Monitoring Chemotherapy and Molecular Targeted Therapy in Solid Tumours using PET

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Co-Chair of Translational Research

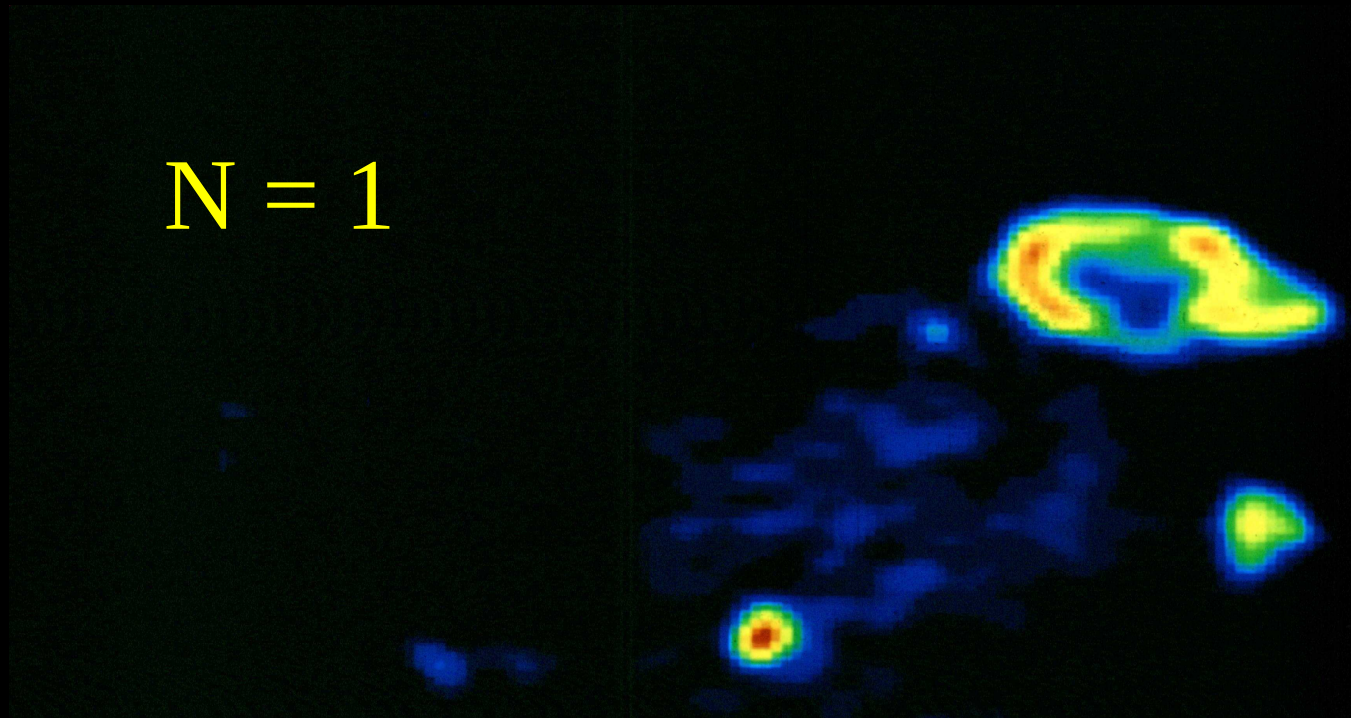
The Peter MacCallum Cancer Centre

Melbourne, Australia

FDG PET Breast Cancer

Wahl, R.L. , 1989

N = 1

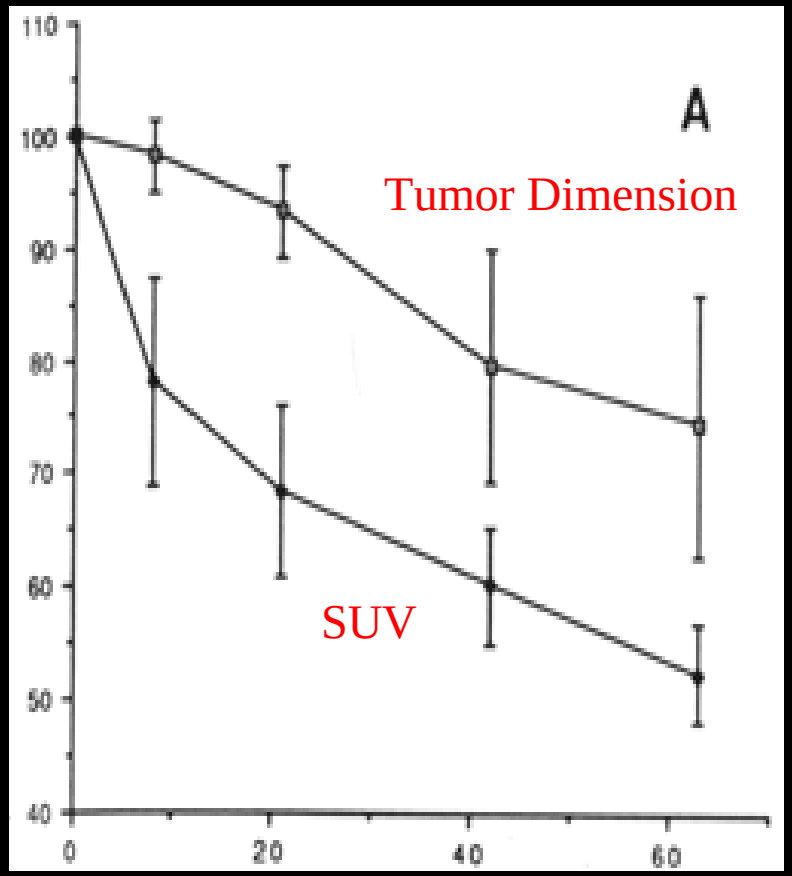


My first experience of PET in cancer evaluation

PET for Therapy Monitoring

Metabolic Response is a Continuum

N = 1



Wahl et al. *J Clin Oncol* 1993;11:2101-11

THE EFFECT OF MEASURING ERROR ON THE RESULTS OF THERAPEUTIC TRIALS IN ADVANCED CANCER

CHARLES G. MOERTEL, MD,* AND JAMES A. HANLEY, PHD†

In this study, 16 experienced oncologists each measured 12 simulated tumor masses employing their usual clinical methods. Unknown to the oncologists, two pairs of these tumors were identical in size. This permitted a total of 64 measurement comparisons of the same investigator measuring the same size mass and 1920 comparisons of different investigators measuring the same size mass. If a 50% reduction in the product of perpendicular diameters is accepted as a criterion, the objective response rate due to measuring error alone was 7.8% by the same investigator and 6.8%by different investigators. If a 25% reduction criterion is used, the respective "placebo" response rates were 19% and 25%. In the clinical setting it is recommended that the 50% reduction criterion be employed and that the investigator should anticipate an objective response rate of 5 to 10% due to human error in tumor measurement.

Cancer 38:388–394, 1976.

Measuring wooden spheres under a foam sheet with palpation and rulers established the methodology for response assessment

Reporting Results of Cancer Treatment

A. B. MILLER, MB, FRCP(C), B. HOOGSTRATEN, MD, M. STAQUET, MD, AND A. WINKLER, MD*

On the initiative of the World Health Organization, two meetings on the Standardization of Reporting Results of Cancer Treatment have been held with representatives and members of several organizations. Recommendations have been developed for standardized approaches to the recording of baseline data relating to the patient, the tumor, laboratory and radiologic data, the reporting of treatment, grading of acute and subacute toxicity, reporting of response, recurrence and disease-free interval, and reporting results of therapy. These recommendations, already endorsed by a number of organizations, are proposed for international acceptance and use to make it possible for investigators to compare validly their results with those of others.

Cancer 47:207–214, 1981.

RARELY

ENLIGHTENING

COMMONLY

INEFFECTIVE

SURVEILLANCE

TECHNIQUE

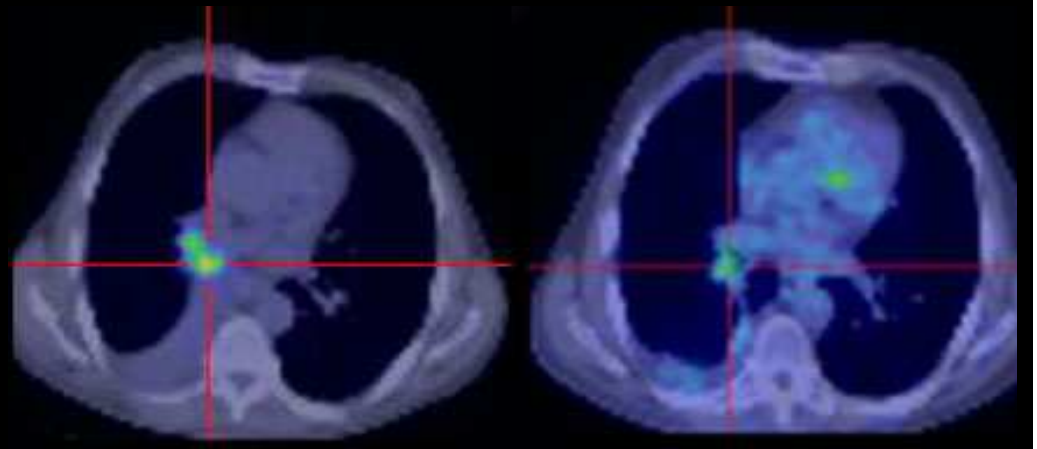
The Importance of Methodology

"However beautiful the strategy, you should occasionally look at the results."
Winston Churchill, British prime minister

PET/CT - Form and Function in Harmony

An Evolution in Technology

but a Revolution in Oncology



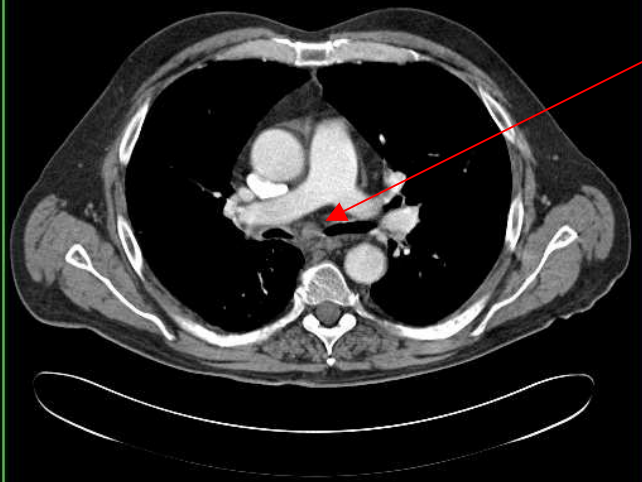
Baseline Post-RT

- Solid tumours can lead to secondary morphological changes in adjacent tissues that confounds initial tumour measurement

Advantages of PET/CT- Lesion Conspicuity

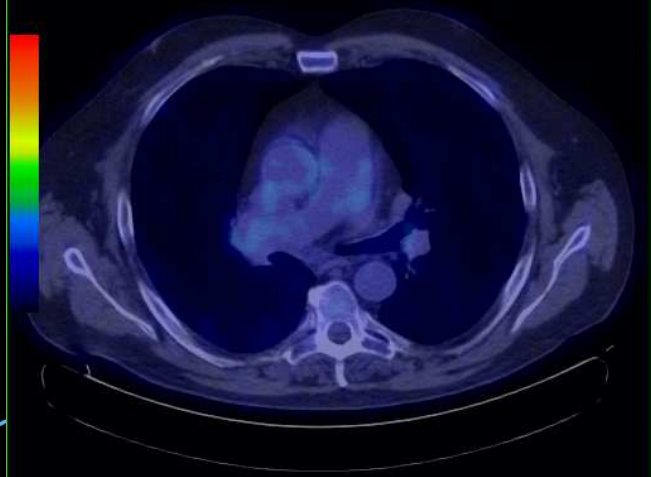
SCR-DxCT

D56-DxCT

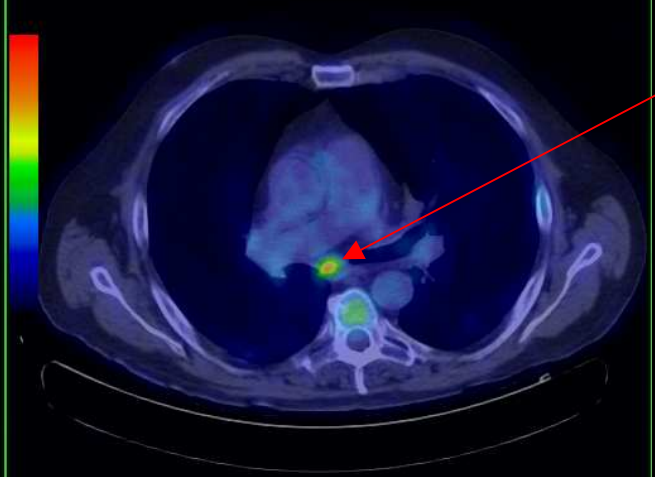


NEWLY ENLARGED LYMPH NODE

SCR-FDG



D56-FDG



PET for Therapy Monitoring of Solid Tumours

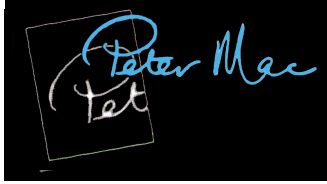
FDG Methodology

- Analysis techniques
  - Qualitative
  - Semi-quantitative
    - Tumor to background ratios (TBR)
    - Standardized uptake value (SUV)
  - Quantitative
    - Compartmental modeling
    - Patlak graphical analysis

