Azienda Ospedaliero-Universitaria di Bologna
Policlinico S.Orsola-Malpighi

ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA

MOLECULAR IMAGING WITH PET/CT: FDG AND BEYOND

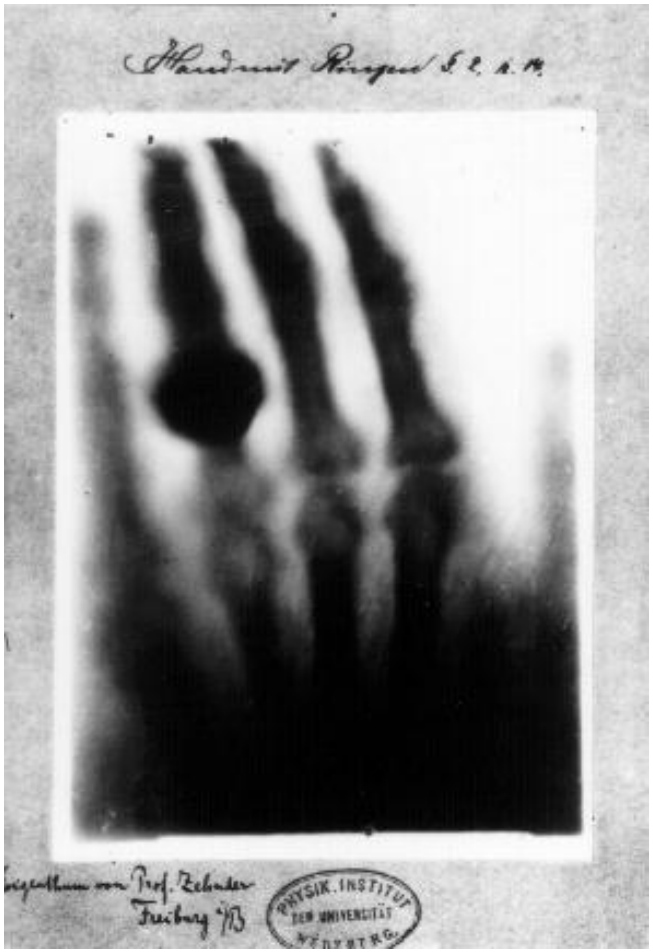
Stefano Fanti

Vienna 28 September 2012

MORPHOLOGICAL IMAGING

FUNCTIONAL IMAGING

MORPHOLOGICAL IMAGING



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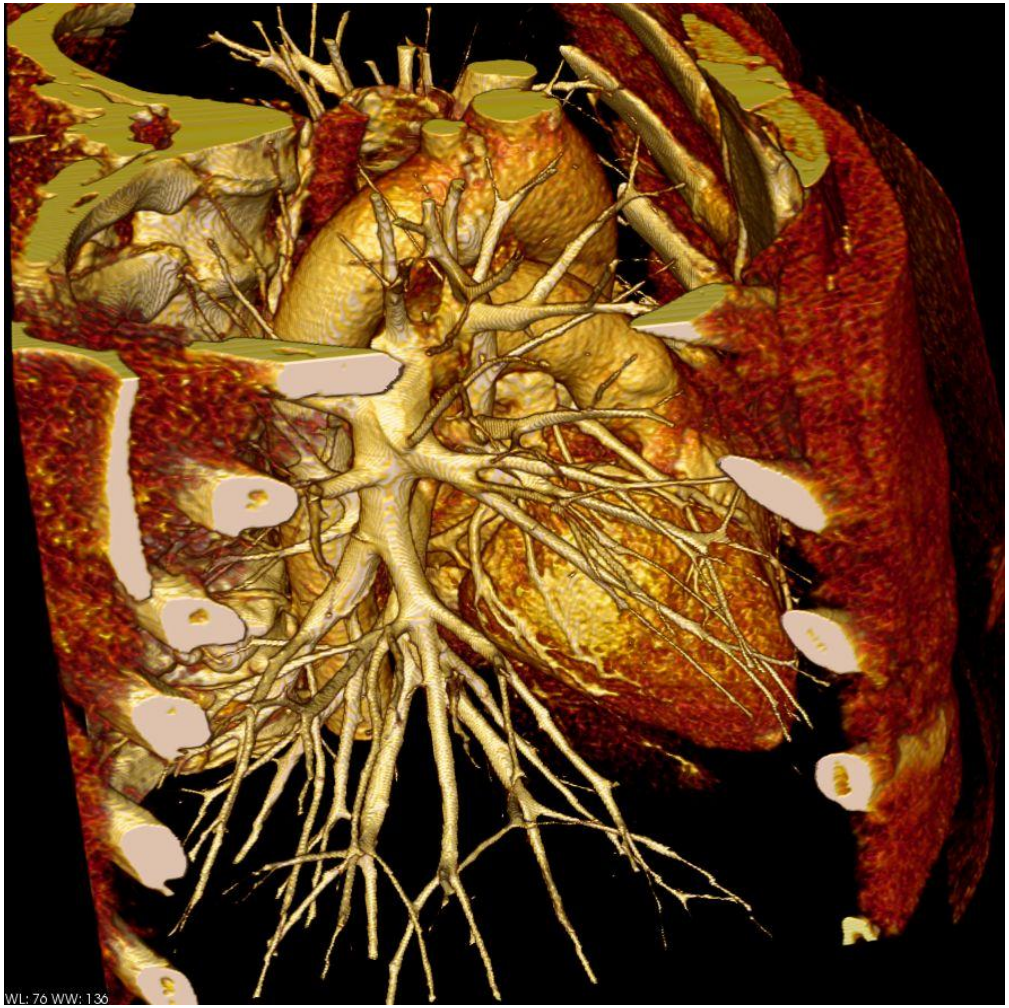

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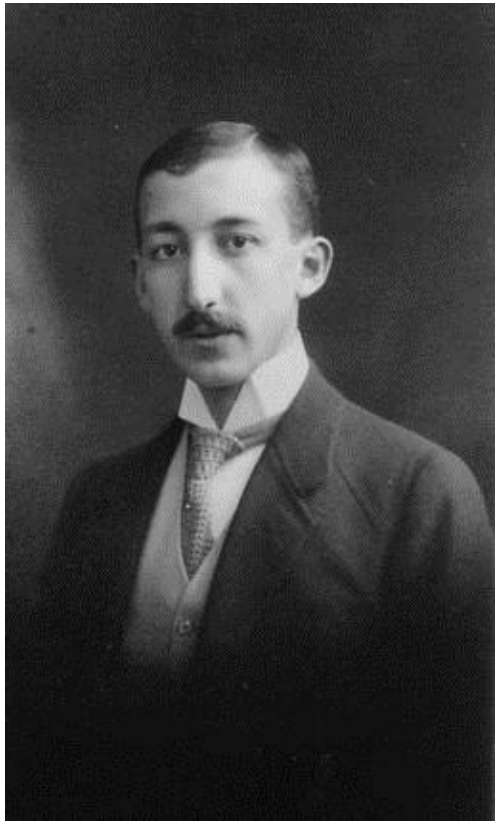


APPLICATION OF RADIOACTIVE INDICATORS IN BIOLOGY[1]

By G. Hevesy

Institute for Theoretical Physics,
The University, Copenhagen, Denmark

Natural radioactive isotopes of some of the heaviest elements are easily available and labelled lead, bismuth, and thorium were used in biological research at an early date. The circulation of lead in plants (1) and that of lead, bismuth, and thorium in both normal (2, 3) and carcinomatous (4) animals was investigated by this method. Extended use was made of radioactive bismuth in the study of the rate of absorption of the various bismuth preparations used in syphilis therapy (5). The discovery of artificial radioactivity and the rapid and successful development following this important event (6) made it possible to obtain "artificial" radioactive isotopes of numerous elements and opened thus a vast field for the application of isotopic indicators in biology. Among the elements of biological importance, hydrogen has no radioactive isotope, while nitrogen, oxygen, and carbon have such short half lives that their application for most purposes is excluded, though the radioactive isotope of carbon has met with some very useful applications (see pp. 658, 659). The discovery of heavy hydrogen and the recent progress (7) in the separation of the isotopes of oxygen, nitrogen, and carbon have made it possible to make use of labelled hydrogen, nitrogen, oxygen, and carbon, the tagged elements being identified by density measurements and mass-spectrographic determinations respectively. No fundamental difference is to be found between the application of radioactive and of stable isotopes as indicators. To limit the scope of discussion, however, it may be preferable to treat the application of radioactive indicators separately from that of the nonradioactive ones. In what follows, we will first discuss the use of radioactive phosphorus for labelling purposes. This isotope has found so far the most extensive application; furthermore, in view of its importance both in the study of inorganic and of organic metabolism, its application presents very suitable examples of the type of problems which can be successfully attacked by the use of tagged elements.

