Beth Israel Deaconess Medical Center
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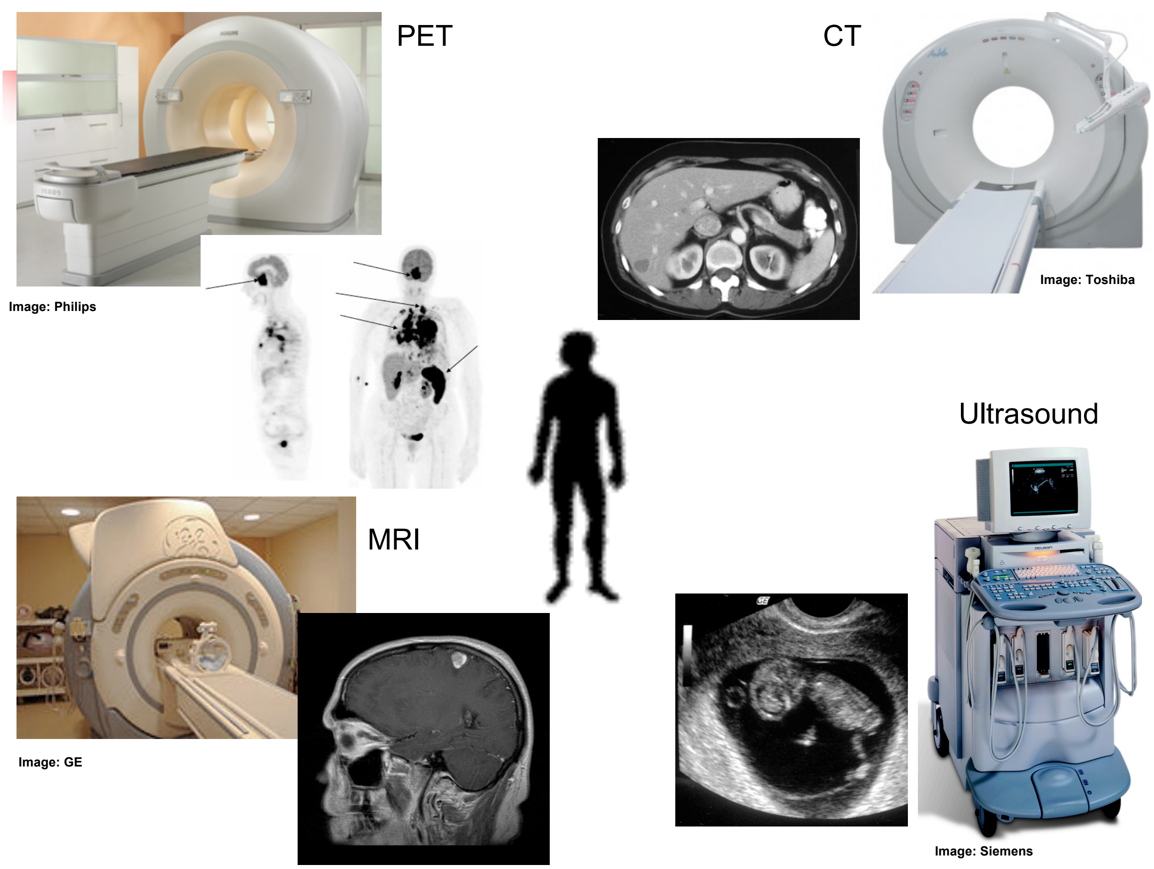
Harvard Medical School

# The Importance of Medical Imaging


Charles R.G. Guttmann, M.D.
Robert E. Lenkinski, PhD

# The Evolution of Clinical Imaging

- Technical advances-improving the technical quality of the images
- Improving the ability to review and interpret the images-digital age

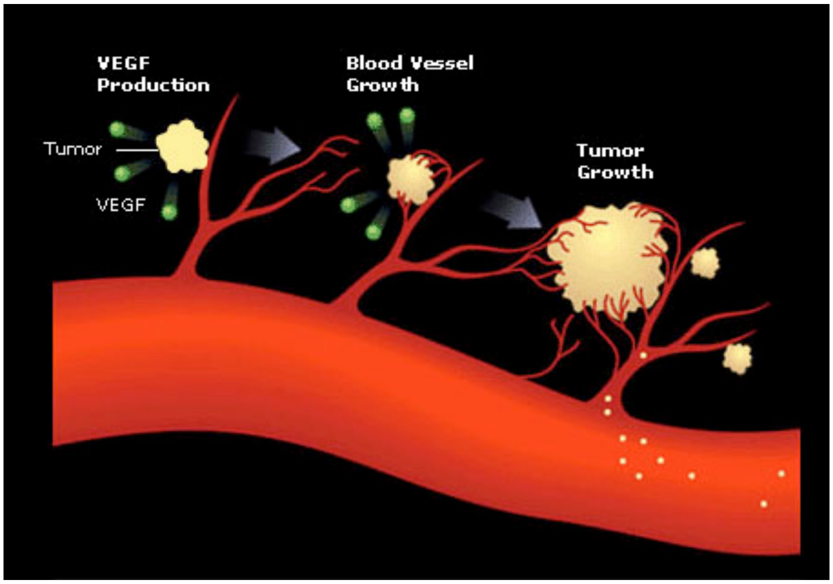
# Trends

- Structure-function (anatomy-physiology/metabolism)
- Diagnostic accuracy (sensitivity-specificity)