PET For Therapeutic Monitoring

Peter Mac Qualitative Response Criteria

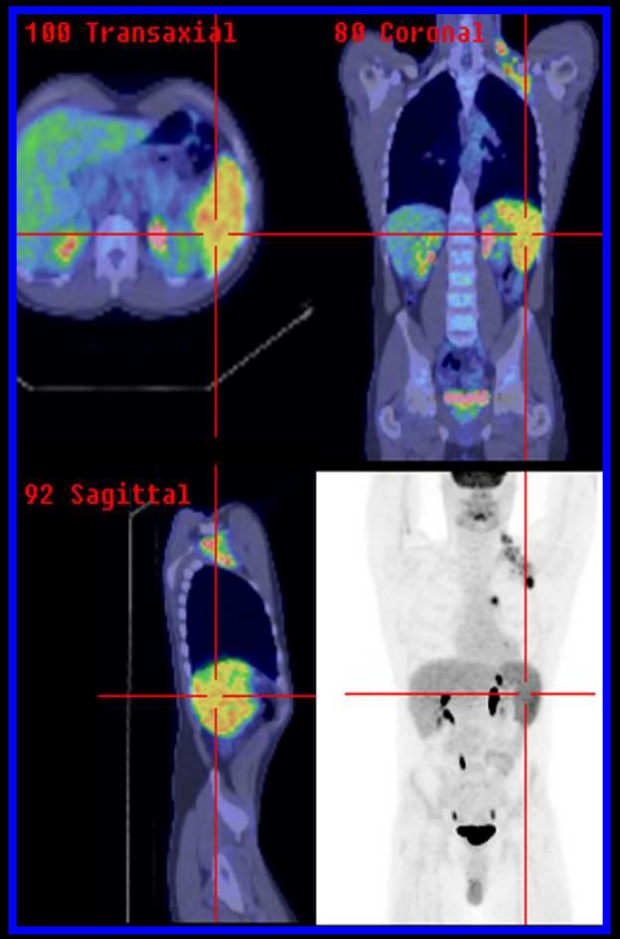
- **Qualitative reporting done based on SUV-calibrated images displayed on same threshold and in standardised rainbow colour-scale**
- **Peter Mac Response Definitions for FDG**
  - **Complete Metabolic Response (CMR)**
    Lesion uptake equal to or less than mediastinal blood pool
  - **Partial Metabolic Response (PMR)**
    Lesion uptake reduced compared to baseline but remains higher than blood pool
  - **Stable Metabolic Disease (SMD)**
    No significant change in extent or intensity of uptake
  - **Progressive Metabolic Disease (PMD)**
    Increase in either intensity or extent of uptake abnormality



MacManus et al. *J Clin Oncol* 2003; 21:1285-92

How To Read PET/CT

Importance of Colour-Scale

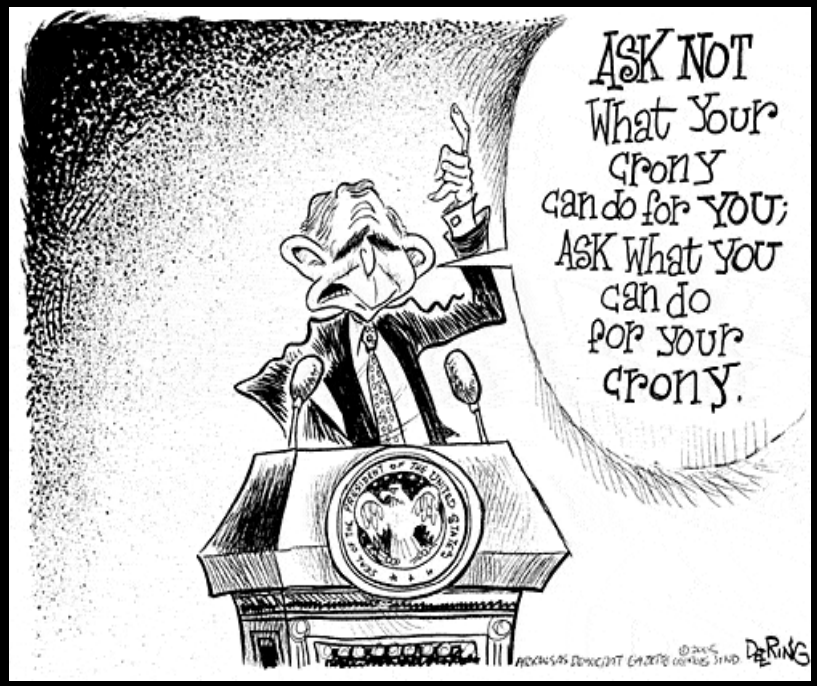


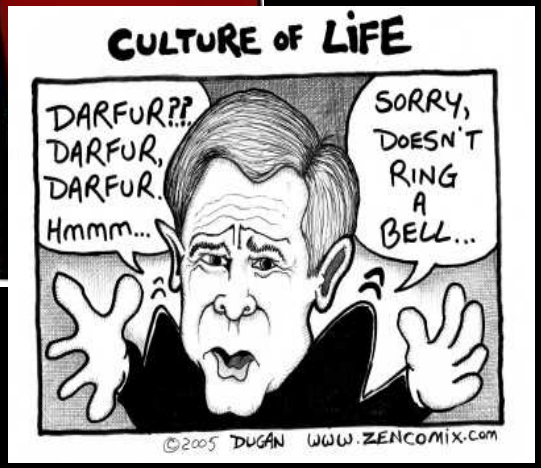
Hot Metal

Rainbow

The Importance of Pattern Recognition

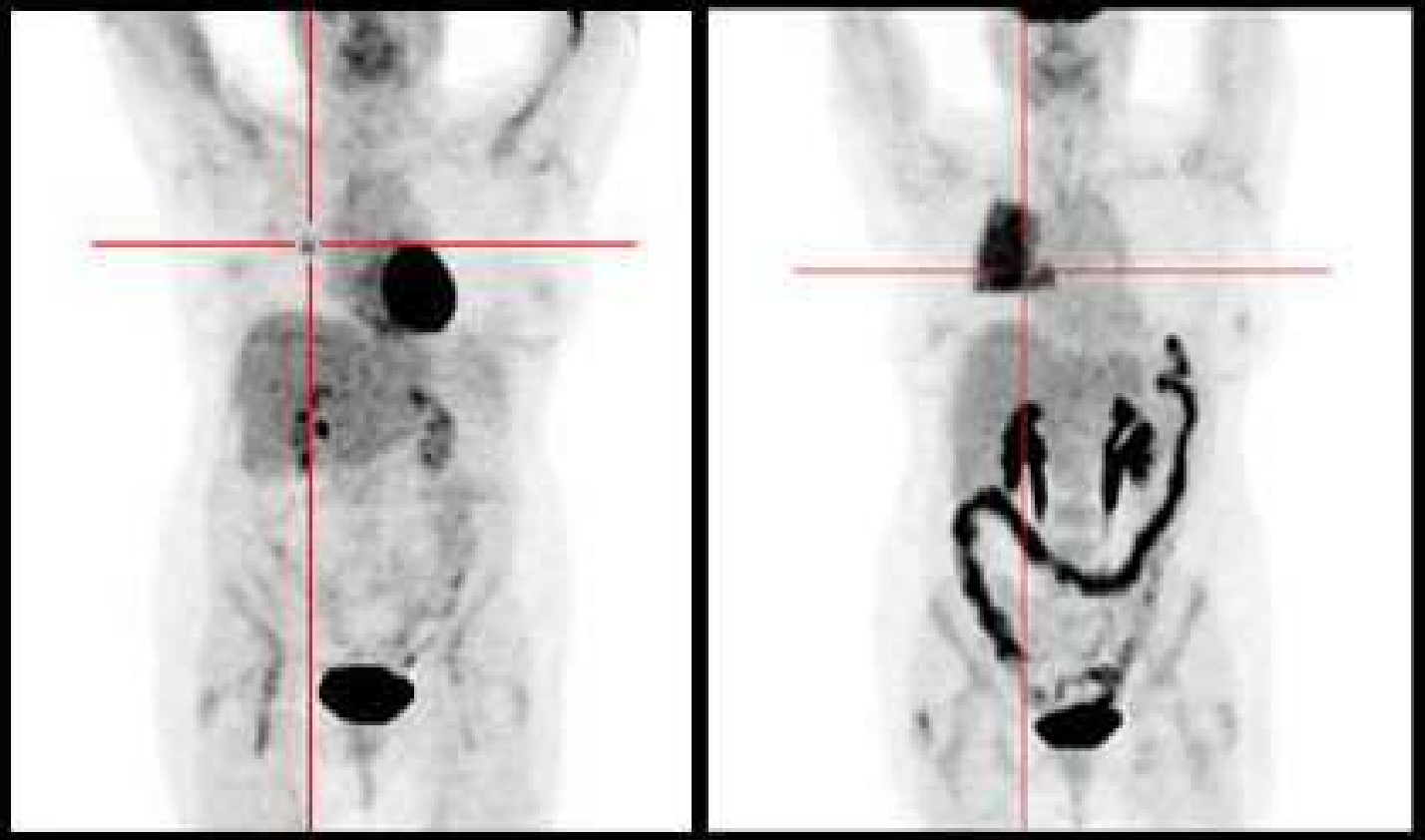
- The human brain is adapted for pattern recognition





The Importance of Pattern Recognition

- Has this patient progressed?



Baseline Post-RT

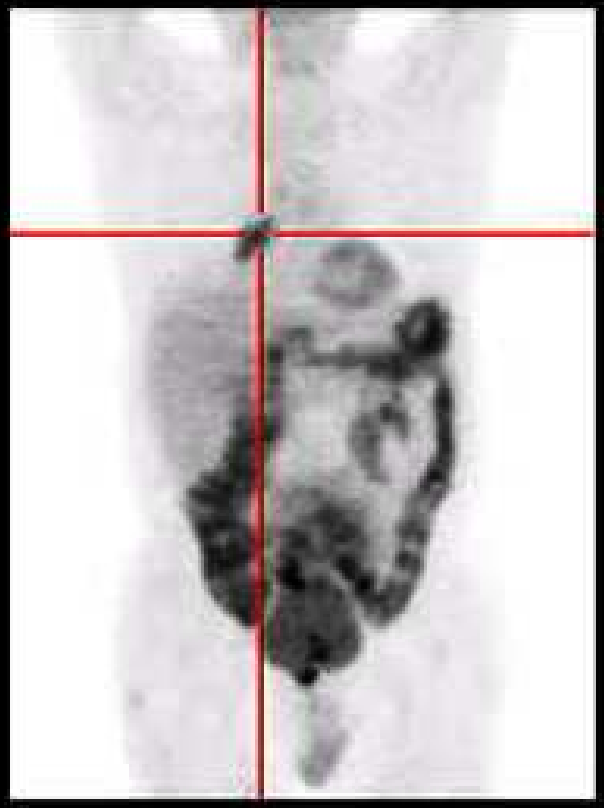
The Importance of Pattern Recognition

- Although patterns are important, mimics abound and interpretation requires interposition of intelligence!