CHOLINE

↓

PHOSPHOLIPID

↓

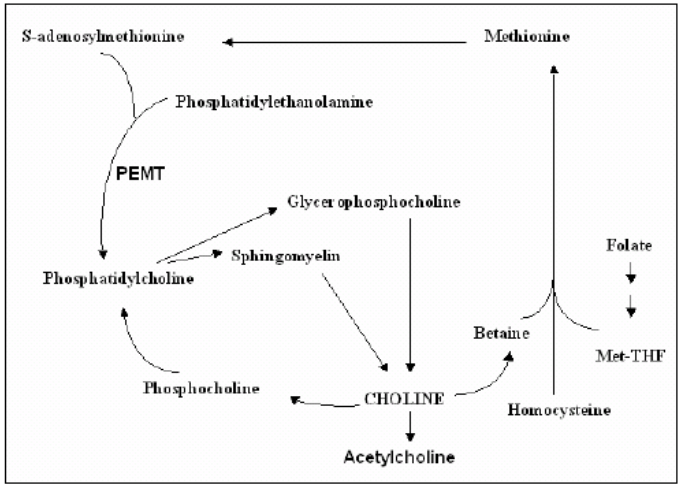
TRACE

CELLS

MEMBRANE

^{11}C-CHOLINE

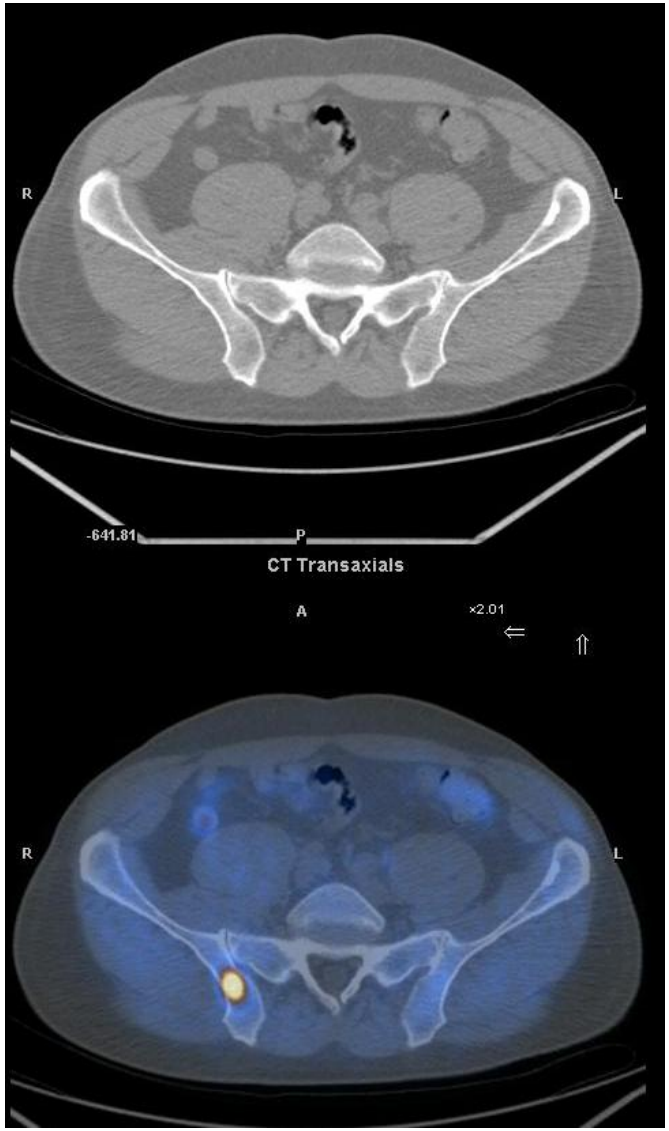
^{18}F-CHOLINE

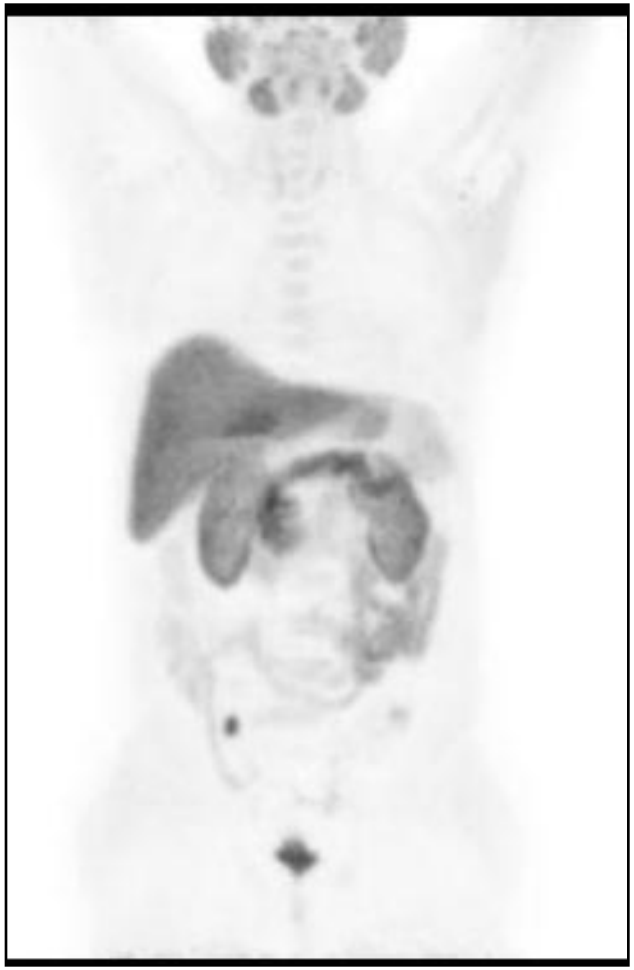


Prostatectomy

PSA 0.9

BS neg



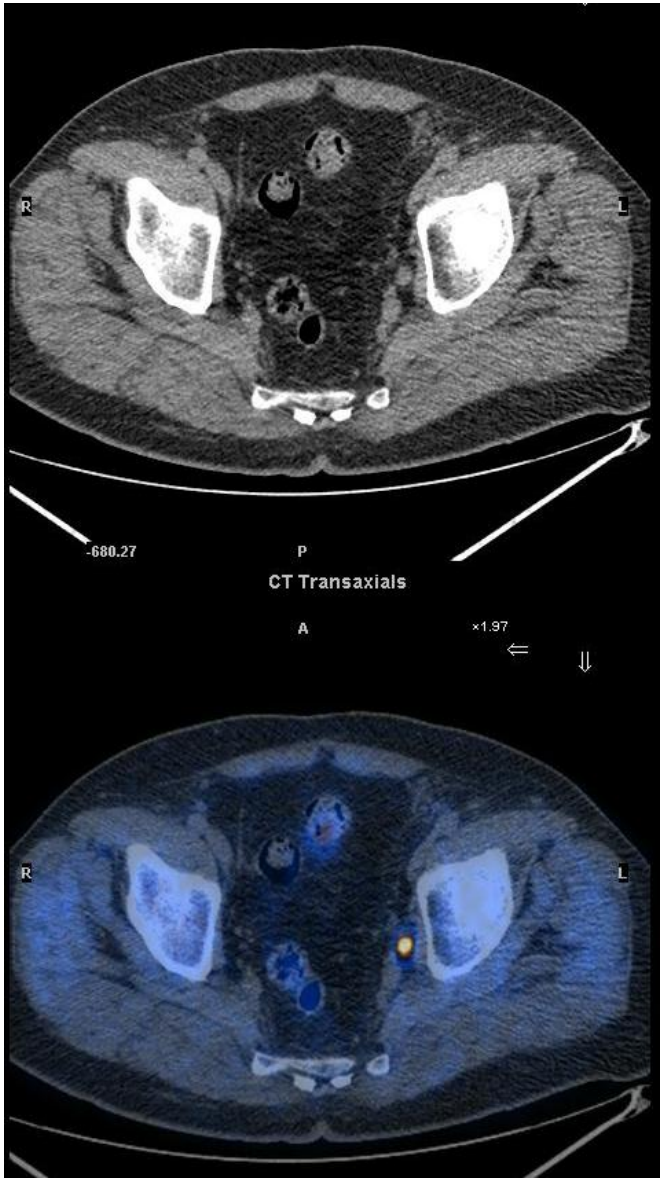


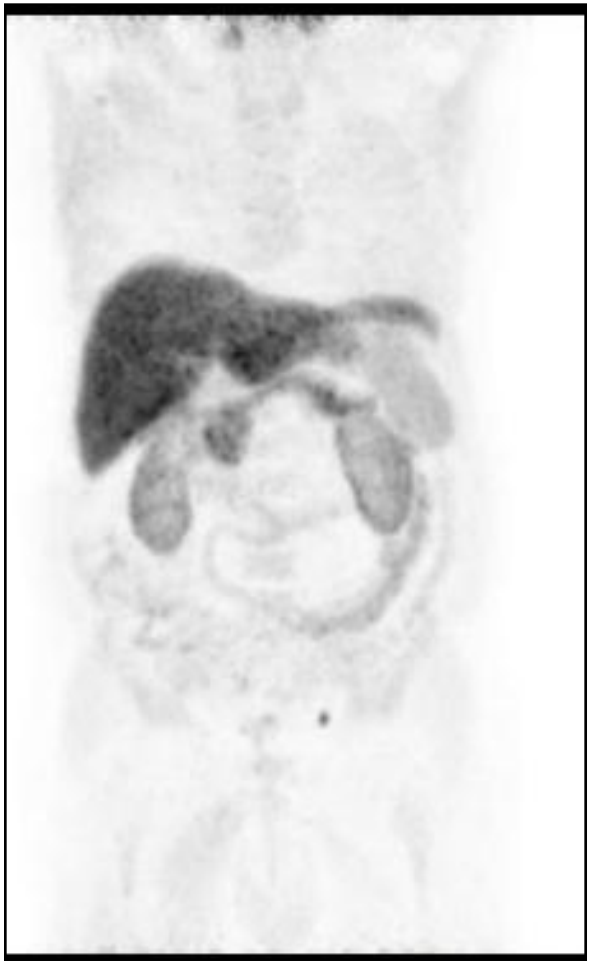
Prostatectomy

PSA 1.3

DT 3 months

BS neg

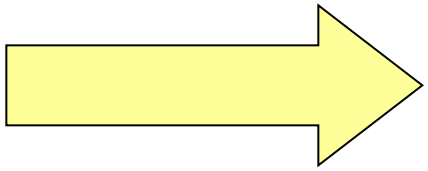




US

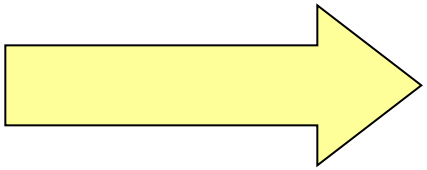
CT

MR



MORPHOLOGICAL IMAGING

NM

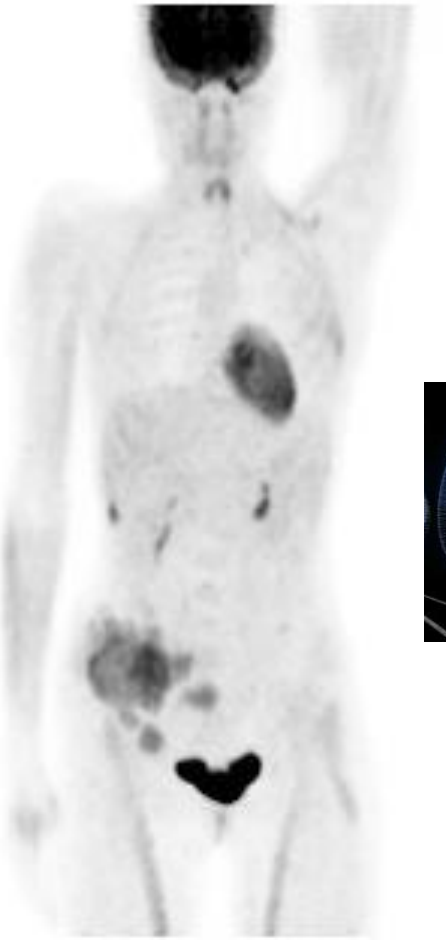


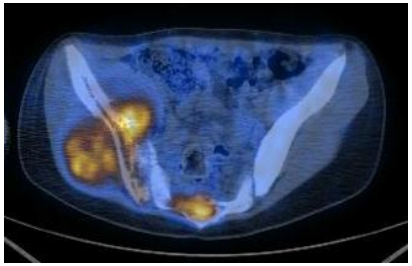
FUNCTIONAL IMAGING

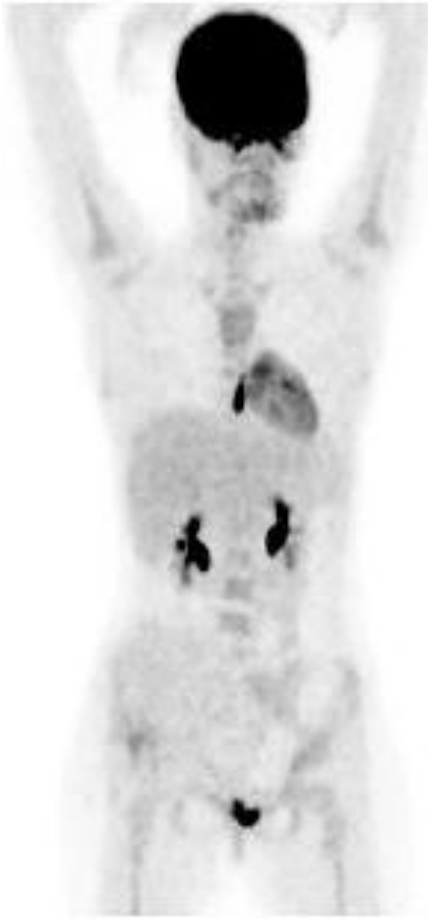
MORPHOLOGICAL IMAGING

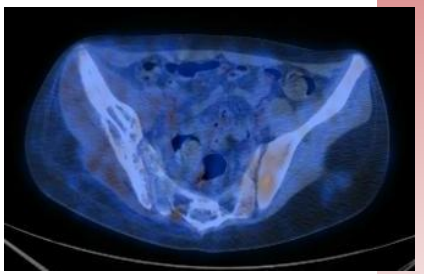
RESPONSE TO THERAPY

FUNCTIONAL IMAGING









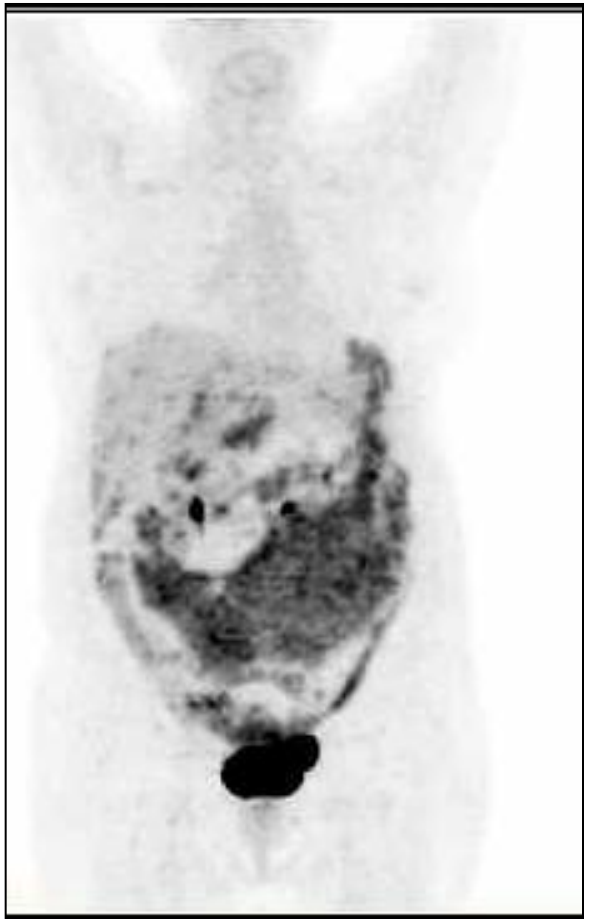
BEFORE TH

SUV max 8

AFTER TH

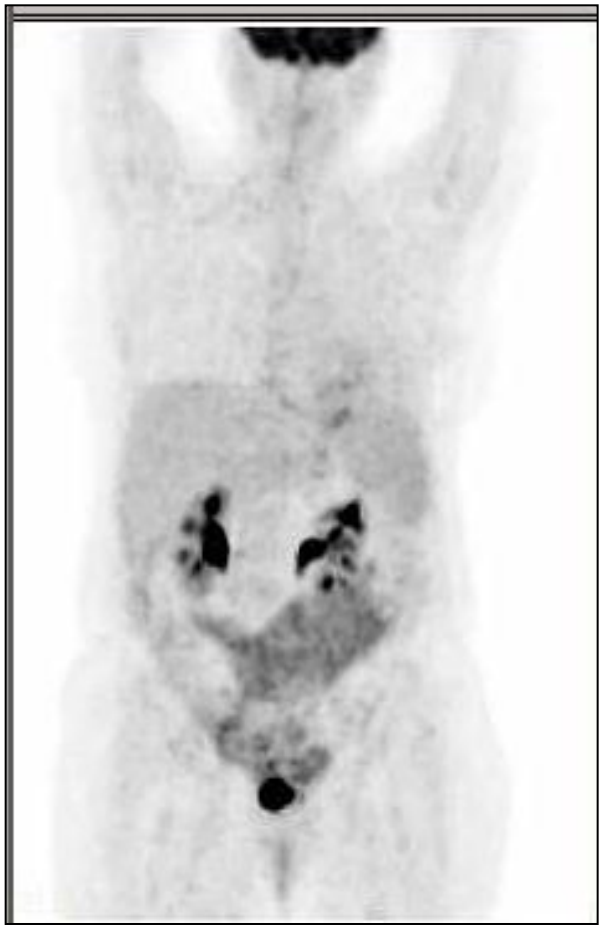
SUV max < 2

EWING'S SARCOMA



BEFORE TH

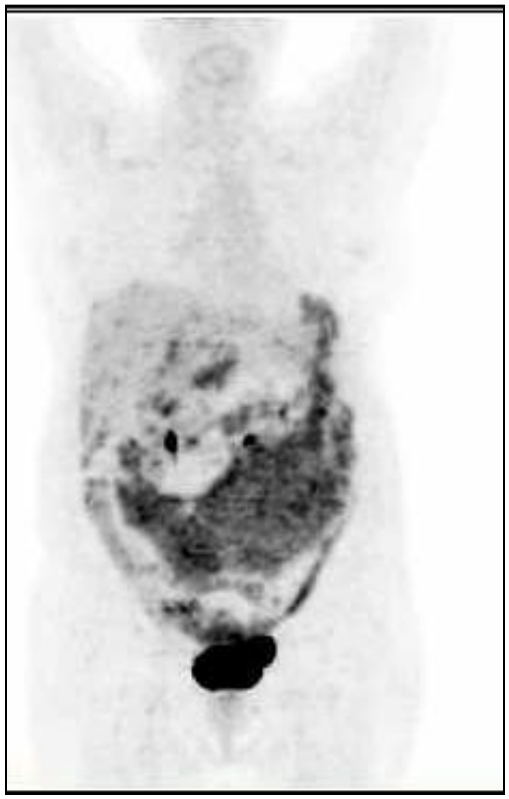
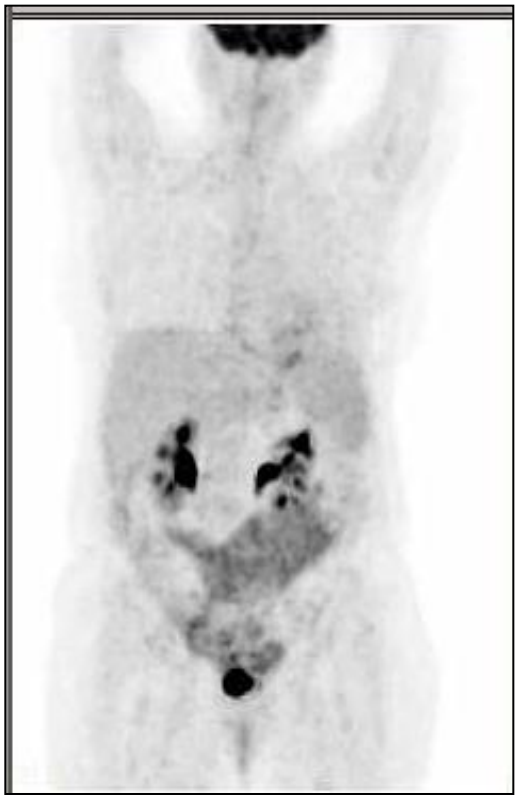
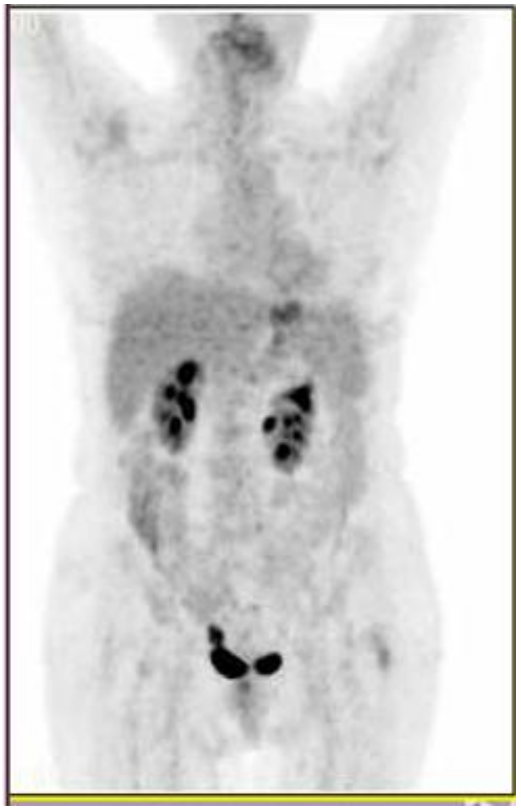
SUV max 20



AFTER 1 C TH

SUV max 6

OVARIAN

OVARIAN

RESPONSE TO THERAPY

LYMPHOMA

Journal of Clinical Oncology

The Official Journal of the American Society of Clinical Oncology

Vol 6, No 6 **June 1988**

EDITORIAL

George P. Canellos
Editor-in-Chief

Residual Mass in Lymphoma May Not Be Residual Disease

The report of Radford et al[6] illustrates two important points in the assessment of patients following any therapy for Hodgkin's disease. First, residual masses in the mediastinum may not represent residual disease since only 18% of their patients with residual abnormalities ever relapsed. Second, the presence of residual radiographic abnormalities might render a patient as a partial or incomplete responder, and thus may be an inaccurate measure of the efficacy of a particular treatment. In the Radford et al series, 45% of patients considered to have incomplete mediastinal remissions eventually achieved a complete remission in a period of 1 year. This suggests that immediate posttherapeutic assessment of extent of response may erroneously judge a treatment as achieving only a partial remission.

