Molecular Imaging in the Development of Cancer Therapeutics

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Cancer Statistics

Cancer Type	5-year Survival Rate
Lung Cancer:	13%
Breast Cancer:	90, 88, 36, 7%
Esophageal Cancer:	10%
Stomach Cancer:	10%
Pancreatic Cancer:	2%
Advanced Colorectal Cancer:	5 -10%
Metastatic Renal Cell Cancer:	3%

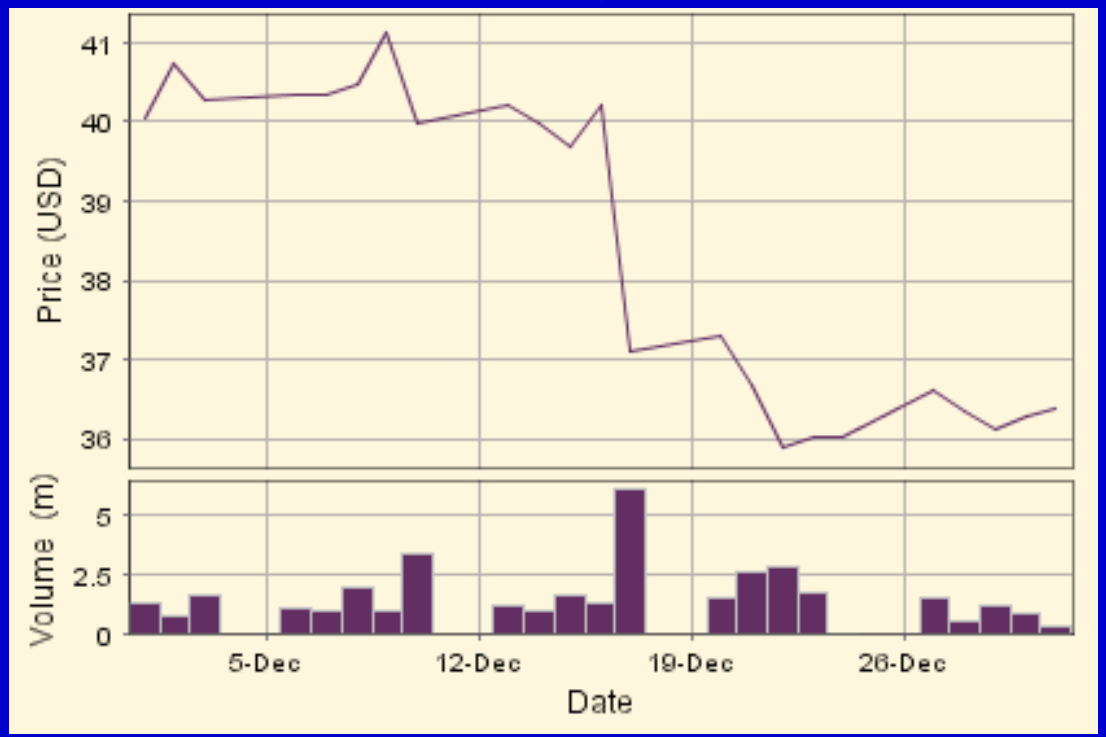
Exceptions: Prostate Cancer (die with rather than from cancer), Testicular Cancer, Lymphoma, and some Leukemias.

ISEL study: Iressa Survival Evaluation in Lung Cancer

- Randomized, double blind, placebo controlled trial
- 1692 patients with metastatic NSCLC
- Refractory to chemotherapy
- Palliative treatment vs. Iressa
- Objective response rate: 8.2%
- Median survival: Iressa: 5.6 months, placebo 5.1 months (p=0.11)

ISEL study and AstraZeneca stock price

ISEL results made public



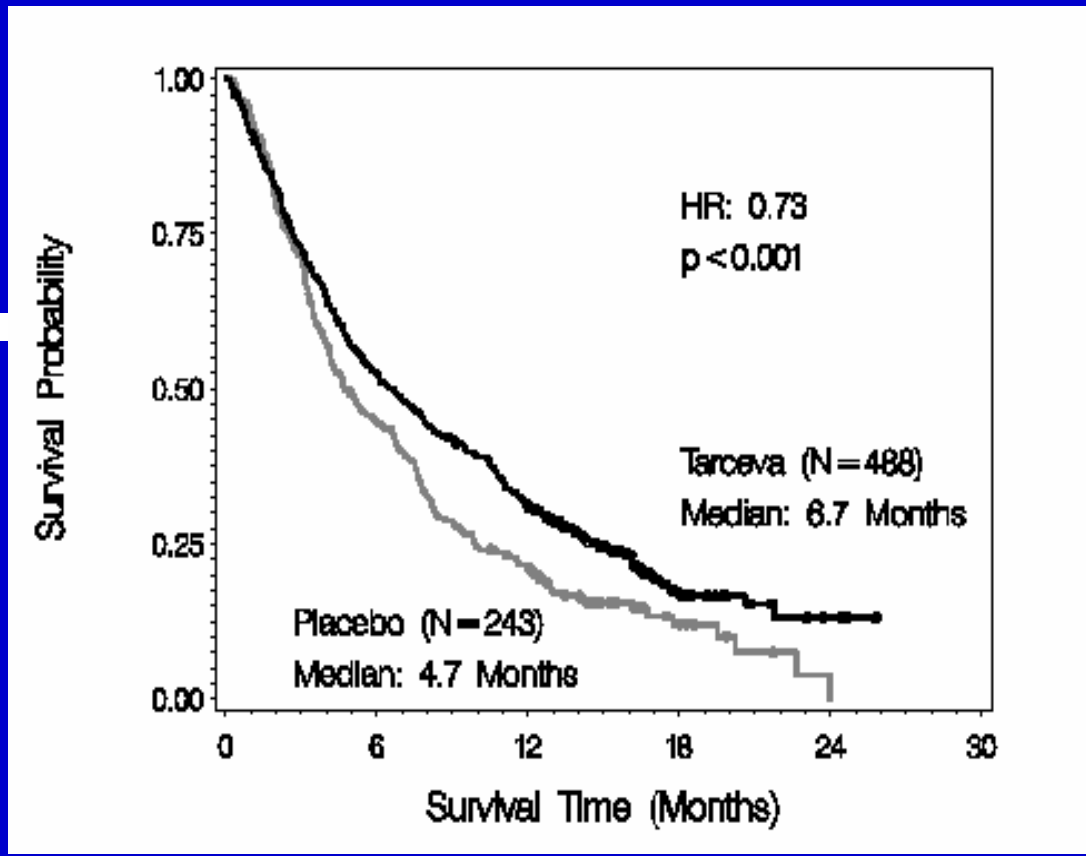
10% loss within 2 days

6.58 billion US$

AZN NASDAQ: December 2004

Erlotinib for Treatment of Advanced NSCLC NCIC CTG trial

- Randomized, placebo controlled study
- 731 patients included
- Erlotinib vs. Placebo
- Response rate: 8.9%
- Survival: 6.7 mo vs. 4.7 months (p<0.001)



