or without concurrent systemic therapy. One hundred twelve consecutive patients who achieved a complete response at the primary site underwent a 12-week posttherapy nodal response assessment with PET and diagnostic CT. Patients with an equivocal PET underwent a repeat PET 4 to 6 weeks later. Patients with residual CT nodal abnormalities deemed PET-negative were uniformly observed regardless of residual nodal size. Median follow-up from commencement of RT was 28 months (range, 13-64 months). Residual CT nodal abnormalities were present in 50 patients (45%): 41 PET-negative and 9 PET-positive. All PET-negative residual CT nodal abnormalities were observed without subsequent isolated nodal failure. PET-directed management of the neck after definitive RT in node-positive HNSCC appropriately spares neck dissections in patients with PET-negative residual CT nodal abnormalities.

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Int J Radiat Oncol Biol Phys. 2011 Jan 13. [Epub ahead of print]

### **Imaging Tumor Perfusion and Oxidative Metabolism in Patients with Head-and-neck Cancer using 1- [(11)C]-acetate PET during Radiotherapy: Preliminary Results.**

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A growing body of in vitro evidence links alterations of the intermediary metabolism in cancer to treatment outcome. This study aimed to characterize tumor oxidative metabolism and perfusion in vivo using dynamic positron emission tomography (PET) with 1- [(11)C]-acetate (ACE) during radiotherapy. Nine patients with head-and-neck cancer were studied. Oxidative metabolic rate ( $k(\text{mono})$ ) and perfusion ( $rF$ ) of the primary tumors were assessed by dynamic ACE-PET at baseline and after 15, 30, and 55 Gy was delivered. Tumor glucose uptake ( $Tglu$ ) was

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evaluated with [(18)F]-fluorodeoxyglucose PET at baseline. Patients were grouped into complete (CR, n = 6) and partial responders (PR, n = 3) to radiotherapy. The 3 PR patients died within a median follow-up period of 33 months. Baseline  $k(\text{mono})$  was almost twice as high in CR as in PR ( $p = 0.02$ ) and  $T_{\text{glu}}$  was lower in CR than in PR ( $p = 0.04$ ).  $k(\text{mono})$  increased during radiotherapy in PR ( $p = 0.004$ ) but remained unchanged in CR. There were no differences in  $rF$  between CR and PR at any dosage.  $k(\text{mono})$  and  $rF$  were coupled in CR ( $p = 0.001$ ), but not in PR. This study shows that radiosensitive tumors might rely predominantly on oxidative metabolism for their bioenergetic needs. The impairment of oxidative metabolism in radioresistant tumors is potentially reversible, suggesting that therapies targeting the intermediary metabolism might improve treatment outcome.