Radionuclide scans have had a mixed acceptance as a staging tool in the past. The use of high-dose (10 mCi) gallium 67 citrate (^{67}Ga) and improved gamma camera detection, as well as single photon emission CT (SPECT) scans have considerably improved the sensitivity of the technique.[16] A retrospective analysis at the DFCI of ^{67}Ga uptake following combination chemotherapy (four cycles) for large-cell lymphoma identified patients likely to relapse when avidity for ^{67}Ga was still present regardless of radiographic appearance.[17] This approach may prove to be the most useful test yet for the identification of viable residual disease in lymphoma.

Gallium-67 Imaging: A Predictor of Residual Tumor Viability and Clinical Outcome in Patients With Diffuse Large-Cell Lymphoma

By William D. Kaplan, Maxine S. Jochelson, Terence S. Herman, Lee M. Nadler, Paul C. Stomper, Tak Takvorian, Janet W. Andersen, and George P. Canellos

Journal of Clinical Oncology, Vol 8, No 12 (December), 1990: pp 1966-1970

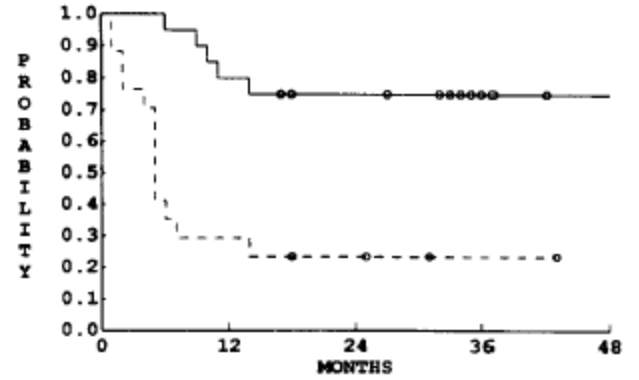


Fig 2. Time to treatment failure for Ga-67–negative patients and Ga-67–positive patients reimaged at a mid-point in therapy. The curves are significantly different ($P = .0004$ by log-rank analysis). CNSR, censured or patient in continuing remission at analysis.

Prognostic Value of PET Using ^{18}F-FDG in Hodgkin's Disease for Posttreatment Evaluation

J Nucl Med 2003; 44:1225–1231

Christian Guay, MD[1]; Mariette Lépine, MD[2]; Jean Verreault, MD[1,3]; and François Bénard, MD[1,3]

TABLE 3
Comparison Between ^{18}F-FDG PET and CT

Imaging	No.	True +	True −	False +	False −	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
PET	48	11	33	1	3	79*	97†	92‡	92*	92†
CT	32	10	8	12	2	83*	40†	45‡	80*	56†

*No statistical difference.
†$P < 0.0005$.
‡$P < 0.05$.
PPV = positive predictive value; NPV = negative predictive value.
Comparison was for 32 patients with available CT scans.

Predictive role of positron emission tomography (PET) in the outcome of lymphoma patients

PL Zinzani*[,1], S Fanti[2], G Battista[3], M Tani[1], P Castellucci[2], V Stefoni[1], L Alinari[1], M Farsad[2], G Musuraca[1], A Gabriele[1], E Marchi[1], C Nanni[2], R Canini[3], N Monetti[2] and M Baccarani[1]

[1]Institute of Hematology and Medical Oncology 'Seràgnoli', University of Bologna, Italy; [2]Department of Nuclear Medicine, University of Bologna, Italy; [3]Department of Radiology, University of Bologna, Italy

Table 2 PET and CT scans: restaging results and clinical outcome

	No. pts	Relapses
CT^-/PET^-	29	0
CT^-/PET^+	5	4 (80%)
CT^+/PET^+	11	10 (91%)
CT^+/PET^-	30	0

VOLUME 25 · NUMBER 5 · FEBRUARY 10 2007

JOURNAL OF CLINICAL ONCOLOGY

SPECIAL ARTICLE

Use of Positron Emission Tomography for Response Assessment of Lymphoma: Consensus of the Imaging Subcommittee of International Harmonization Project in Lymphoma

Malik E. Juweid, Sigrid Stroobants, Otto S. Hoekstra, Felix M. Mottaghy, Markus Dietlein, Ali Guermazi, Gregory A. Wiseman, Lale Kostakoglu, Klemens Scheidhauer, Andreas Buck, Ralph Naumann, Karoline Spaepen, Rodney J. Hicks, Wolfgang A. Weber, Sven N. Reske, Markus Schwaiger, Lawrence H. Schwartz, Josee M. Zijlstra, Barry A. Siegel, and Bruce D. Cheson

RECOMMENDATIONS

1. Use of PET for Response Assessment of Lymphoma at the Conclusion of Therapy

Numerous studies have demonstrated the value of PET or PET/CT for response assessment of HL and diffuse large B-cell NHL (DLBCL) at the conclusion of front-line, salvage, or high-dose therapy.[5-16] Based on the meta-analysis by Zijlstra et al,[5] pooled sensitivity and specificity of FDG-PET for detection of residual disease after completion of first-line therapy were 84% (95% CI, 71% to 92%) and 90% (95% CI, 84% to 94%), respectively, for HL, and 72% (95% CI, 61% to 82%) and 100% (95% CI, 97% to 100%), respectively, for aggressive NHL. Accurate information regarding tumor status after treatment of these lymphoma subtypes is critical because these are curable lymphomas. The value of PET in this setting is its ability to distinguish between viable tumor and necrosis or fibrosis in residual masses often present after treatment in patients without any other clinical or biochemical evidence of disease.[6-17] Conventional anatomic imaging modalities generally are unable to make this distinction because the morphologic features of these tissues are usually indistinguishable. False-positive PET findings at the site of residual masses can be seen, however, and have been discussed in detail by Juweid and Cheson,[1,2] among others.

The role of PET for response assessment of aggressive NHL subtypes other than DLBCL and of indolent and mantle-cell lymphomas, is less clear. For these generally incurable NHLs, progression-free or overall survival is usually the primary end point in clinical trials evaluating their response to treatment.[18] However, if overall objective response rate and, particularly, complete response rate are major end points in certain clinical trials, PET may be used for their more accurate determination.[18]

LYMPHOMA

SOLID TUMORS

VOLUME 24 · NUMBER 34 · DECEMBER 1 2008

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Monitoring of Early Response to Neoadjuvant Chemotherapy in Stage II and III Breast Cancer by [^{18}F]Fluorodeoxyglucose Positron Emission Tomography

Caroline Rousseau, Anne Devillers, Christine Sagan, Ludovic Ferrer, Boumédiène Bridji, Loïc Campion, Myriam Ricaud, Emmanuelle Bourbouloux, Isabelle Doutriaux, Martine Clouet, Dominique Berton-Rigaud, Catherine Bouriel, Valérie Delecroix, Etienne Garin, Sophie Rouquette, Isabelle Resche, Pierre Kerbrat, Jean François Chatal, and Mario Campone

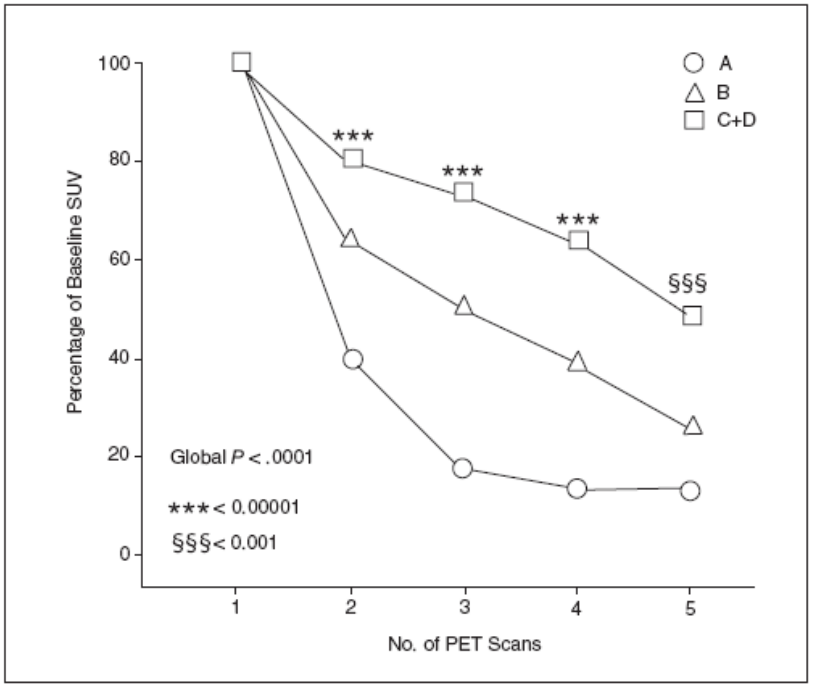


Fig 4. Changes in the relative standardized uptake value (SUV; mean) during neoadjuvant chemotherapy in responders (Sataloff grade A + B response) and nonresponders (Sataloff grade C + D response). PET, positron emission tomography.

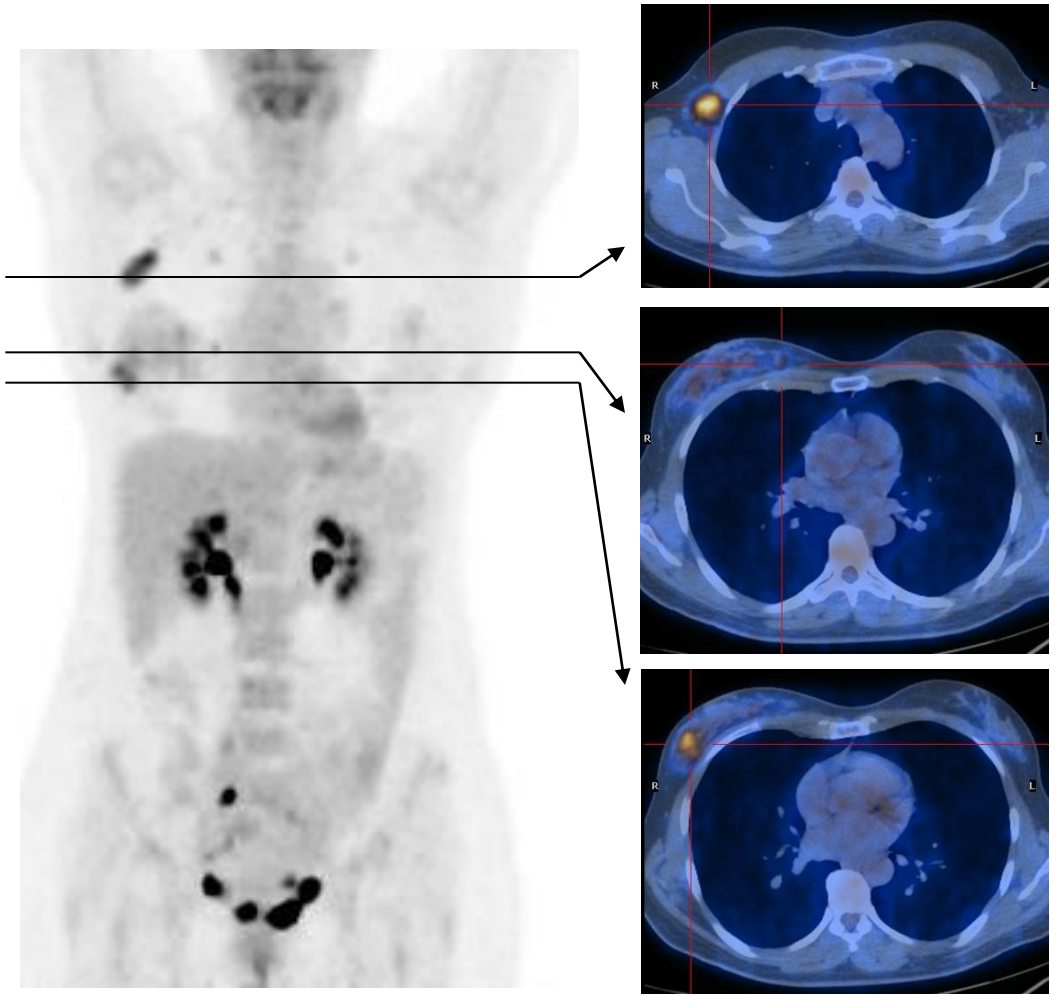
BREAST

STAGING

FDG PET/CT:

2 AREAS OF INCREASED UPTAKE IN THE RIGHT BREAST (SUV max 4.4) AND POSITIVE AXILLARY LYMPH NODES (SUV max 6.9). THIS IS CONSISTENT WITH CANCER.

CONTRALATERAL SUV MAX 1.3



NEOADJUVANT CHEMOTHERAPY

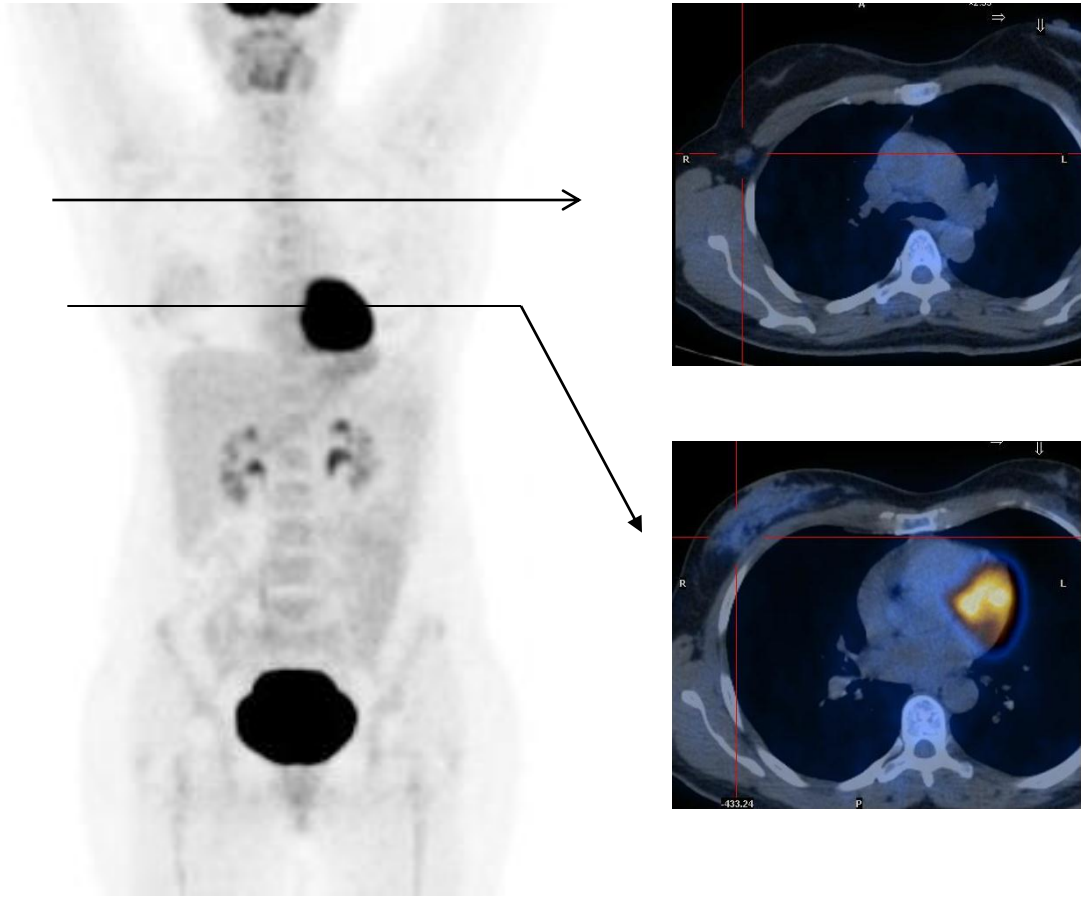
EARLY DURING TH

FDG PET/CT:

MILD RIGH BREAST RESIDUAL UPTAKE (SUV max 1.6), NEGATIVE AXILLARY NODES.

