Η συμβολή της Τομογραφίας Εκπομπής Ποζιτρονίων στην εκτίμηση της αποτελεσματικότητας των θεραπευτικών παρεμβάσεων

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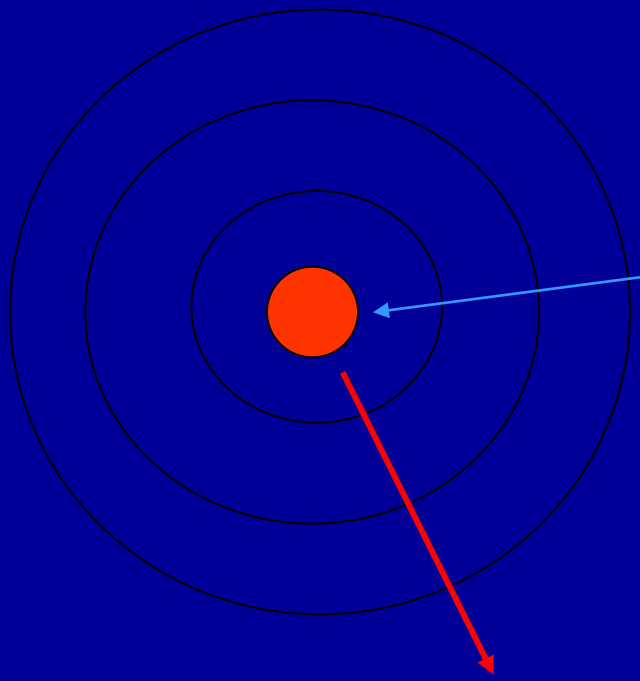
ΙΔΡΥΜΑ ΙΑΤΡΟΒΙΟΛΟΓΙΚΩΝ ΕΡΕΥΝΩΝ

PET and treatment response

- Fundamentals
- Oncology
- Sarcoidosis
- IBD
- RA
- CVD



unstable nucleus

positron emitted

β^+

β^+/e^-

511keV

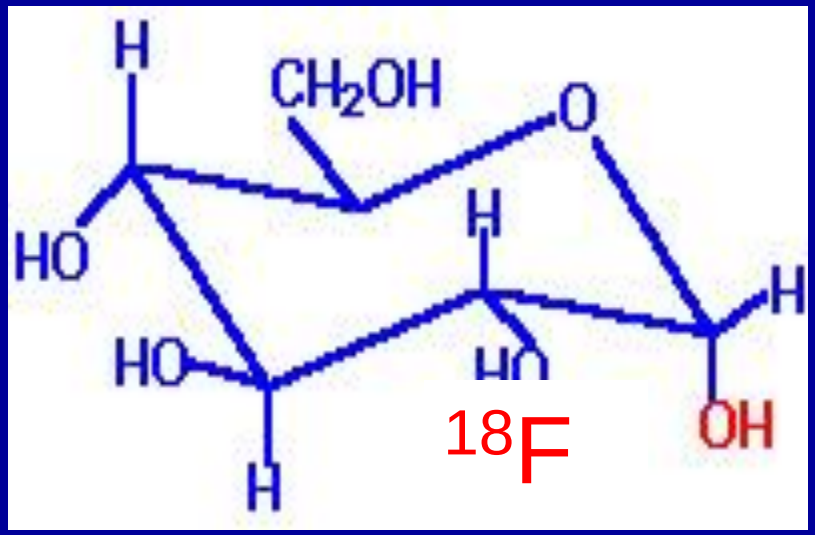
511keV

annihilation with electron & production of two 511keV gamma photons

Radioisotopes

Radioisotope	Half life (min)	Maximum Energy (MeV)
F-18	110	0.635
C-11	20.4	0.96
N-13	9.96	1.19
O-15	2.07	1.72
Ga-68	68.3	1.9
Rb-82	1.25	3.35

F-18 Deoxy-Glucose (FDG) PET Imaging



FDG…

- is a positron emitter
- has a half-life of 110 minutes
- can be imaged by PET

Tracers other than FDG

- Glucose metabolism using ^{18}F-FDG

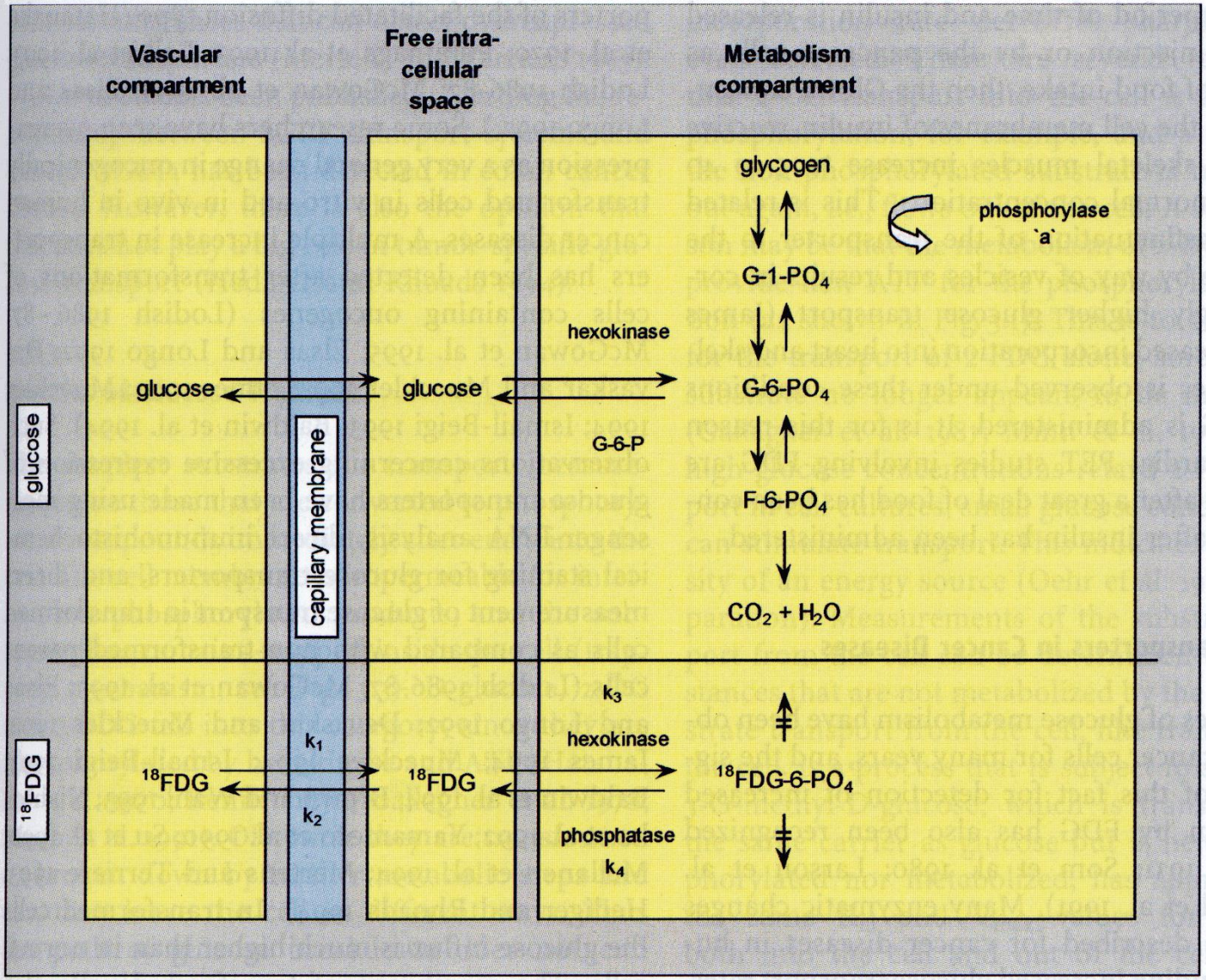
- Cell proliferation
  - ^{18}F Fluro- L-Thymidine (FLT) for assessment of cellular-proliferative activity
  - FLT: in principle, an attractive tracer for monitoring tumor treatment response
- Somatostatin receptors
  - ^{68}Ga-D-Phe1-Tyr3-octreotide (^{68}Ga-DOTATOC) and Gluc-Lys(18F-fluoropropionyl-TOCA

- ^{18}F-Choline (precursor for phospholipids) for prostate cancer
- ^{18}F-Fluoride for bone assessment (like a bone scan)
- ^{18}F-fluoromisonidazole (^{18}F-FMISO), ^{18}F arginine glycine–aspartic acid (^{18}F galacto RGD), ^{18}F annexin etc...