Mutations of the EGFR Kinase Domain and Response to EGFR-Kinase Inhibitors

Authors	Journal	Year	N	PPV	NPV
Paez et al.	Science	2004	9	100%	100%
Lynch et al.	NEJM	2004	16	100%	88%
Pao et al.	PNAS	2004	17	100%	83%
Han et al.	JCO	2005	90	64%	86%
Cappuzzo et al.	JNCI	2005	89	53%	94%
Tsao et al.	NEJM	2005	100	16%	93%

PPV: positive predictive value for response

NPV: negative predictive value for response

The Problem

- Pharmaceutical Industry has Problems
  - Drug discovery and development is expensive (1 Billion Dollars/drug to market)
  - Most of the patents expire
  - Success rate is low
  - Only marginal survival improvements in cancer

  Biological Problem: most frequently there are many mutations

Can Imaging Contribute do Drug Response Prediction and Evaluation

- *Predicting Treatment Responses*

Imaging the expression of a therapeutic target

Example I: Tyrosine Kinase Inhibitors: *F18-Iressa*

Monitoring Treatment Responses with FDG PET

Esophageal Cancer

Lung Cancer

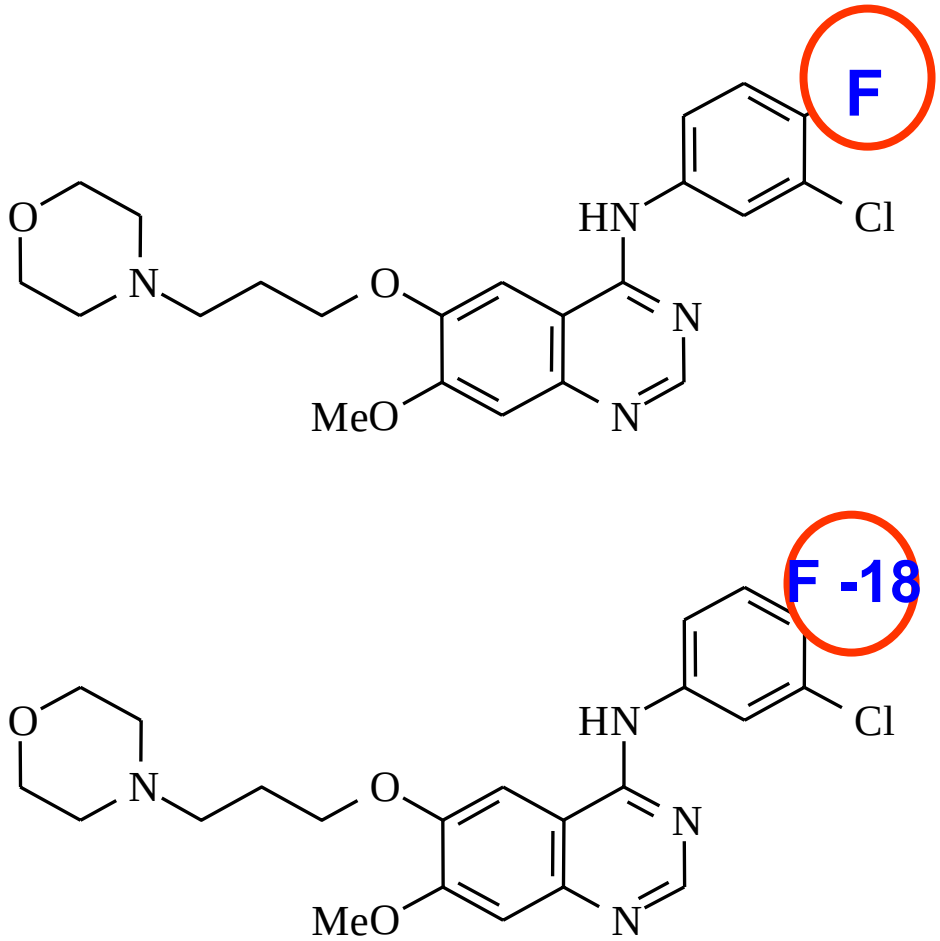
Sarcoma

Glioblastoma

Gefitinib can be Radiolabeled with F-18 without Changing its Chemical Properties

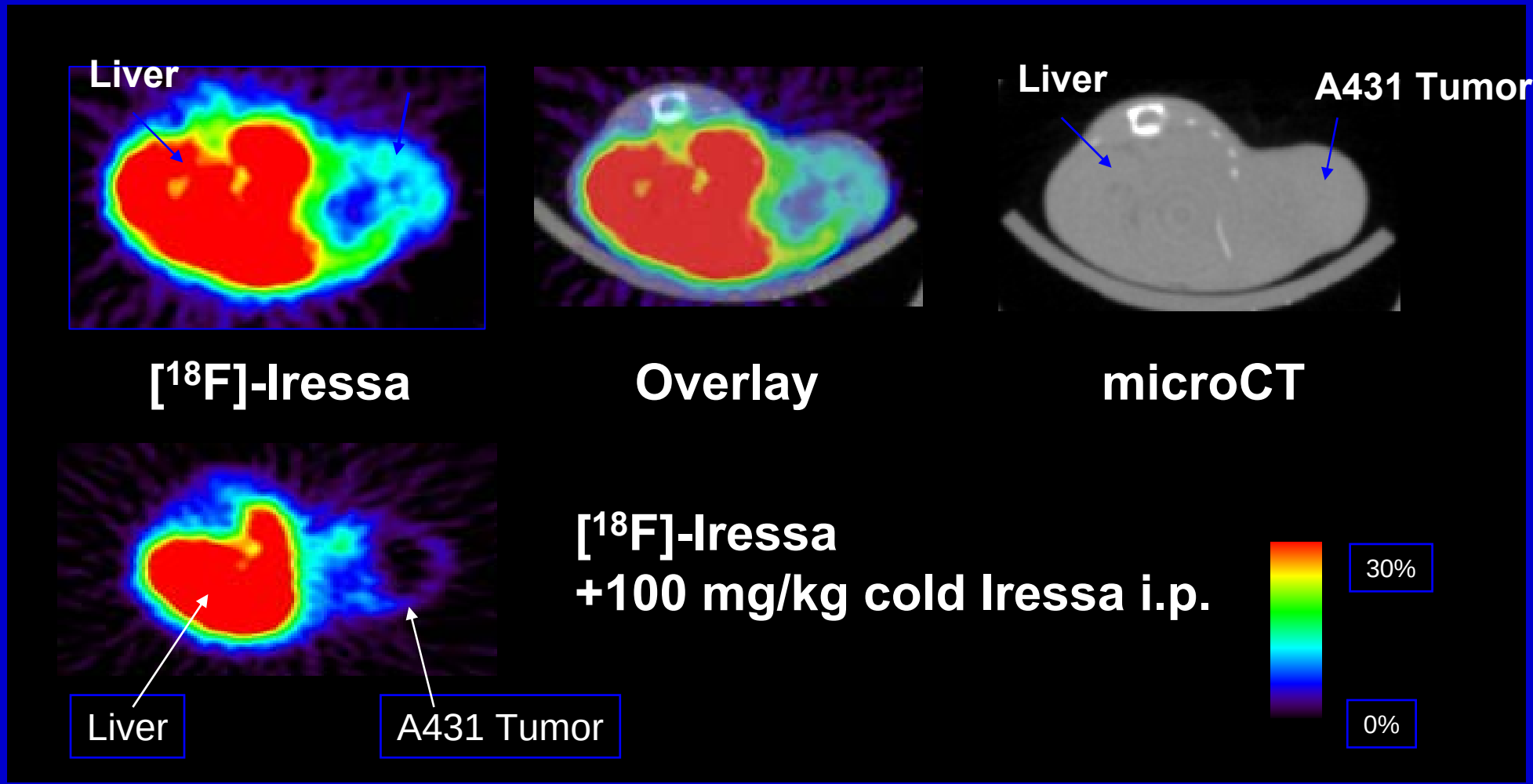
Gefitinib

[^{18}F]Gefitinib



Seimbille 2004

Unexpected Tumor uptake of [^{18}F]Iressa with and without pretreatment with cold Iressa



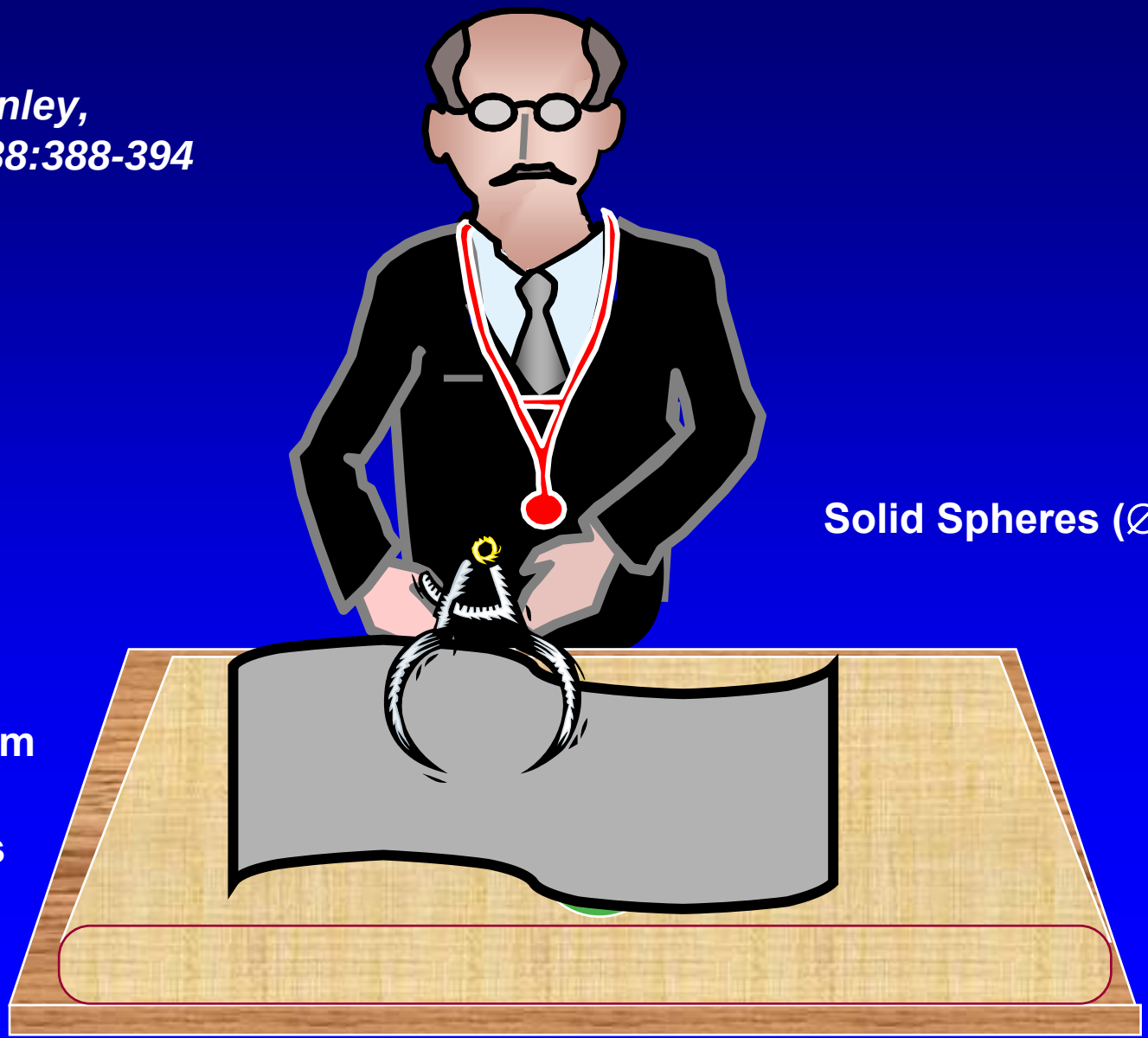
A431 cell lines are sensitive to Iressa

Clinical Trials for Evaluating Drug Responses = Treatment monitoring

- Why?: Limitations of RECIST
- How?:
  - Quantitative? Kinetic modeling?
    Semiquantitative? (SUV)?
- When?: ?