CONTRALATERAL SUV max 0.6

THIS IS CONSISTENT WITH PARTIAL RESPONSE.



VOLUME 27 · NUMBER 4 · FEBRUARY 1 2009

JOURNAL OF CLINICAL ONCOLOGY

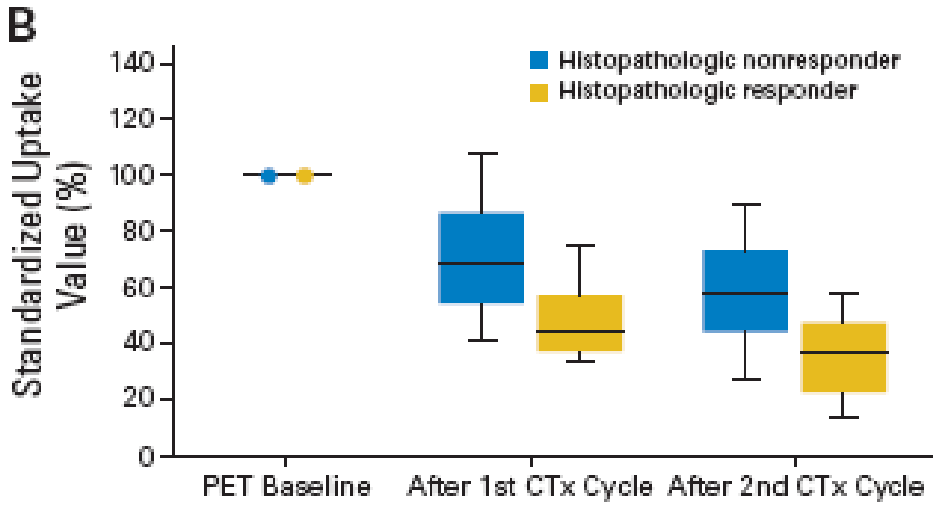
ORIGINAL REPORT

Monitoring Primary Systemic Therapy of Large and Locally Advanced Breast Cancer by Using Sequential Positron Emission Tomography Imaging With [^{18}F]Fluorodeoxyglucose

Jörg Schwarz-Dose, Michael Untch, Reinhold Tiling, Stefanie Sassen, Sven Mahner, Steffen Kahlert, Nadia Harbeck, Annette Lebeau, Winfried Brenner, Markus Schwaiger, Fritz Jaenicke, and Norbert Avril

Conclusion

FDG-PET allows for prediction of treatment response by the level of FDG uptake in terms of SUV at baseline and after each cycle of chemotherapy. Moreover, relative changes in SUV after the first and second cycle are a strong predictor of response. Thus, FDG-PET may be helpful for individual treatment stratification in breast cancer patients.



BREAST

Positron Emission Tomography Is Superior to Computed Tomography Scanning for Response-Assessment After Radical Radiotherapy or Chemoradiotherapy in Patients With Non–Small-Cell Lung Cancer

By Michael P. Mac Manus, Rodney J. Hicks, Jane P. Matthews, Allan McKenzie, Danny Rischin, Eeva K. Salminen, and David L. Ball

Journal of Clinical Oncology, Vol 21, No 7 (April 1), 2003: pp 1285-1292

Results: **Median survival after follow-up PET was 24 months. There was poor agreement between PET and CT responses (weighted kappa = 0.35), which were identical in only 40% of patients. There were significantly more complete responders on PET (n = 34) than CT (n = 10), whereas fewer patients were judged to be nonresponders (12 patients on PET *v* 20 on CT) or nonassessable (zero patients on PET *v* six on CT) by PET. Both CT and PET responses were individually significantly associated with survival duration; but on multifactor analysis that included the known prognostic factors of CT response, performance status, weight loss, and stage, only PET response was significantly associated with survival duration ($P < .0001$).**

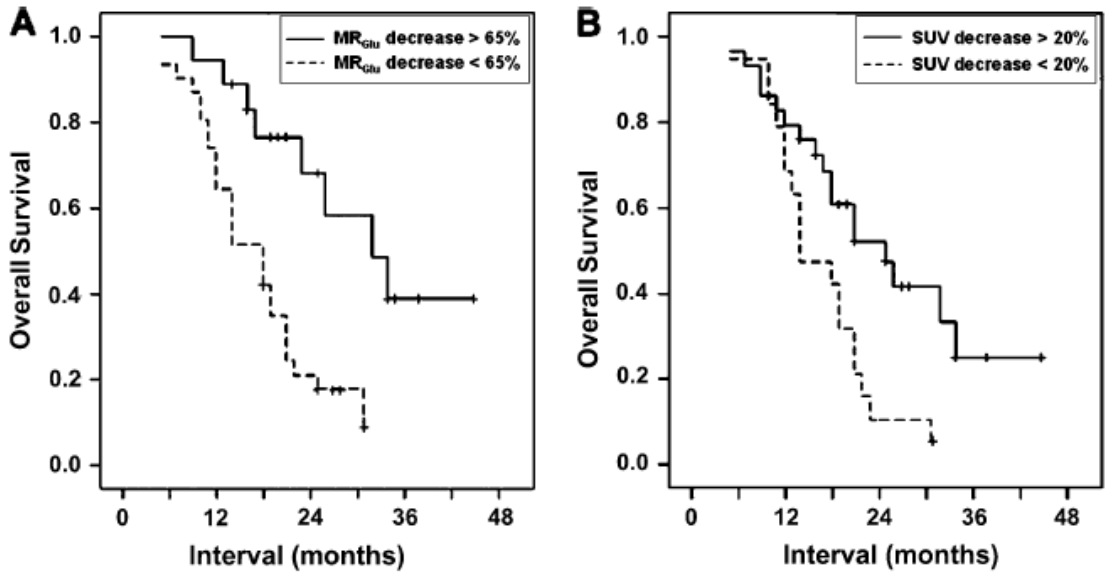
Conclusion: **In NSCLC, a single, early, posttreatment PET scan is a better predictor of survival than CT response, stage, or pretreatment performance status.**

NSCLC

Chemotherapy response evaluation with FDG–PET in patients with colorectal cancer

L. F. de Geus-Oei[1]*, H. W. M. van Laarhoven[2], E. P. Visser[1], R. Hermsen[1], B. A. van Hoorn[1], Y. J. L. Kamm[2], P. F. M. Krabbe[3], F. H. M. Corstens[1], C. J. A. Punt[2] & W. J. G. Oyen[1]

Annals of Oncology 19: 348–352, 2008



Conclusion: The degree of chemotherapy-induced changes in tumor glucose metabolism is highly predictive for patient outcome. The use of FDG–PET for therapy monitoring seems clinically feasible since simplified methods (SUV) are sufficiently reliable.

COLORECTAL

Int J Radiat Oncol Biol Phys. 2011 May 1;80(1):91-6. Epub 2010 Jun 3.

Prediction of response to neoadjuvant radiotherapy in patients with locally advanced rectal cancer by means of sequential 18FDG-PET.

Everaert H, Hoorens A, Vanhove C, Sermeus A, Ceulemans G, Engels B, Vermeersch M, Verellen D, Urbain D, Storme G, De Ridder M.

Department of Nuclear Medicine, UZ Brussel, Vrije Universiteit Brussel, Brussels, Belgium.

Ann Surg Oncol. 2011 Oct;18(10):2783-9. Epub 2011 Apr 8.

Evaluation of ^{18}F-FDG-PET for early detection of suboptimal response of rectal cancer to preoperative chemoradiotherapy: a prospective analysis.

Leibold T, Akhurst TJ, Chessin DB, Yeung HW, Macapinlac H, Shia J, Minsky BD, Saltz LB, Riedel E, Mazumdar M, Paty PB, Weiser MR, Wong WD, Larson SM, Guillem JG.

Department of Surgery (Colorectal Service), Memorial Sloan-Kettering Cancer Center, New York, NY, USA.

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.

Department of Surgical Oncology, Peter MacCallum Cancer Centre, St. Andrew's Place, East Melbourne, Victoria, Australia.

Int J Radiat Oncol Biol Phys. 2012 Feb 1;82(2):871-6. Epub 2011 Mar 5.

PET-based treatment response evaluation in rectal cancer: prediction and validation.

Janssen MH, Öllers 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. marco.janssen@maastro.nl

Radiat Oncol. 2010 Dec 15;5:119.

The value of metabolic imaging to predict tumour response after chemoradiation in locally advanced rectal cancer.

Palma P, Conde-Muíño R, Rodríguez-Fernández A, Segura-Jiménez I, Sánchez-Sánchez R, Martín-Cano J, Gómez-Río M, Ferrón JA, Llamas-Elvira JM.

Division of Colon &Rectal Surgery - Department of Surgery, HUVN Granada, Spain. pablopalma@andaluciajunta.es

Mol Imaging Biol. 2011 Oct;13(5):1011-9.

Comparison of different SUV-based methods for response prediction to neoadjuvant radiochemotherapy in locally advanced rectal cancer by FDG-PET and MRI.

Herrmann K, Bundschuh RA, Rosenberg R, Schmidt S, Praus C, Souvatzoglou M, Becker K, Schuster T, Essler M, Wieder HA, Friess H, Ziegler SI, Schwaiger M, Krause BJ.

Department of Nuclear Medicine, Klinikum rechts der Isar der Technischen Universität München, Munich, Germany. ken.herrmann@tum.de

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Results: 1 to 20 of 206

Monitoring and Predicting Response to Therapy with ^{18}F-FDG PET in Colorectal Cancer: A Systematic Review

Lioe-Fee de Geus-Oei[1], Dennis Vriens[1], Hanneke W.M. van Laarhoven[2], Winette T.A. van der Graaf[2], and Wim J.G. Oyen[1]

[1]*Department of Nuclear Medicine, Radboud University, Nijmegen Medical Centre, Nijmegen, The Netherlands; and*
[2]*Department of Medical Oncology, Radboud University, Nijmegen Medical Centre, Nijmegen, The Netherlands*

CONCLUSION

Published data indicate that ^{18}F-FDG PET has a high predictive value in the therapeutic management of colorectal cancer. This technique could be an asset for improving patient care by reducing the effort, costs, and morbidity associated with ineffective treatment in nonresponders. The available studies on chemotherapy response monitoring in advanced colorectal cancer and on preoperative radiotherapy and multimodality treatment response evaluation in primary rectal cancer indicate that ^{18}F-FDG PET is a significant predictor of therapy outcome in both situations. In primary rectal cancer, ^{18}F-FDG PET is

TABLE 3. (Preoperative) Multimodality and Radiotherapy Treatment Response Evaluation in Primary Rectal Cancer

Stage	Authors	Year	Reference	No. of patients	Therapy	Timing after therapy of PET evaluation	PET response criteria	Outcome measures	Results	*P*
Recurrent nonresectable tumor	Engenhart et al.	1992	40	21	Radiotherapy	8–9 wk	SUV normalization to background	Local control	PPV 20%; NPV 67%	
cT3NXM0	Schiepers et al.	1999	41	9	Radiotherapy	2–3 wk	$-\Delta MR_{glu}$	Histopathology, cell kinetics	Accuracy 80%	
cT3 or N1	Guillem et al.	2000	49	15	Chemoradiation	4–5 wk	−ΔSUV, visual response score, −ΔTLG	Histopathology	PPV 100%	
cT2, cT3, cT4, N1, N2, or N3	Oku et al.	2002	46	40	Radiotherapy	3–5 wk	SUV cutoff level after radiotherapy 3.2; SUV ratio	Recurrence, CT shrinkage rate	Responders <3.2; nonresponders >3.2 Correlation −0.383	0.046 0.014
cT3 or cT4	Amthauer et al.	2004	44	20	Chemoradiation + hyperthermia	2–4 wk	$-\Delta SUV_{max,BSA}$ > 36%	Histopathology	PPV 93%; NPV 100%	<0.001
cT2NXM0, cT3NXM0, or cT4NXM0	Calvo et al.	2004	50	25	Chemoradiation	4–5 wk	$-\Delta SUV_{max}$	Histopathology (T downstaging)	Responders −3.3; nonresponders −1.9	0.03
cT3, cT4, or N1	Guillem et al.	2004	51	15	Chemoradiation	4–5 wk	$-\Delta SUV_{max} \geq$ 62.5%, visual response score, −ΔTLG ≥ 69.5%	Recurrence, overall survival, recurrence-free survival	Responders −69%; nonresponders 37%	0.004
cT3 or cT4	Denecke et al.	2005	52	23	Chemoradiation + hyperthermia	2–4 wk	$-\Delta SUV_{max}$ > 36%	Histopathology (T downstaging)	Responders −60%; nonresponders −37% PPV 77%; NPV 100%	0.03 0.002
uT3, uT4, or N1	Konski et al.	2005	53	20	Chemoradiation	3–4 wk	$-\Delta SUV_{max}$	Histopathology	Responders −75%; nonresponders −52%	0.24
cT3, cT4, or N1	Cascini et al.	2006	54	33	Chemoradiation	Day 12 during and after	$-\Delta SUV_{mean}$ > 52% (after 12 d)	Histopathology (tumor regression grade)	Responders −63%; nonresponders −22%; accuracy 100%	<0.0001
cT3, cT4, N1M0, N2M0, or N3M0	Capirci et al.	2006	55	88	Chemoradiation	5–6 wk	PET-positive	5-y overall survival	PET-negative: 5-y OS 91%; PET-positive: 5-y DFS 62%	0.024
							PET-negative (SUV_{max} < 0.9)	5-y disease-free survival	PET-negative: 5-y DFS 81%; PET-positive: 5-y OS 72%	0.003
cT3NXM0 or cT4NXM0	Kalff et al.	2006	56	34	Chemoradiation	7–43 d	Visual response score	Overall survival Progression-free survival	CMR: 3-y PFS 100%; PMR: 3-y OS 79% CMR: 3-y OS 100%; PMR: 3-y PFS 47%	<0.0001 <0.0001
cT3 or cT4	Capirci et al.	2007	57	45	Chemoradiation	5–6 wk	$-\Delta SUV_{max}$ > 66.2%	Histopathology (tumor regression grade, T downstaging)	Responders −76%; nonresponders −47%; PPV 77%; NPV 89%; accuracy 80%	0.0015
cT3, cT4, or N1	Melton et al.	2007	58	21	Chemoradiation	4–5 wk	$-\Delta SUV_{max}$ > 70%, visual response score, −ΔTLG, −ΔCT/−ΔPET volume	Histopathology (T downstaging)	Responders −72%; nonresponders −44%; PPV 58%; NPV 100%	<0.001
cT3 or cT4	Kristiansen et al.	2008	59	30	Chemoradiation	7 wk	Visual response on PET/CT	Histopathology (tumor regression grade)	PPV 50%; NPV 58%	
uT2N+ or uT3N0+	Siegel et al.	2008	47	32	Short course of radiotherapy	Days 7–8 after start	$-\Delta SUV_{max}$ > 40%	Histopathology (tumor regression grade)	No correlation between PET responses and outcome measures	NS
uT3, uT4, or N1	Nakagawa et al.	2008	48	59	Radiotherapy	2–3 wk	SUV cutoff level after radiotherapy 5	Median survival	Responders 95 mo; nonresponders 42 mo	0.042
								5-y overall survival	Responders 70%; nonresponders 44%	
							SUV ratio < 100%		Relative risk 0.239	0.028
								Histopathology	Significant correlation	0.047
cT3 or cT4	Vliegen et al.	2008	60	20	Chemoradiation	4–6 wk	$-\Delta SUV_{max}$	Histopathology (tumor regression grade)	Responders −83%; nonresponders −59%	0.025
cT3NX, cT4NX, or N1	Konski et al.	2008	61	53	Chemoradiation	3–4 wk	$-\Delta SUV_{max}$	Histopathology, disease-free survival	Responders −67%; nonresponders −55%	0.08

PPV = positive predictive value; NPV = negative predictive value; ΔMR_{glu} = fractional change in MR_{glu}; ΔSUV = fractional change in SUV; SUV ratio = ratio of SUV between follow-up and baseline scans; $\Delta SUV_{max,BSA}$ = ΔSUV_{max} corrected for body surface area; ΔSUV_{max} = fractional change in SUV_{max}; ΔSUV_{mean} = fractional change in SUV_{mean}; OS = overall survival; DFS = disease-free survival; CMR = complete metabolic response; PFS = progression-free survival; PMR = partial metabolic response; ΔCT/ΔPET volume = change in lesion volume based on CT or PET measurements; NS = not significant.