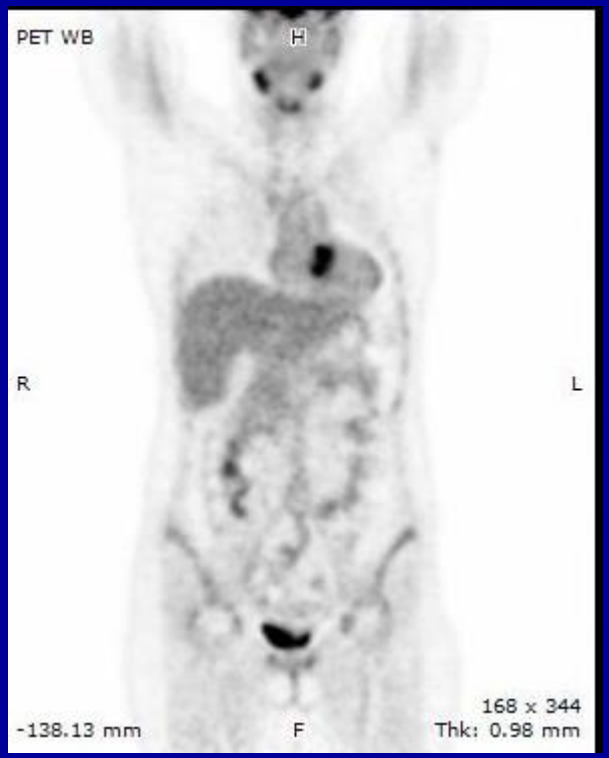
FDG Transport into the cells

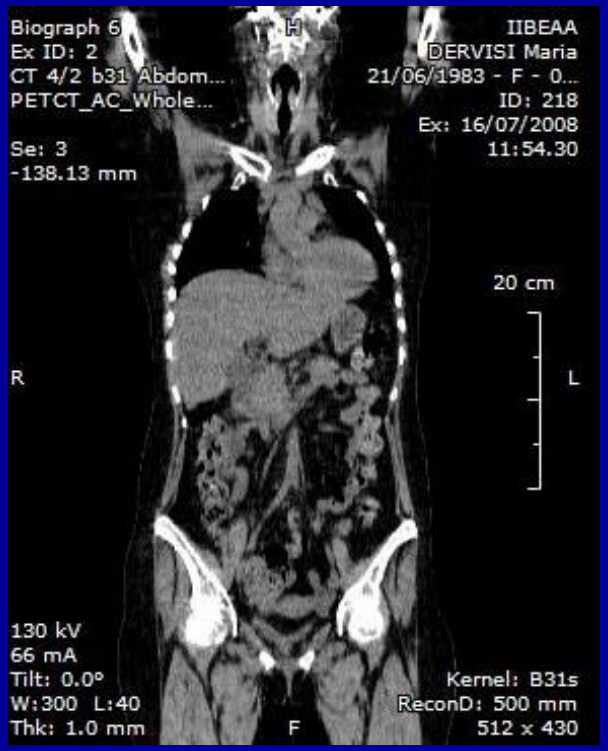
Table 3.1. Glucose Transport Systems

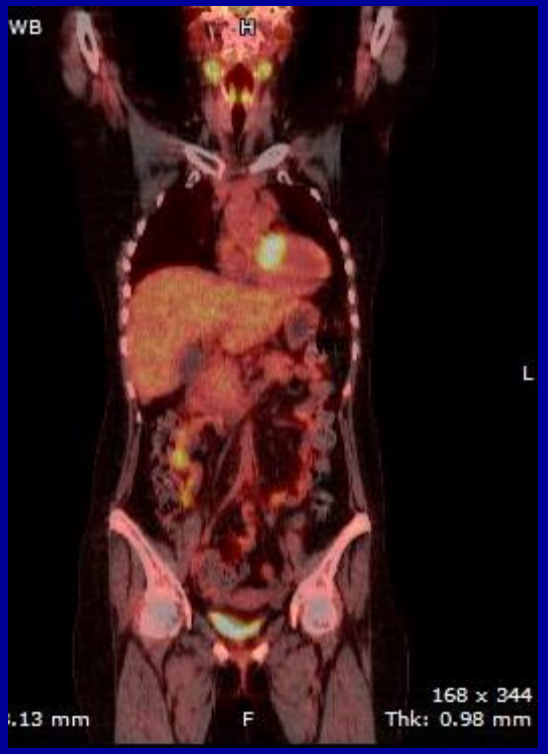
Transporter System	Occurrence	No. of Amino Acids	Chromosome Location	Kinetics	Insulin-Sensitive
I. Na^+-glucose cotransport or symport				**Transport to concentration gradient**	
SGLT 1 Na^+/glucose cotransporter	Small intestine Proximal renal tubule	664	22		
SGLT-2 Na^+/glucose cotransporter	Distal renal tubule				
II. Facilitated diffusion				**Passive transfer along a gradient**	
	Red blood cells	492	1	K_m 5–30 mM	–
Glut-1	Brain, kidney, colon, fetal tissue, placenta			Asymmetrical K_m in $<<$Km out	–
Glut-2	*Liver*, β-cells, kidney, small intestine	524	3	K_m liver 60 mM Symmetrical	–
Glut-3	*Fetal muscle*, brain, placenta, kidney (fibroblasts, smooth muscle tissue)	496	12	K_m 10 mM	–
Glut-4	Cardiac muscle, skeletal muscle, fat cells	509	17	K_m 2 – 5 mM	+ (20–30)
Glut-5	Small intestine	501	1	High affinity for fructose	–


Vascular compartment
Free intra-cellular space
Metabolism compartment
glycogen
phosphorylase `a`
G-1-PO4
hexokinase
glucose
glucose
G-6-PO4
G-6-P
F-6-PO4
CO2 + H2O
glucose
capillary membrane
k3
k1
hexokinase
18FDG
18FDG
18FDG-6-PO4
k2
phosphatase
k4
18FDG

Example of FDG-PET normal scan







PET-FDG in Oncology

- Metabolic Imaging of the malignancies
- Malignant cells have higher metabolic rate and take up more FDG

Understanding the signal seen with FDG PET

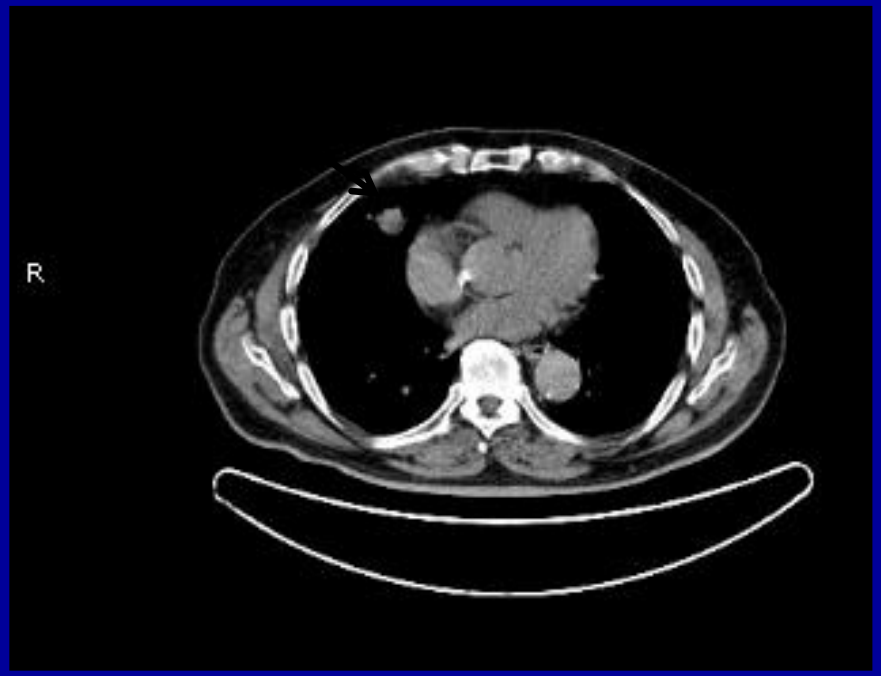
- Malignant cells have a higher glycolytic rate
  - Hypoxia, activation of hypoxia inducible factors (HIFs)
  - ⇑Gluts-1, 3 in the cell membrane are responsible for ⇑FDG uptake
  - ⇑ hexokinase activity
  - Microvessel density
  - Total number of tumor cells/proliferation rate
  - Histology
- Identification of a lesion depends on the intensity of metabolic activity, resolution limits of PET and background activity in surrounding tissues

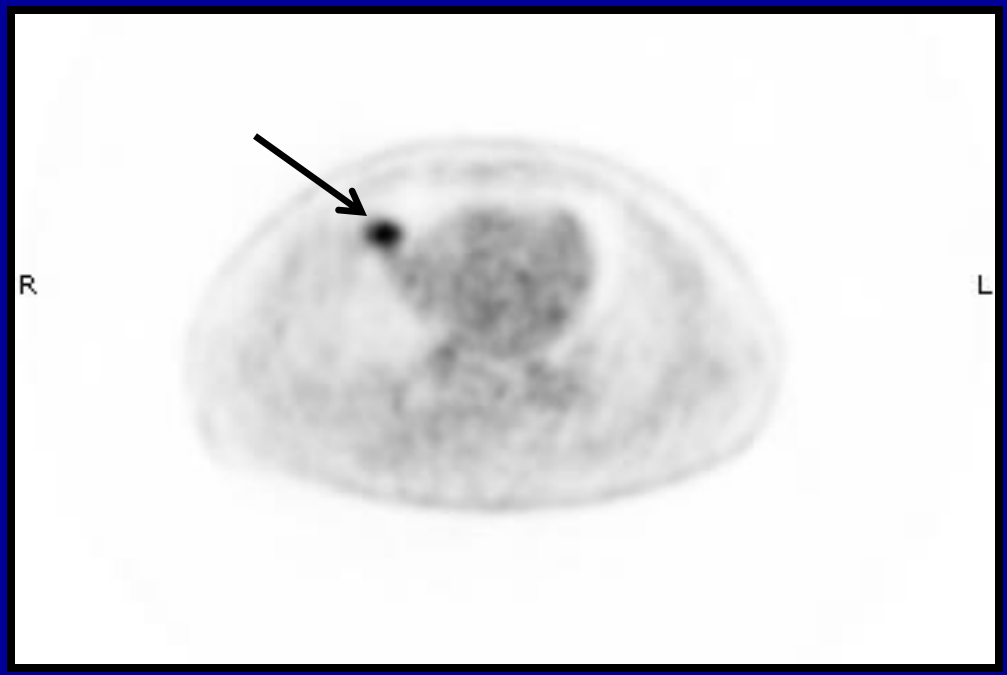
SUV- standard uptake value

- SUV = $[FDG]_{tissue}$(μCi/g)/(injected dose(mCi)/wt(g)) * calibration factor
  - Dependent on
    - Time from injecting to scanning
    - Plasma glucose
    - Partial volume effect
    - Reconstruction method
  - Reproducibility in the region of 15-20%

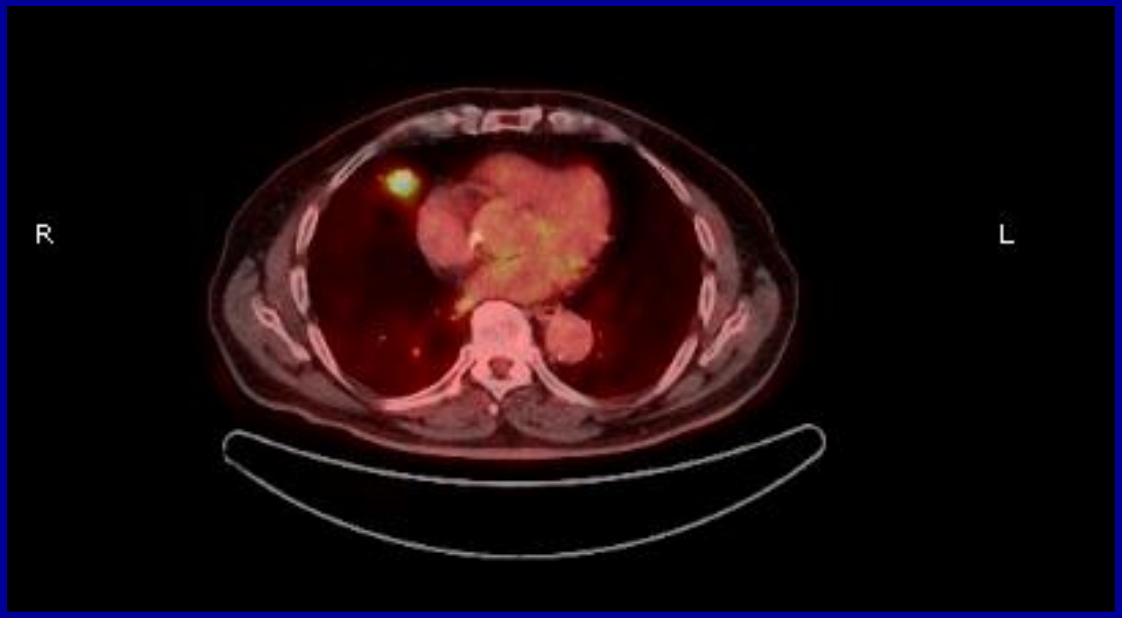
Utility of PET/CT in cancer

- Benign vs. malignant
- Detecting the primary tumour when unknown
- Correct staging
- Recurrence
- Therapy planning
- Therapy monitoring or follow-up





Μονήρης πνευμονικός όζος



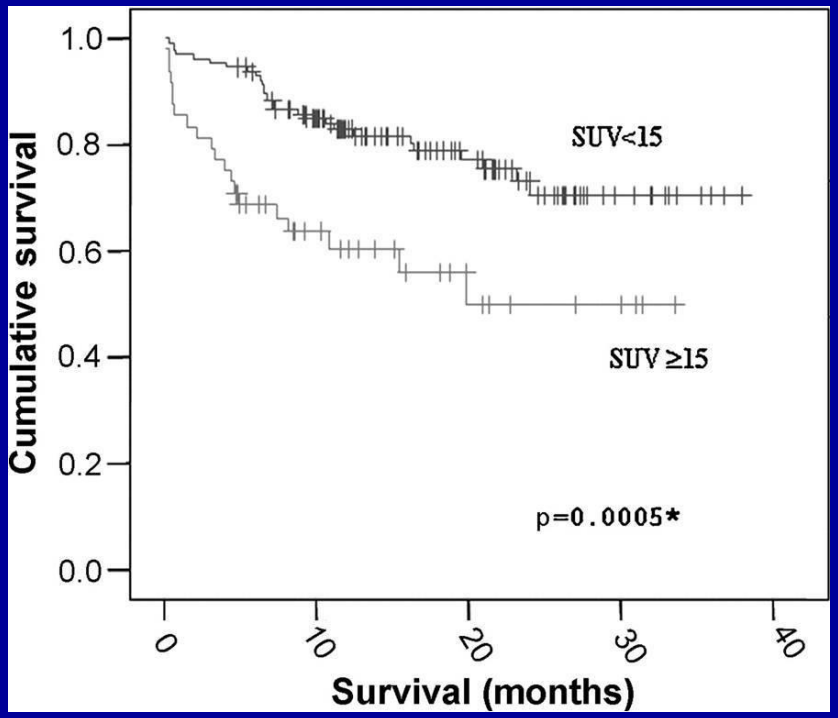
SUVmax=5.6

Κακοήθεια

Prognostic significance of standardised uptake value (SUV) of primary non-small cell lung cancer (NSLC) on PET

176 consecutive patients with histologically proven NSCLC

SUVmax was significantly higher in centrally located tumours, tumours 4.0 cm, squamous cell subtype, poorly differentiated tumours, advanced T stage, advanced nodal stage, pleural invasion, and patients requiring complex surgical resection.