## The Continued Evolution of Clinical Imaging

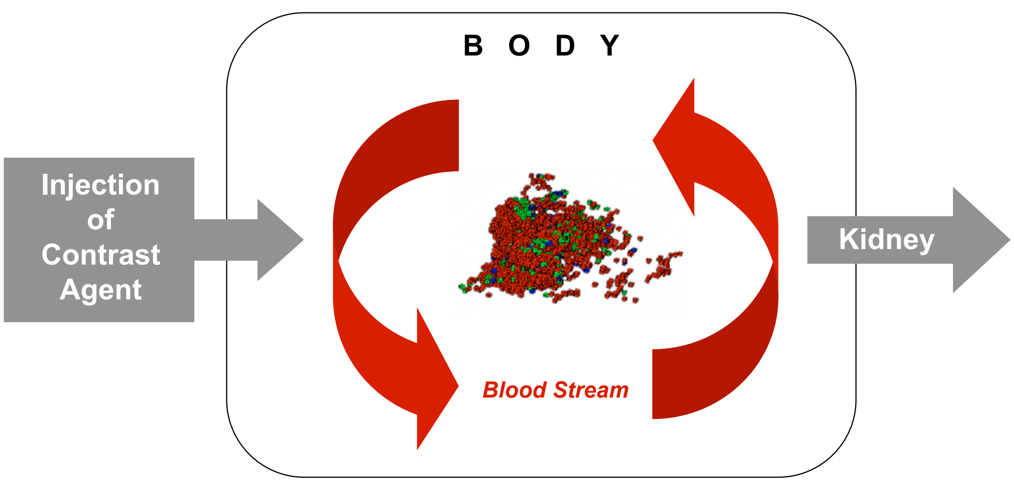
- Extracting the maximum amount of diagnostic information from the images
- Relating imaging features to pathology, physiology, and biology

***Contrast Enhanced MRI of the Breast Has Diagnostic Value***




# Behavior of Contrast Agent in Body

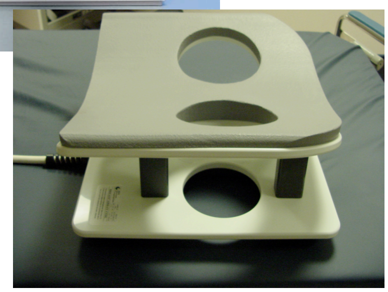
- **Depends on:**
  - **Cellular density or "Extracellular Volume Fraction"**
  - **Blood vessel permeability "Microvascular Permeability"**



# Dynamic Contrast Enhanced MRI (DCEMRI)

Components

- “High-field” MRI machine (1.0 tesla or greater)
- Standard breast coil
- Gadolinium contrast agent (GdDTPA)
- Images taken at several time points (spatial vs temporal resolution
- Software algorithm processes data for either parametric maps or semi-quantitative plots


Christiane Katharina Kuhl, MD
Peter Mielcareck, MD
Sven Klaschik, MD
Claudia Leutner, MD
Eva Wardelmann, MD
Jürgen Gieseke, PhD
Hans H. Schild, MD


## Dynamic Breast MR Imaging: Are Signal Intensity Time Course Data Useful for Differential Diagnosis of Enhancing Lesions?[1]


Radiology 1999; 211:101–110

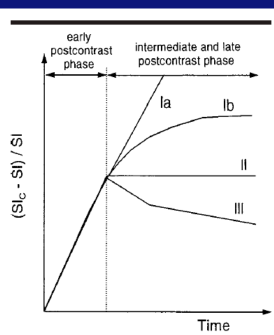




**Figure 1.** Schematic drawing of the time–signal intensity curve types. Type I corresponds to a straight (*Ia*) or curved (*Ib*) line; enhancement continues over the entire dynamic study. Type II is a plateau curve with a sharp bend after the initial upstroke. Type III is a washout time course ($([SI_c - SI]/SI)$).

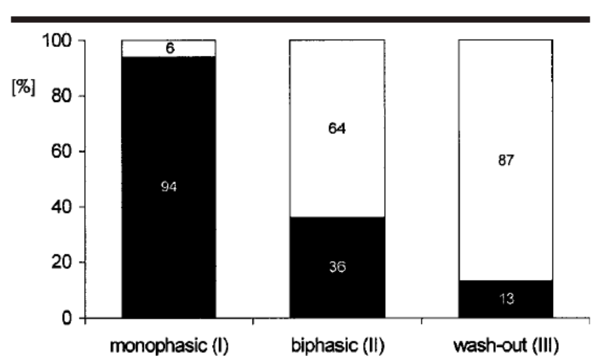



**Figure 4.** Bar graph shows the prevalence of benign (black bars) and malignant (white bars) lesions for the three different signal intensity time courses.

## Color Coding by the 3TP Algorithm

**Time Points**

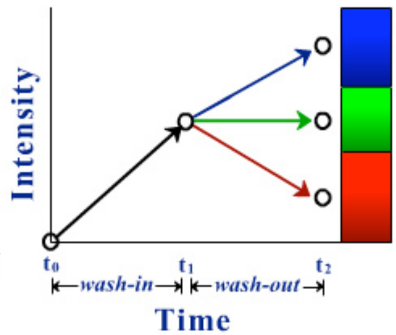
$t_0$ = 0 minutes
$t_1$ = 2 minutes

**Wash-in rate**

color intensity
(256 shades)

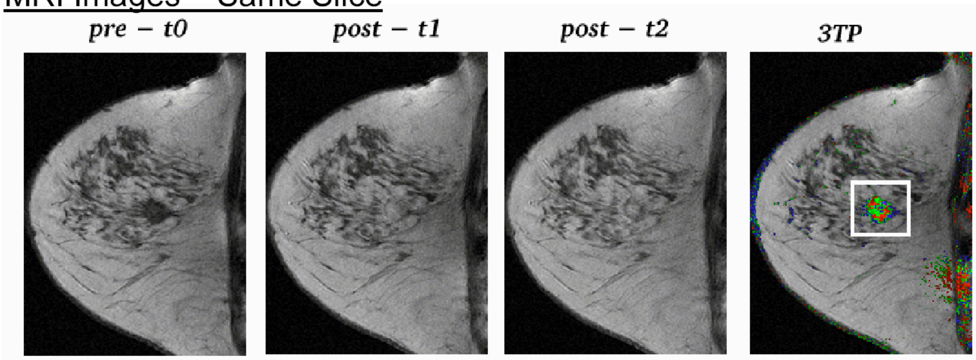
**Wash-out pattern**

determines color
(3 shades)