History of Response Criteria

Moertel and Hanley,
Cancer (1976) 38:388-394



Solid Spheres (∅ 1.8-14.5 cm)

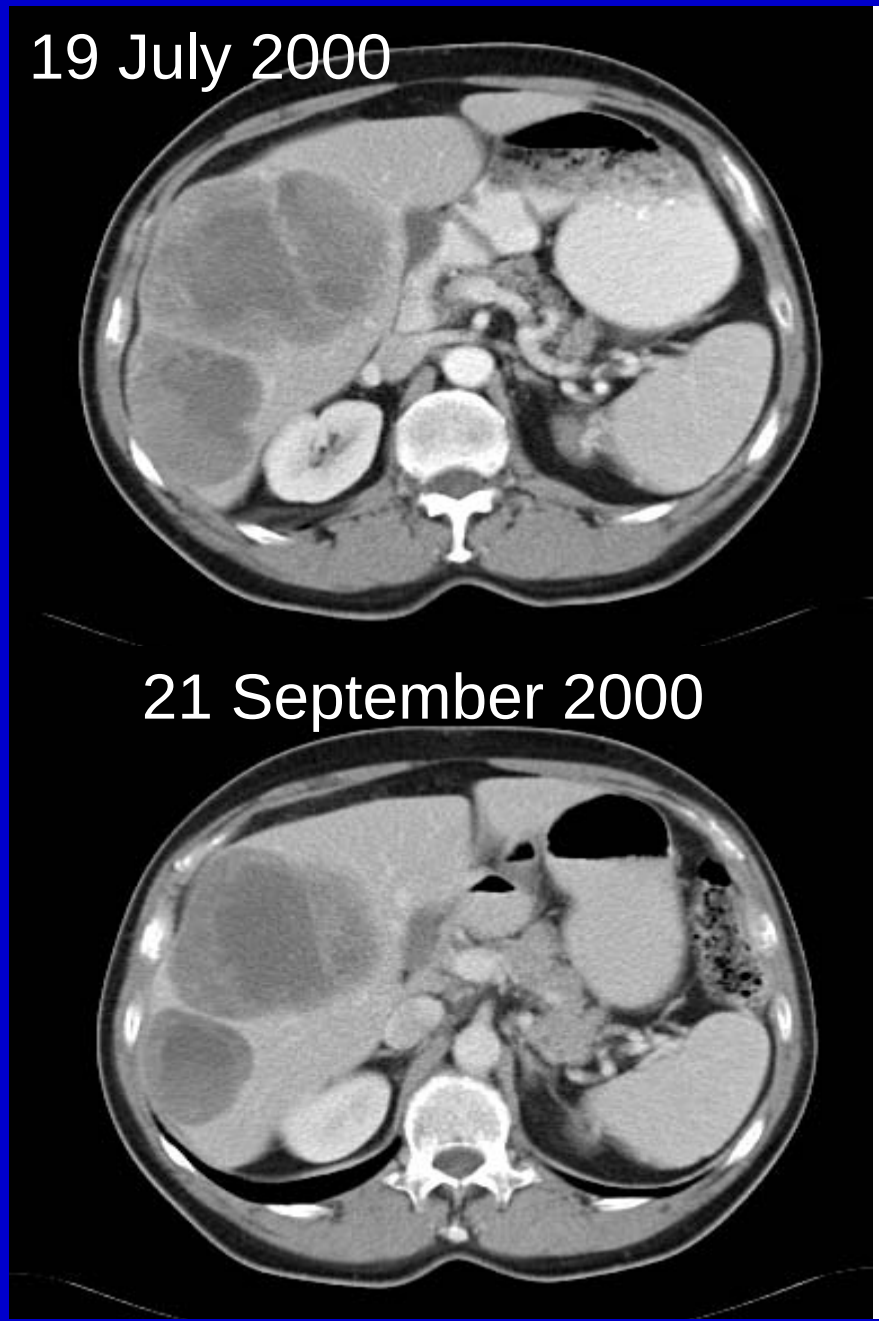
Rubber Foam

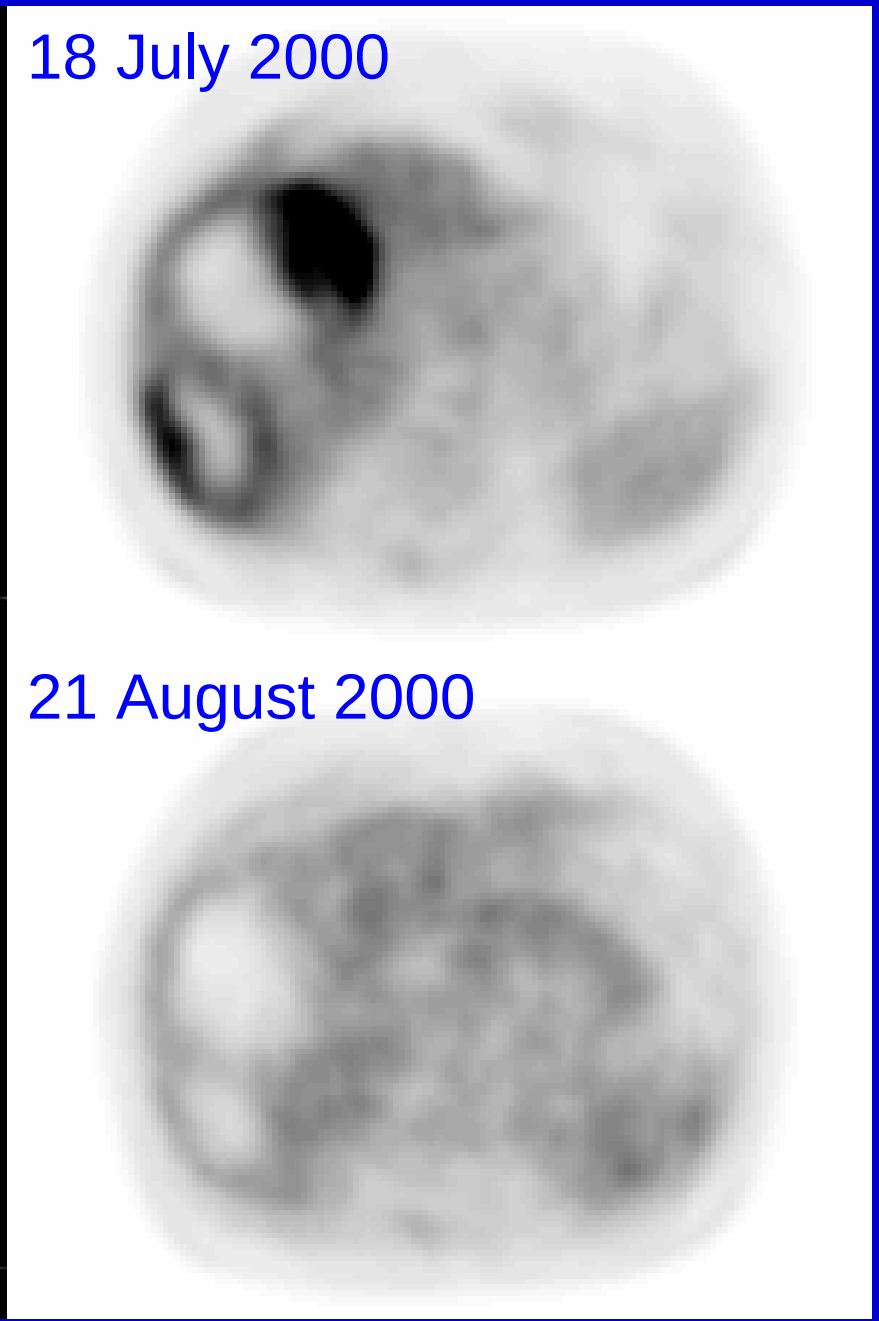
Soft Mattress

Limitations of morphological Criteria to Monitor Cytotoxic Therapy

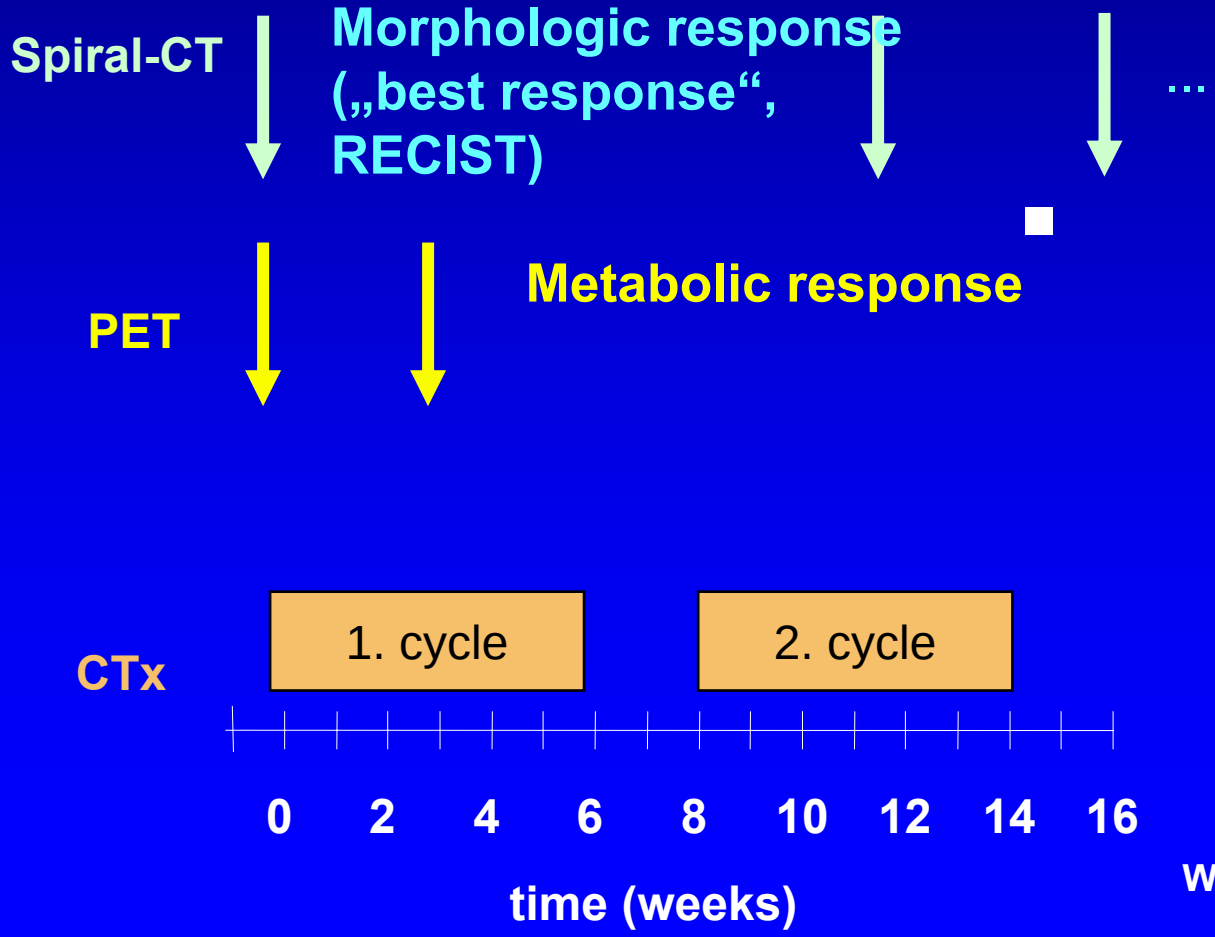
- Historical and arbitrary definition
- Not well correlated with patient outcome