Kaplan–Meier survival curve for all patients

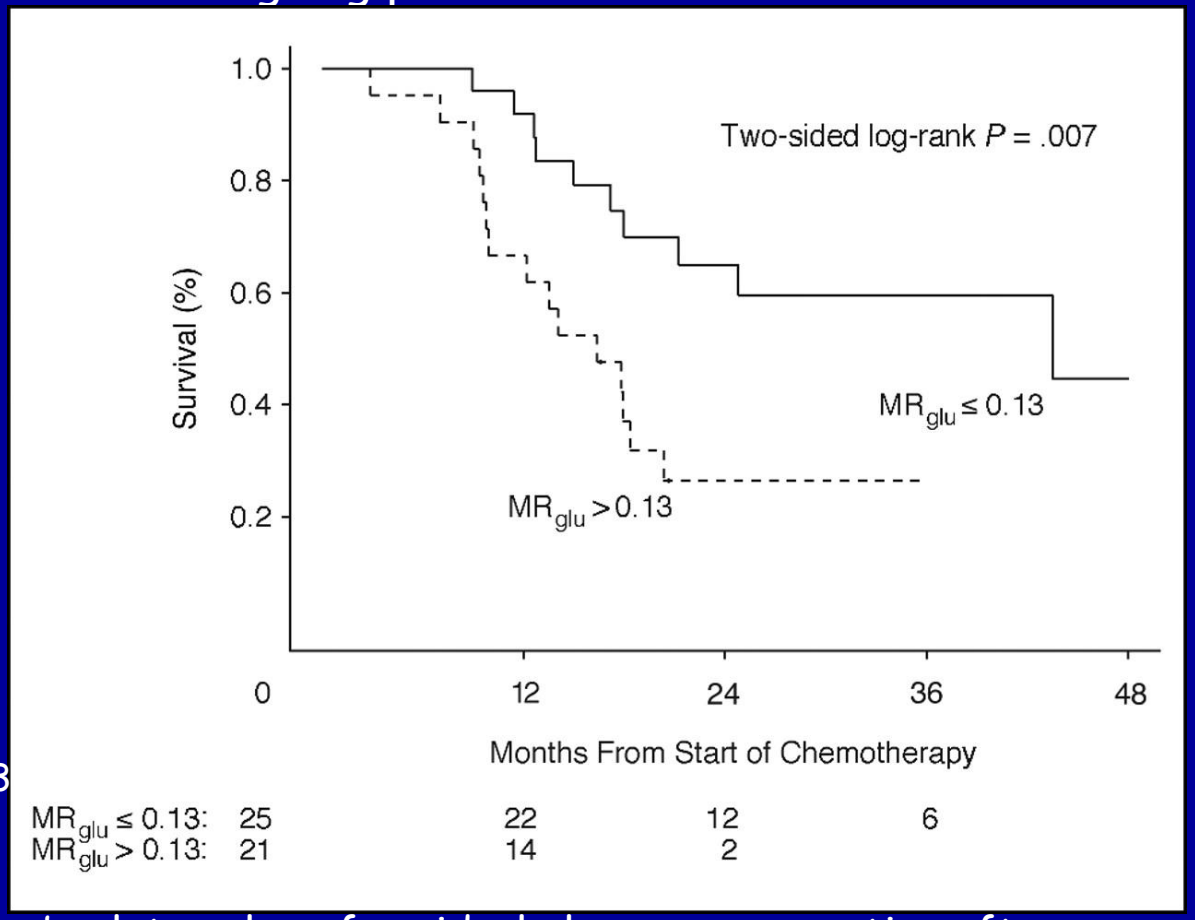
Al-Sarraf N et al. Eur J Cardiothorac Surg 2008;34:892-897

Effect of treatment-Ca Lung

Stage	Study	No. of patients	Criteria for response on PET	Outcome measure	*P*
IIIA	Vansteenkiste et al.	15	50% ↙ in SUV	Overall survival	0.03
I–III	MacManus et al.	73	CMR	Overall survival	0.0004
IIIB–IV	Weber et al.	57	20% ↙ in SUV	Overall survival	0.005
IIB–III	Hellwig et al.	47	SUV < 4	Overall survival	<0.001
IIIA	Hoekstra et al.	47	MR_{glu} < 0.13 µmol/mL/min	Overall survival	0.0003
III	Eschmann et al.	70	CMR or 80% ↙ in SUV	Overall survival	0.005
IB–IV	de Geus-Oei et al.	51	MR_{glu} > 47%	Overall survival	0.017
IIIB–IV	Nahmias et al.	16	↙ in SUV at wk 1–3	Overall survival	0.0016
IB–IIIB	.Tanvetyanon et al.	89	CMR or PMR	Overall survival	NS

Prognostic Relevance of Response Evaluation Using FDG PET in Patients With Locally Advanced NSCLC

To determine the accuracy of early (after one cycle) response measurements using ^{18}FDG PET with respect to survival of patients with stage IIIA-N2 NSCLC undergoing platinum-based induction chemotherapy

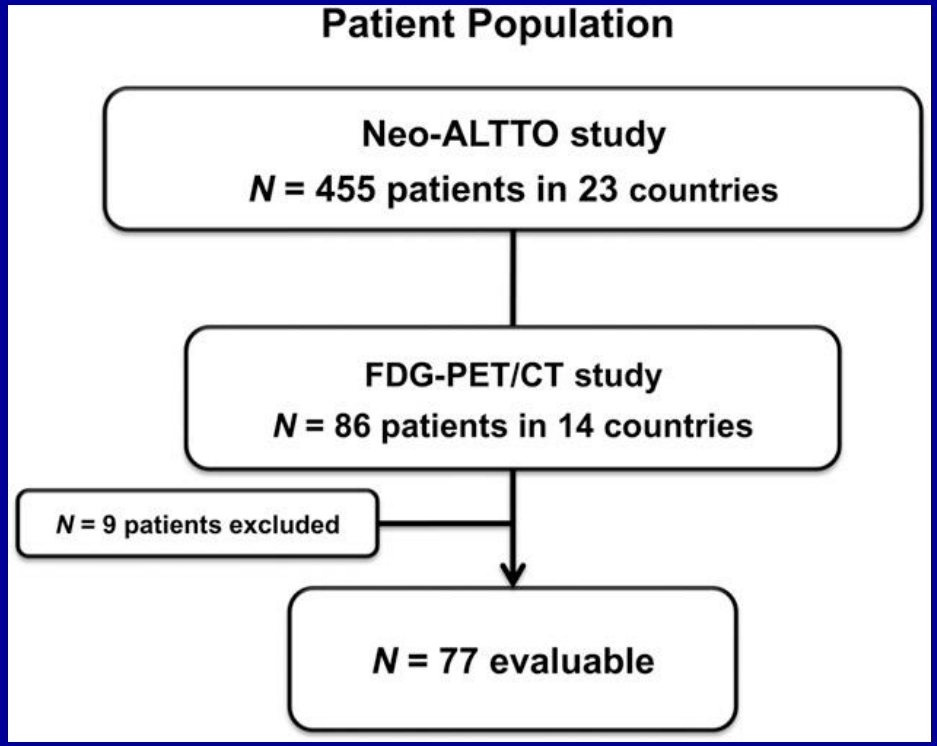


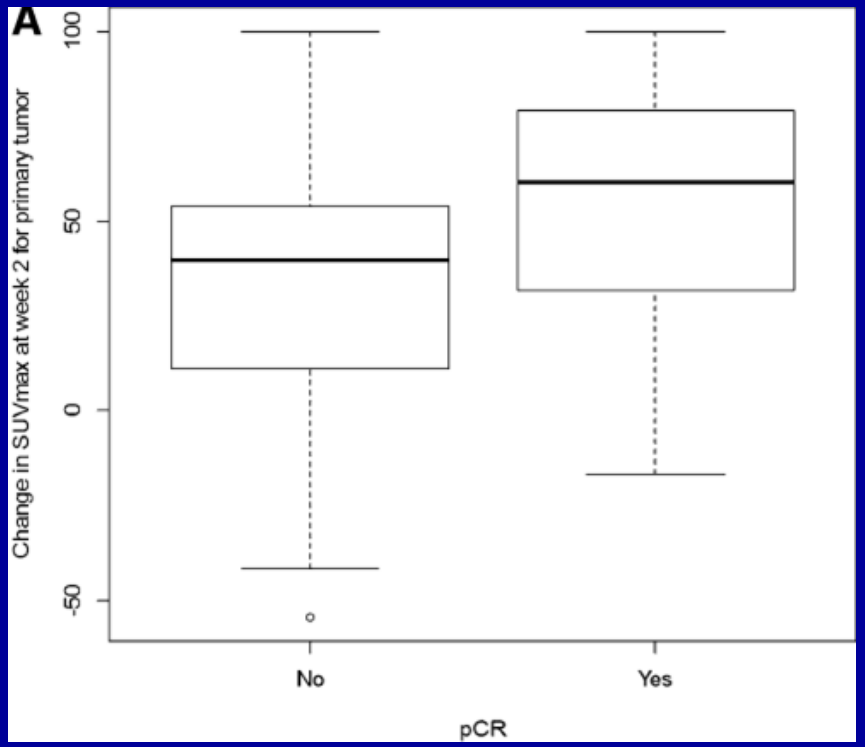
MR_{glu} threshold of 0.13 μmol/mL/min

Survival by absolute value of residual glucose consumption after one course of induction chemotherapy

Hoekstra C J et al. JCO 2005

Early Prediction of Response to Neoadjuvant Lapatinib, Trastuzumab and Their Combination in HER2* + Breast Cancer