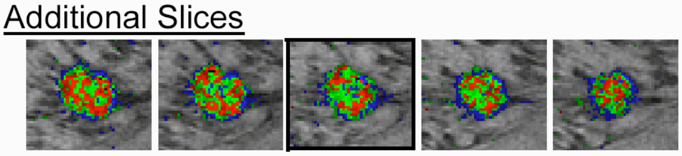



# Breast Cases: Cancer

MRI Images – Same Slice

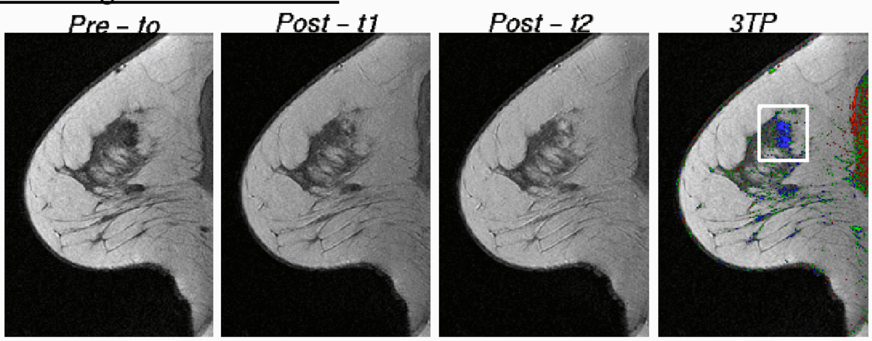



Additional Slices

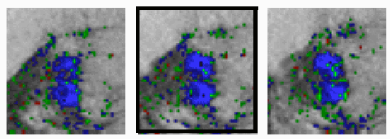


# Breast Cases: Fibroadenoma

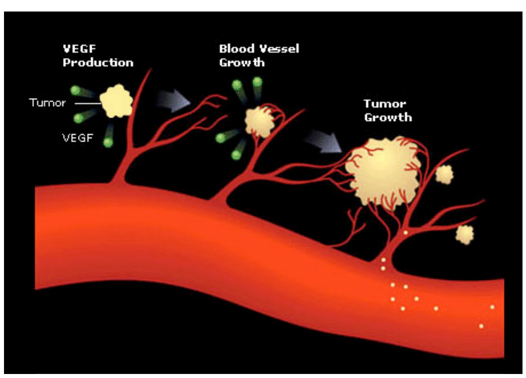
MRI Images – Same Slice



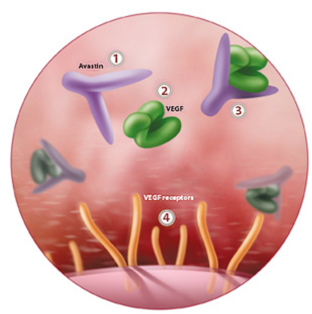

Individual Slices



VEGF Mediated Angiogenesis




Anti-Angiogenesis



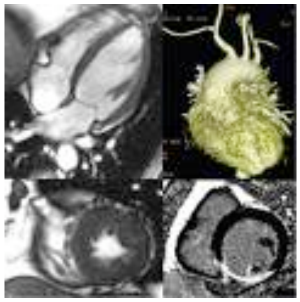

Imaging angiogenesis-MR-DSC, DCE, ASL

Brain Tumors-GBM's

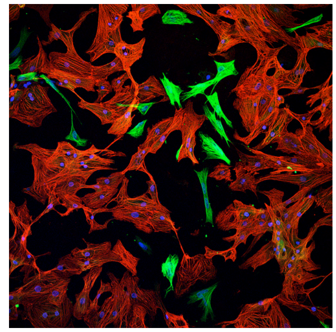
Paradoxical improvement in imaging parameters followed by clinical progression or worsening of Imaging parameters with no tumor progression

## Beyond "Radiologic-Pathologic Correlation"[1]

King C. P. Li, MD, MBA



Scale



Cardiomyocytes (red) and fibroblasts (green) isolated from chicken embryo heart.

# Radiogenomics in Diagnosis

# Decoding global gene expression programs in liver cancer by noninvasive imaging

Eran Segal[1], Claude B Sirlin[2], Clara Ooi[4], Adam S Adler[5], Jeremy Gollub[6], Xin Chen[8], Bryan K Chan[2], George R Matcuk[7], Christopher T Barry[3], Howard Y Chang[5] & Michael D Kuo[2]