Early Prediction of Response to Sunitinib After Imatinib Failure by ^{18}F-Fluorodeoxyglucose Positron Emission Tomography in Patients With Gastrointestinal Stromal Tumor

John O. Prior, Michael Montemurro, Maria-Victoria Orcurto, Olivier Michielin, François Luthi, Jean Benhattar, Louis Guillou, Valérie Elsig, Roger Stupp, Angelika Bischof Delaloye, and Serge Leyvraz

Positron emission tomography for monitoring response to neoadjuvant therapy in patients with oesophageal and gastro-oesophageal junction carcinoma

S.A. Suttie [a,*], A.E. Welch [b], K.G.M. Park [c]

Early evaluation of neoadjuvant chemotherapy response using FDG-PET/CT predicts survival prognosis in patients with head and neck squamous cell carcinoma

Masahiro Kikuchi · Yuji Nakamoto · Shogo Shinohara · Keizo Fujiwara · Hiroshi Yamazaki · Yuji Kanazawa · Risa Kurihara · Ippei Kishimoto · Hiroyuki Harada · Yasushi Naito

^{18}F-FDG-PET/CT Imaging as an Early Survival Predictor in Patients with Primary High-Grade Soft Tissue Sarcomas Undergoing Neoadjuvant Therapy

Ken Herrmann[1], Matthias R. Benz[1], Johannes Czernin[1], Martin S. Allen-Auerbach[1], William D. Tap[2], Sarah M. Dry[5], Tibor Schuster[6], Jeff J. Eckardt[3], Michael E. Phelps[1], Wolfgang A. Weber[1,7], and Fritz C. Eilber[1,4]

[18F]FDG-PET/CT monitoring early identifies advanced ovarian cancer patients who will benefit from prolonged neo-adjuvant chemotherapy.

Martoni AA, Fanti S, Zamagni C, Rosati M, De Iaco P, D'Errico Grigioni A, Castellucci P, Quercia S, Musto A, Ricci Maccarini L, Lopci E, Bernardi A.

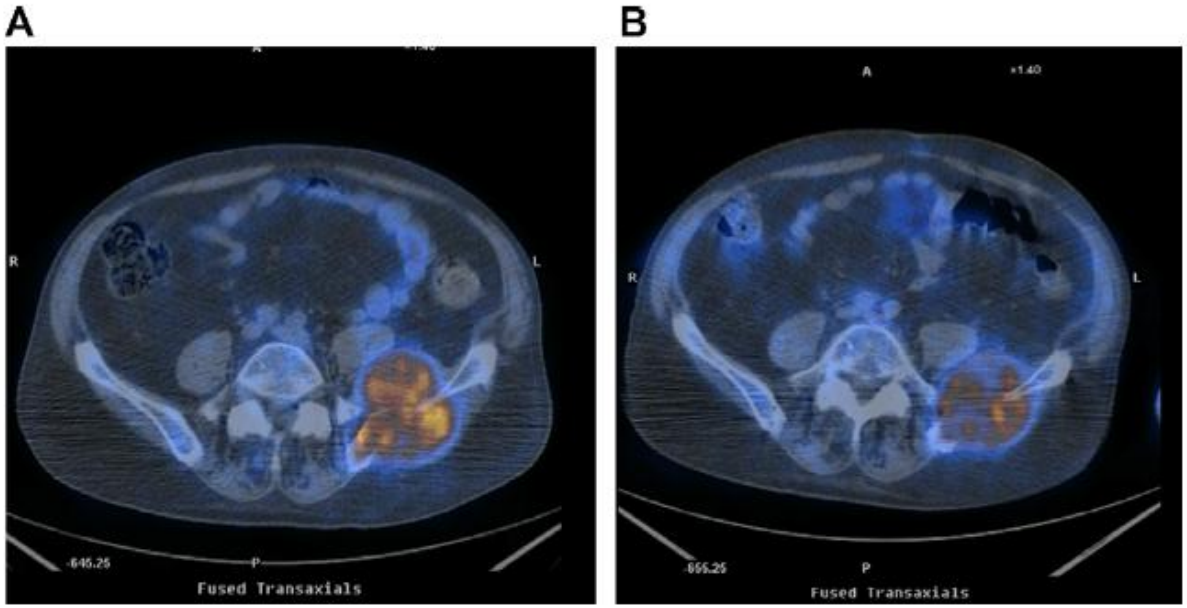
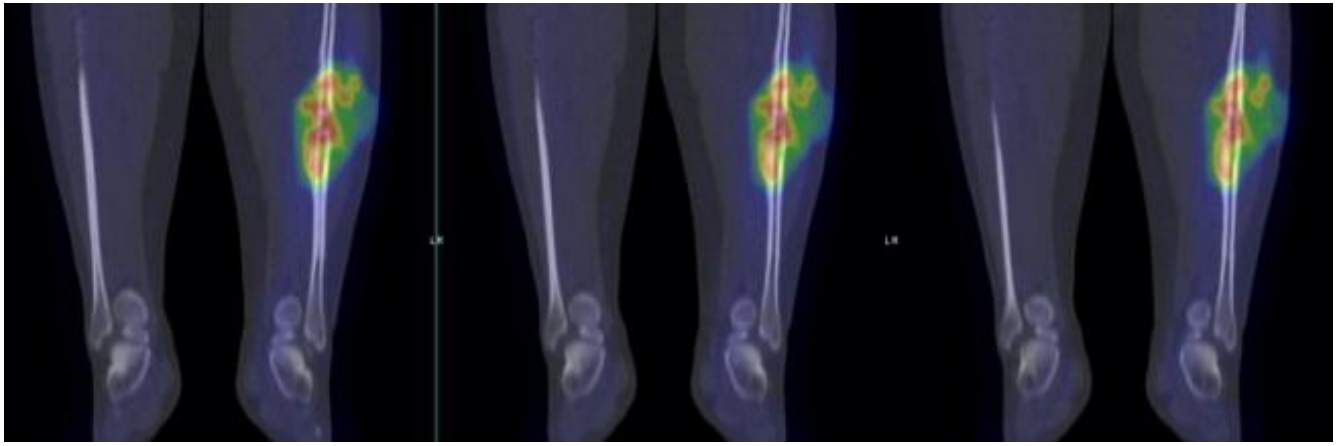


Figure 2 FDG PET in a patient affected by RCC: partial metabolic response of right muscle lesion after sunitinib treatment. (A) PET: before sunitinib treatment. (B) PET: after sunitinib treatment.

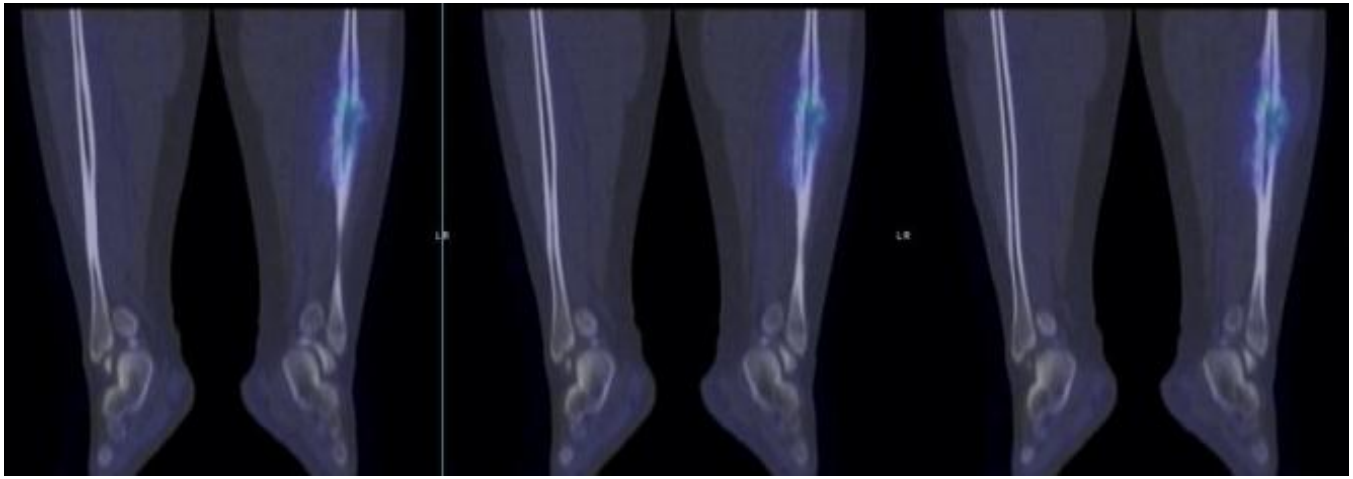
RECIST

EORTC

PERCIST



BEFORE TH
SUV max 6.1



AFTER TH
SUV max 1.8

OSTEOSARCOMA

Special Paper

Can Positron Emission Tomography (PET) be Used to Detect Subclinical Response to Cancer Therapy?

P. Price and T. Jones on behalf of the EC PET Oncology Concerted Action and the EORTC PET Study Group

At the EORTC NCI New Drug Development Meeting in Amsterdam in 1994, a workshop, suggested by the EC PET (positron emission tomography) Oncology concerted action, was held to bring together many of those European PET centres investigating the use of [^{18}F]FDG ([^{18}F]2-fluoro-2 deoxyglucose) PET scanning as a measure of response to cancer therapy. Of the current 31 PET centres in Europe invited to contribute, 15 centres already had data and others expressed interest. Many of the groups were collaborating with local oncologists to measure tumour response to chemotherapy (12 groups) and radiotherapy (three groups) with this technique. Despite variations of methodology, and difficulties in data interpretation, assessment of tumour [^{18}F]FDG uptake was thought to be a reasonable method for the functional imaging of tumours, assessing metabolic rate and providing a measure of tumour response. Broadly, pooling experience, it would appear that changes in [^{18}F]FDG tumour uptake following one or two cycles of chemotherapy treatment was related to ultimate clinical responses. Patients showing most reduction in [^{18}F]FDG uptake achieved the best clinical responses. Data were also available on the effect of chemotherapy on normal tissues and some data on the effect of radiotherapy and tumour response. It was concluded that changes in [^{18}F]FDG uptake as measured with PET may provide useful information on clinical as well as subclinical response of tumours to anticancer therapy. This could be useful as a guide to early response to therapy as well as providing functional assessment of residual masses of disease. More specific markers of cellular proliferation e.g. [^{11}C]thymidine, or [^{11}C]- amino acids may provide even more accurate information. A strategy was outlined whereby PET scanning protocols could parallel EORTC early clinical trials so that [^{18}F]FDG response information could supplement phase I and II clinical studies. Following these developments, an EORTC study group was formed under the auspices of the EORTC research branch, and the strategy for future development in Europe outlined.

From RECIST to PERCIST: Evolving Considerations for PET Response Criteria in Solid Tumors

Richard L. Wahl[1,2], Heather Jacene[1], Yvette Kasamon[2], and Martin A. Lodge[1]

May 1 2009, Volume 50, Suppl_1

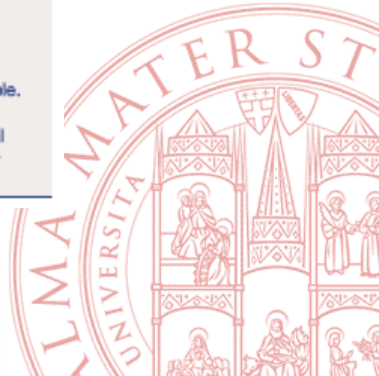
Introduction to PERCIST 1.0

Based on the extensive literature now supporting the use of ^{18}F-FDG PET to assess early treatment response as well as the known limitations of anatomic imaging, updated draft PET criteria are proposed that may be useful for consideration in clinical trials and possibly clinical practice. We have called these draft criteria "PERCIST"—Positron Emission tomography Response Criteria In Solid Tumors. The RECIST committee did not have a role in developing these criteria, but while we were developing them we acknowledged and appreciated the careful work and approaches of the RECIST committee. We also recognized that, as with RECIST, criteria such as PERCIST will need updates and validation in differing settings. With apologies to the RECIST group, we believed that the name *PERCIST* seemed quite appropriate as a complement to the well-developed anatomic criteria now in widespread use and recently updated.