*Human Epidermal Growth Factor Receptor-2

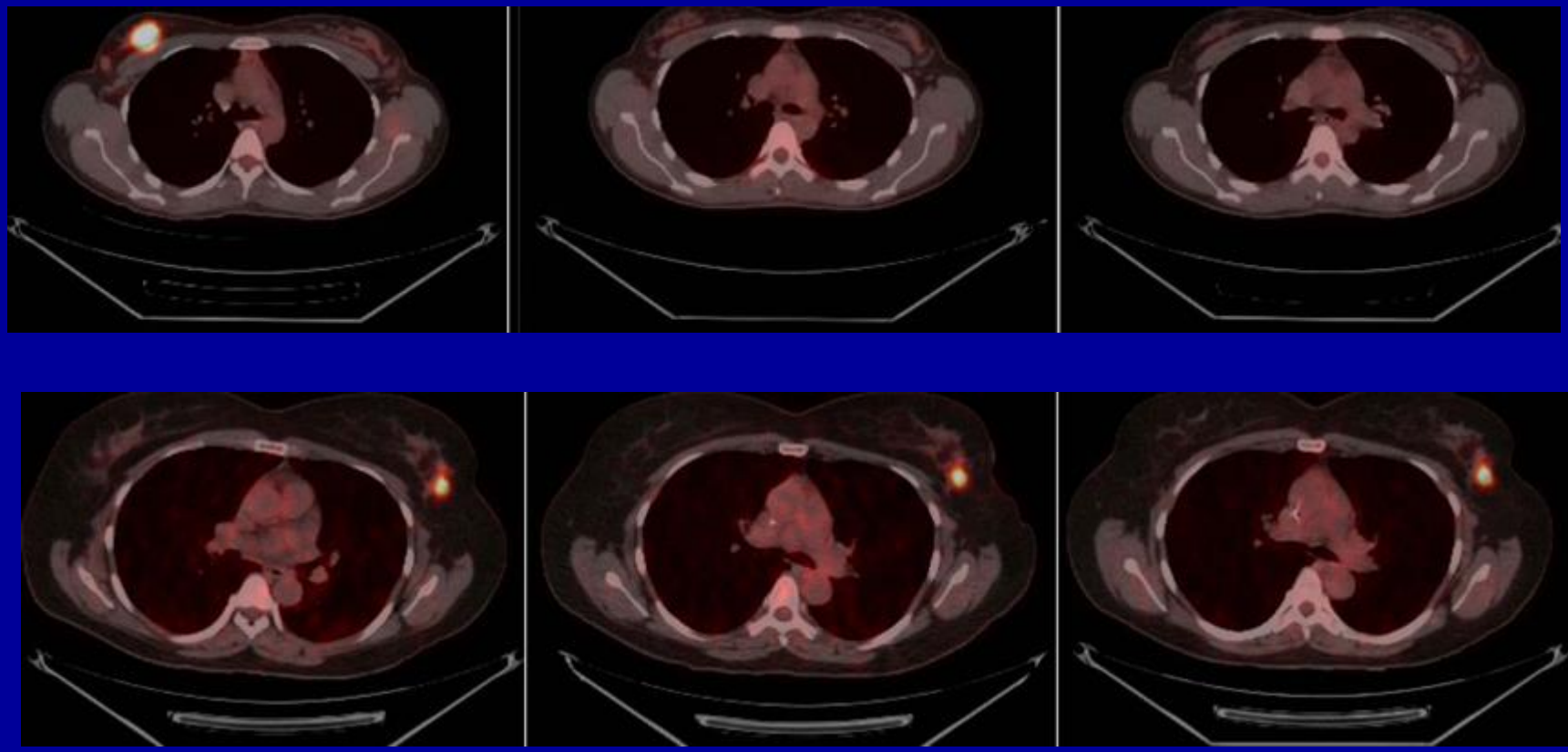
pCR: pathologic complete response

Mean SUVmax reductions were 54.3% versus 32.8% at week 2

J Gebhart et al J Nucl Med 2013 doi:10.2967/jnumed.112.119271

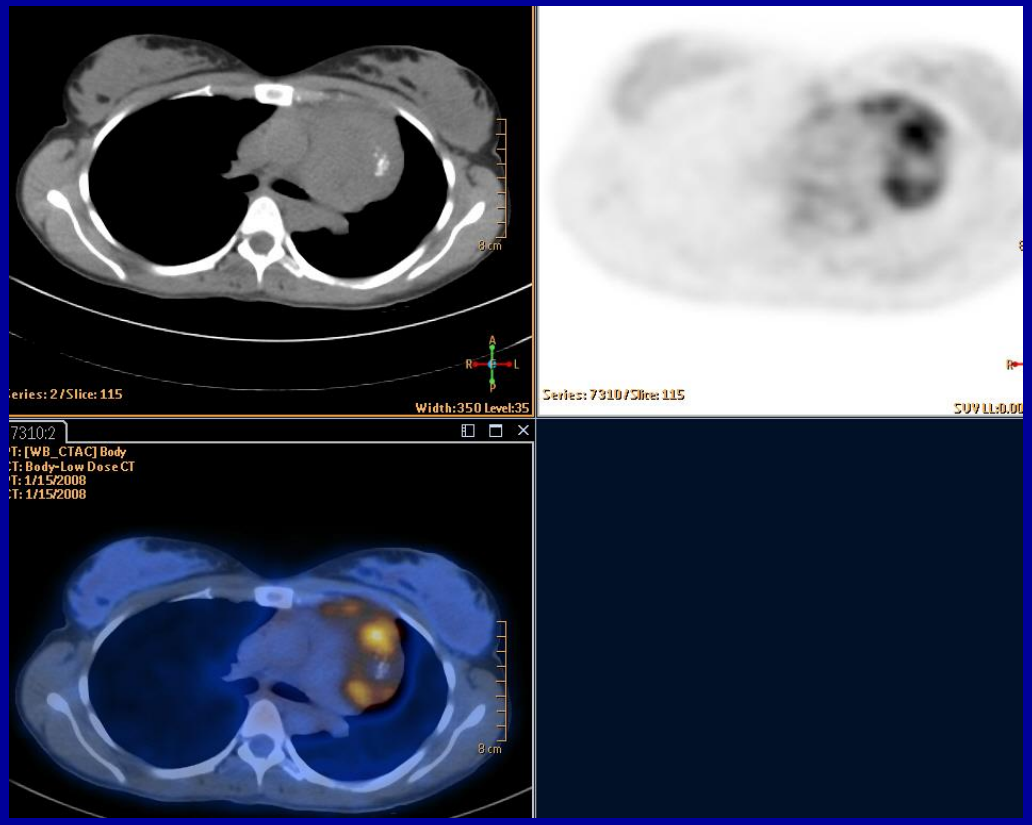
Early Prediction of Response to Neoadjuvant Lapatinib, Trastuzumab and Their Combination in HER2 + Breast Cancer

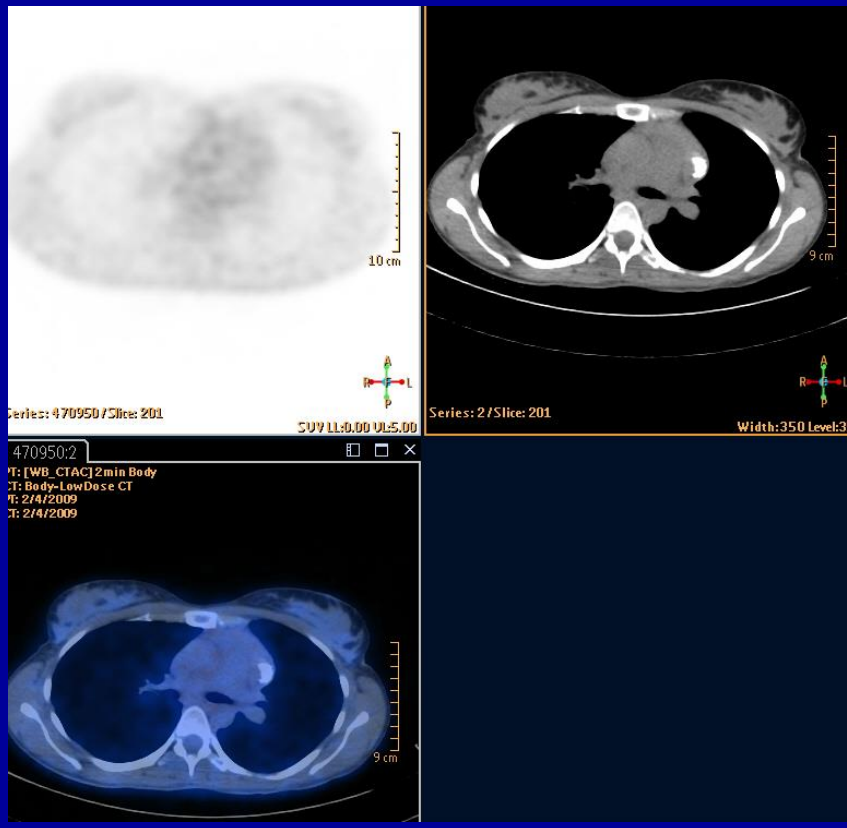
The presence of response at week 2 (SUV at least 15% lower compared to baseline value) was predictive of response at week 6, with a positive predictive value of 78.5%



Absence of response in the primary tumor at week 2 was predictive of non-response at week 6, with a negative predictive value of 90%

Assessment of response to treatment in lymphoma





Pre-treatment Scan

Post-treatment Scan

Sensitivity results of both ^{18}F-FDG PET/CT and Ga^{67} scintigraphy in detecting active sarcoidosis

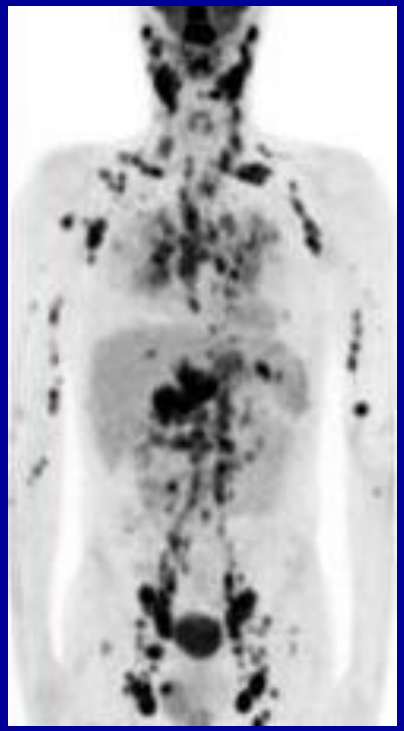
Location of biopsy-proven sarcoidosis involvement	^{18}F-FDG PET/CT			^{67}Ga scintigraphy		
	No. of examined Patient	No. of biopsied sites	Sensitivity (%)	No. of examined patient	No. of biopsied sites	Sensitivity (%)
Thoracic	13	13	100	7	7	71
Sinonasal	5	5	100	4	4	75
Pharyngo-laryngeal	5	5	80	3	3	67
Thoracic & extra-thoracic	20	31	87	12	21	67
Thoracic & extra-thoracic	12	21	86	12	21	67

Increased FDG uptake correlates with CD4/CD8 and neutrophils

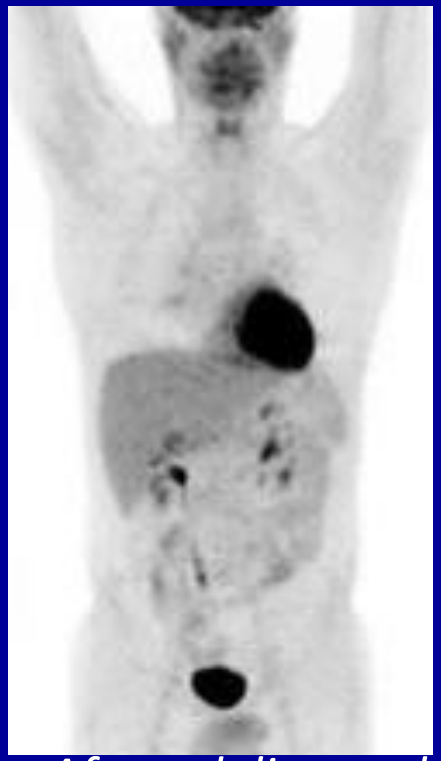
JJ Braun et al. Eur J Nucl Med Mol Imaging (2008) 35:1537-1543

Effect of the TNF-a inhibitor adalimumab in patients with recalcitrant sarcoidosis

Patients continued medication with steroids and antimetabolites and received adalimumab 40 mg subcutaneously every other week.