- Reduction of tumor size by effective therapy takes considerable time (weeks/months)
  - –> Non-responding patients undergo prolonged treatment without benefit
  - –> Responding patients are erroneously classified as non-responding

J.K.





Response Prediction in NSCLC



Objectives

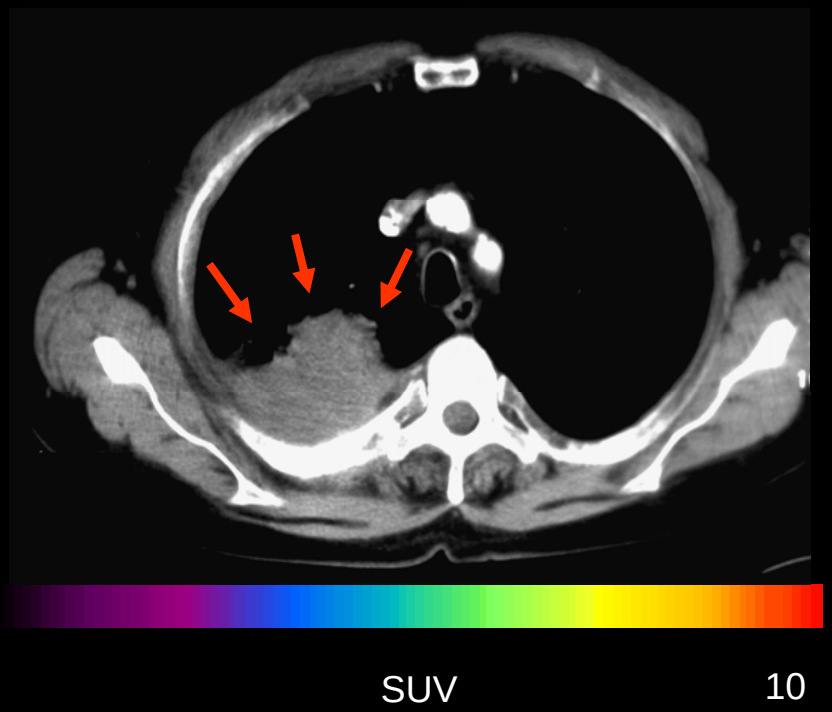
- to correlate changes of tumor metabolic during therapy with subsequent response
- compare different parameters of tumor glucose use