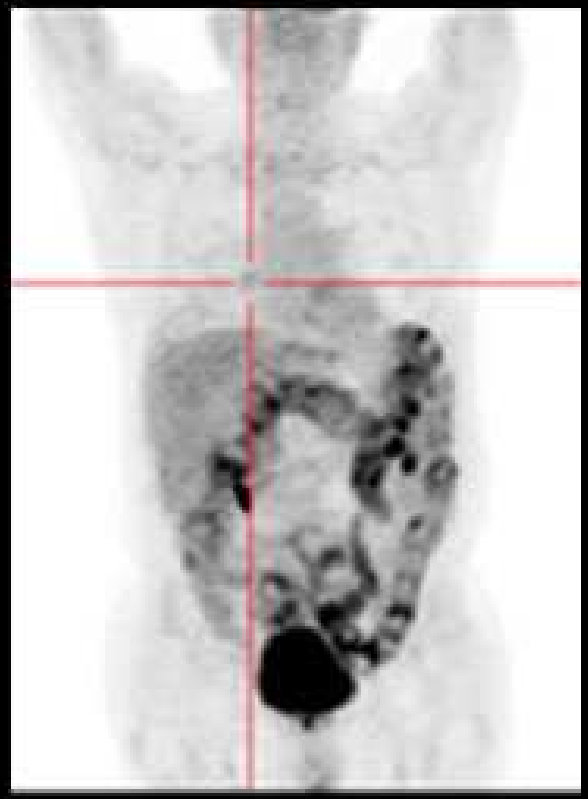
PET for Therapy Monitoring

Lung Cancer

- NSCLC of the right hilum
- Treated with radical radiotherapy and Iressa
- PMR



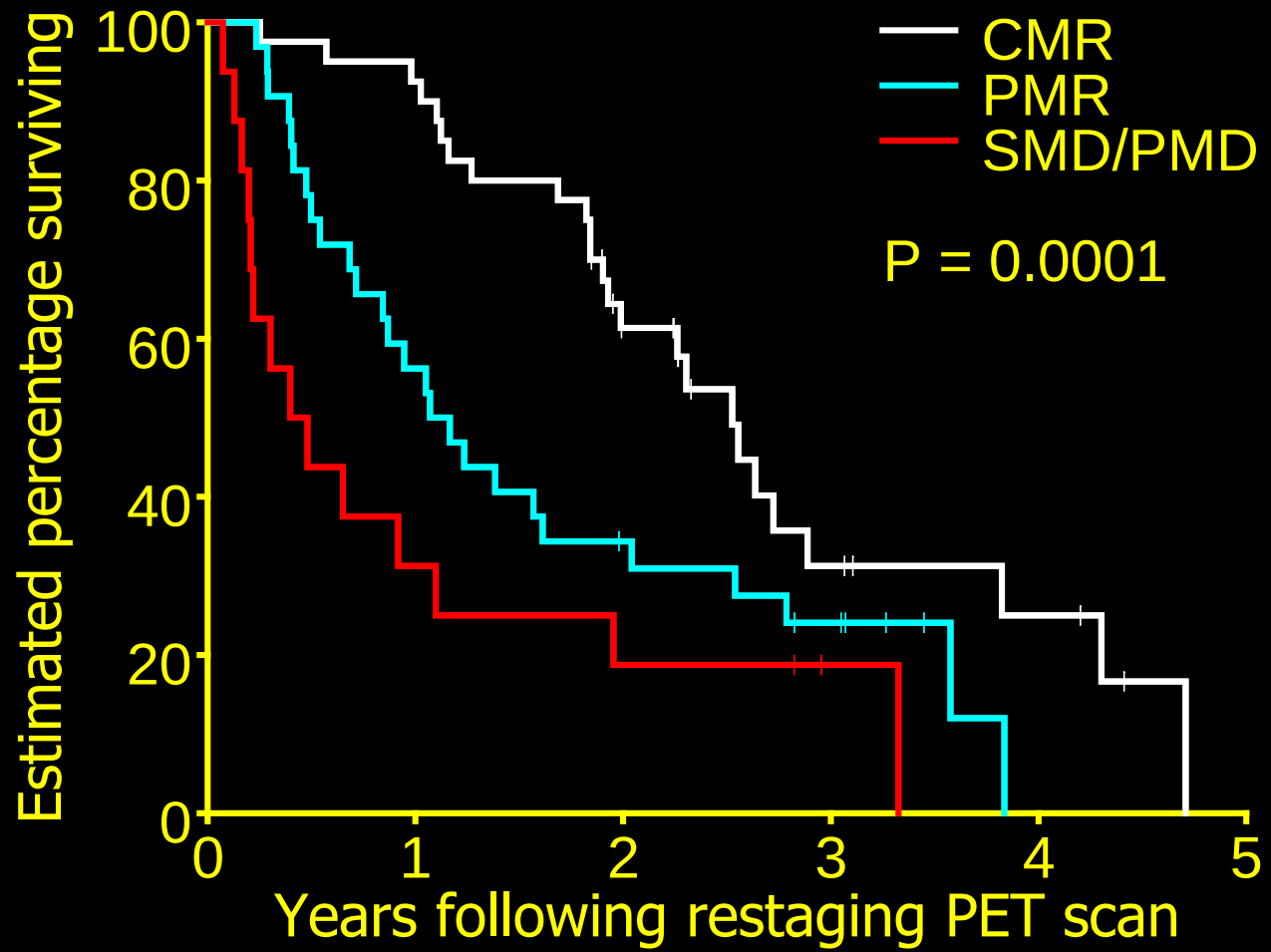
Baseline



Post-RT

PET for Therapy Monitoring

Lung Cancer



MacManus et al, J Clin Oncol 2003

PET for Therapy Monitoring

Lung Cancer

Multifactor Analysis of Survival

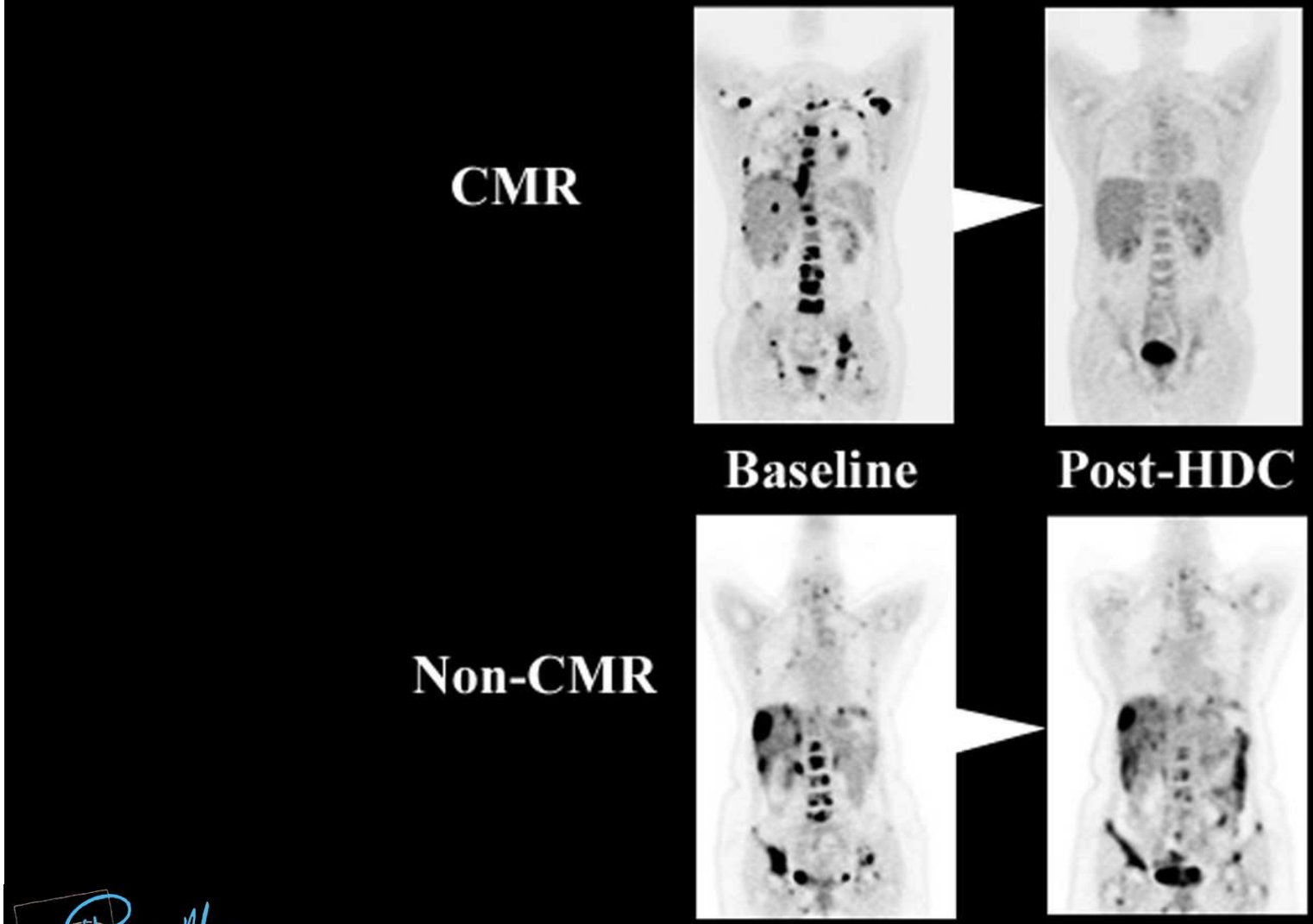
Factor	P -value
ECOG	0.077
Wt loss some/none	0.96
Stage	0.46
CT Response	0.066
Evaluable CT Response	0.033
PET Response	0.0005
PET Response per Category	< 0.0001