9/10 responders



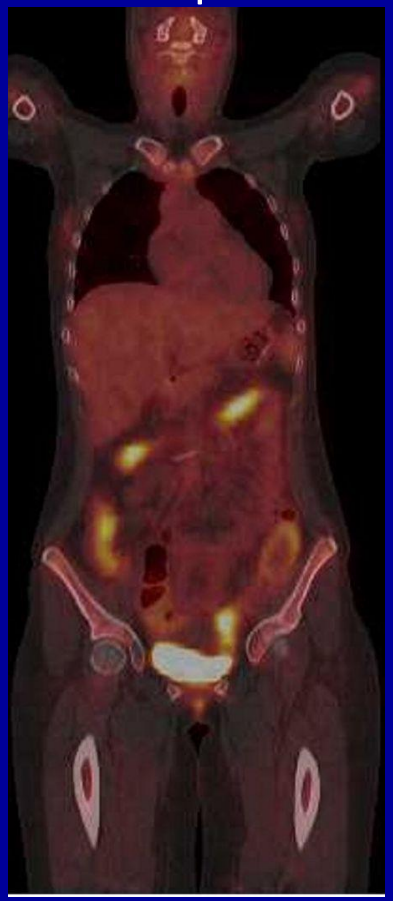
SF-36 score Improved in 8patients

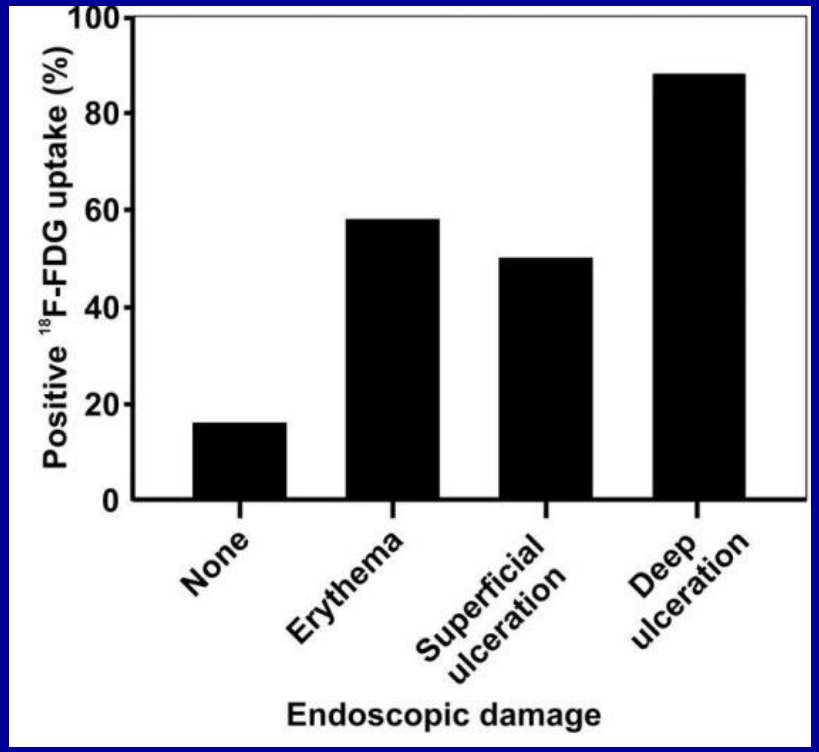
Before adalimumab	*After adalimumab*	*P value**
SUVmean 6.5 (1.5–13.2)	2.9 (1.2–10.3)	<0.017
SUVmax 14.1 (3.0–36.4)	7.0 (2.0–29.9)	<0.028

N Milman et al Clin Respir J 2012

FDG PET/CT Imaging to Monitor Lesion Activity in Intestinal Inflammation

^{18}F-FDG PET/CT scans of 25 Crohn disease patients were analyzed and colonic ^{18}F-FDG uptake was correlated to endoscopically assessed damage



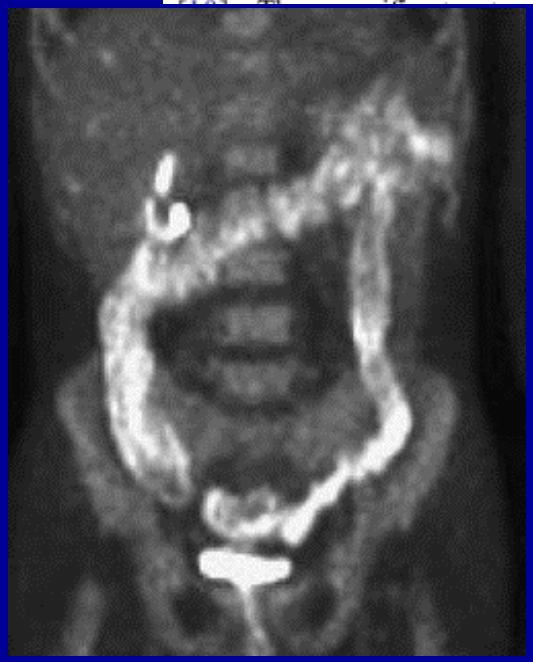


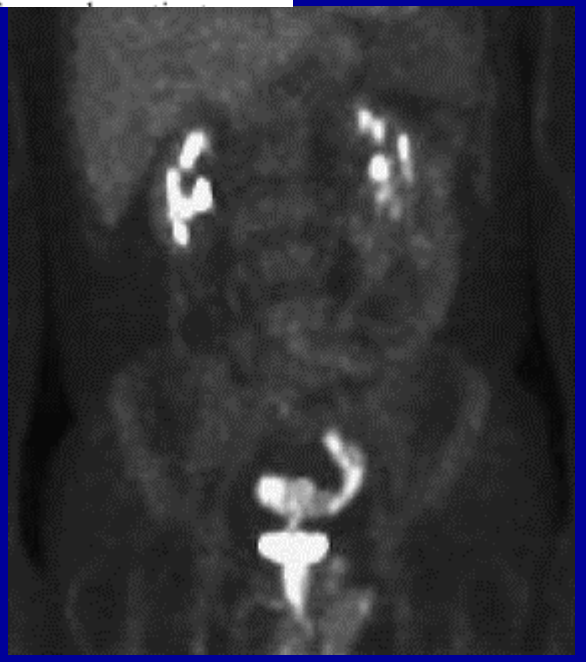
PET/CT was considered positive if the SUVmax for the segment analyzed was higher than 4

D Bettenworth et al J Nucl Med 2013; 54:748-755

PET/CT in the evaluation of inflammatory bowel disease: studies in patients before and after treatment

Physician global assessment scores were calculated for each patient before and after treatment. There were six categories from which an overall score was generated including points for the following: general well-being (0–4), abdominal pain (0–3), diarrhea (average number of liquid stools/24 h), blood in stool (0–2), abdominal mass (0–3), and complications (one per complication of eight possible)



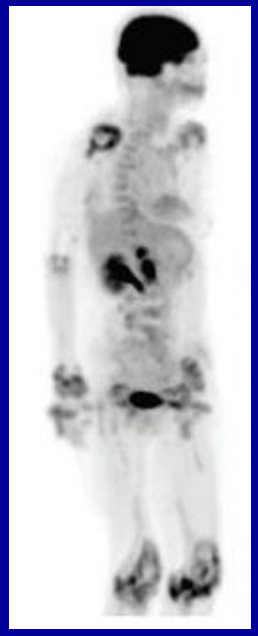


All patients showed significant improvement in physician global assessment scores

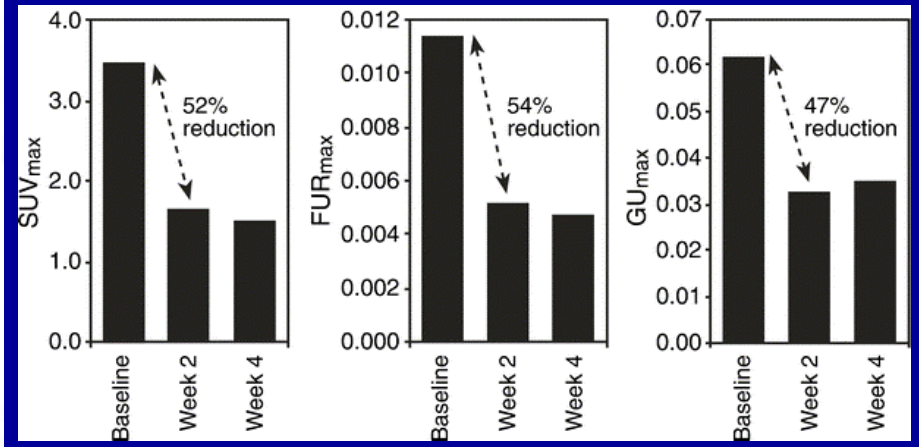
B. J. Spier et al Mol Imaging Biol (2010)

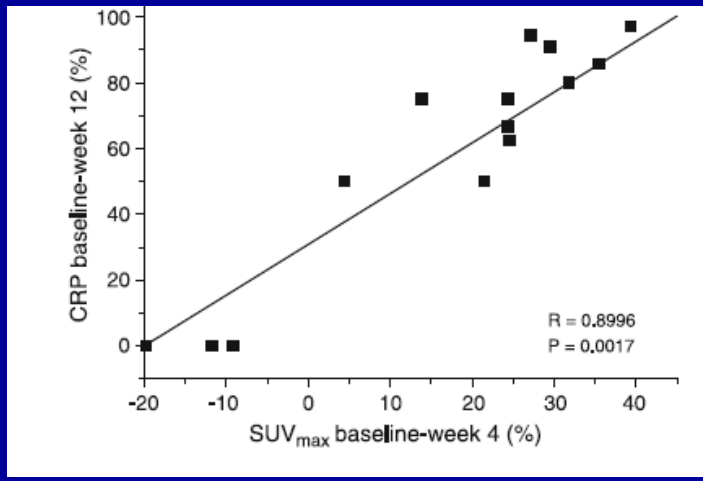
Correlation of 18F-FDG PET/CT assessments with disease activity and markers of inflammation in early rheumatoid arthritis following the initiation of combination therapy with triple oral antirheumatic drugs

17 patients with active RA in whom combination therapy was initiated with methotrexate, sulfasalazine, hydroxychloroquine and low-dose oral prednisolone. Clinical disease activity was assessed at screening, at baseline and after 2, 4, 8 and 12 weeks of therapy.