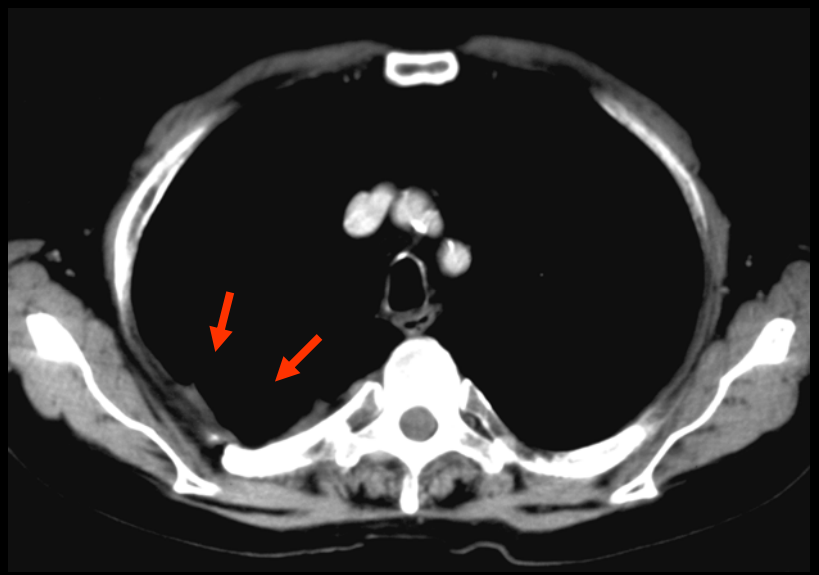
Weber, Petersen et al. J Clin Oncol (2003) 2651-2657