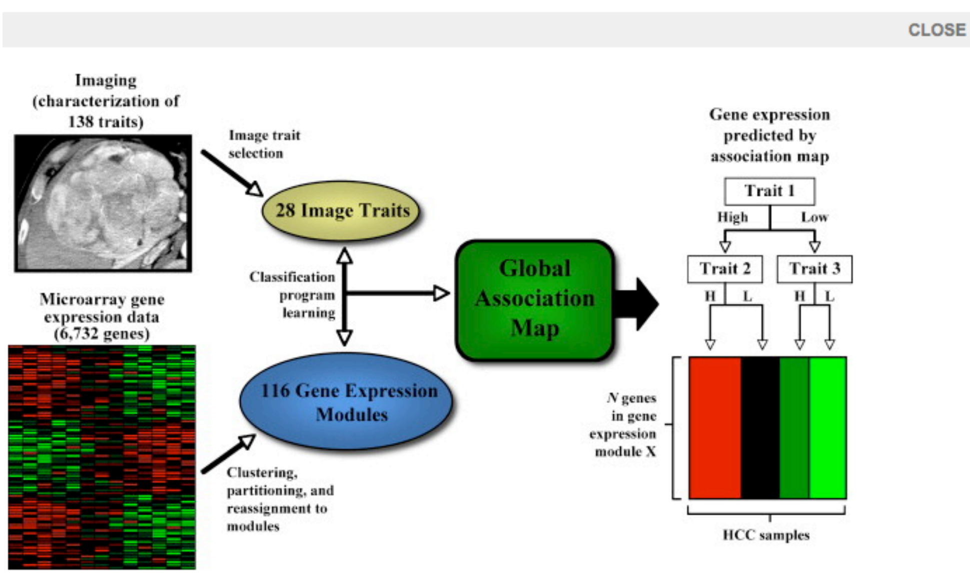


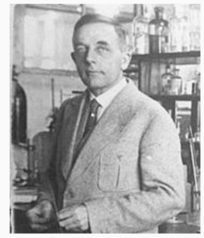

Fig. 2. Knowledge of imaging traits allows approximate reconstruction of a given HCC sample's gene expression pattern, as reported by Segal et al. [8]. The authors created a global "association map" between imaging features and gene expression. Expression variation of 6732 genes, as measured by microarray data and captured by 116 gene expression "modules", was sufficiently reconstructed by a combination of only 28 imaging traits. The decision tree of imaging trait expression patterns is used to predict variation of expression in a given gene expression module. Each split in the tree is determined by variation of an imaging trait, while each terminus identifies a group of samples that share a similar expression pattern of genes in a particular gene expression module.

Otto Warburg, 1931

Cancer cells will undergo glycolysis even in the presence of oxygen

Opposite of the Pasteur effect

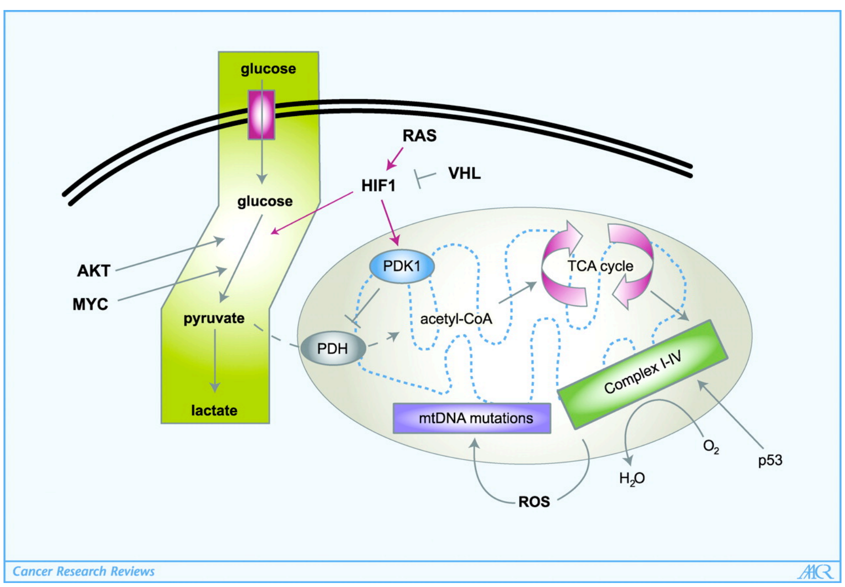
**Otto Heinrich Warburg**



Otto Heinrich Warburg

| | |
|---|---|
| **Born** | October 8, 1883<br>Freiburg, Baden, Germany |
| **Died** | August 1, 1970 (aged 86)<br>Berlin, West Germany |
| **Nationality** | German |
| **Fields** | Cell biology |
| **Institutions** | Kaiser Wilhelm Institute for Biology |
| **Alma mater** | University of Berlin<br>University of Heidelberg |
| **Doctoral advisor** | Emil Fischer<br>Ludolf von Krehl |
| **Known for** | Pathogenesis of cancer |
| **Notable awards** | Nobel Prize in Physiology or Medicine (1931) |