Treatment response was assessed using ACR criteria and DAS



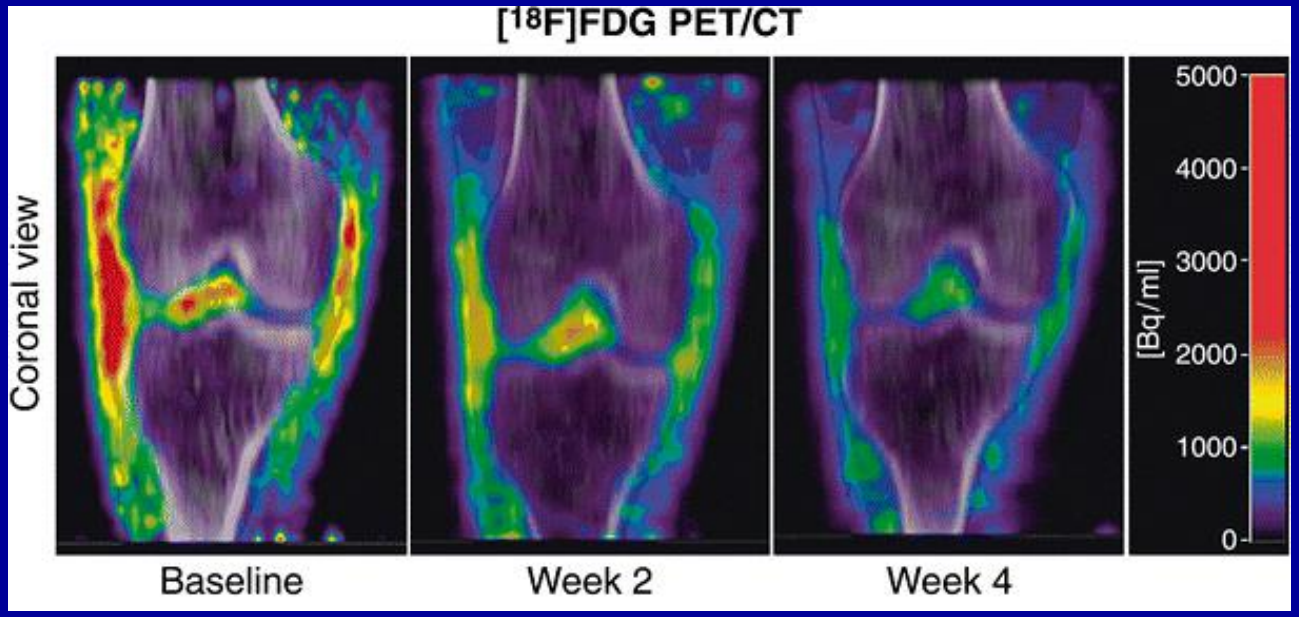


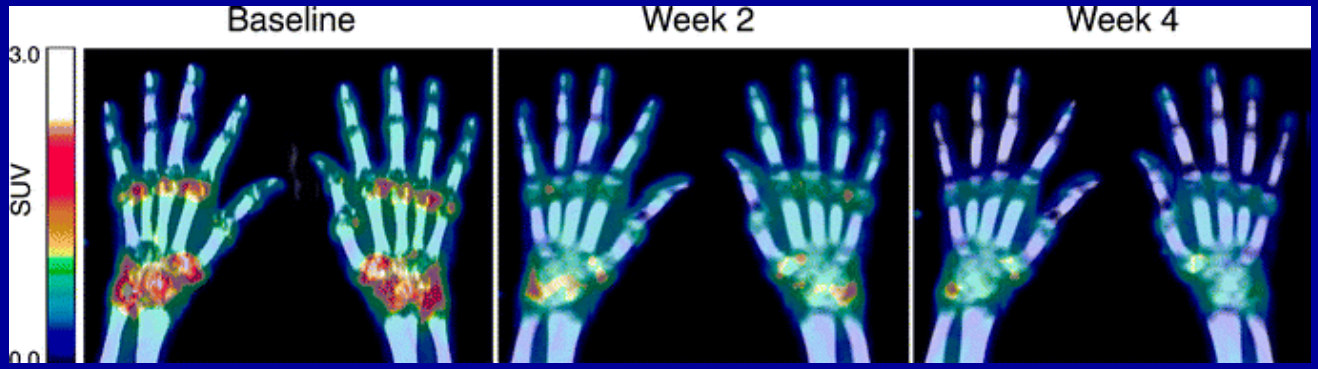
*FUR: fractional uptake rate

*GU: glucose uptake rate

A Roivainen et al. E JNMMI 2013

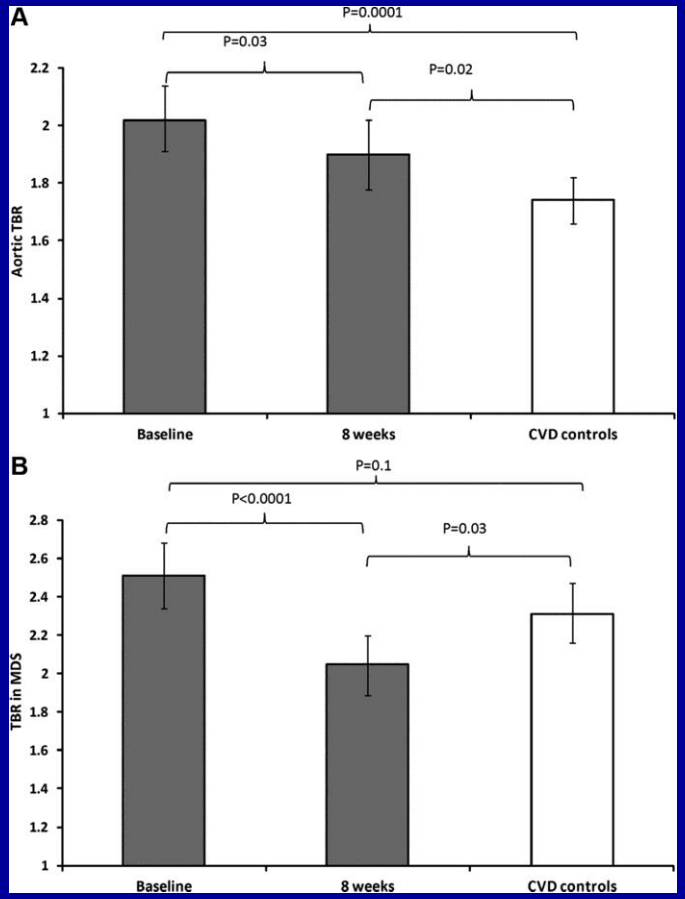
Correlation of 18F-FDG PET/CT assessments with disease activity and markers of inflammation in early rheumatoid arthritis following the initiation of combination therapy with triple oral antirheumatic drugs





Anti-Tumor Necrosis Factor-α Therapy Reduces Aortic Inflammation and Stiffness in Patients With Rheumatoid Arthritis

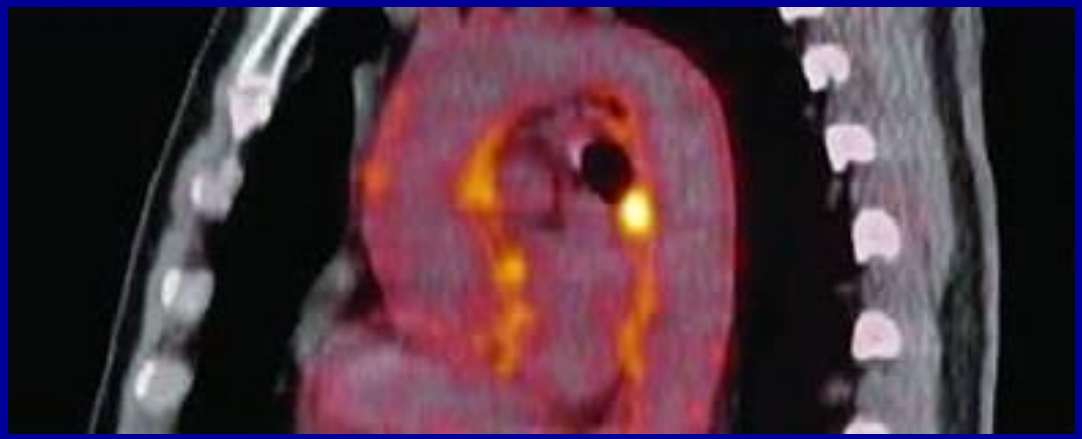
Aortic inflammation was quantified in 17 patients with RA, before and after 8w

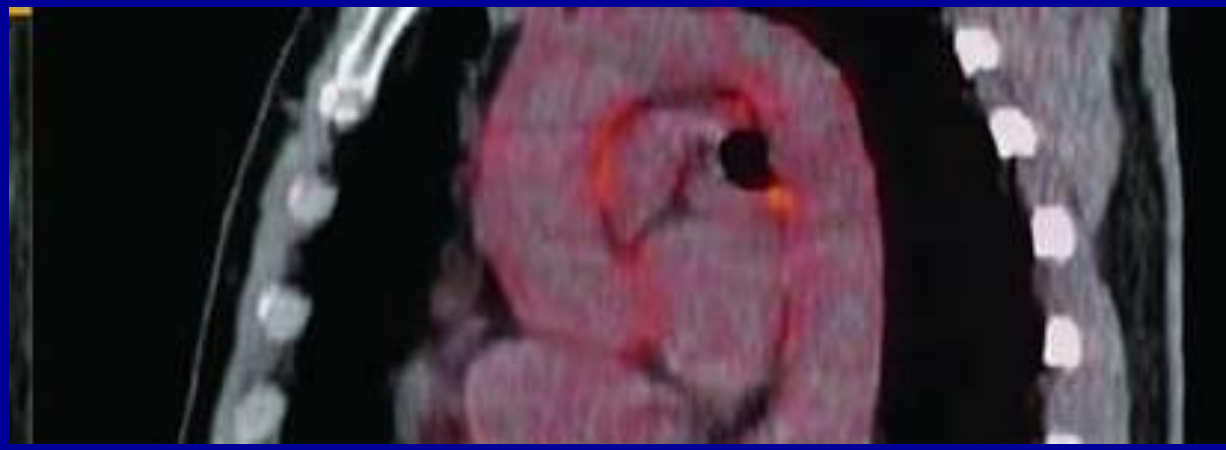


	Baseline	8 wk	*P*
DAS28 score	6.52±0.78	4.38±1.61	<0.0001
CRP, mg/L*	11.0 (4.0–29.0)	3.0 (2.0–10.0)	0.007
ESR, mm/h*	22 (8.5–41.0)	13.0 (7.0–17.0)	0.04
MAP, mm Hg	104±11	104±12	0.9
Augmentation index, %	31±11	33±11	0.4
Brachial PWV, m/s	9.00±1.23	8.56±1.11	0.06
Aortic PWV, m/s	9.09±1.77	8.63±1.42	0.04
Baseline diameter, mm	3.94±0.59	3.91±0.68	0.8
FMD, %	3.54±2.34	6.66±3.17	0.003
GTN response, %	9.53±4.26	8.29±5.63	0.9

Mäki-Petäjä K M et al. Circulation 2012;126:2473-2480

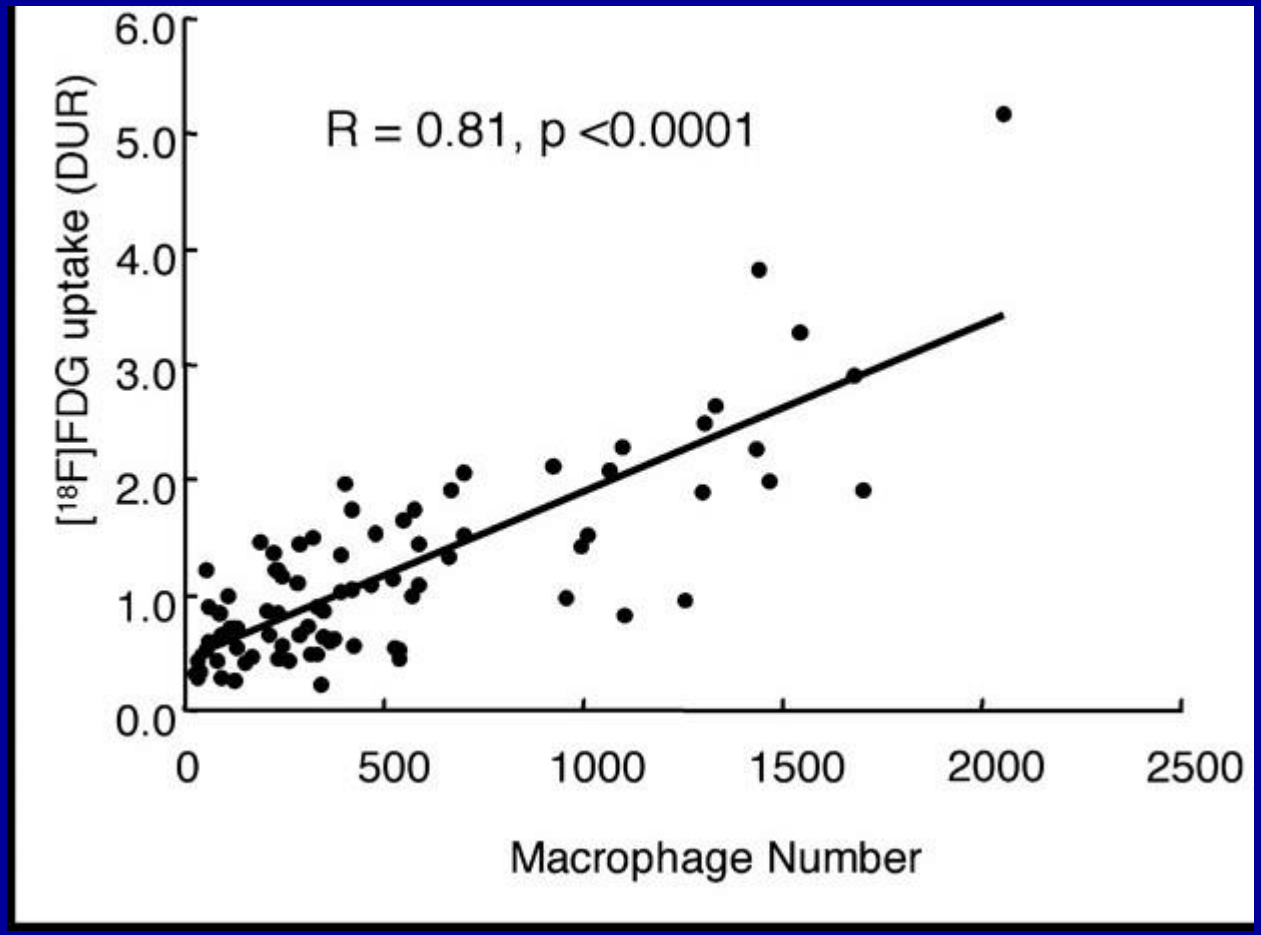
Anti-Tumor Necrosis Factor-α Therapy Reduces Aortic Inflammation and Stiffness in Patients With Rheumatoid Arthritis