NSCLC: Good partial response to chemotherapy

prior to therapy

at three month

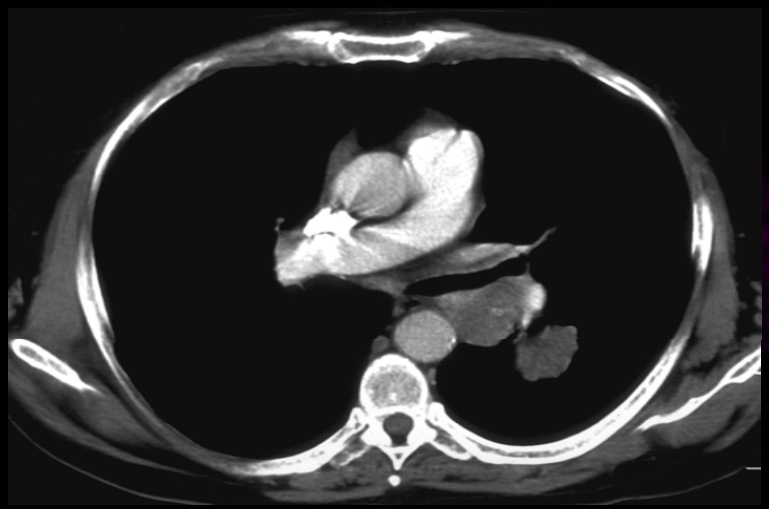


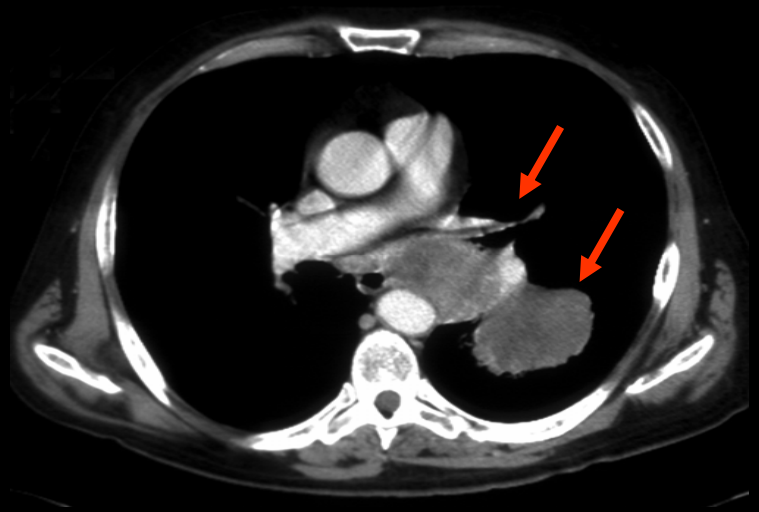


NSCLC: Progression during chemotherapy

prior to therapy

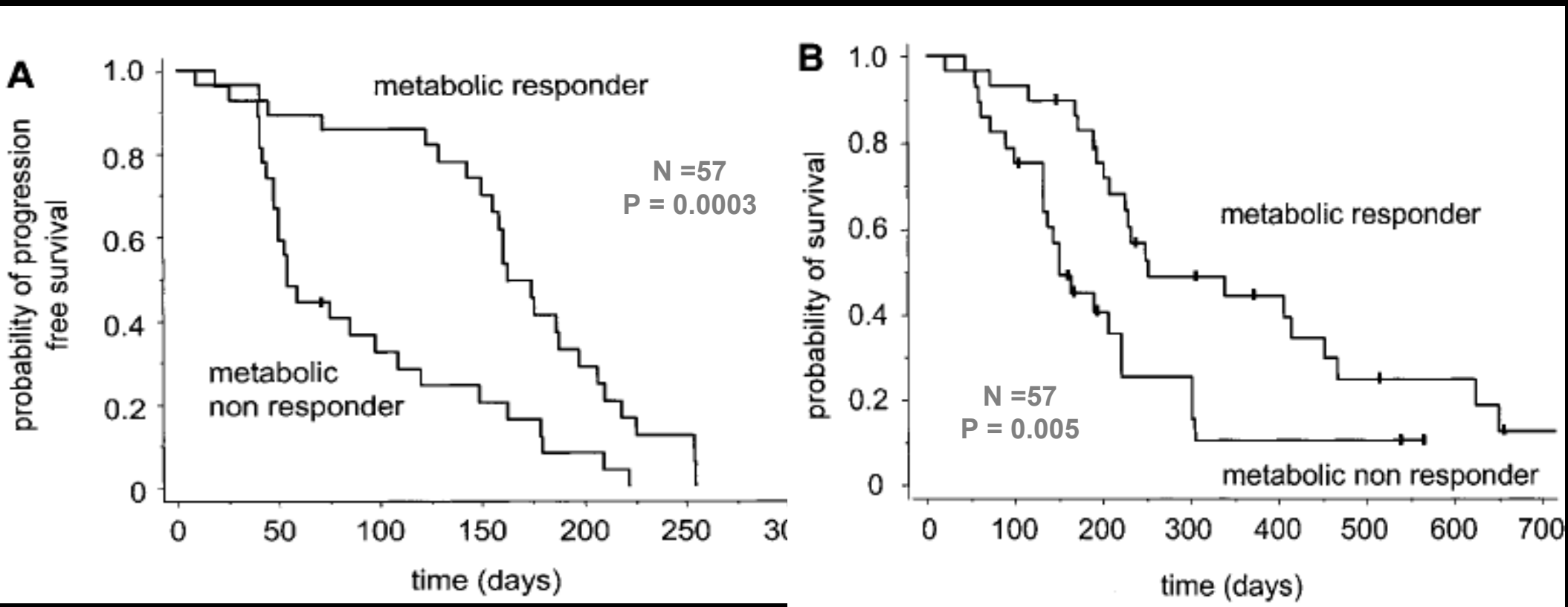
at three month





0 SUV 12

Response by FDG-PET and survival

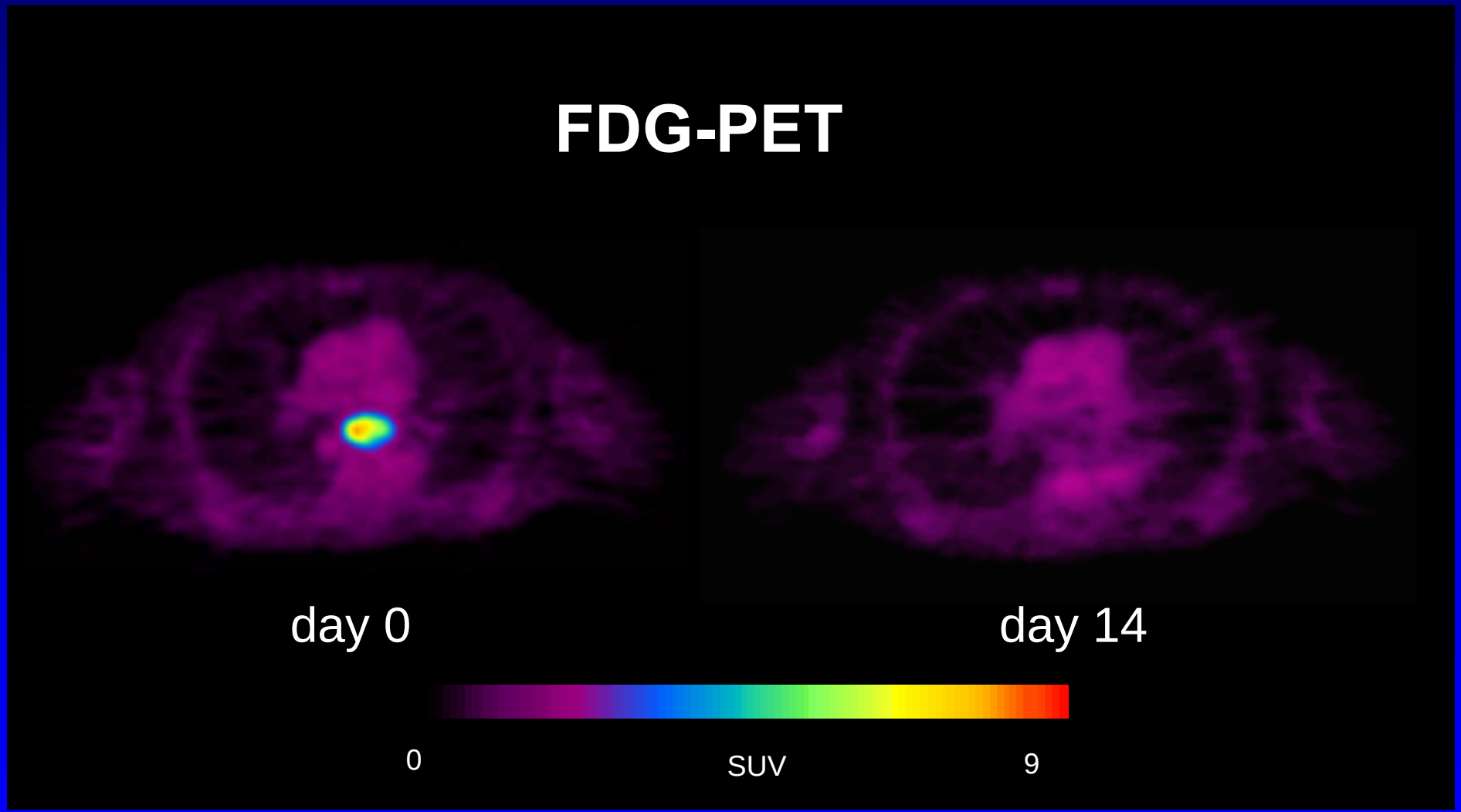


Weber et al; J Clin Oncol (2003) 2651-2657

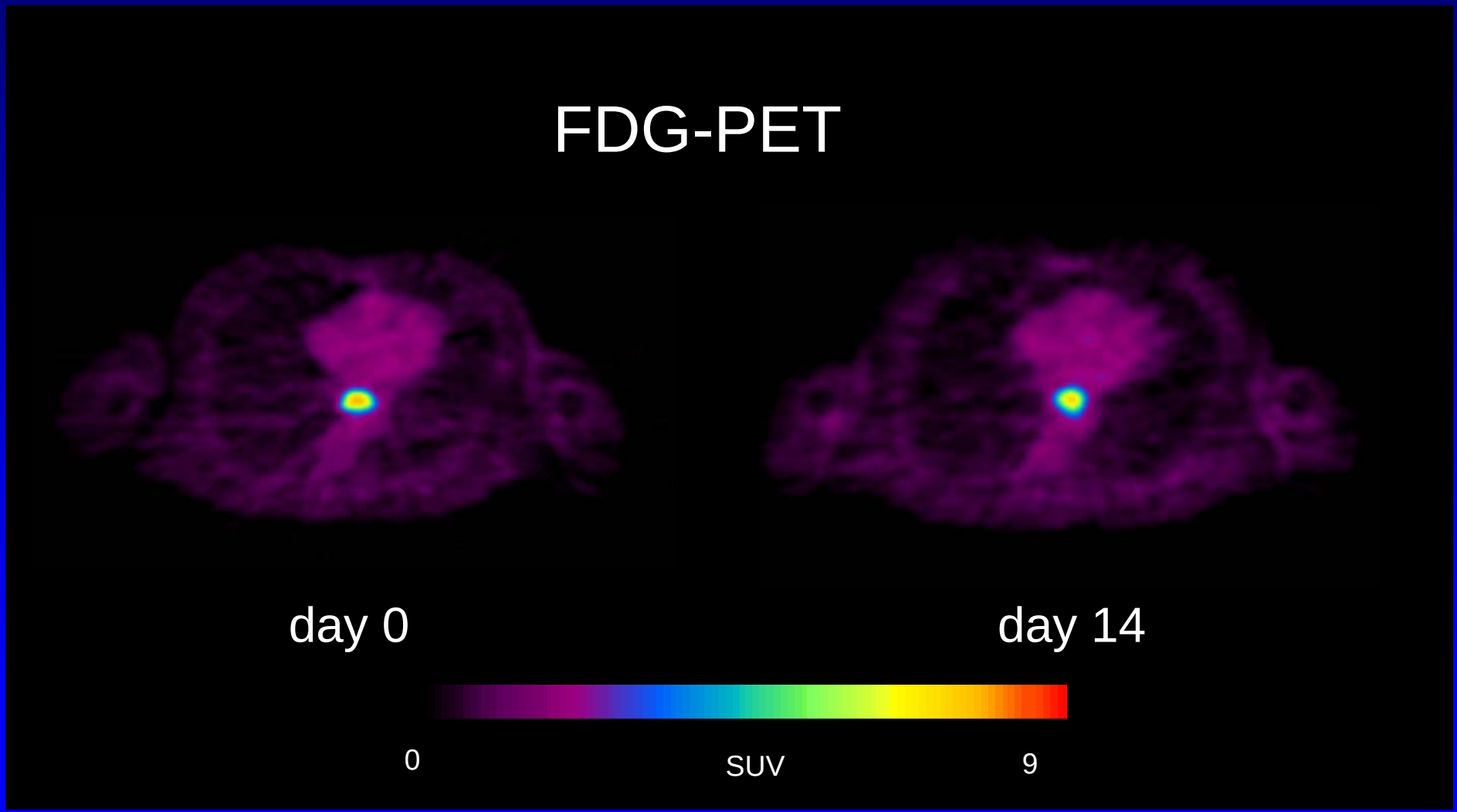