EORTC

PERCIST

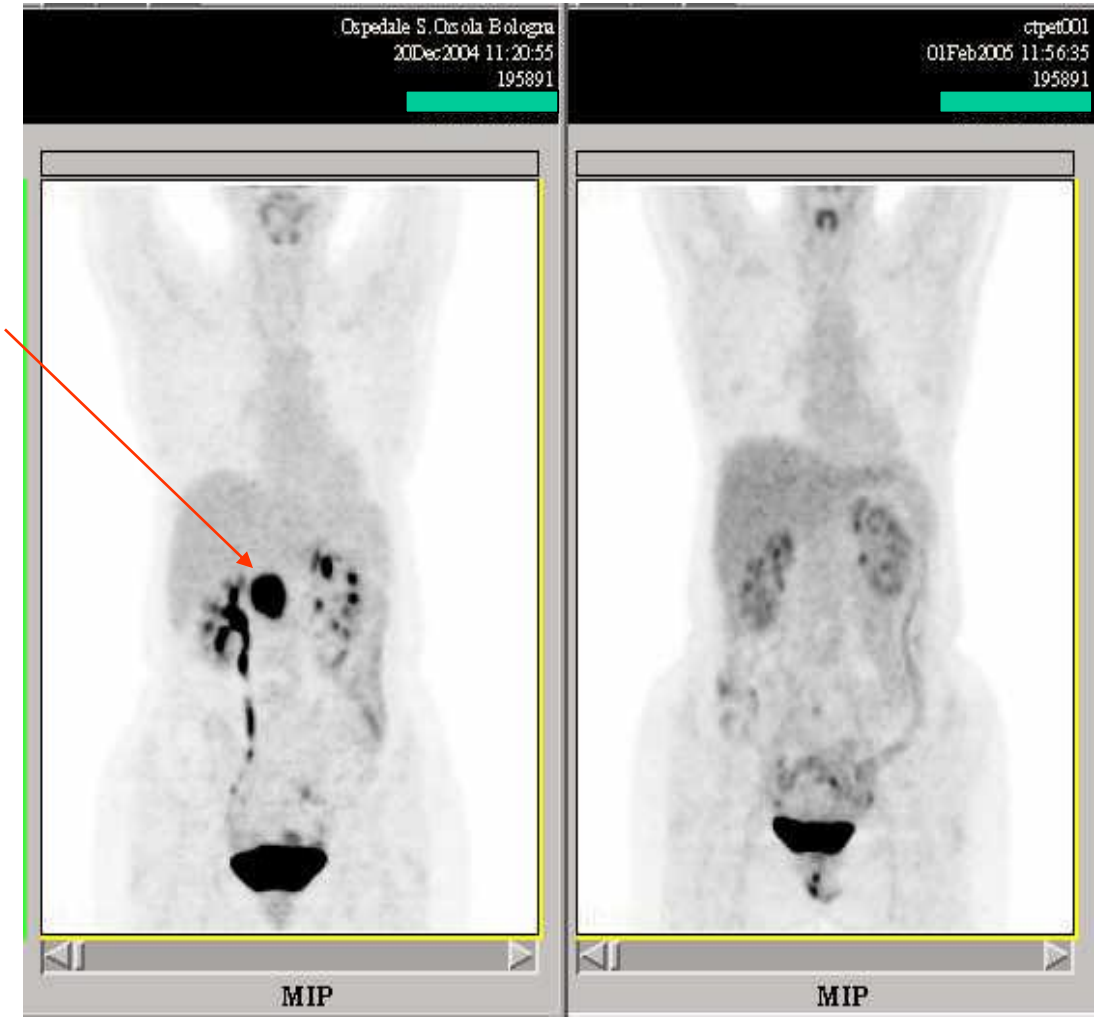
Characteristic	EORTC	PERCIST 1.0
	PMR: reduction of minimum of 15% ± 25% in tumor ^{18}F-FDG SUV after 1 cycle of chemotherapy, and >25% after more than 1 treatment cycle; reduction in extent of tumor ^{18}F-FDG uptake is not a requirement for PMR.	PMR: reduction of minimum of 30% in target measurable tumor ^{18}F-FDG SUL peak. Absolute drop in SUL must be at least 0.8 SUL units, as well. Measurement is commonly in same lesion as baseline but can be another lesion if that lesion was previously present and is the most active lesion after treatment. ROI does not have to be in precisely same area as baseline scan, though typically it is. No increase, >30% in SUL or size of target or nontarget lesions (i.e., no PD by RECIST or IWC) (if PD anatomically, must verify with follow-up). Reduction in extent of tumor ^{18}F-FDG uptake is not requirement for PMR. Percentage decline in SUL should be recorded, as well as (ideally) time in weeks after treatment was begun (i.e., PMR −40, 3). No new lesions.
	SMD: increase in tumor ^{18}F-FDG SUV < 25% or decrease of <15% and no visible increase in extent of ^{18}F-FDG tumor uptake (20% in longest dimension).	SMD: not CMR, PMR, or PMD. SUL peak in metabolic target lesion should be recorded, as well as (ideally) time from start of most recent therapy, in weeks (i.e., SMD −15, 7).
	PMD: increase in ^{18}F-FDG tumor SUV of >25% within tumor region defined on baseline scan; visible increase in extent of ^{18}F-FDG tumor uptake (20% in longest dimension) or appearance of new ^{18}F-FDG uptake in metastatic lesions.	PMD: >30% increase in ^{18}F-FDG SUL peak, with >0.8 SUL unit increase in tumor SUV peak from baseline scan in pattern typical of tumor and not of infection/treatment effect. OR: Visible increase in extent of ^{18}F-FDG tumor uptake (75% in TLG volume with no decline in SUL. OR: New ^{18}F-FDG–avid lesions that are typical of cancer and not related to treatment effect or infection. PMD other than new visceral lesions should be confirmed on follow-up study within 1 mo unless PMD also is clearly associated with progressive disease by RECIST 1.1. PMD should be reported to include percentage change in SUV peak, (ideally, time after treatment, in weeks) and whether new lesions are present/absent and their number (i.e., PMD, +35, 4, new: 5). Because SUL is continuous variable, dividing response criteria into limited number of somewhat arbitrary response categories loses much data. For this reason, PERCIST preserves percentage declines in SUV peak in each reported category. Because rapidity with which scan normalizes is important (faster appears better), PERCIST asks for time from start of treatment as part of reporting. For example, CMR 90, 1, is probably superior to CMR 90, 10, especially if latter patient were SMD 20, 1. More than one measurement of PET response may be needed at differing times, and it may be treatment type–dependent. PERCIST 1.0 evaluates SUL peak of only hottest tumor. This is possible limitation of approach, but lesions and their responses are highly correlated in general. Additional data are required to determine how many lesions should be assessed over 1. A suggested option is to include the 5 hottest lesions, or the 5 observed on RECIST 1.1 that are most measurable. Percentage change in SUL can be reported for single lesion with largest increase in uptake or smallest decline in uptake. Additional studies will be needed to define how many lesions are optimal for assessment.



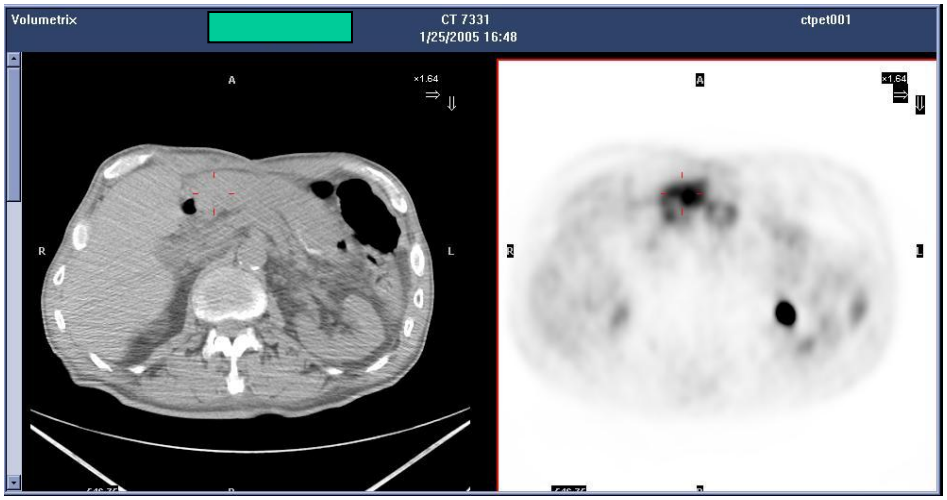
EORTC

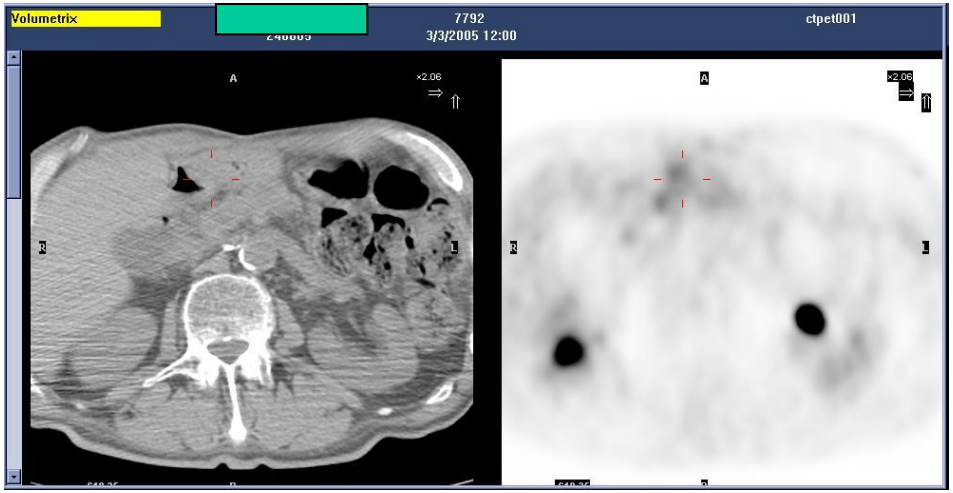
criteria for evaluating metabolic response to therapy using FDG PET:

- **CR:** same metabolic rate as normal tissue
- **PR:** after I cycle 15-25% decrease in SUV
  after II cycle > 25% decrease in SUV
- **PD:** > 25% increase of SUV or apparence of new lesions
- **SD**: difference of –15% to +25% in SUV ; same extension

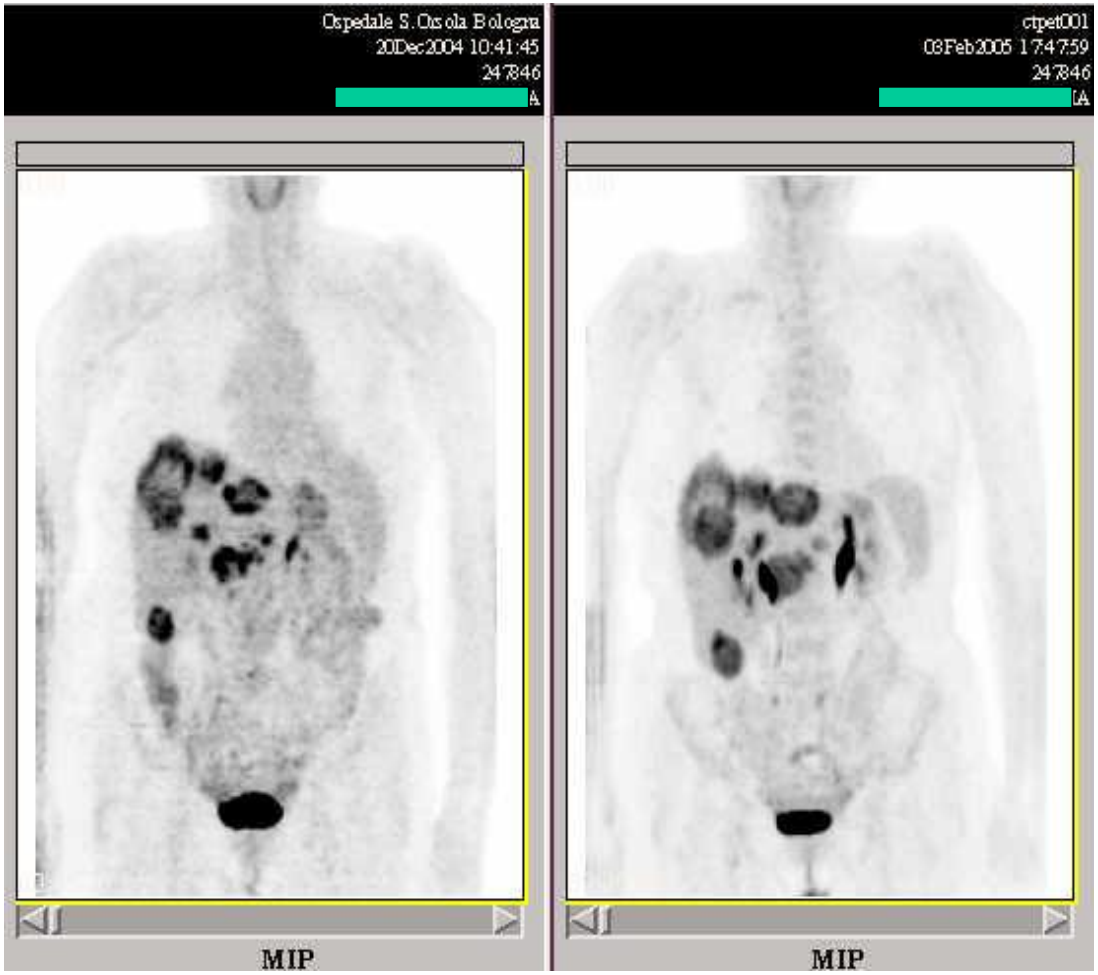


GASTRIC CANCER: Folcetux before and after (40 days)
COMPLETE RESPONSE





GASTRIC CANCER: Folcetux before and after (35 days)
PARTIAL RESPONSE

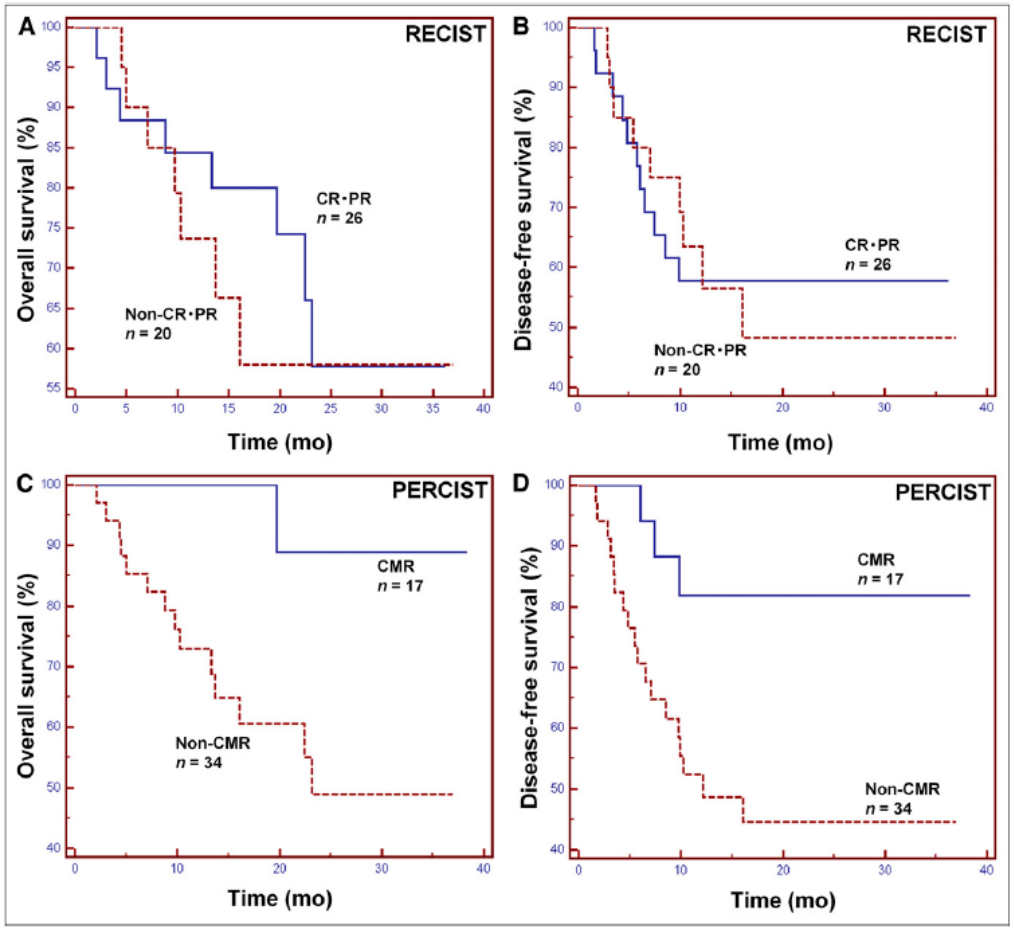


GASTRIC CANCER: Folcetux before and after (43 days)
STABLE DISEASE

Evaluation of Response to Neoadjuvant Chemotherapy for Esophageal Cancer: PET Response Criteria in Solid Tumors Versus Response Evaluation Criteria in Solid Tumors