Mäki-Petäjä K M et al. Circulation 2012;126:2473-2480

^{18}F-FDG Accumulation in Atherosclerotic Plaques

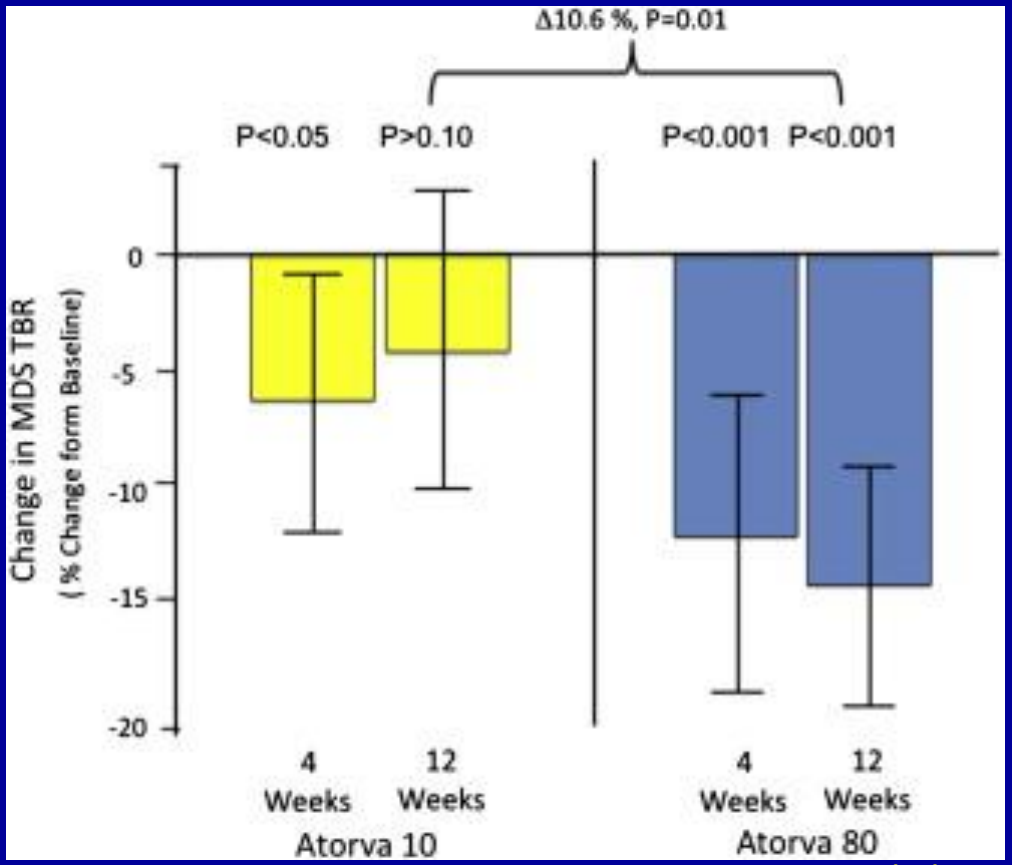


Correlation Between ^{18}F-FDG Uptake and macrophages from a rabbit model of atherosclerosis

J Nucl Med 2004; 45:1245-50

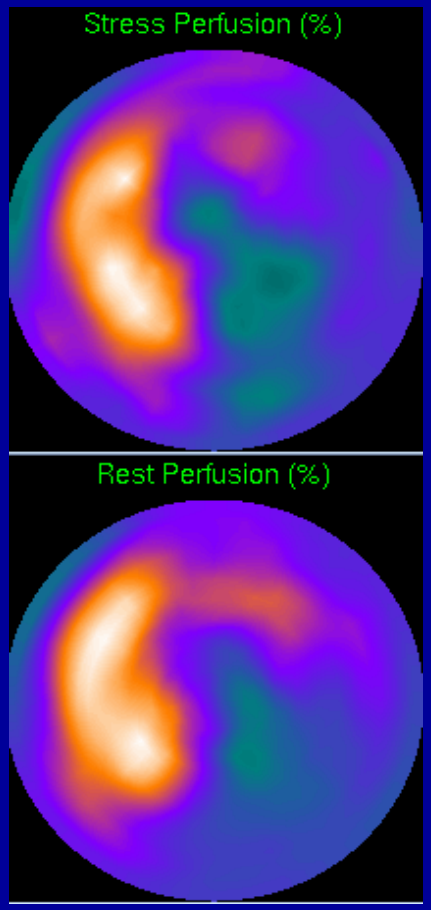
Intensification of Statin Therapy Results in a Rapid Reduction in Atherosclerotic Inflammation Results of a Multicenter FDG-PET

FDG imagjng of the ascending thoracic aorta and carotid arteries at baseline, 4, and 12 weeks after randomization and target-to-background ratio of FDG uptake within the artery wall was assessed in 76 pts

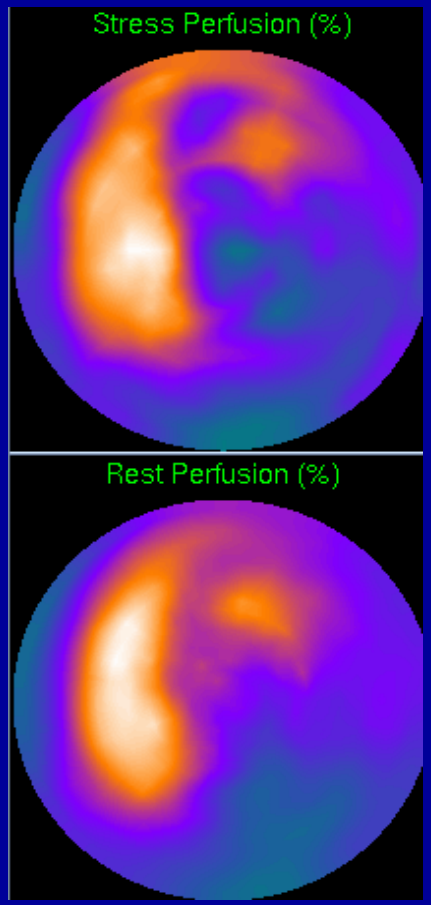


A Tawakol et al J Am Coll Cardiol 2013

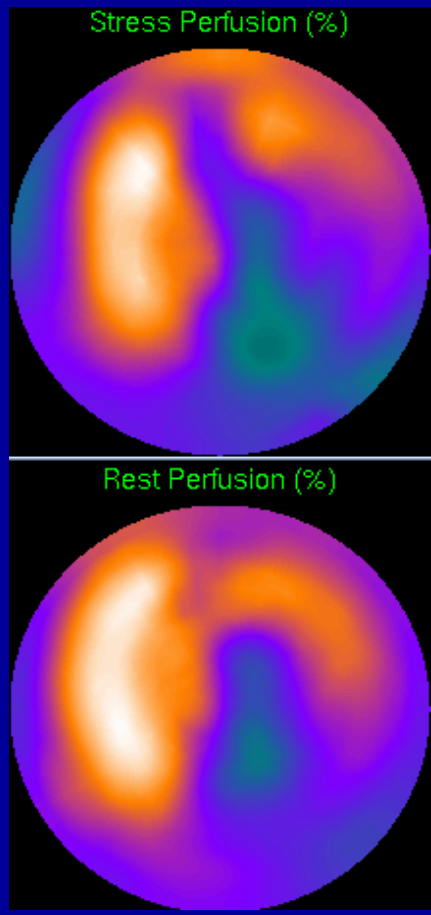
Monitoring the effect of Stem cell therapy



Before



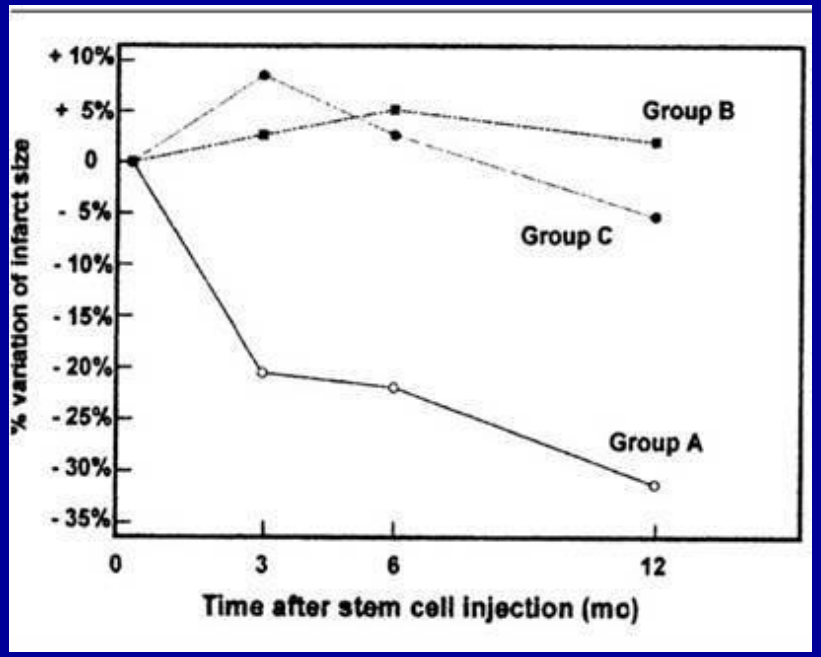
6 months

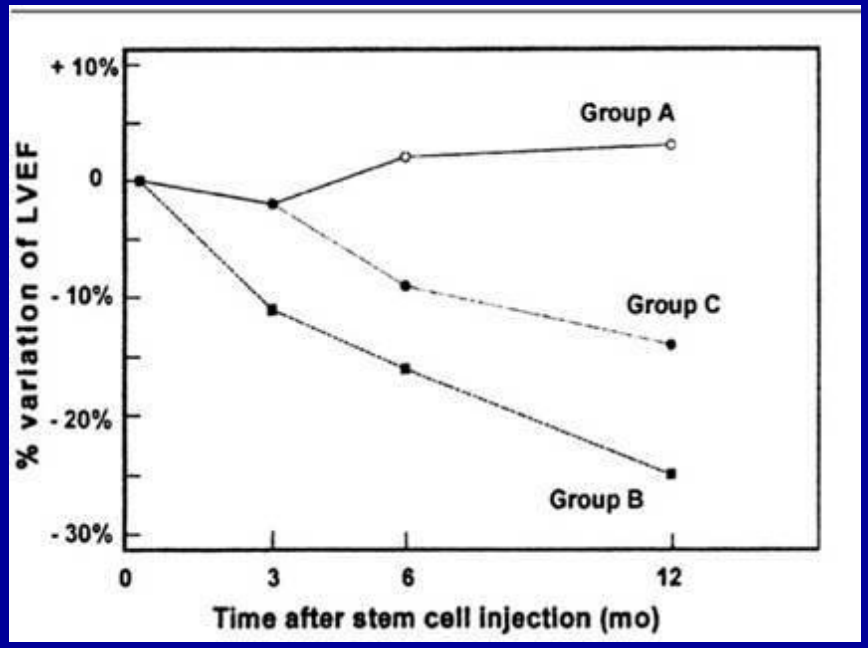


18 months

PET with 13N-ammonia and 18F-FDG in the assessment of myocardial perfusion and metabolism in patients with recent AMI and intracoronary stem cell injection