- Survival by PET response in 88 patients receiving rRT

MacManus et al, *J Clin Oncol* 2003

PET for Therapy Monitoring

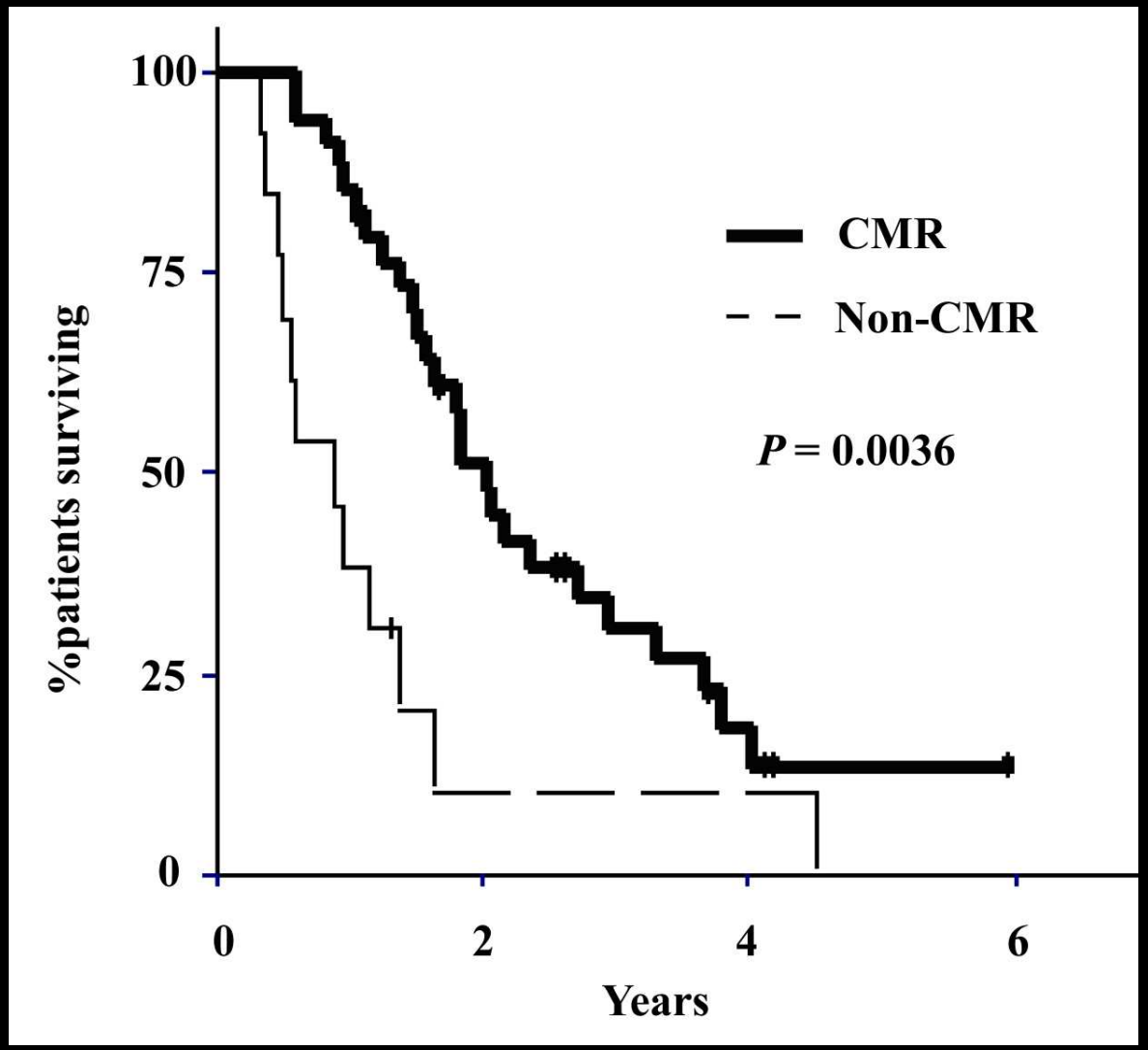
Post-Treatment FDG in Breast Cancer



Cachin et al. *J Clin Oncol* 2006;24:3026-3031

PET for Therapy Monitoring

Post-Treatment FDG in Breast Cancer



Cachin et al. *J Clin Oncol* 2006;24:3026-3031

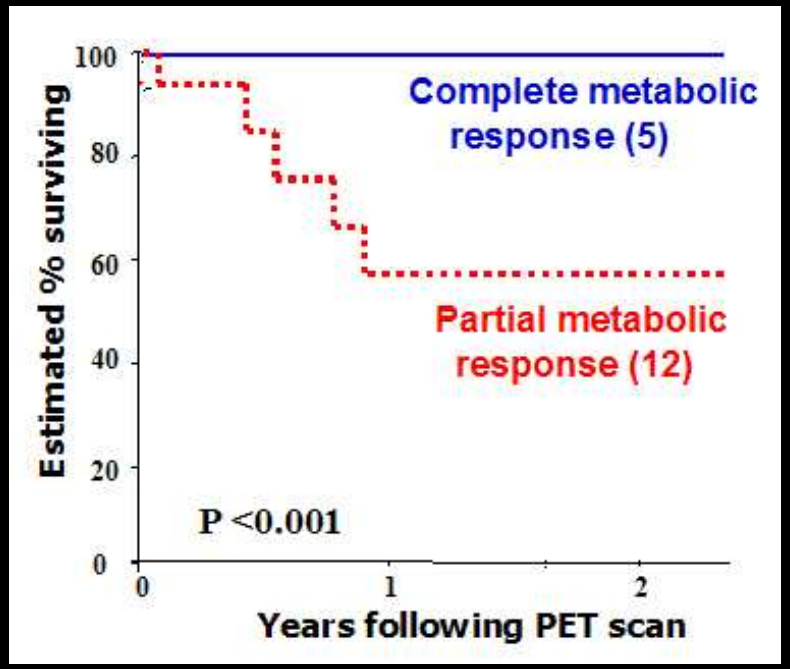
PET for Therapy Monitoring

Esophageal Cancer

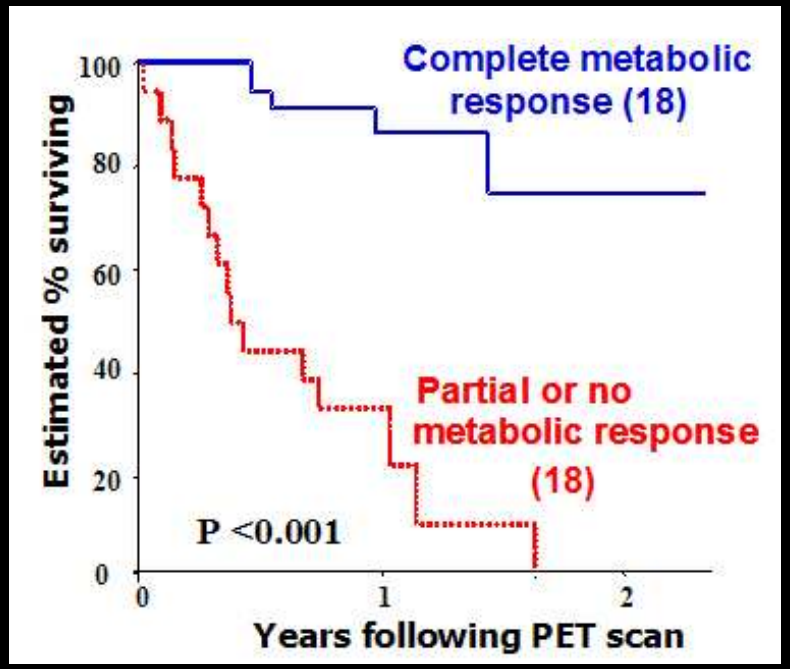
Results

Survival by PET response post-CRT

Resection of tumor site



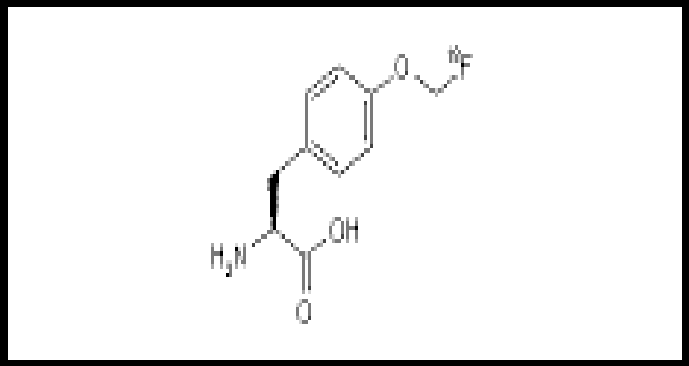
No Resection

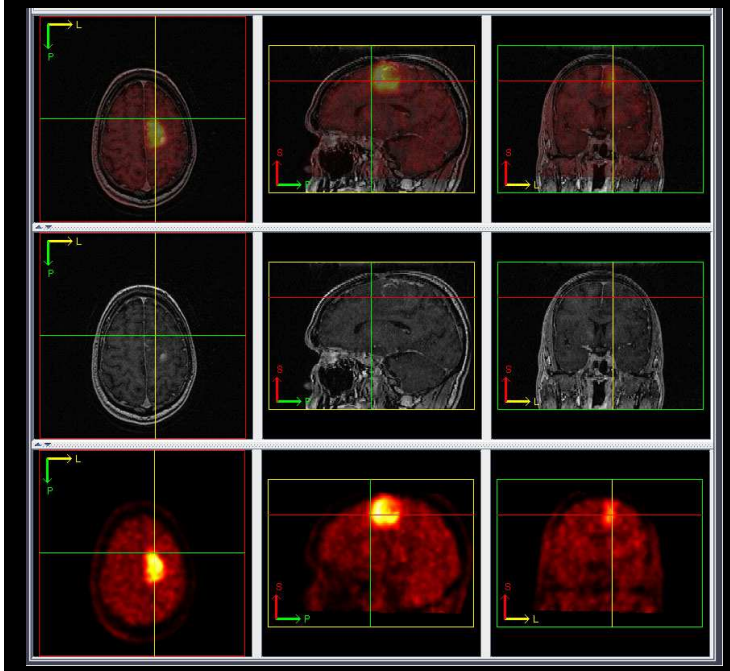


In 53 patients with locally-advanced disease

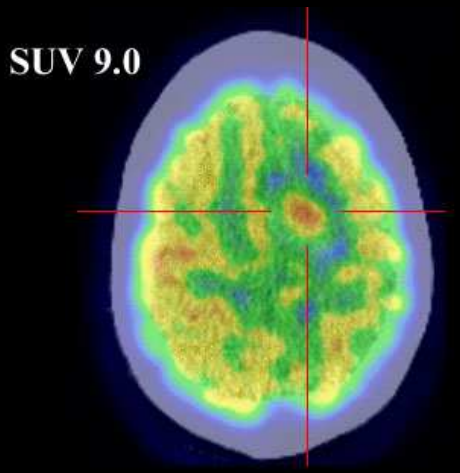
Duong et al. 2006;33:770-778

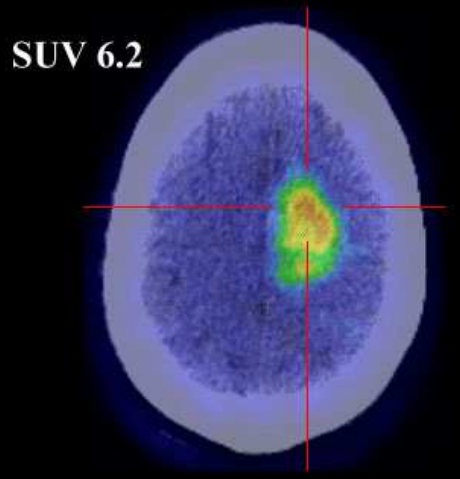
Flouroethyltyrosine FET





FET-MRI fusion

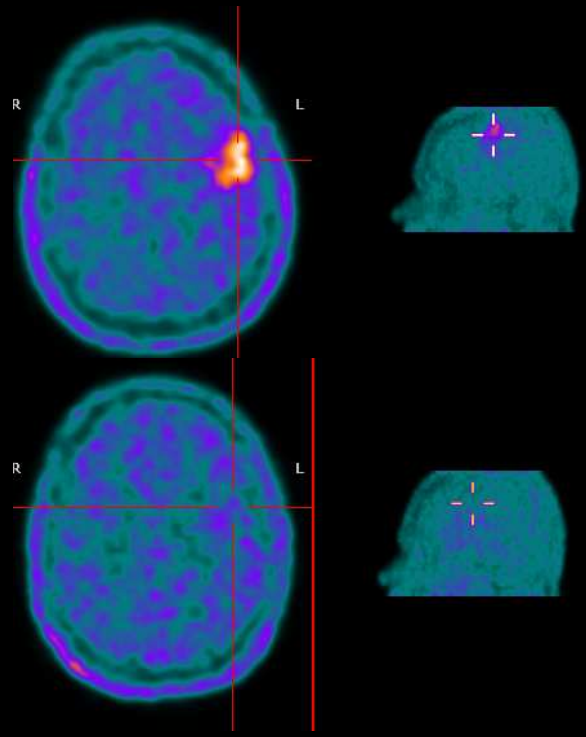




PMCC FET PET Pilot Study in Brain Tumours
Therapeutic Monitoring

Baseline FET

Post-CRT FET



- Left frontal grade II WHO oligoastrocytoma
- Treated by chemo-radiation following debulking surgery

PET in Therapeutic Monitoring

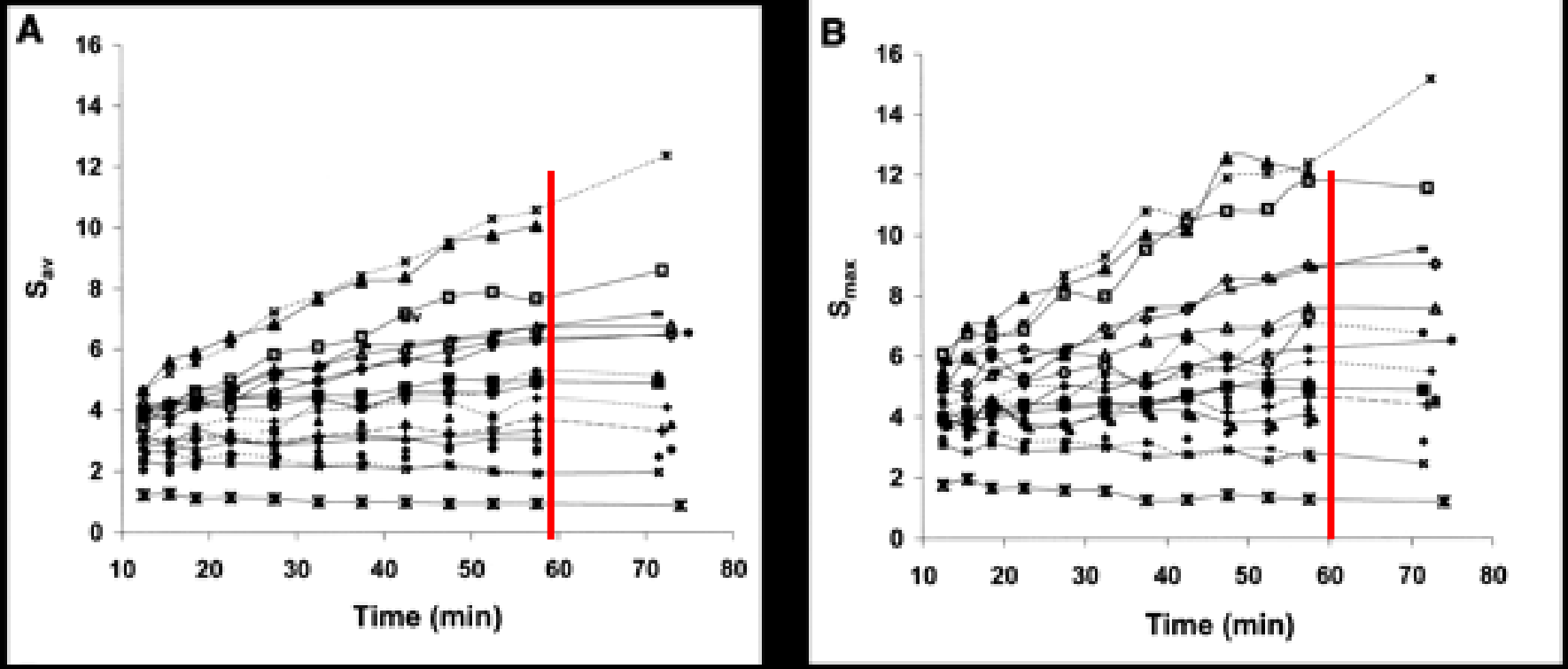
- Standardisation required to;
  - interpret results in clinical trials
  - Compare different trials
  - Implement prospective evaluation
- Initial criteria of Young et al. EJC 1999
  - CMR- disappearance
  - PMR Decrease of 15-25% after 1 cycle, >25% after 2 or more cycles
  - PMD - Increase of >25% or new lesion
  - SD, neither PMR or PMD

"Committee- a group of men who individually can do nothing but as a group decide that nothing can be done."

Fred Allen (American Humorist), 1894-1956

PET for Therapy Monitoring

FDG Methodology

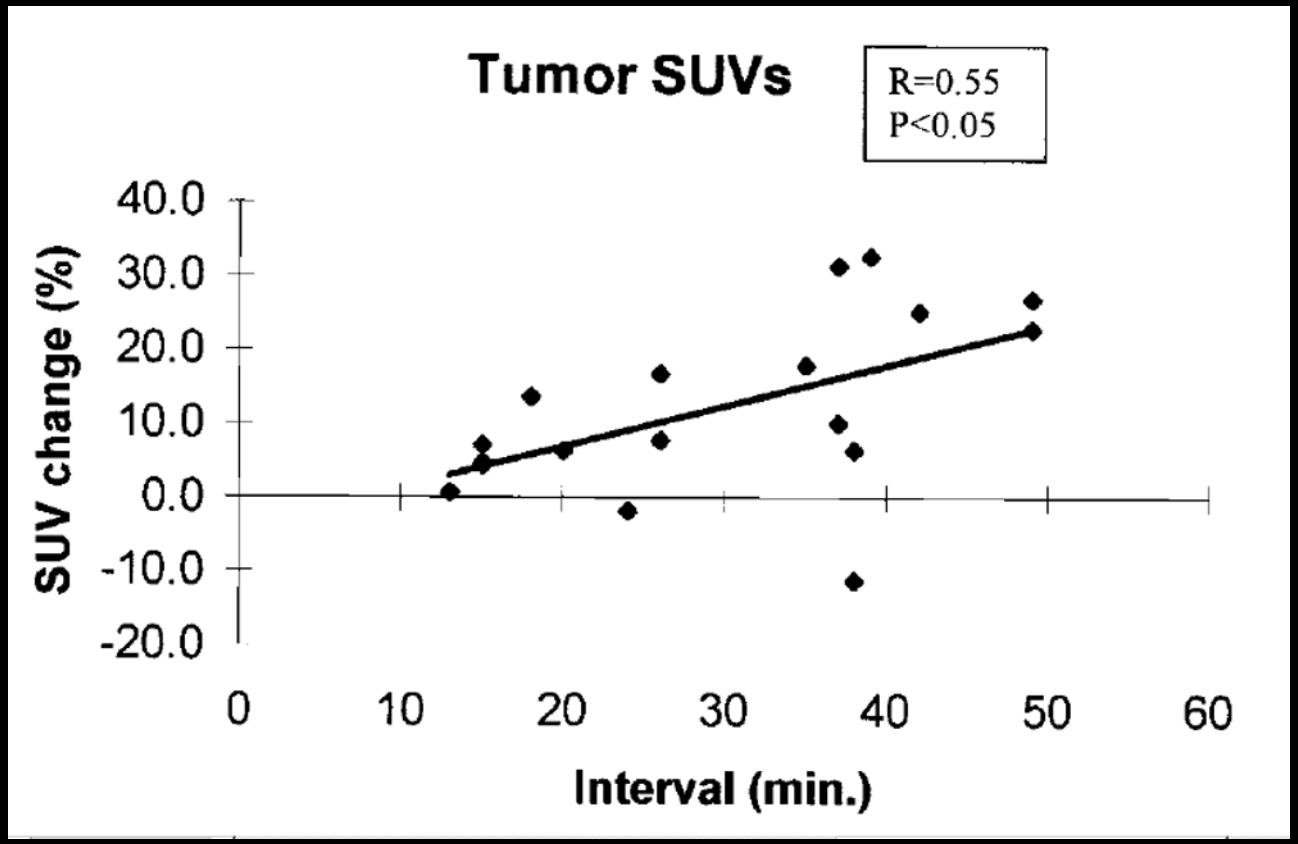


Beaulieu et al. JNM 2003:44:1044-50

Change in SUV over time in breast cancer

PET for Therapy Monitoring

FDG Methodology

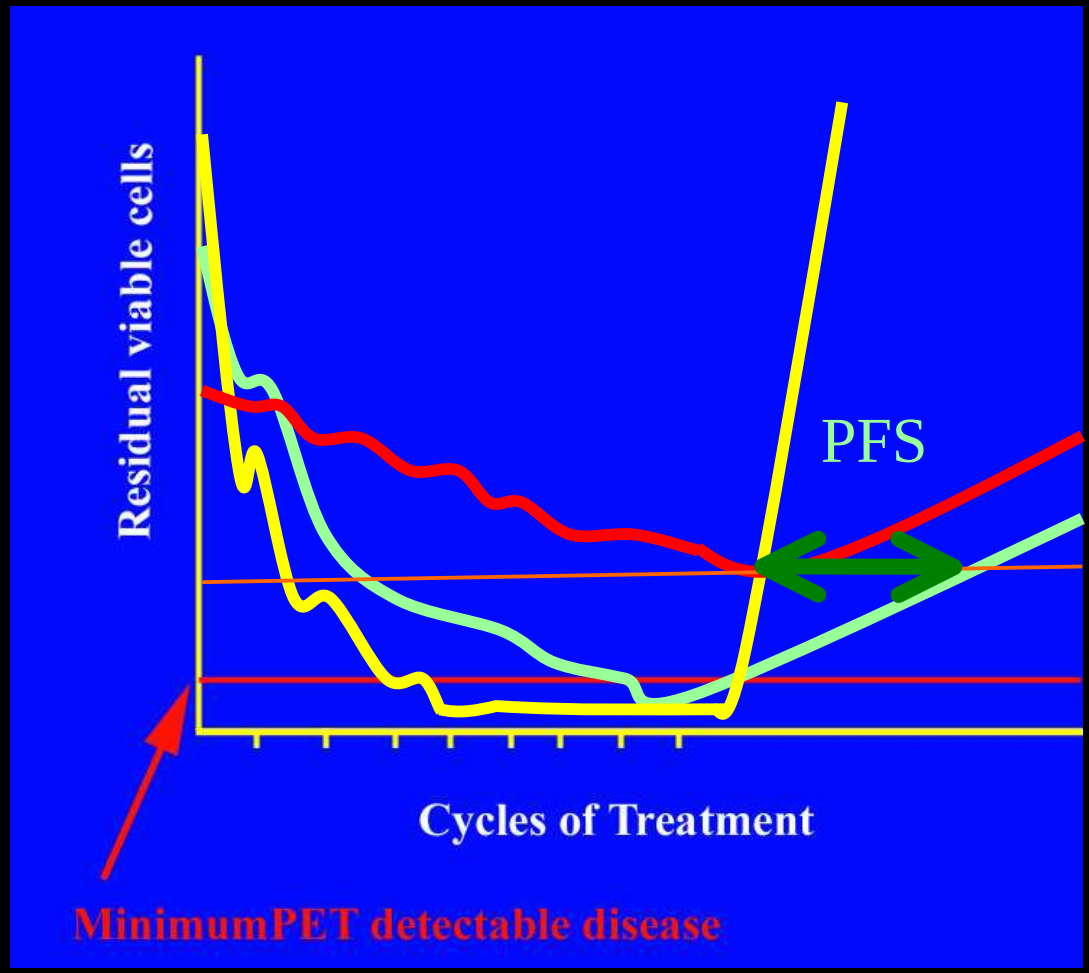


Hustinx et al. EJNM 1999:26:1345-8

Change in SUV between median 70 (range 47-112) and 98 (range 77-142) minutes post-injection of FDG