Masahiro Yanagawa*[1], Mitsuaki Tatsumi*[1,2], Hiroshi Miyata[3], Eiichi Morii[4], Noriyuki Tomiyama[1], Tadashi Watabe[2], Kayako Isohashi[2], Hiroki Kato[2], Eku Shimosegawa[2], Makoto Yamasaki[3], Masaki Mori[3], Yuichiro Doki[3], and Jun Hatazawa[2]

THE JOURNAL OF NUCLEAR MEDICINE • Vol. 53 • No. 6 • June 2012

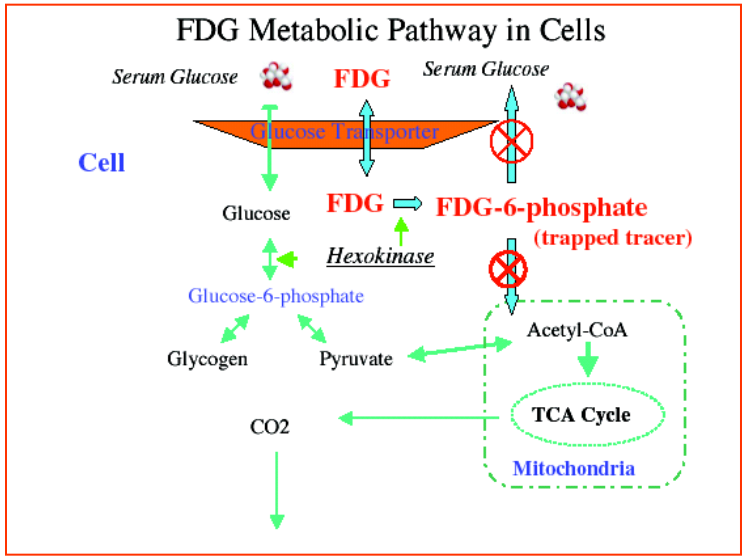


Quantification of FDG uptake: calculation of SUV

Standardized Uptake Value (SUV)

Measure of radiotracer biodistribution in the body and at level of lesions

$$SUV = \frac{\text{mean ROI activity (mCi/ml)}}{\text{injected dose (mCi)/body weight (g)}}$$



Variations in PET/CT Methodology for Oncologic Imaging at U.S. Academic Medical Centers: An Imaging Response Assessment Team Survey

THE JOURNAL OF NUCLEAR MEDICINE • Vol. 52 • No. 2 • February 2011

Michael M. Graham[1], Ramsey D. Badawi[2], and Richard L. Wahl[3]

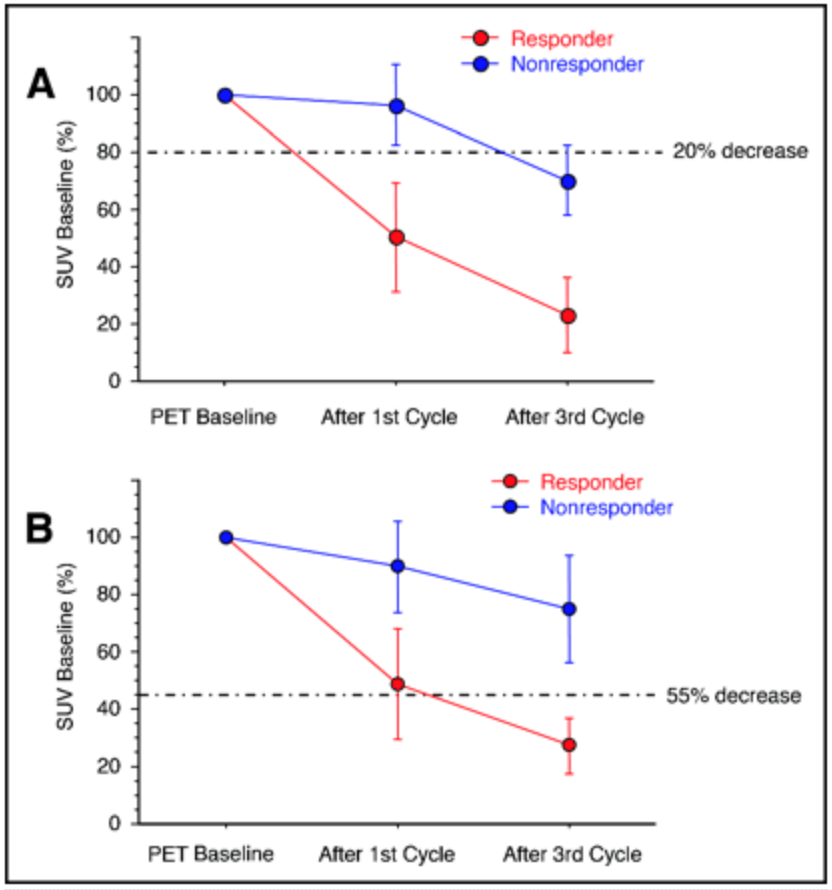
CONCLUSION

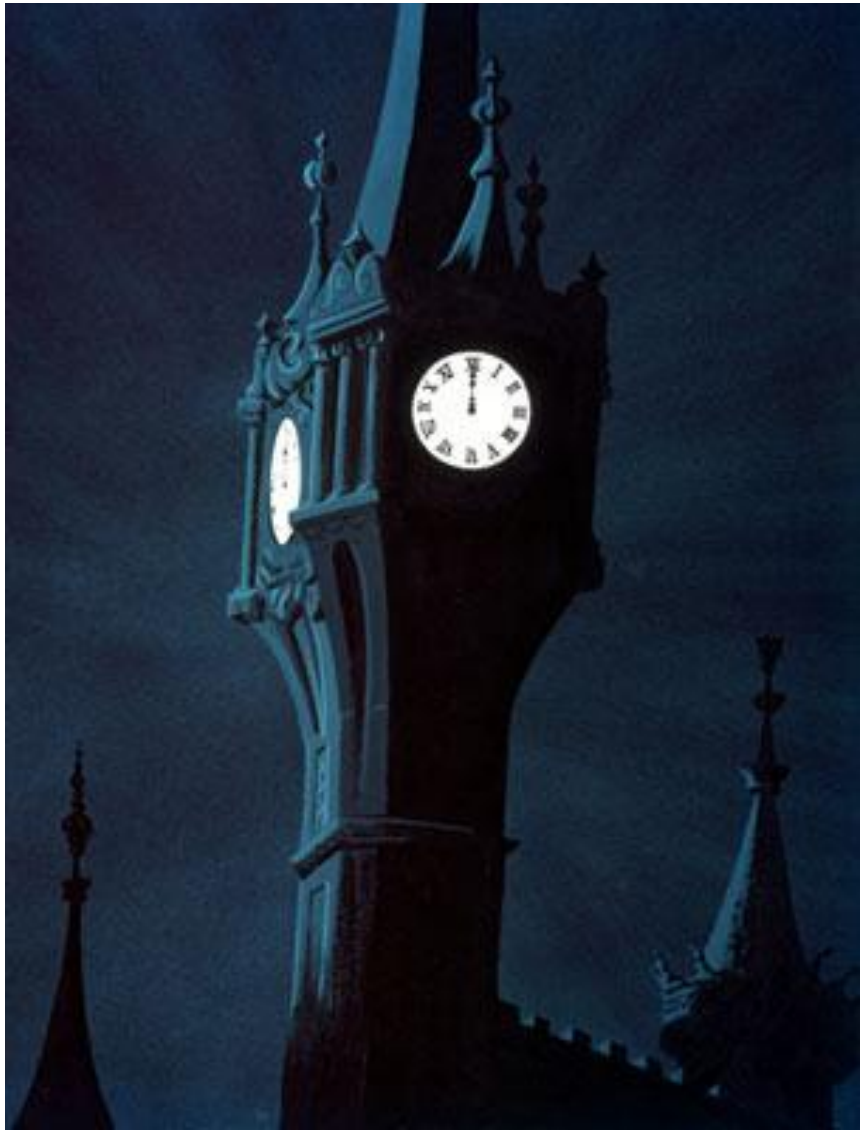
A survey applied mainly to academic PET centers participating in the IRAT network showed considerable variability in patient preparation, ^{18}F-FDG dose, CT technique, tracer uptake, imaging time, reconstruction methods, and suitability of PACS for PET/CT display. The existence of this variance despite professional guidelines suggests that results from quantitative PET analyses are likely to differ widely across centers. These data indicate that additional standardization is needed to bring about results—particularly quantitative results—that are more comparable among sites.

Prediction of Response to Neoadjuvant Chemotherapy by Sequential F-18-Fluorodeoxyglucose Positron Emission Tomography in Patients With Advanced-Stage Ovarian Cancer

Norbert Avril, Stefanie Sassen, Barbara Schmalfeldt, Joerg Naehrig, Stephan Rutke, Wolfgang A. Weber, Martin Werner, Henner Graeff, Markus Schwaiger and Walther Kuhn

J Clin Oncol. 2005 Oct 20;23(30):7445-53. Epub 2005 Sep 12.



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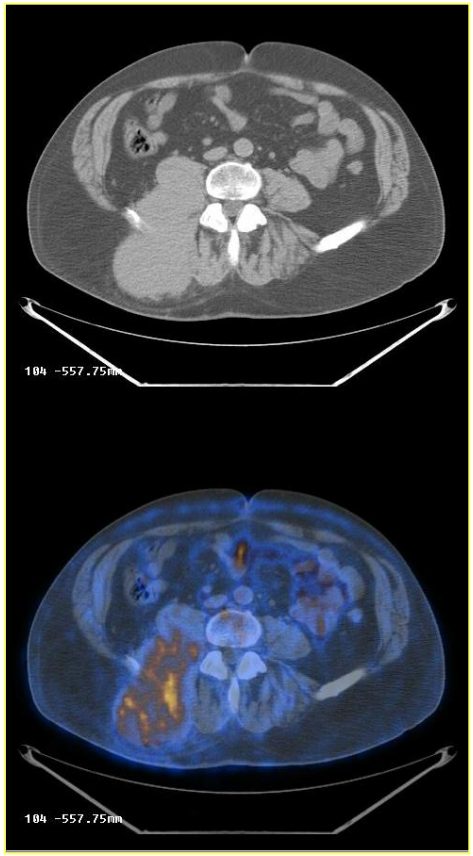
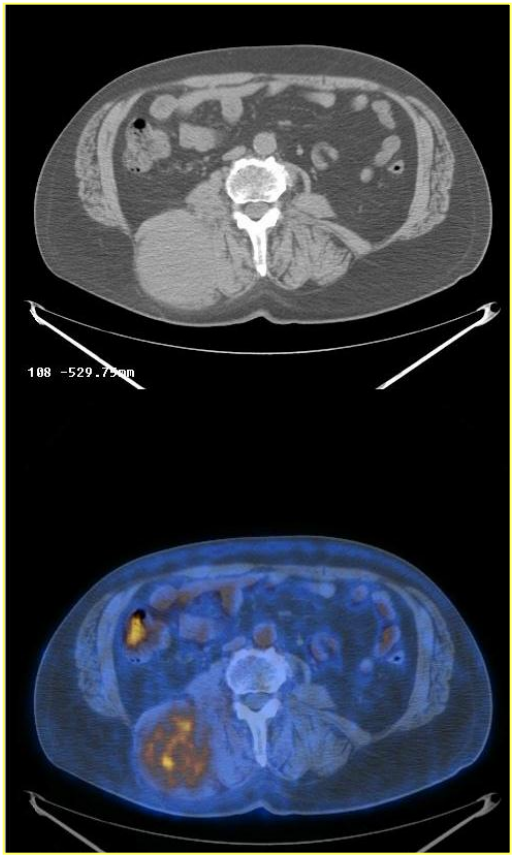
FDG PRE



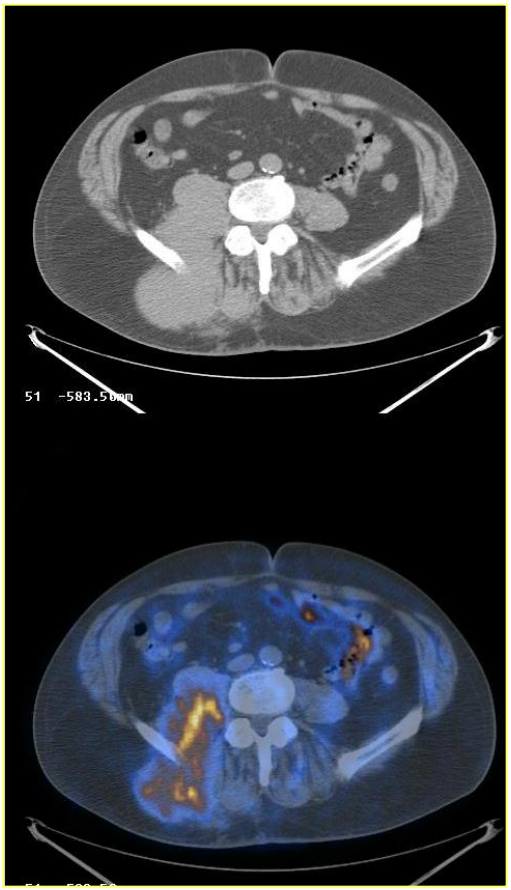
SUVmax 5.5

FDG POST



SUVmax 4.5

MET PRE



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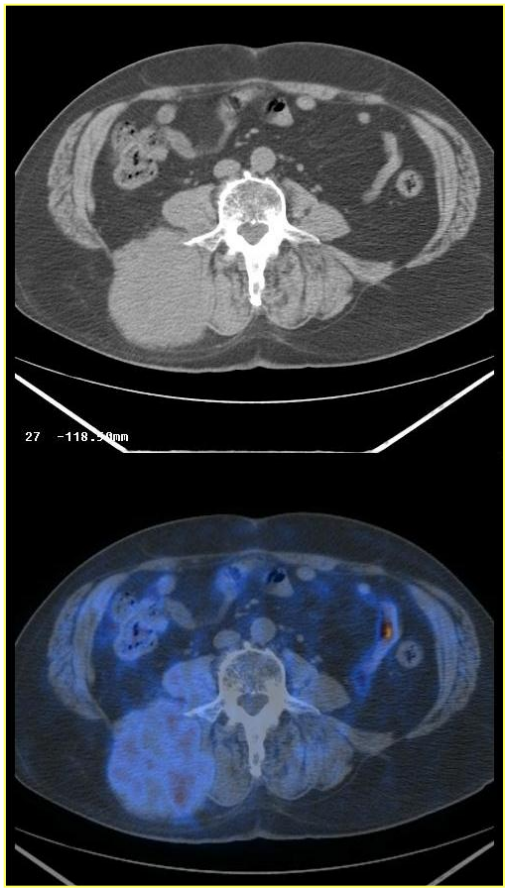


SUVmax 4.2

Tumor-Specific Positron Emission Tomography Imaging in Patients: [^{18}F] Fluorodeoxyglucose and Beyond

David A. Mankoff, Janet F. Eary, Jeanne M. Link, Mark Muzi, Joseph G. Rajendran, Alexander M. Spence, and Kenneth A. Krohn

Clin Cancer Res 2007;13(12) June 15, 2007

Biochemical and molecular imaging of cancer using positron emission tomography (PET) plays an increasing role in the care of cancer patients. Most clinical work to date uses the glucose analogue [^{18}F]fluorodeoxyglucose (FDG) to detect accelerated and aberrant glycolysis present in most tumors. Although clinical FDG PET has been used largely to detect and localize cancer, more detailed studies have yielded biological insights and showed the utility of FDG as a prognostic marker and as a tool for therapeutic response evaluation. As cancer therapy becomes more targeted and individualized, it is likely that PET radiopharmaceuticals other than FDG, aimed at more specific aspects of cancer biology, will also play a role in guiding cancer therapy. Clinical trials designed to test and validate new PET agents will need to incorporate rigorous quantitative image analysis and adapt to the evolving use of imaging as a biomarker and will need to incorporate cancer outcomes, such as survival into study design.