**Figure 1. Molecular underpinnings of the Warburg effect**



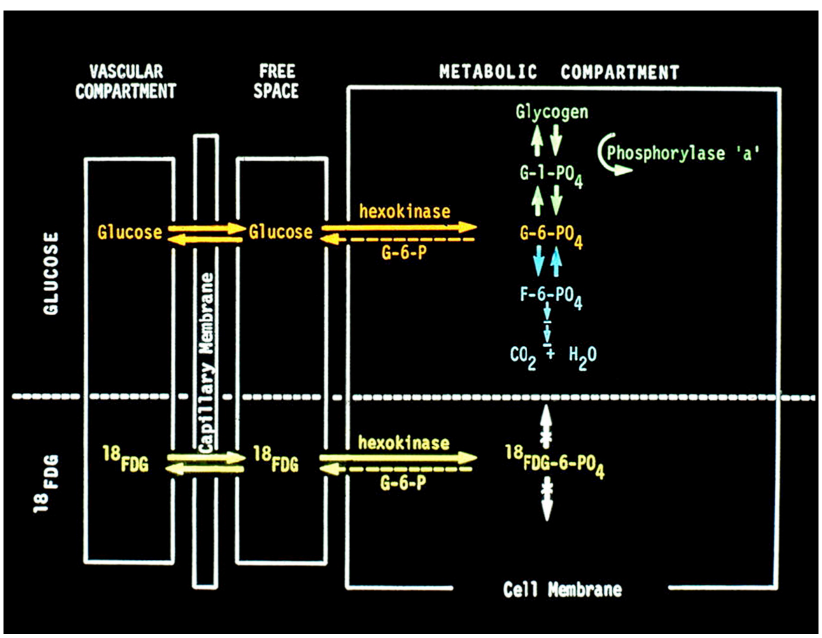

**Kim, J.-w. et al. Cancer Res 2006;66:8927-8930**

Cancer Research

## Good News

We can image glycolysis with FDG PET

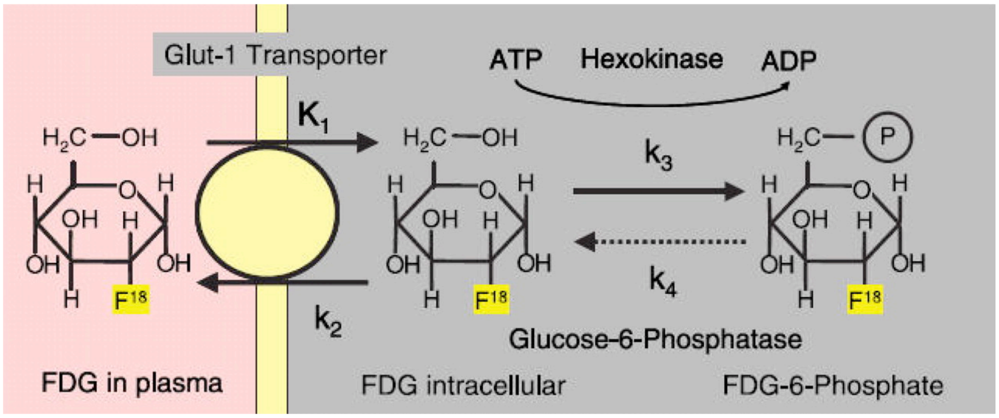
**Glucose and FDG metabolism.**




**Hoffman J M , Gambhir S S Radiology 2007;244:39-47**

Radiology

## Glucose and FDG metabolism.




Hoffman J M , Gambhir S S Radiology 2007;244:39-47

Radiology



# Glycolyisis is common trait of metastatic cancers

ELSEVIER
SCIENCE @ DIRECT®
GENOMICS
Genomics 84 (2004) 1014–1020
www.elsevier.com/locate/ygeno

Genes of glycolysis are ubiquitously overexpressed in 24 cancer classes

B. Altenberg[a,*], K.O. Greulich[b]

[a] Bioinformatics Group, European Molecular Biology Laboratory, Meyerhofstrasse 1, D-69117 Heidelberg, Germany
[b] Department of Single Cell and Single Molecule Techniques, Institute for Molecular Biotechnology, Beutenbergstrasse 11, D-07745 Jena, Germany

Received 27 July 2004; accepted 8 August 2004
Available online 25 September 2004

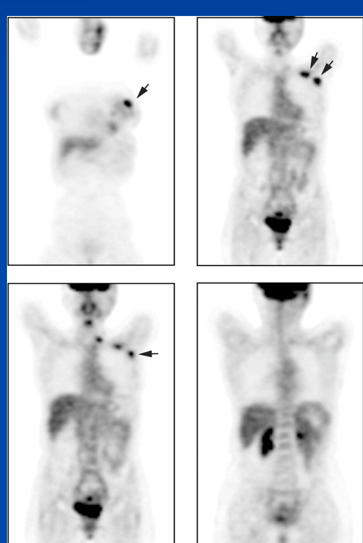
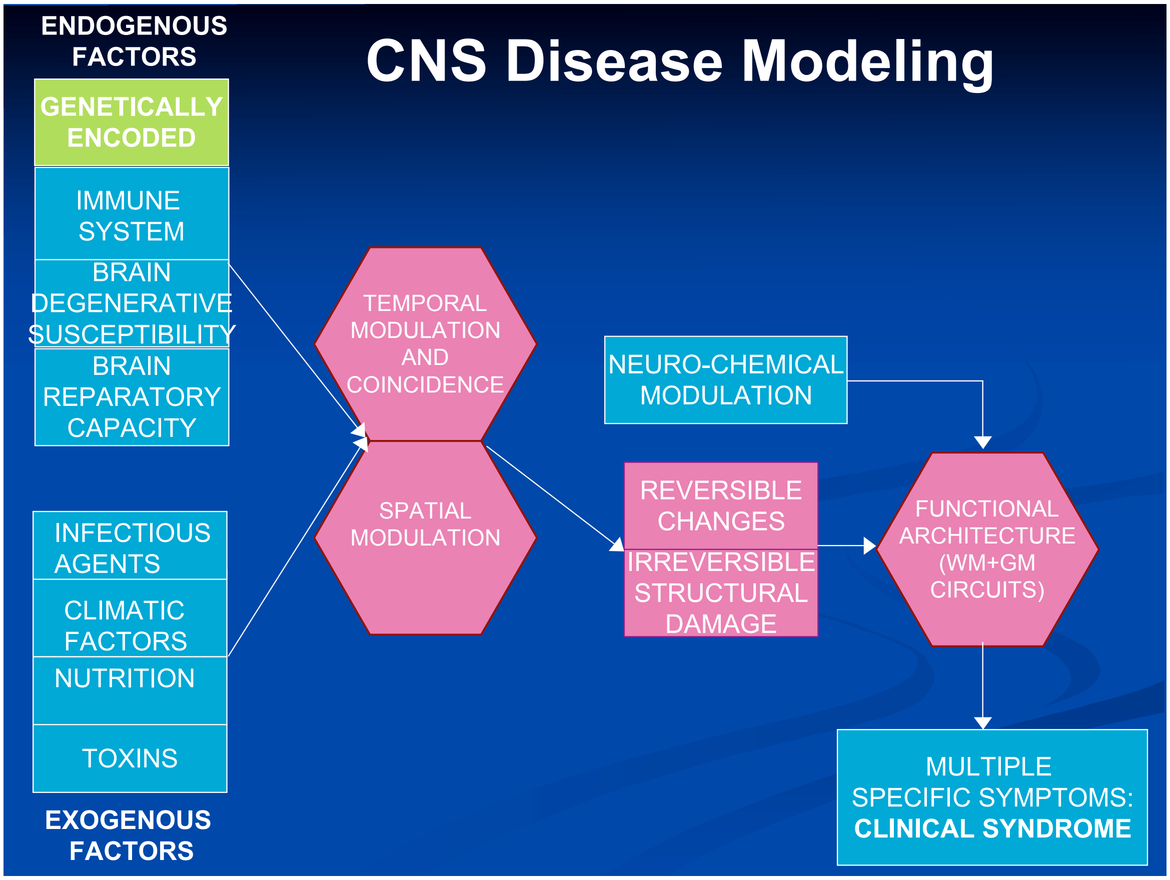