Imaging of Cancer

Importance of Disease Biology



Rate of cell depopulation and repopulation determines survival advantage of PET responders versus non-responders


www.timeasia.com
MAY 28, 2001
TIME
JAPAN'S REBEL GOVERNOR
MERCURY POISON IN INDONESIA
THERE IS NEW AMMUNITION IN THE WAR AGAINST CANCER.
THESE ARE THE BULLETS.
Revolutionary new pills like GLIVEC combat cancer by targeting only the diseased cells. Is this the breakthrough we've been waiting for?
NVR SI
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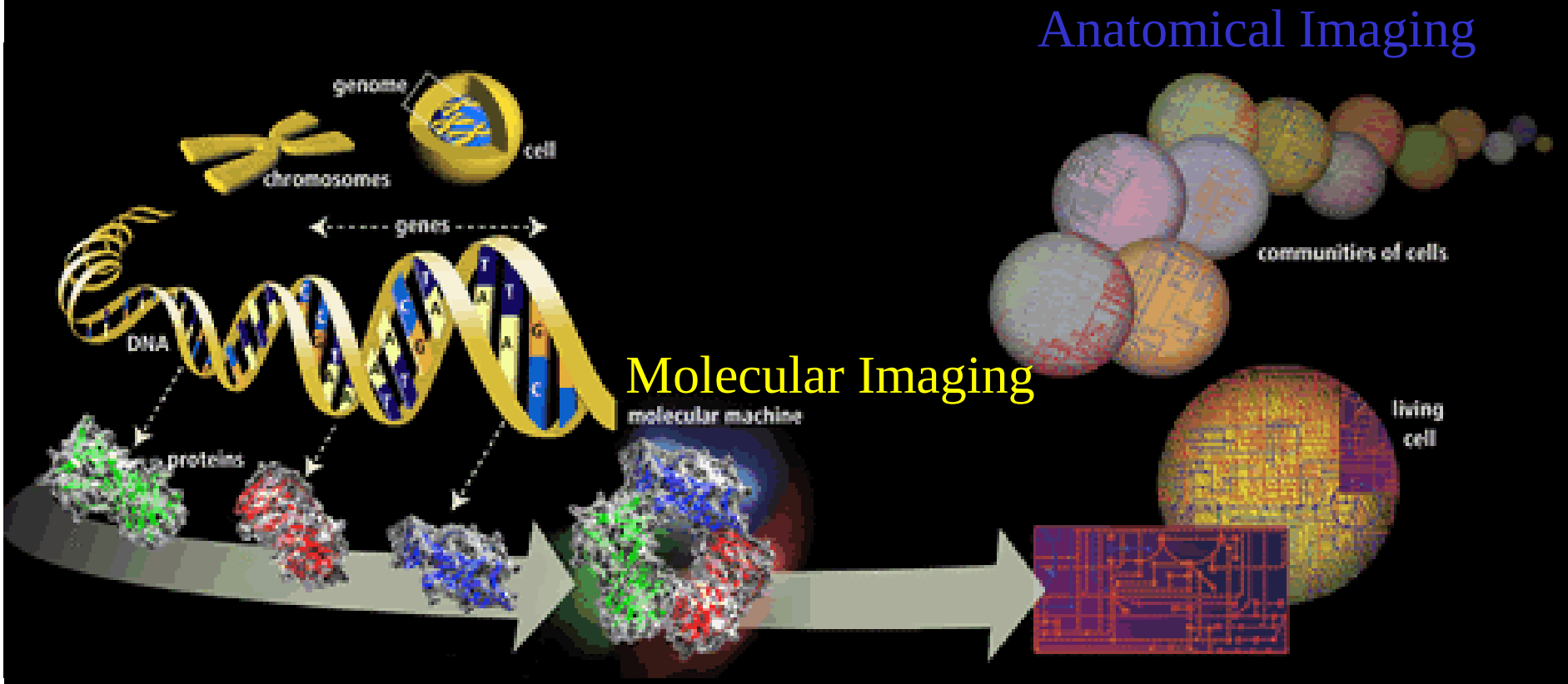
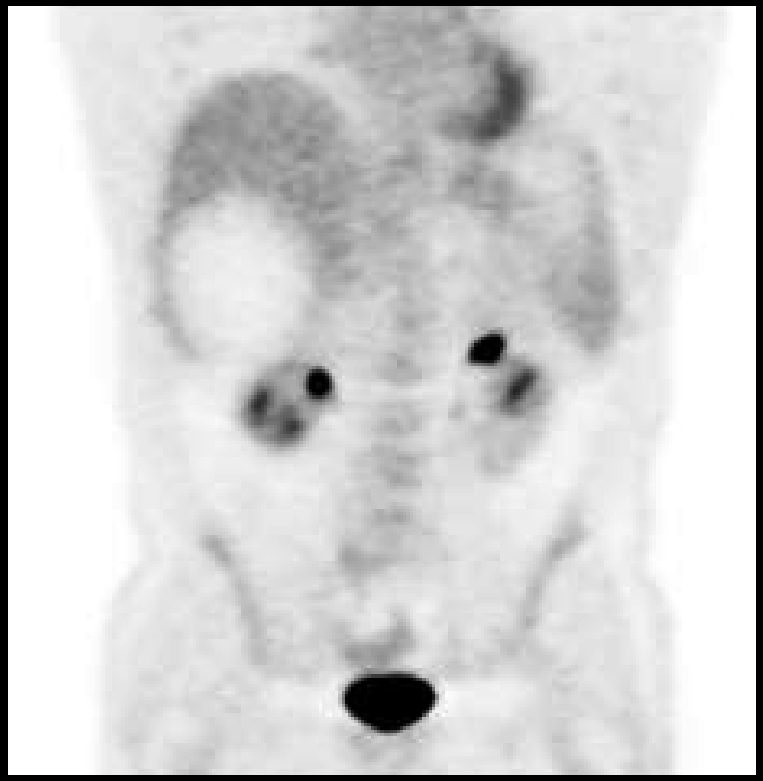
The New Molecular Paradigm



A new era of personalised
"molecular medicine"!

The Power of Metabolic Imaging
FDG PET for Therapeutic Monitoring

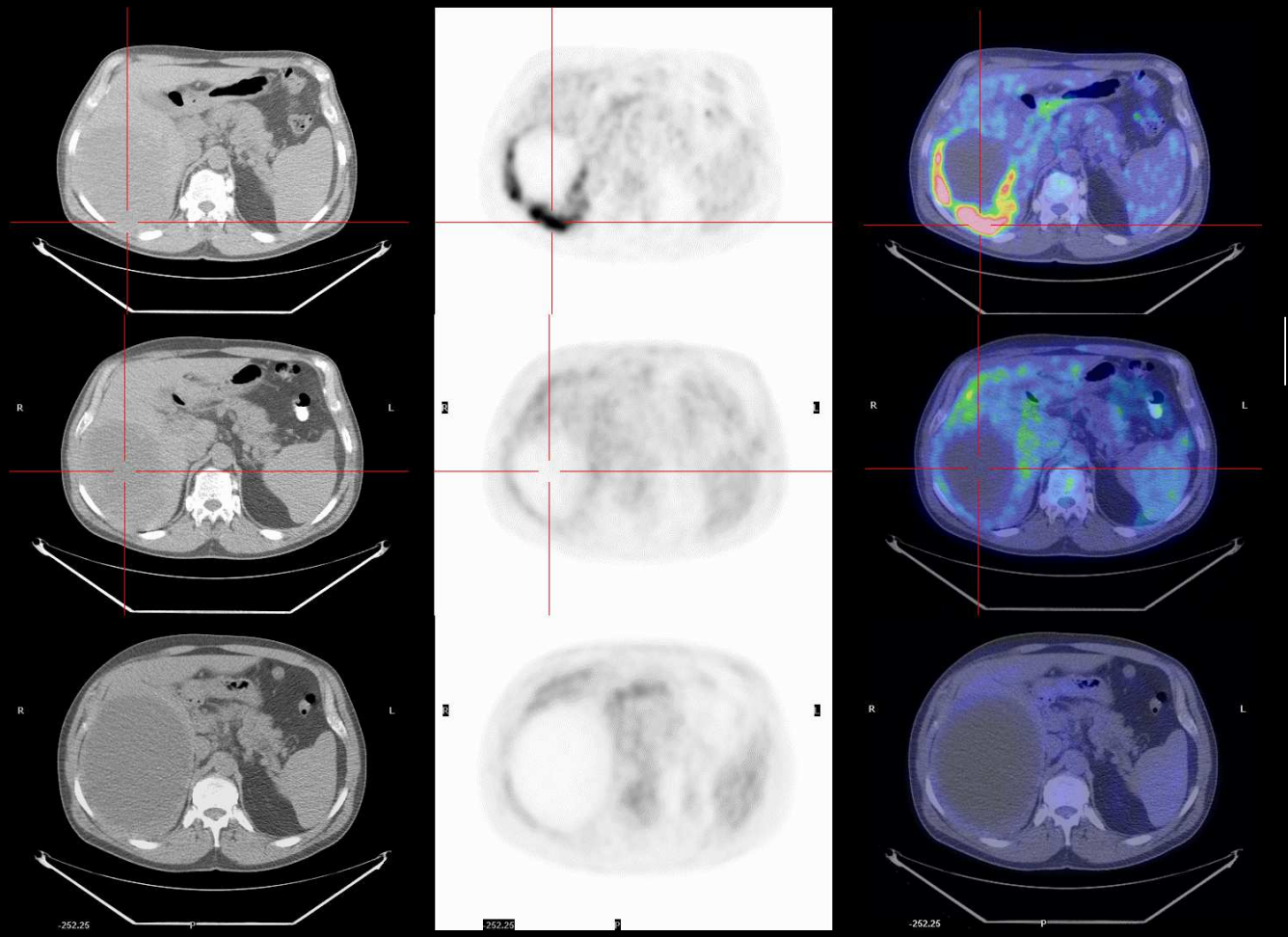


Before Imatinib

One day after Imatinib

Gastrointestinal stromal tumor (GIST)

Discordance in Metabolic and Anatomic Response

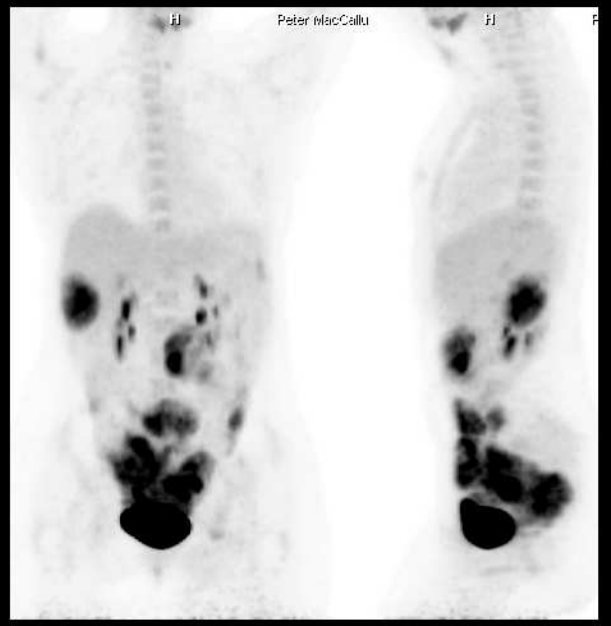


Clinical response in GIST treated with imatinib concordant with metabolic response but not RECIST