15 patients were randomly assigned to 3 groups based on different treatments Group A: bone marrow-derived stem cells; Group B: peripheral blood-derived stem cells; group C: standard therapy alone





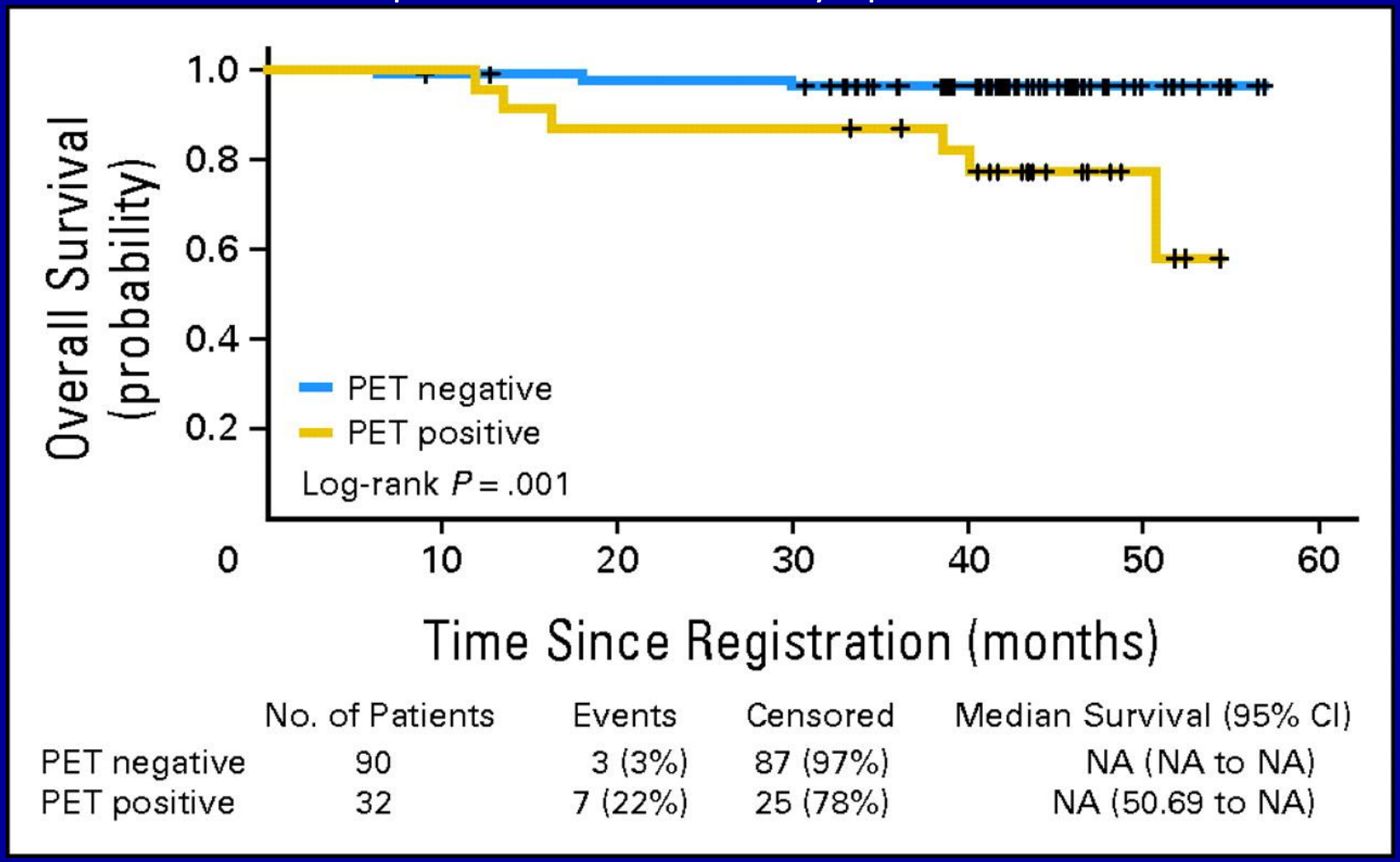
Castellani M et al. J Nucl Med 2010

In memory of my father
Dimitrios C Anagnostopoulos

THANK YOU

Prognostic impact of post -induction positron emission tomography–computed tomography (PET-CT) on overall survival (OS)

122 PET-CT scans performed at the end of the induction immunochemotherapy in patients with follicular lymphoma



	No. of Patients	Events	Censored	Median Survival (95% CI)
PET negative	90	3 (3%)	87 (97%)	NA (NA to NA)
PET positive	32	7 (22%)	25 (78%)	NA (50.69 to NA)

Trotman J et al. JCO 2011;29:3194-3200

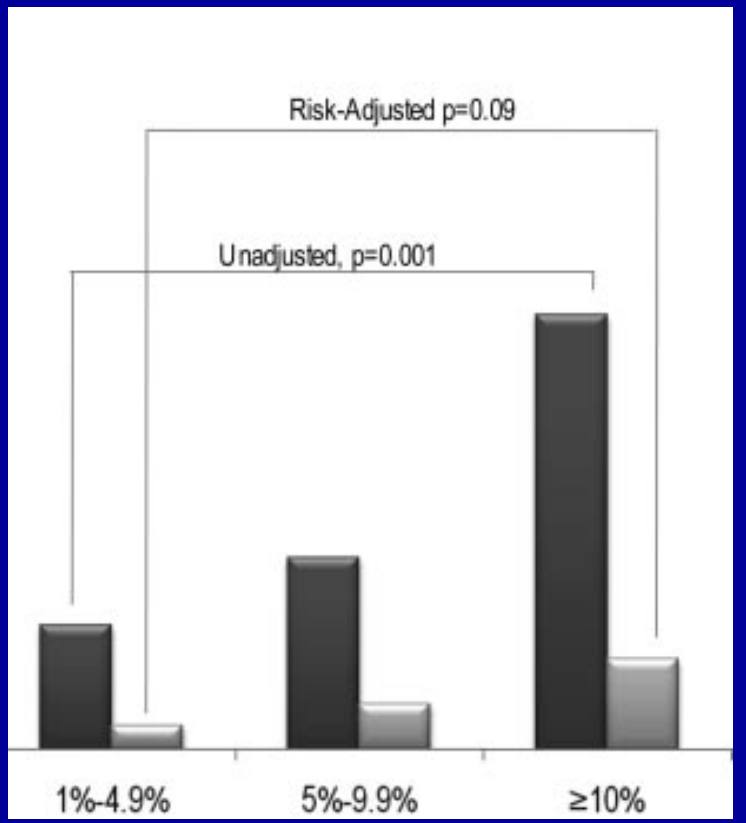
COURAGE (Nuclear sub-study)

Clinical Outcomes Utilising Revascularization and Aggressive drug Evaluation

314 patients randomised to OMT or OMT+PCI

Follow up period; 374+50d

	PCI+OMT	OMT	
Overall (n=314)	n=159	n=155	0.047
No ischemia	15.2%	8.8%	
Minimal ischemia	40.0%	39.8%	
Mild ischemia	29.0%	24.4%	
Moderate to severe ischemia	15.8%	27.0%	
Ischemia reduction > 5% (n=82)	n=53	n=29	0.04
No ischemia	31.4%	17.8%	
Minimal ischemia	26.6%	28.5%	
Mild ischemia	36.5%	43.0%	
Moderate to severe ischemia	5.5%	10.7%	

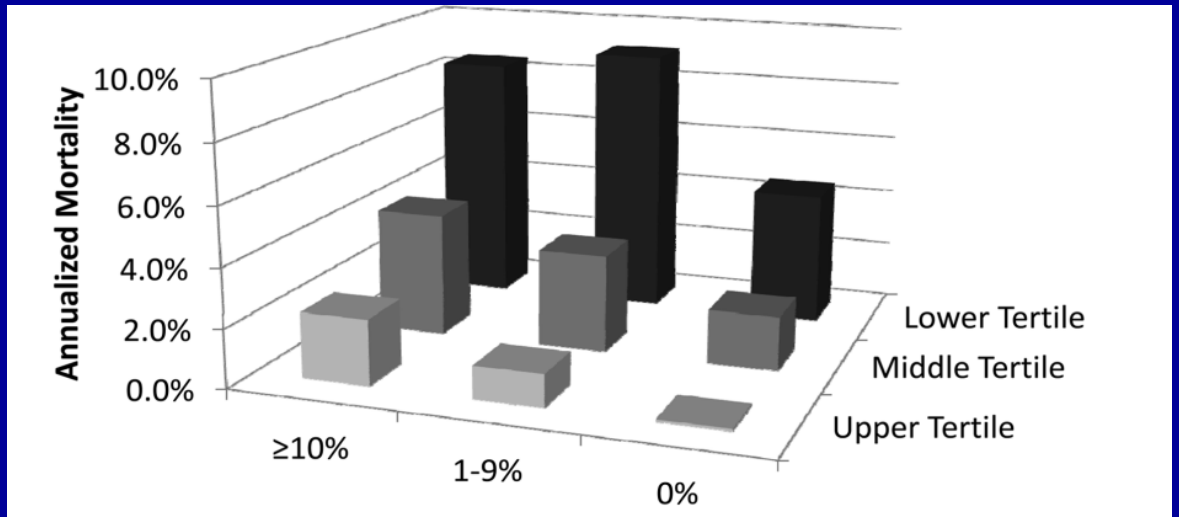


Residual Ischemia on 6- to 18-Month Follow-Up MPS

Shaw LJ, et al. Circulation 2008; 117:1283-91

Improved Cardiac Risk Assessment With Noninvasive Measures of Coronary Flow Reserve

2783 consecutive patients referred for rest/stress PET were followed up for a median of 1.4 years
Primary end point: cardiac death



	≥10%	(n)	1-9%	(n)	0%	(n)
Upper Tertile	2.2%	(50)	1.1%	(197)	0.1%	(681)
Middle Tertile	4.2%	(119)	3.3%	(234)	1.8%	(575)
Lower Tertile	8.5%	(232)	9.1%	(298)	4.5%	(397)

Highest tertile of CFR (values > 2), lowest tertile (values <1.5)

VL. Murthy et al. Circulation 2011;124:2215-2224

ISCHEMIA trial

- ISCHEMIA is an international comparative effectiveness study.
- Participants will be recruited following clinically indicated stress testing but before catheterization and randomized in a 1:1 fashion to an invasive (INV) or Conservative (CON) strategy
- Approximately 8,000 participants randomized
- Primary objective: to determine whether an INV strategy of routine early cardiac catheterization with intent for optimal revascularization in addition to optimal medical therapy in patients with stable ischemic heart disease (SIHD) and at least moderate ischemia on stress imaging (≥10% myocardium) reduces the incidence of the composite of cardiovascular death or nonfatal myocardial infarction compared with a CON) strategy of optimal medical therapy alone.