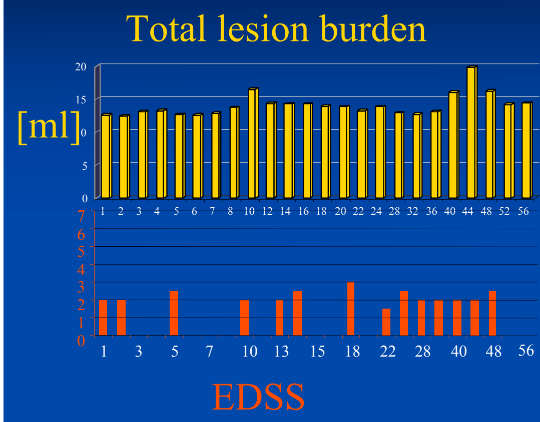
**Table 4. Sensitivity and Specificity of FDG PET for detection of metastases** (data culled from reference *(39)*)

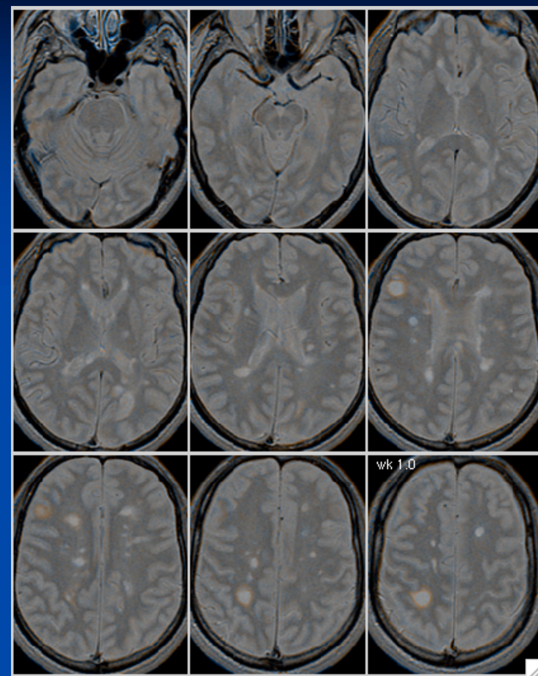
| Cancer metastasis | Sens | | Spec | |
|---|---|---|---|---|
| | Range | median | range | median |
| NSCLC - mediastinal | 67-100 | 94 | 84-100 | 100 |
| CRC - LN & hepatic | 73-100 | 95 | 96-100 | 100 |
| Melanoma | 70-100 | 100 | 77-100 | 100 |
| Lymphoma | 50-100 | 80 | 87-100 | 92 |
| Breast | 83-100 | 97 | 75-100 | 97 |
| Cervical – LN | 3-100 | 72 | 92-100 | 100 |
| Esophageal – distant | 69-100 | 91 | 67-93 | 91 |
| Prostate – LN & bone | 40-75 | 65 | n/a | |