PET-CT of GIST

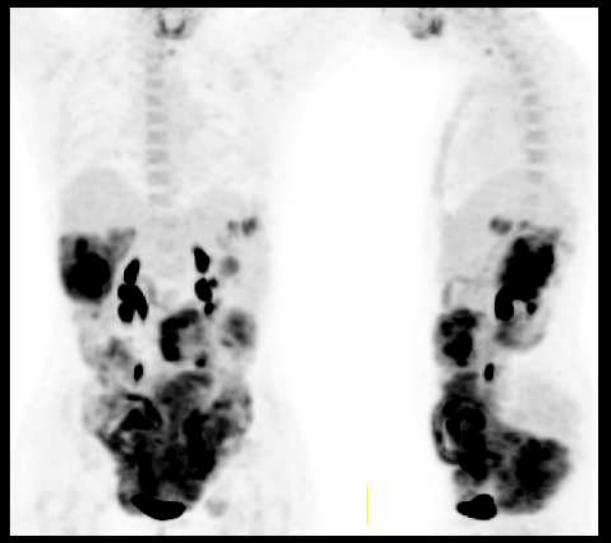
- Poor therapeutic response to imatnib

October 2008



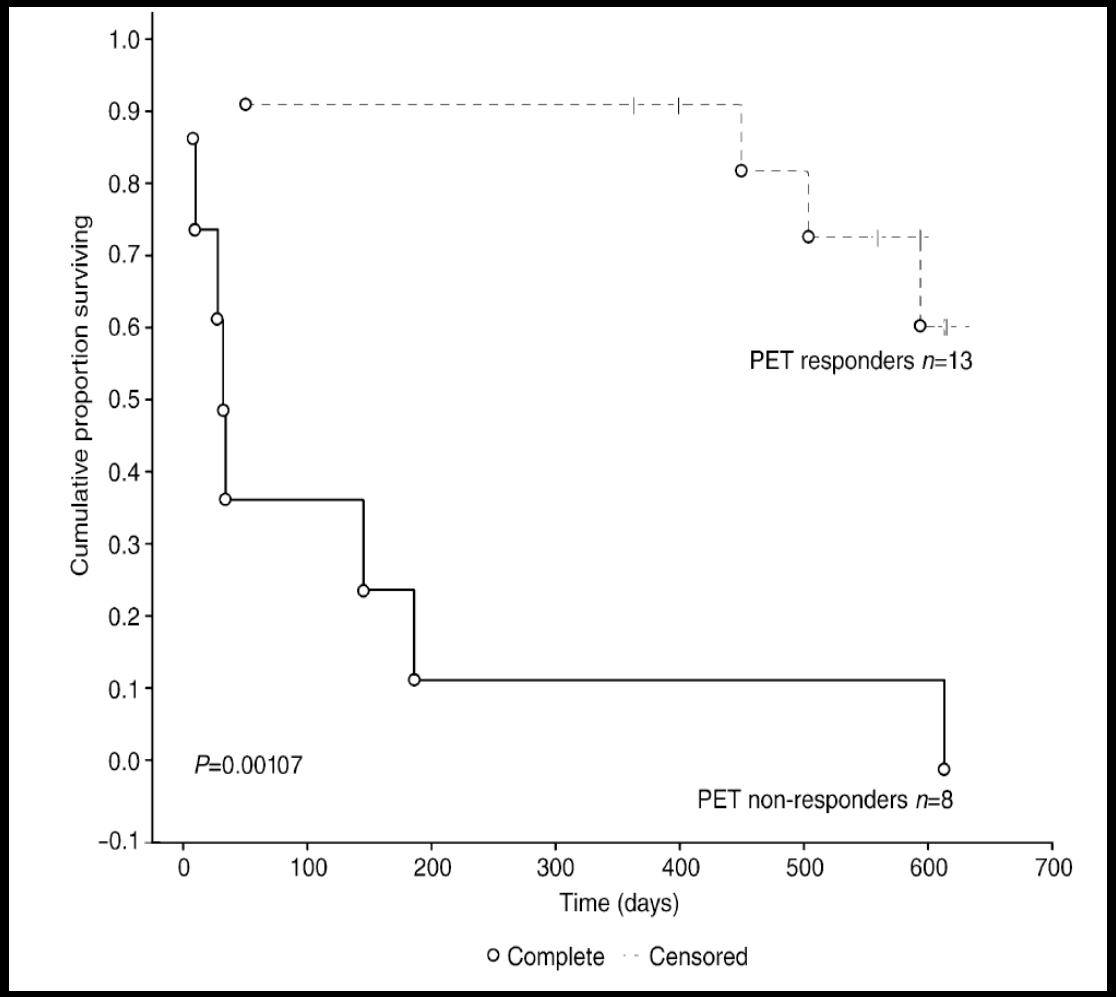
Anterior MIP Left Lateral MIP

January 2009



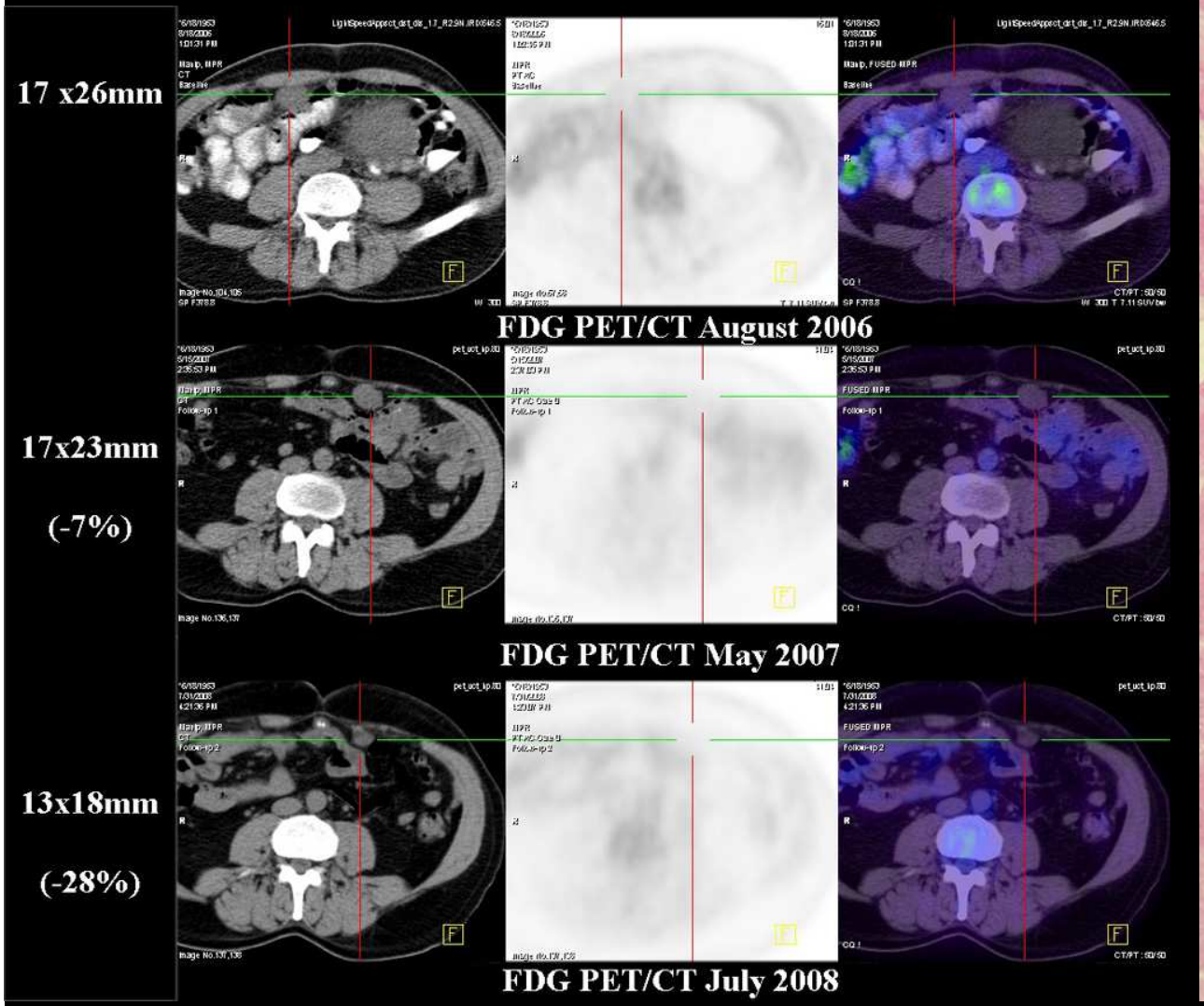
PET for Therapy Monitoring

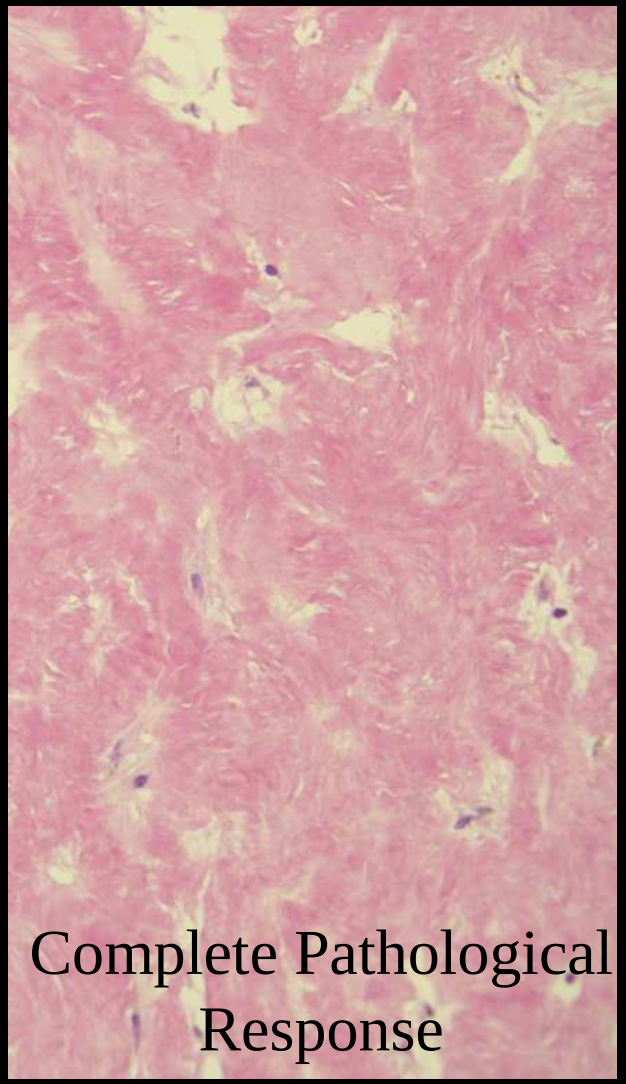
The Prognostic Significance of Metabolic Response in GIST



Stroobants et al, *European Journal of Cancer*, 2003

FDG PET for Therapeutic Monitoring





Complete Pathological Response

Discordance between metabolic and structural responses in GIST tumour treated with imatinib (Sustained CMR but never achieved PR)

FDG PET for Therapeutic Monitoring

71x100mm

Baseline FDG PET/CT August 2006 (Recently started Imatinib)

36x44mm

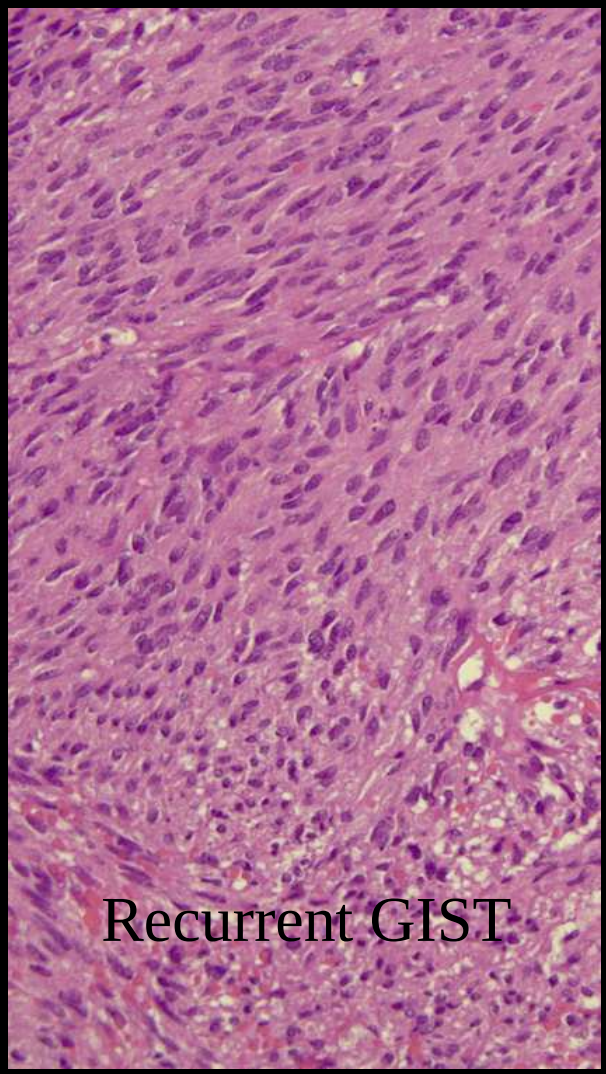
(-53%)

Surveillance FDG PET/CT May 2007 (Ongoing Imatinib)

24x33mm

(-67%)

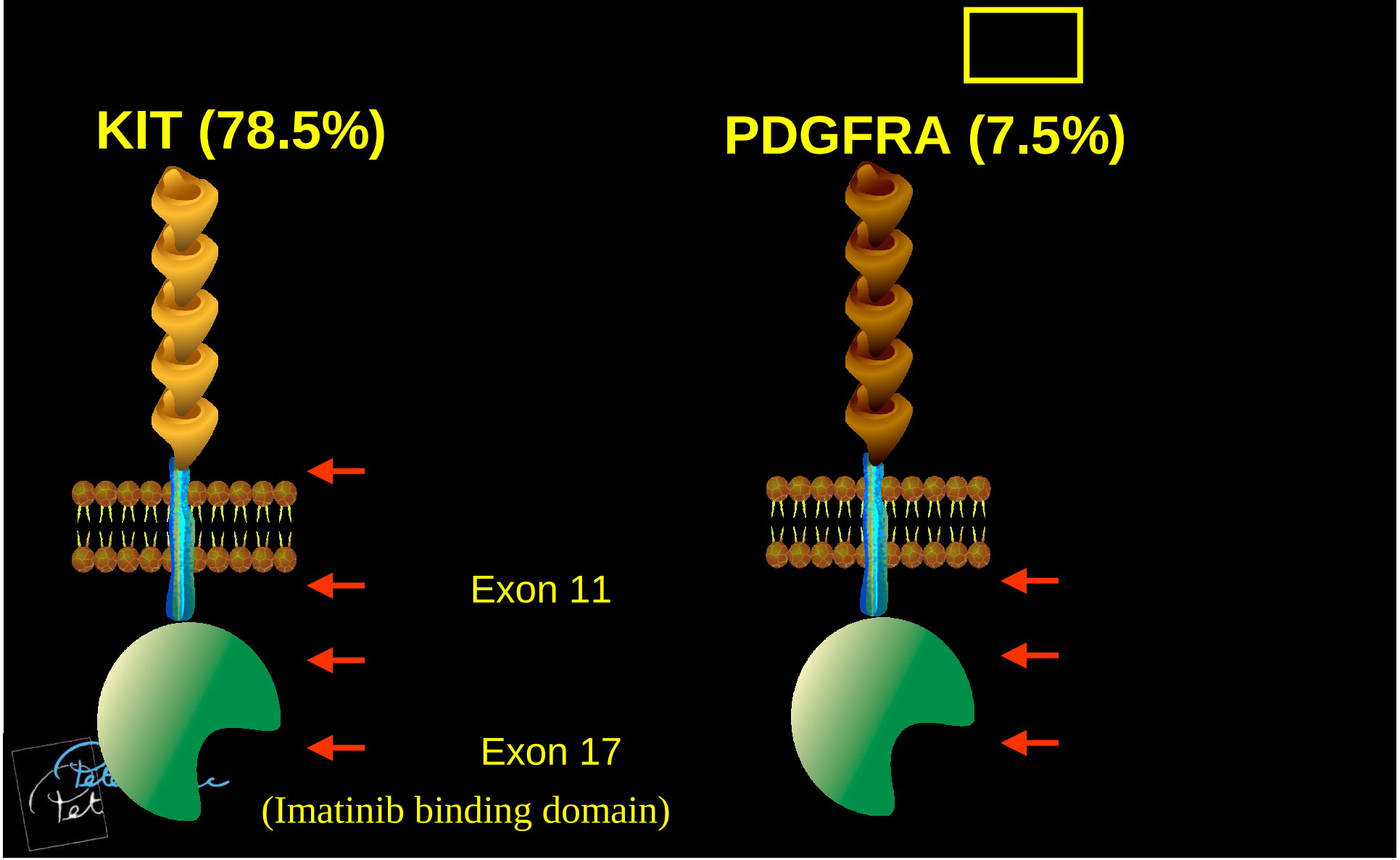
Surveillance FDG PET/CT July 2008 (Ongoing Imatinib)