Conventional and novel PET tracers for imaging in oncology in the era of molecular therapy

Cancer Treatment Reviews (2008) 34, 103–121

M.A. Pantaleo [a,*], M. Nannini [a], A. Maleddu [a], S. Fanti [b], V. Ambrosini [b], C. Nanni [b], S. Boschi [b], G. Biasco [a]

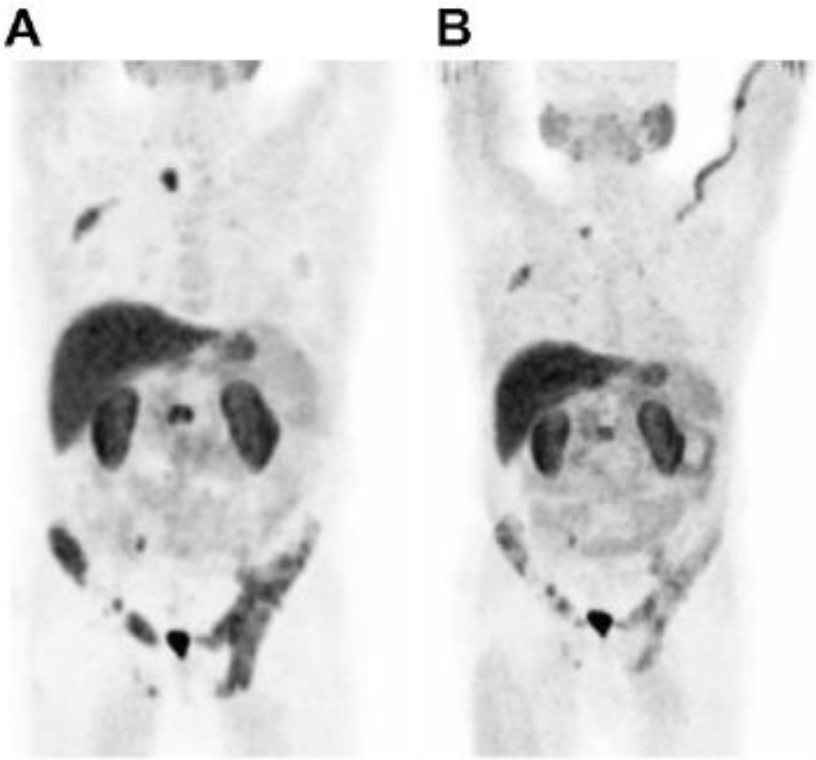


Figure 3 ^{11}C-choline PET in a patient affected by prostate cancer with multiple bone lesions (right V rib, right collar-bone, pelvis, L1 vertebre): metabolic response of the pelvis after chemotherapy and zoledronic acid. (A) PET: before treatment. (B) PET: after treatment.

[^{18}F]FLT: An imaging biomarker of tumour proliferation for assessment of tumour response to treatment

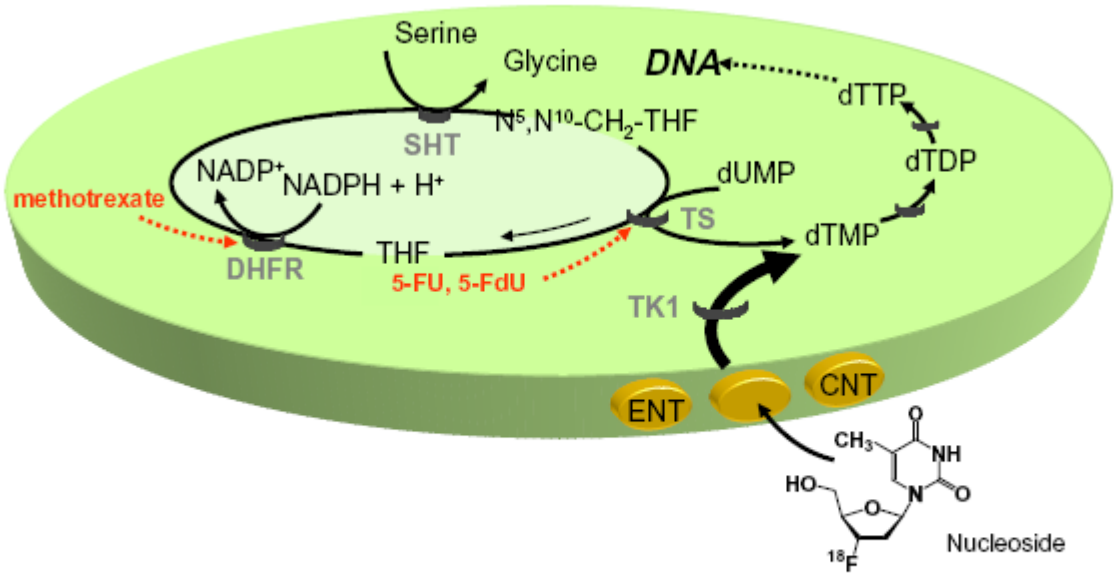
Dmitry Soloviev[a, c], David Lewis[a, c], Davina Honess[a, c], Eric Aboagye[b, c]

European Journal of Cancer
Volume 48, Issue 4, March 2012, Pages 416–424

Molecular imaging of proliferation in vivo: Positron emission tomography with [^{18}F]fluorothymidine

Methods 48 (2009) 205–215

Andreas K. Buck[a,*], Ken Herrmann[a], Changxian Shen[c], Tobias Dechow[b], Markus Schwaiger[a], Hans-Jürgen Wester[a]



SHT: serine hydroxymethyl transferase
TK1: thymidine kinase
ENT: equilibrative nucleoside transporter
DHFR: dihydrofolate reductase
dUMP: deoxyuridine monophosphate
CNT: concentrative nucleoside transporter
TS: thymidylate synthase
dTMP: deoxythymidine monophosphate (thymidylate)

Quantitative Analysis of Response to Treatment with Erlotinib in Advanced Non–Small Cell Lung Cancer Using ^{18}F-FDG and 3′-Deoxy-3′-^{18}F-Fluorothymidine PET

Deniz Kahraman[1,2], Matthias Scheffler[2,3], Thomas Zander[2,3], Lucia Nogova[2,3], Adriaan A. Lammertsma[4], Ronald Boellaard[4], Bernd Neumaier[5], Roland T. Ullrich[2,3,5], Arne Holstein[1,2], Markus Dietlein[1,2], Jürgen Wolf[2,3], and Carsten Kobe[1,2]

THE JOURNAL OF NUCLEAR MEDICINE • Vol. 52 • No. 12 • December 2011

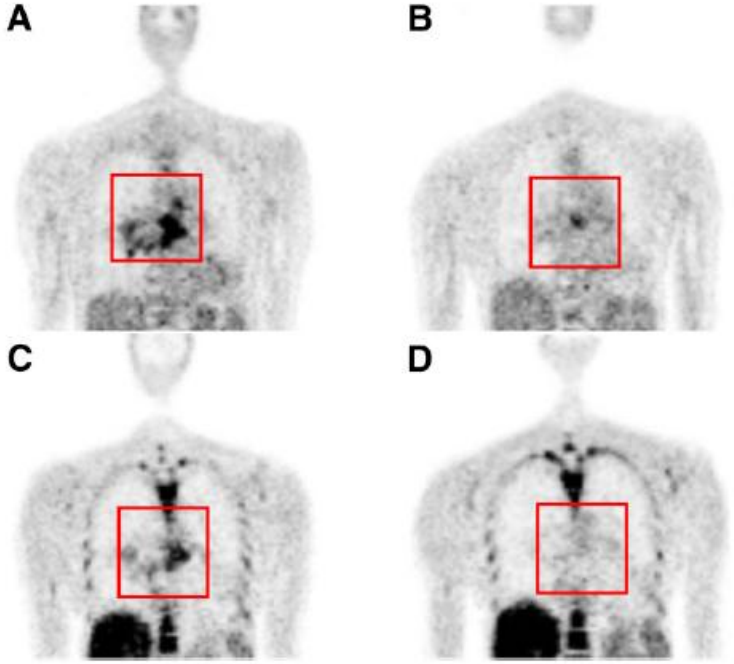


FIGURE 1. ^{18}F-FDG PET (A) and ^{18}F-FLT PET (C) before start of treatment, and ^{18}F-FDG PET (B) and ^{18}F-FLT PET (D) after 1 wk of treatment with erlotinib.

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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

Thomas Zander, Matthias Scheffler, Lucia Nogova, Carsten Kobe, Walburga Engel-Riedel, Martin Hellmich, Irini Papachristou, Karin Toepelt, Andreas Draube, Lukas Heukamp, Reinhard Buettner, Yon D. Ko, Roland T. Ullrich, Egbert Smit, Ronald Boellaard, Adriaan A. Lammertsma, Michael Hallek, Andreas H. Jacobs, Andreas Schlesinger, Karin Schulte, Silvia Querings, Erich Stoelben, Bernd Neumaier, Roman K. Thomas, Markus Dietlein, and Jürgen Wolf

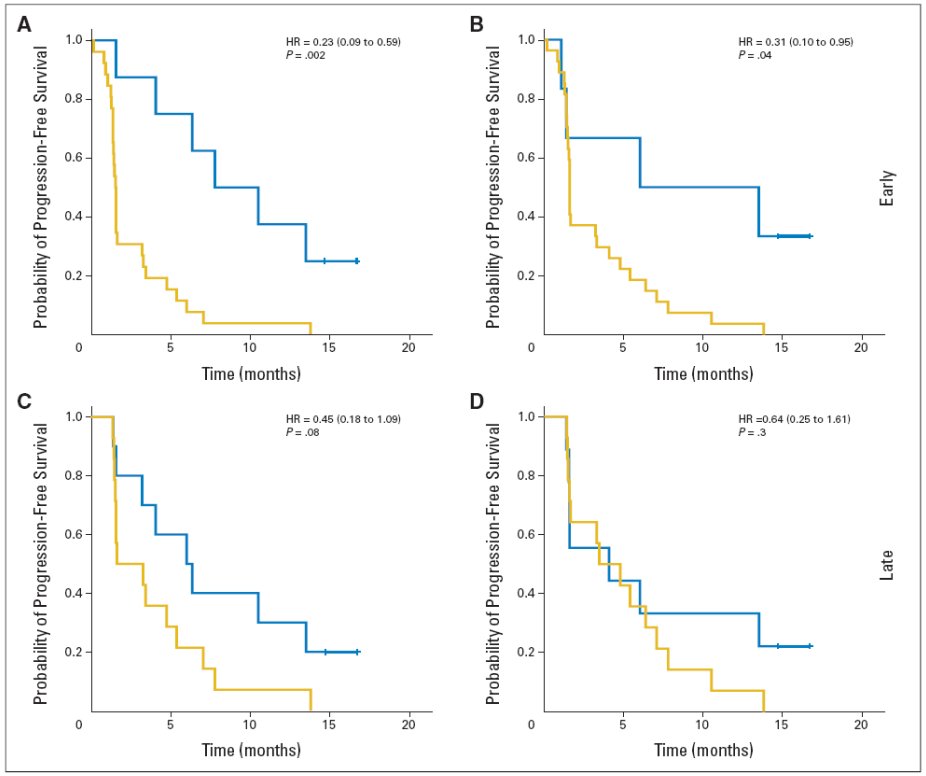

Fig 3. Early reduction in (A) 2′-deoxy-2′-[^{18}F]fluoro-D-glucose FDG and (B) 3′-[^{18}F]fluoro-3′-deoxy-L-thymidine (FLT) uptake is associated with longer progression-free survival. Late reduction in (C) FDG and (D) FLT positron emission tomography is not associated with progression-free survival. A cutoff of ≥ 30% reduction in standardized uptake value peak (SUV_{peak}) was used for classifying patients. Blue lines, metabolic response; gold lines, nonmetabolic response. HR, hazard ratio.

Pharmacodynamic Study Using FLT PET/CT in Patients with Renal Cell Cancer and Other Solid Malignancies Treated with Sunitinib Malate

Clin Cancer Res; 17(24) December 15, 2011

Glenn Liu[1,2,3], Robert Jeraj[1,2,4,5], Matt Vanderhoek[4], Scott Perlman[1,2,5], Jill Kolesar[1,7], Michael Harrison[1,2,3], Urban Simoncic[4], Jens Eickhoff[1,6], Lakeesha Carmichael[1,6], Bo Chao[3], Rebecca Marnocha[1,7], Percy Ivy[8], and George Wilding[1,3]

In summary, we have shown that during sunitinib treatment on both the 4/2 and 2/1 schedules, there are statistically significant increases in median sunitinib concentrations and median serum VEGF levels, and a median decrease in cellular proliferation as measured by SUV_{mean} and SUV_{max}. Change in VEGF during sunitinib treatment predicted change in SUV_{mean} during sunitinib withdrawal, which fits with the biologically plausible hypothesis that the rise in VEGF ligand during treatment may drive tumor flare during the withdrawal period. Finally, there was a suggestion of a more brisk proliferative flare in nonresponders compared with responders. This suggests that patients with a robust compensatory response to treatment-induced hypoxia (e.g., large flare) might develop early treatment failure as a result.

[^{18}F]Fluorothymidine Positron Emission Tomography before and 7 Days after Gefitinib Treatment Predicts Response in Patients with Advanced Adenocarcinoma of the Lung

Hee-Jung Sohn,[1] You-Jung Yang,[2] Jin-Sook Ryu,[2] Seung Jun Oh,[2] Ki Chun Im,[2] Dae Hyuk Moon,[2] Dae Ho Lee,[1] Cheolwon Suh,[1] Jung-Shin Lee,[1] and Sang-We Kim[1]

Clin Cancer Res 2008;14(22) November 15, 2008

Validity of Simplified 3′-Deoxy-3′-[^{18}F] Fluorothymidine Uptake Measures for Monitoring Response to Chemotherapy in Locally Advanced Breast Cancer

Mol Imaging Biol (2012)

Mark Lubberink,[1,2,5] Wieteke Direcks,[1] Jasper Emmering,[1] Harm van Tinteren,[4] Otto S. Hoekstra,[1] Jacobus J. van der Hoeven,[3] Carla F. M. Molthoff,[1] Adriaan A. Lammertsma[1]

Usefulness of 3′-Deoxy-3′-^{18}F-Fluorothymidine PET for Predicting Early Response to Chemoradiotherapy in Head and Neck Cancer

THE JOURNAL OF NUCLEAR MEDICINE • Vol. 53 • No. 10 • October 2012

Takehito Kishino[1], Hiroshi Hoshikawa[1], Yoshihiro Nishiyama[2], Yuka Yamamoto[2], and Nozomu Mori[1]

Evaluation of 2-Deoxy-2-[^{18}F]Fluoro-D-glucose- and 3′-Deoxy-3′-[^{18}F]Fluorothymidine–Positron Emission Tomography as Biomarkers of Therapy Response in Platinum-Resistant Ovarian Cancer

Mol Imaging Biol (2012)

Meg Perumal,[1] Euan A. Stronach,[2] Hani Gabra,[2] Eric O. Aboagye[1]

FDG

LYMPHOMA

END TREATMENT

SOLID TUMORS

DURING TREATMENT

FLT

OTHER

SOLID TUMORS

EARLY DURING TREATMENT

THANK YOU