*J. Nuc. Med. 49(2):24S-42S, 2008*




# Time Series Analysis: Can "Chronobiopsy" of individual lesions predict pathological stage and disease progression?




# Timing and Sequence of Pathological Processes

## Inflammation

~ days - weeks

- Blood Brain Barrier breakdown
- Edema
- Cellular Infiltration

## Degeneration

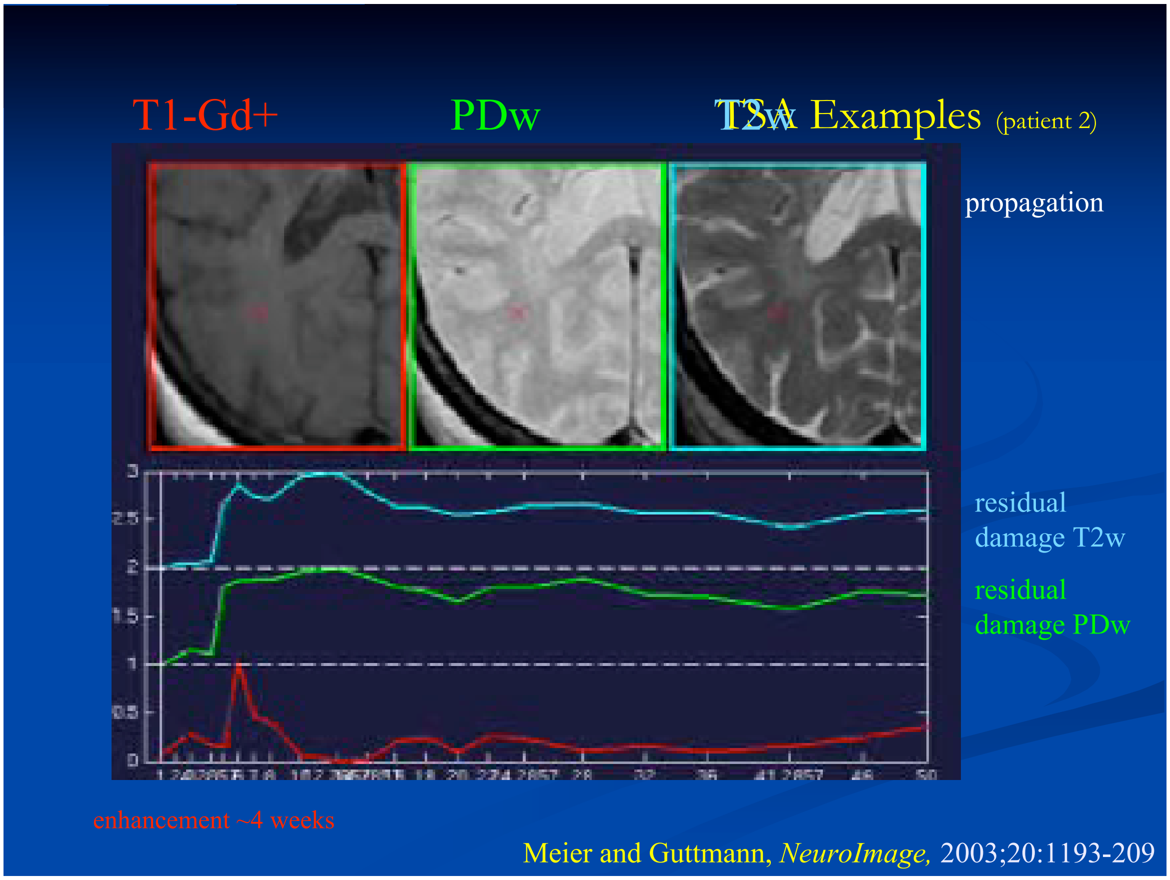
~ **weeks**-months

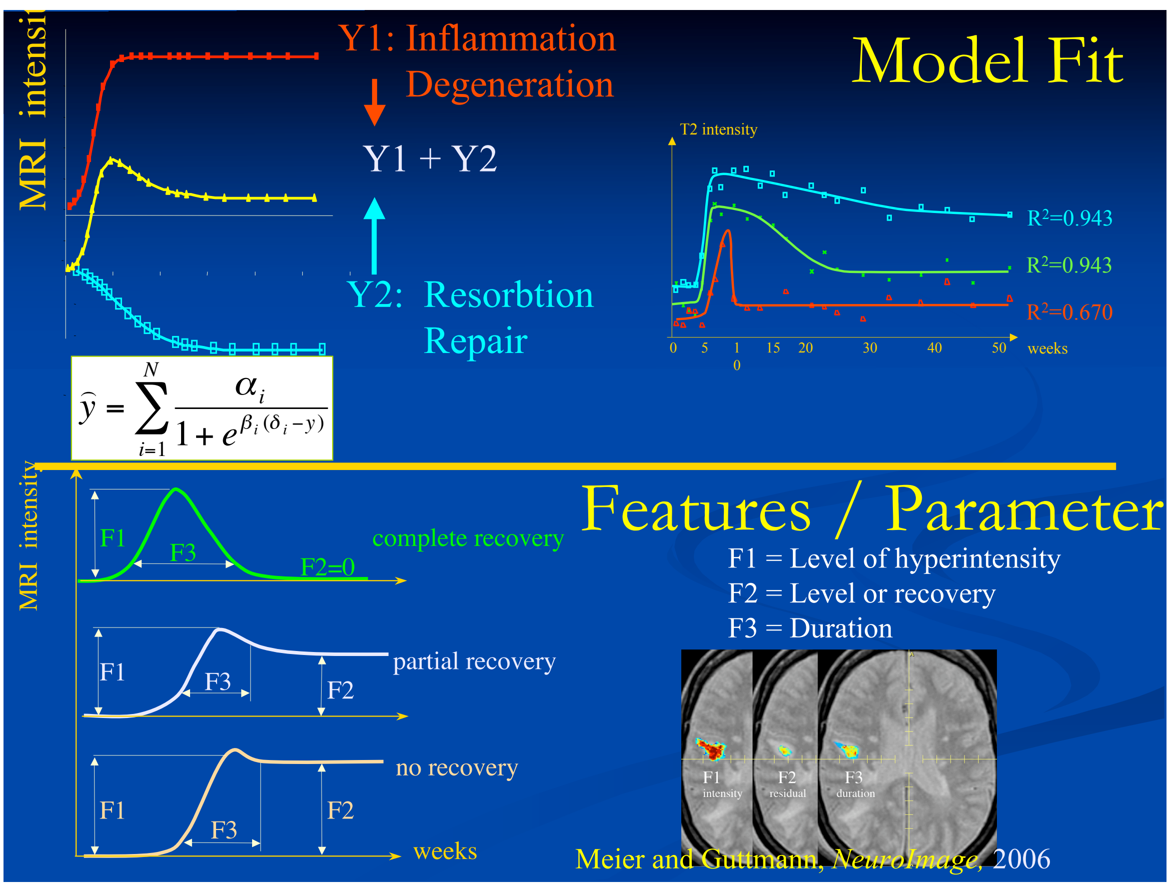
- Demyelination
- Axonal/Neuronal Damage

## Repair

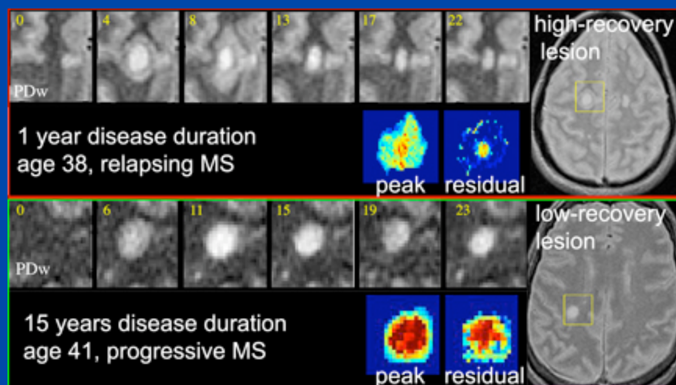
~ **months-years?**

- Macrophage activity
- Astrocytosis
- Remyelination
- Axonal Repair?