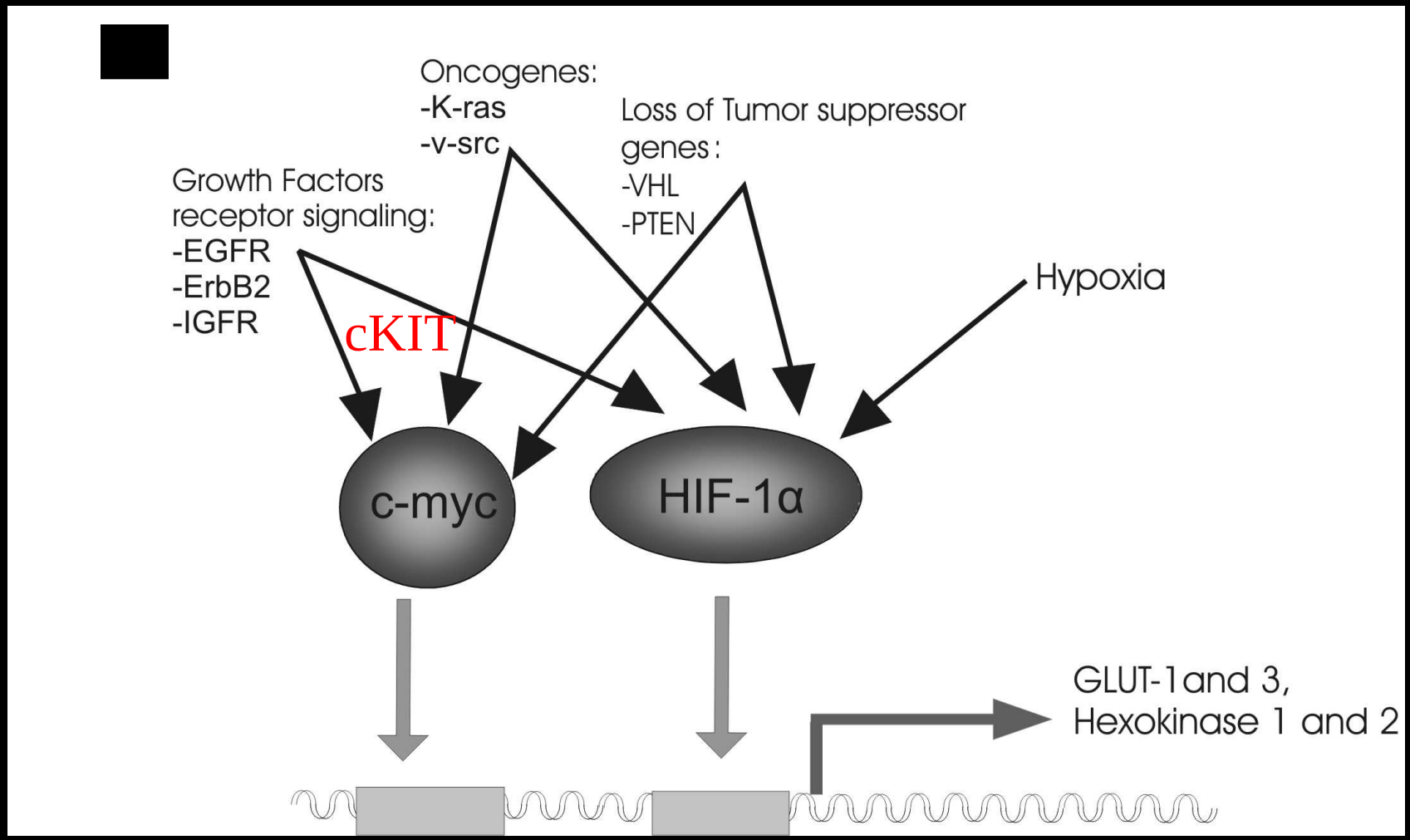
Recurrent GIST

Discordance between metabolic and structural responses in GIST tumour treated with imatinib (Relapsed despite progressive PR)

KIT and PDGFRA Mutations in 950 GISTs



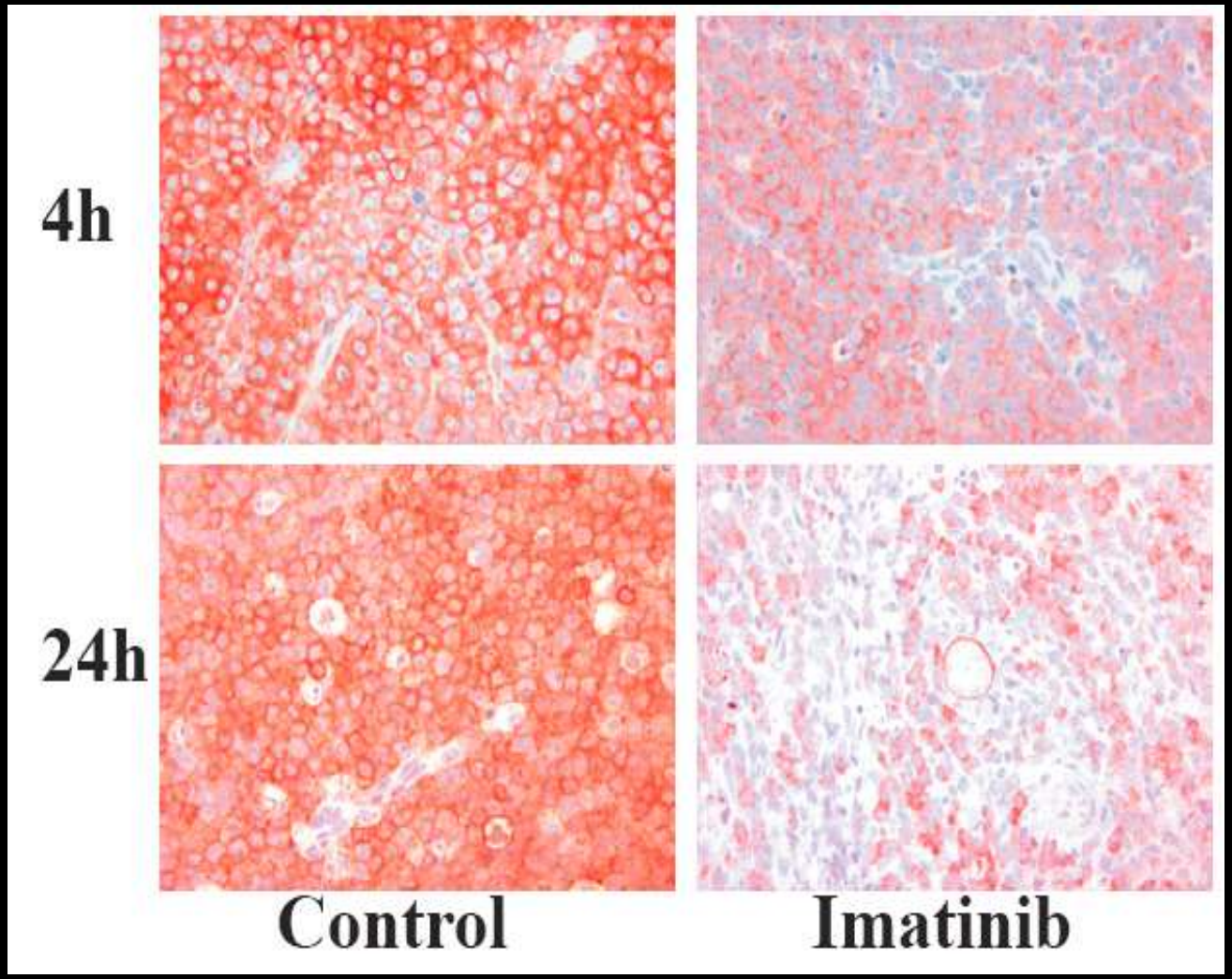
FDG PET
Mechanisms of Enhanced Tumoral Uptake



Key role of oncogenes and hypoxia link FDG uptake to poor prognosis

Solomon B et al. *Biodrugs* 2003; 17:339-354

Why is FDG response to imatinib so rapid?

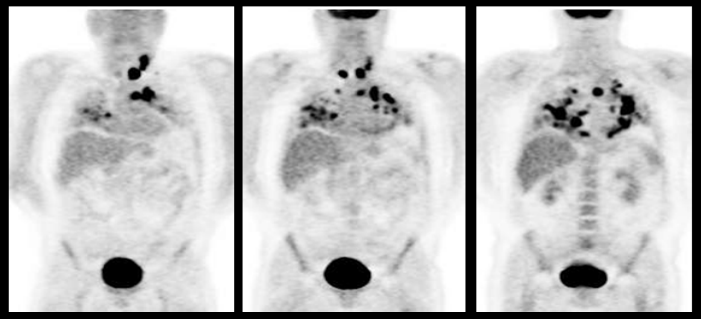


Cullinane, Dorow et al. *Cancer Research* 2005; 65:9633-6

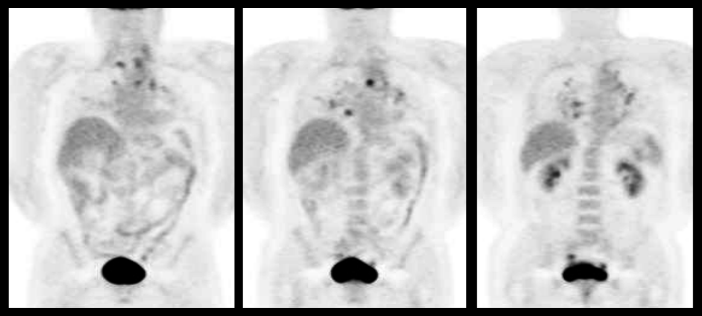
PET For Therapeutic Monitoring

Availability of *Ex Vivo* Biomarker Validation

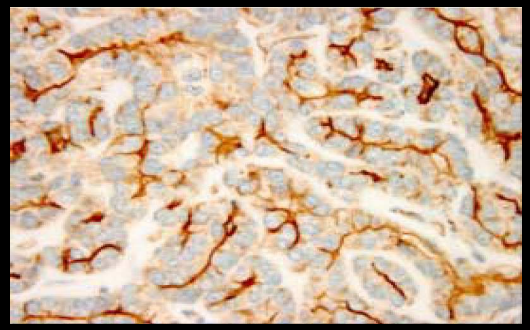
Baseline FDG PET

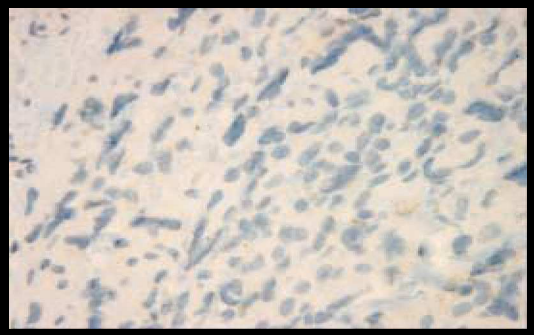


Week 4

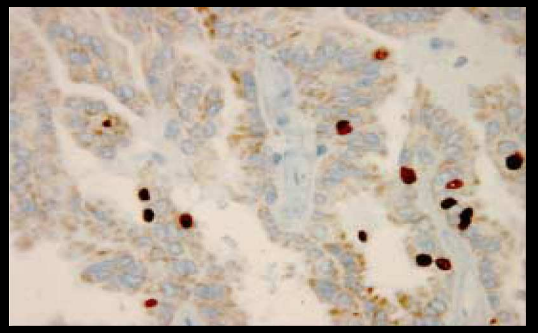


pVEGFR2





Ki67

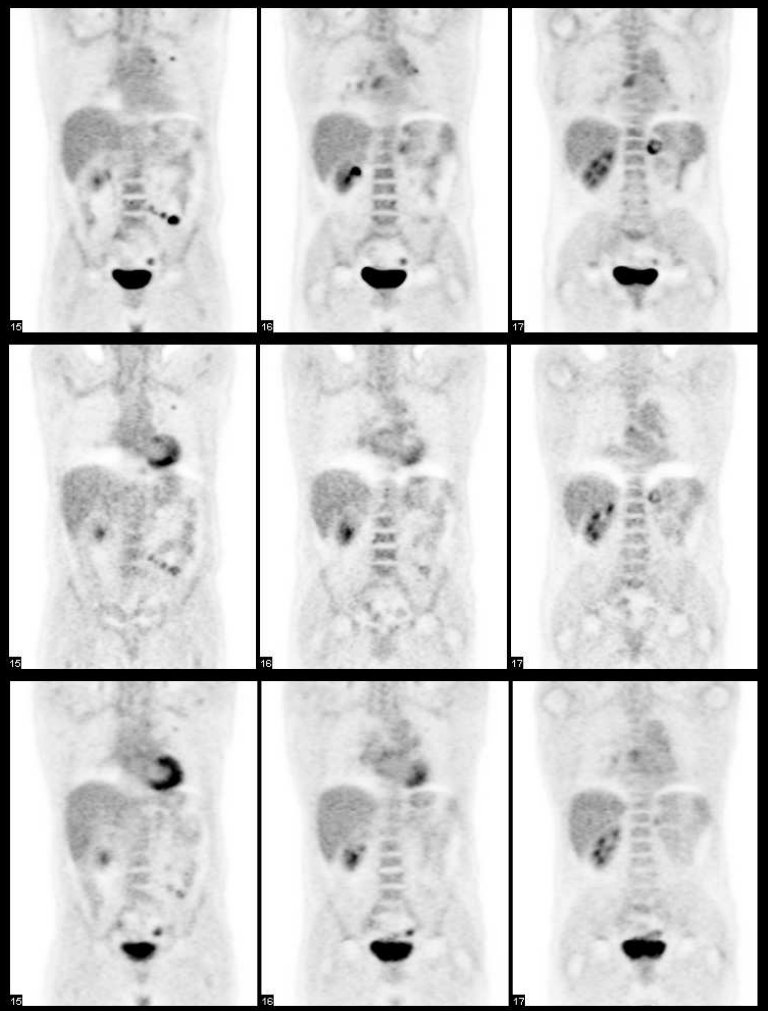


- Metastatic thyroid cancer treated with an anti-angiogenesis agent
- Excellent clinical and radiological response predicted by early qualitative response but not by SUVmax response

PET for Therapy Monitoring

FDG PET - Role in Novel Therapies

- Metastatic renal cell carcinoma
- Novel anti-angiogenesis agent in phase I development
- FDG PET used for assessment of drug activity



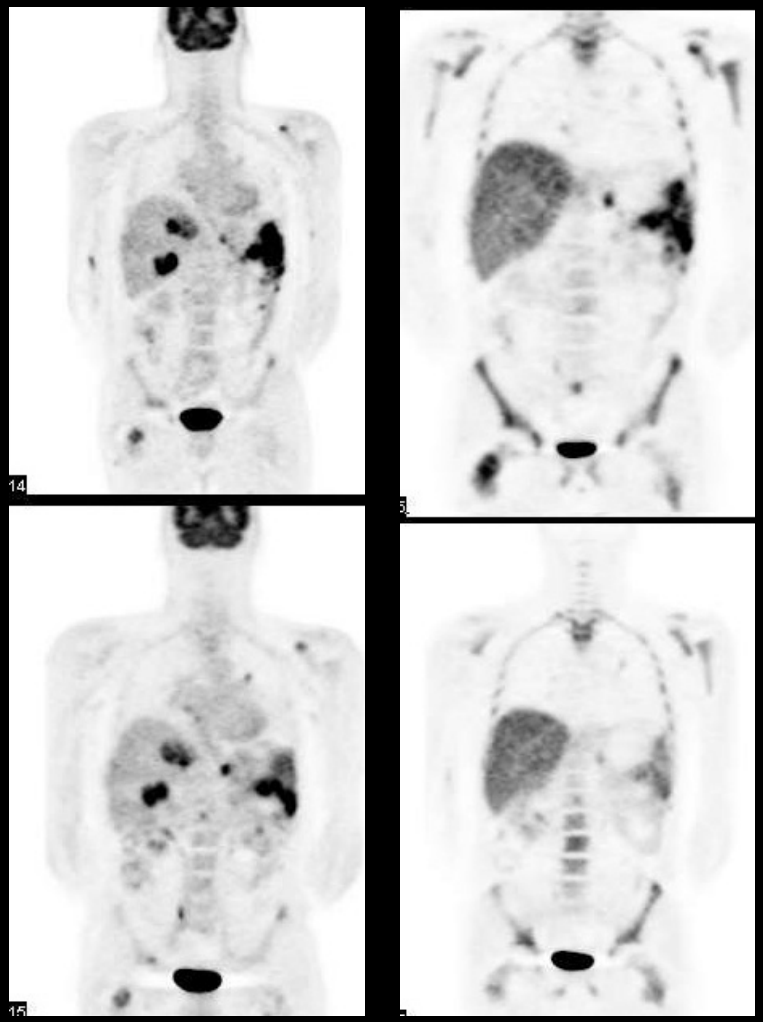
PET For Therapeutic Monitoring

Comparison of FDG and FLT Response

Baseline FDG PET

SU-11248-pt-35

Week 4 FDG PET



Baseline FLT PET

Week 2 FLT PET

- **Metastatic malignant melanoma**
- **Bone and liver mets better seen on FDG PET**

Evaluating New Treatments

Malignant melanoma

New targeted therapy for mutant gene expressed in >40% of cases

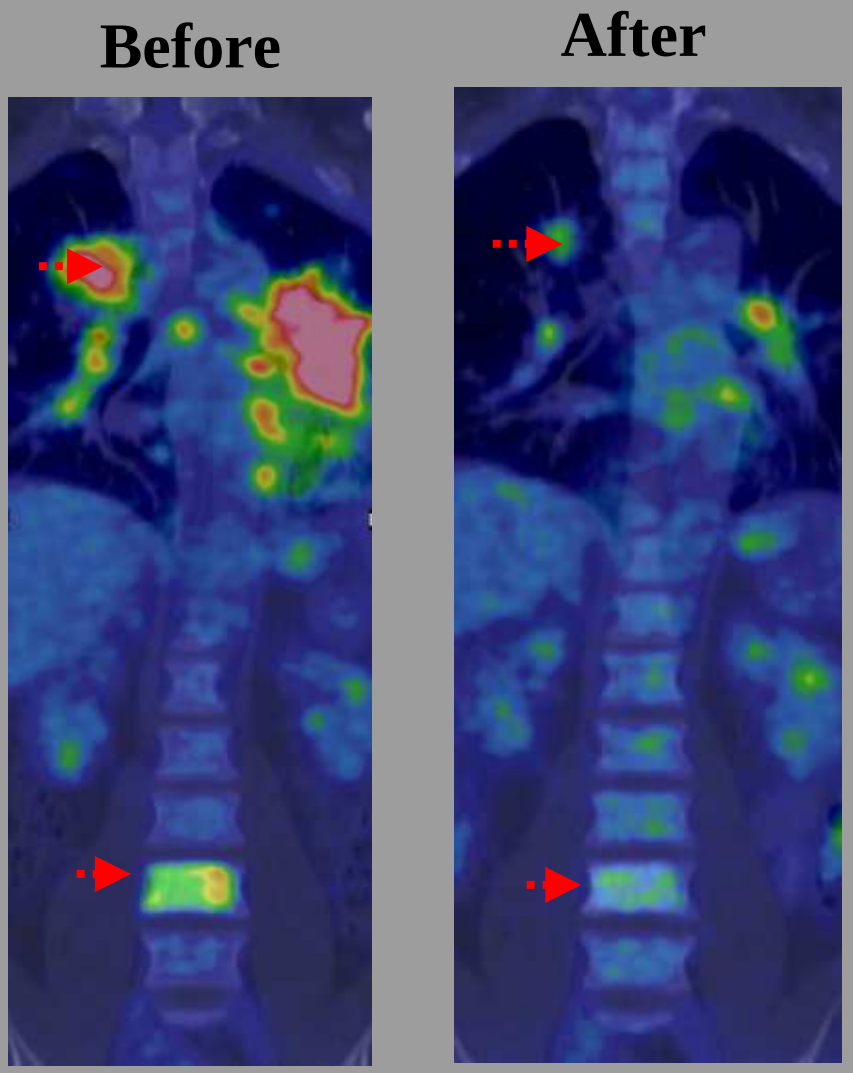
"Why not go out on a limb? Isn't that where the fruit is?"

Frank Scully, American writer

Evaluating New Treatments

Lung cancer

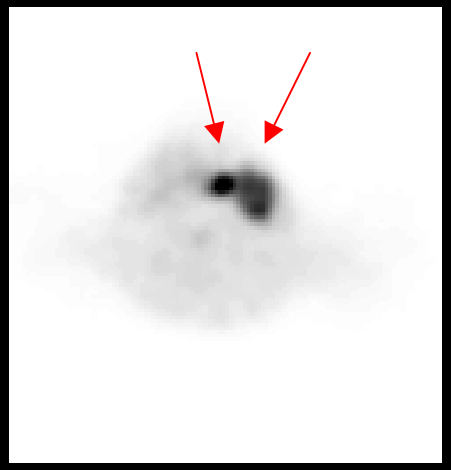
New targeted therapy for a mutant gene (ALK fusion gene) expressed in <5% of cases



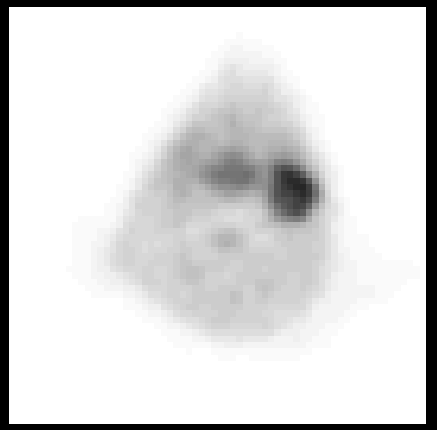
PET for Therapy Monitoring

New Targets Require New Tracers

FDG
(Glucose)

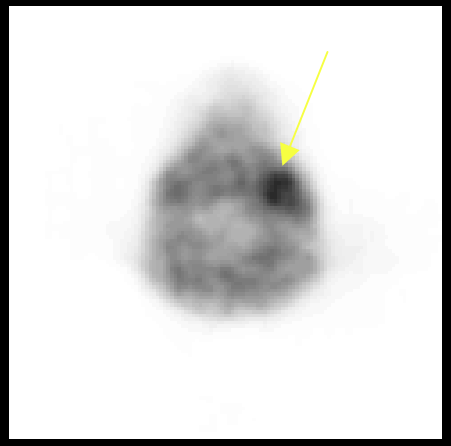


2 tumour sites



Only 1 responds

FMISO
(Hypoxia)



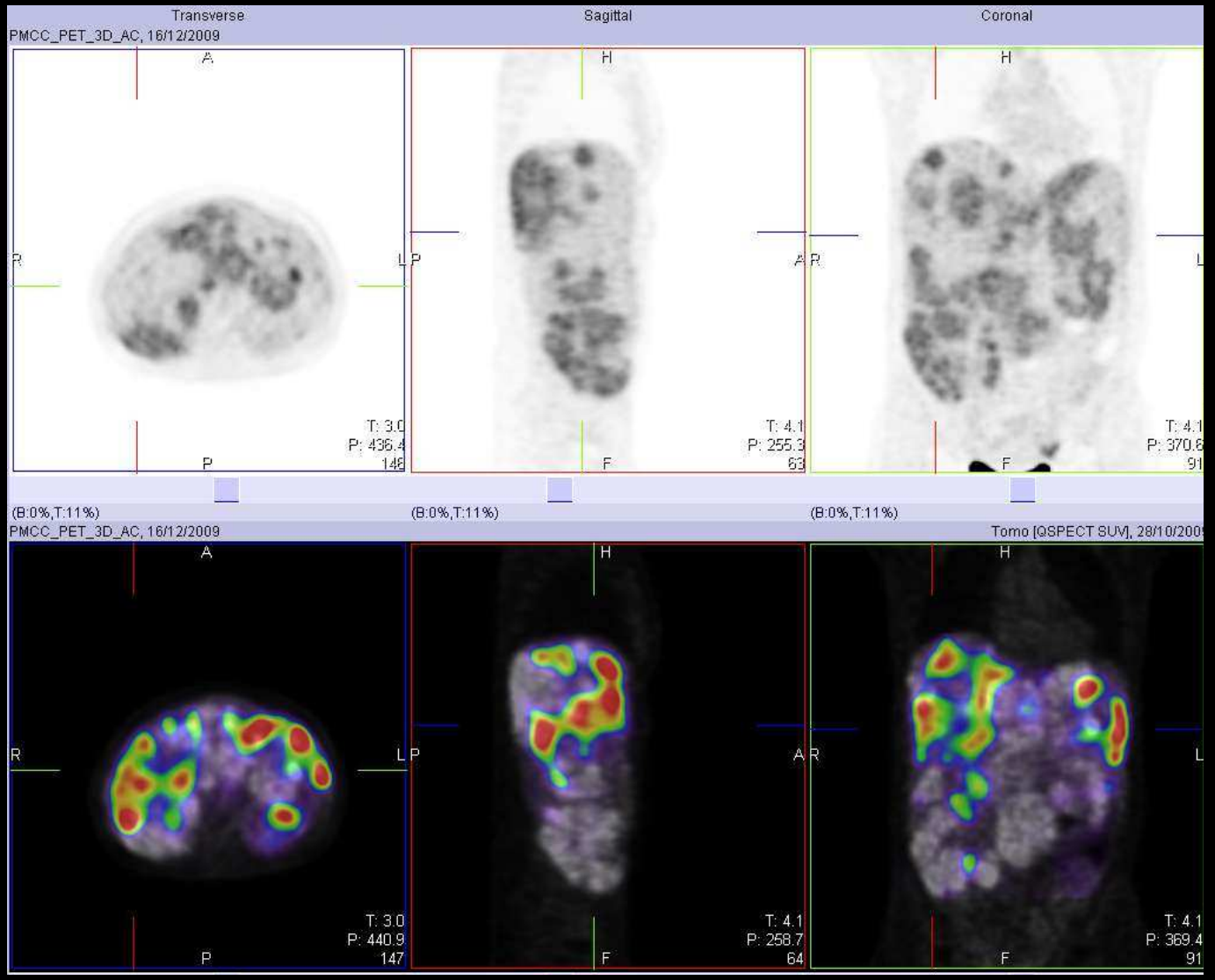
Only 1 site lacks oxygen

Lack of oxygen limits effectiveness of current therapies but provides a target for new drugs!

Concept of Clonal De-Differentiation

FDG

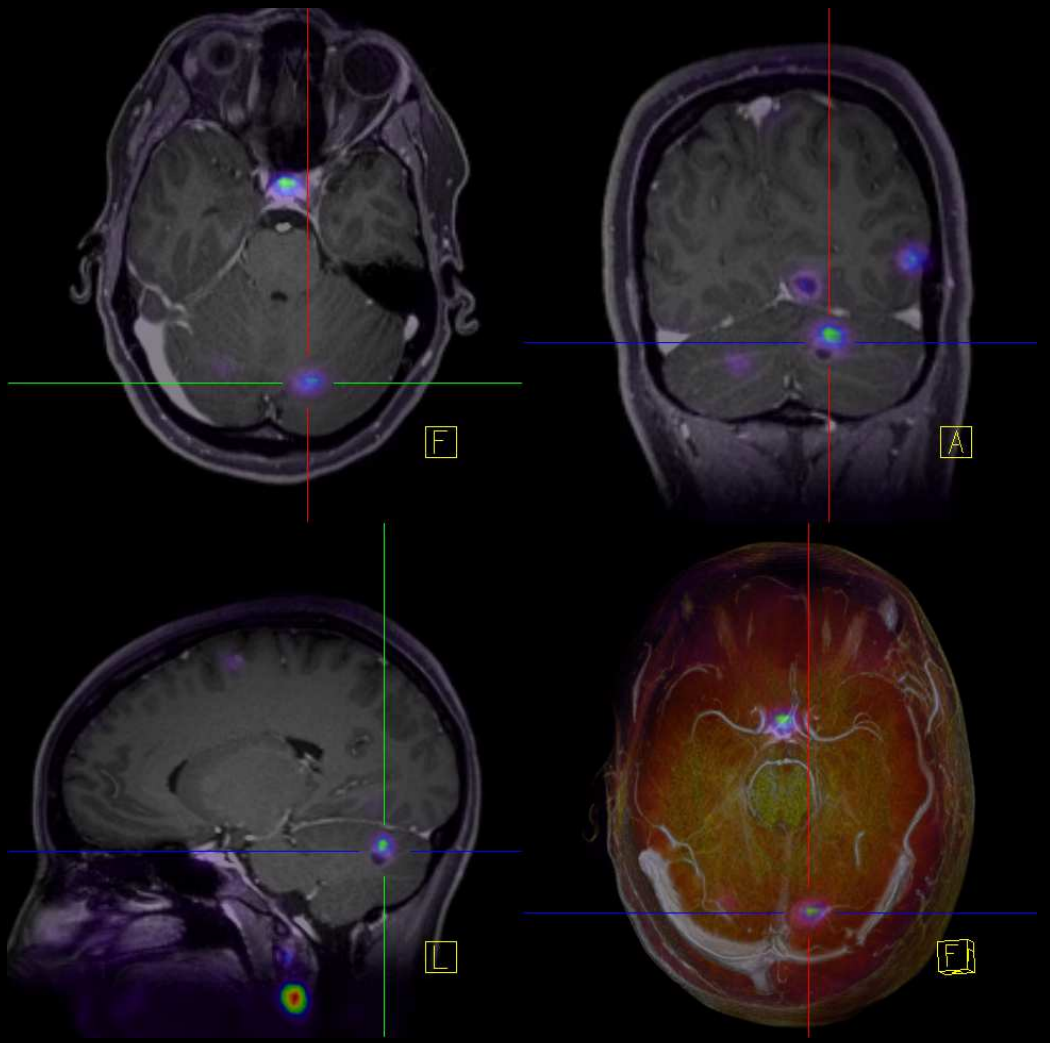
Fused Ga-68 octreotate (colour) and FDG



Future Directions

More specific biological probes

- Receptor ligands, e.g. somatostatin receptor ligands (Ga-68 octreotate)
- Hypoxia , e.g FMISO



PET for Therapy Monitoring

Summary

- Treatment options are becoming more complex
- Better treatment selection is required
- Early monitoring of response can identify non-responders sparing further futile toxicity
- Optimum timing of monitoring scan is probably disease and therapy dependent
- Molecular biology and molecular imaging are complementary tools in the new era of molecular medicine

Now we only need to convince the regulators!