T1-Gd+
PDw
T2w
T2A Examples (patient 2)
propagation
residual damage T2w
residual damage PDw
enhancement ~4 weeks
Meier and Guttmann, *NeuroImage,* 2003;20:1193-209


Model Fit
MRI intensi
Y1: Inflammation
Degeneration
Y1 + Y2
Y2: Resorbtion
Repair
$\hat{y} = \sum_{i=1}^{N} \frac{\alpha_i}{1 + e^{\beta_i(\delta_i - y)}}$
T2 intensity
$R^2$=0.943
$R^2$=0.943
$R^2$=0.670
0 5 10 15 20 30 40 50 weeks
Features / Parameter
F1 = Level of hyperintensity
F2 = Level or recovery
F3 = Duration
MRI intensity
F1
F3
F2=0
complete recovery
partial recovery
no recovery
F2
weeks
F1 intensity
F2 residual
F3 duration
Meier and Guttmann, *NeuroImage,* 2006

- reduced short-term lesion recovery was associated with greater atrophy rates and disability.
- smaller lesions disproportionally more damaging: leaving more residual, associated with greater disability.

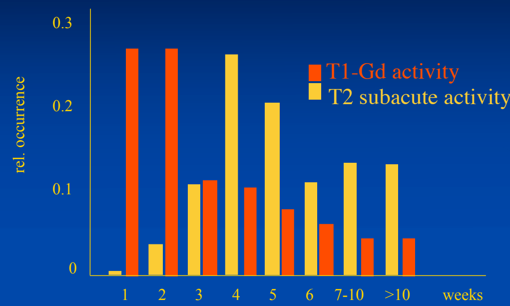



Meier,Weiner, Guttmann, *AJNR,* 2007, 28:1956-63

# Spatial Analysis: Does normal cerebral perfusion predict lesion prevalence at different locations?

# Fact: Repair Does Occur in MS

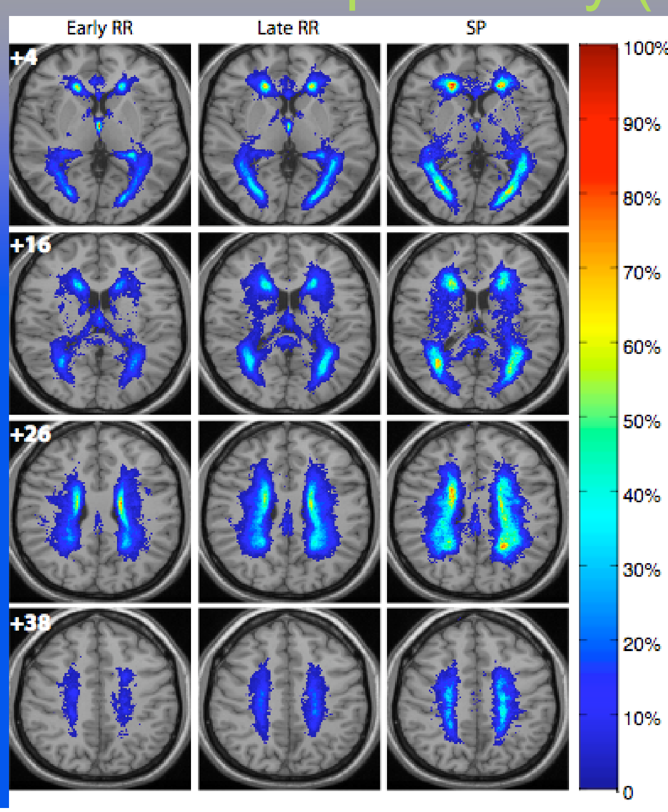
1. When?

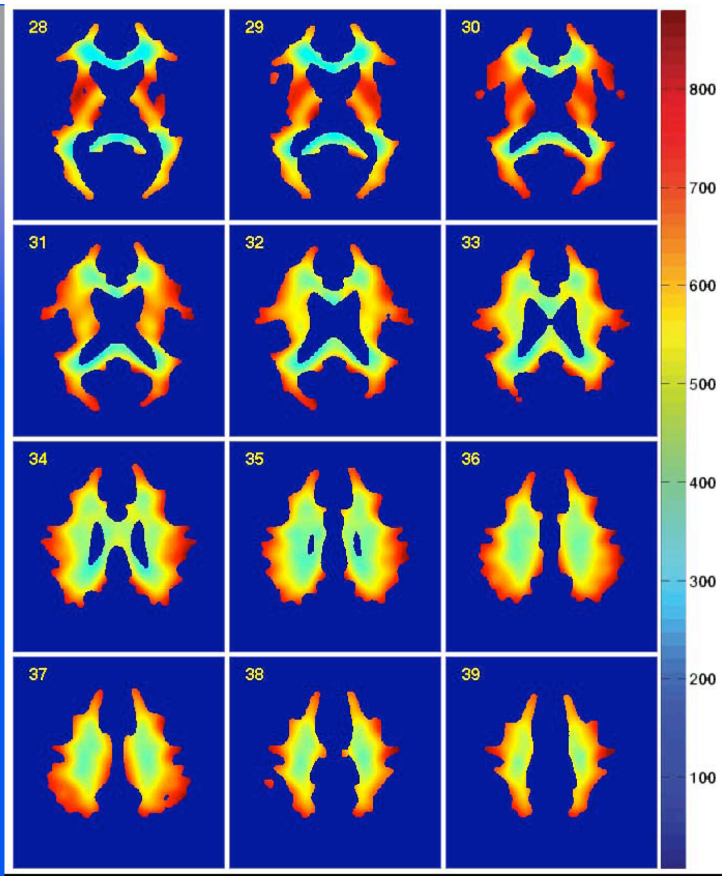



2. Under what Conditions?

Does perfusion modulate brain repair?

# Voxel Based Morphometry (VBM)






Based Morphometry (CBM)

Healthy Perfusion Atlas

Tc-99m SPECT

N = 47