Prediction in Patients with Esophageal Cancer

- 40 patients (3 female, 37 male, age 55 ± 11 years)
- locally advanced adenocarcinomas of the esophagogastric junction ($T_{3,4}$,N+)
- preoperative chemotherapy (cis-Platin, 5FU, Paclitaxel)
- FDG-PET prior to and 14 days after initiation of therapy
- correlation of changes in FDG-uptake with histopathological tumor regression and patient survival

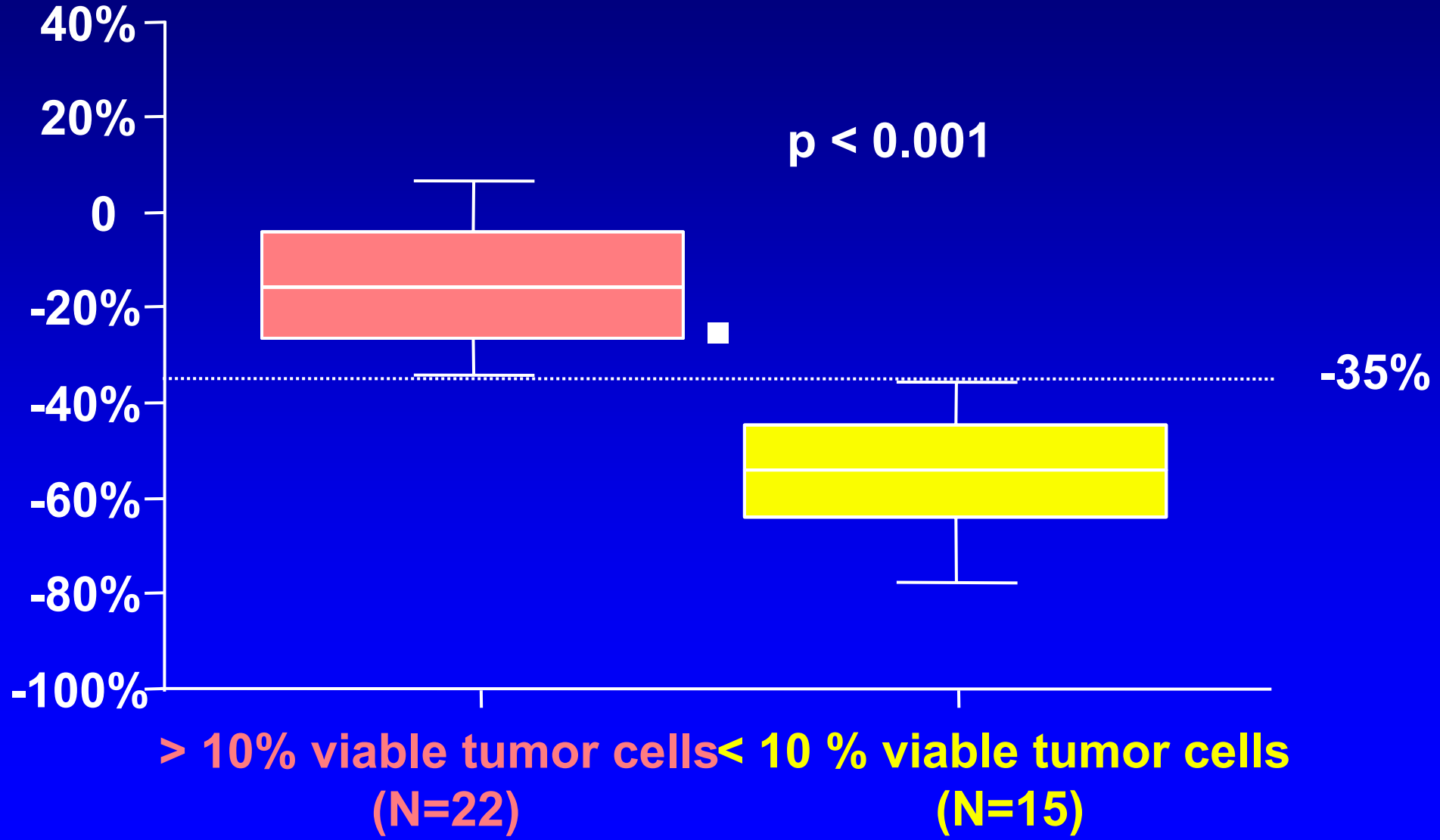
Treatment Responder



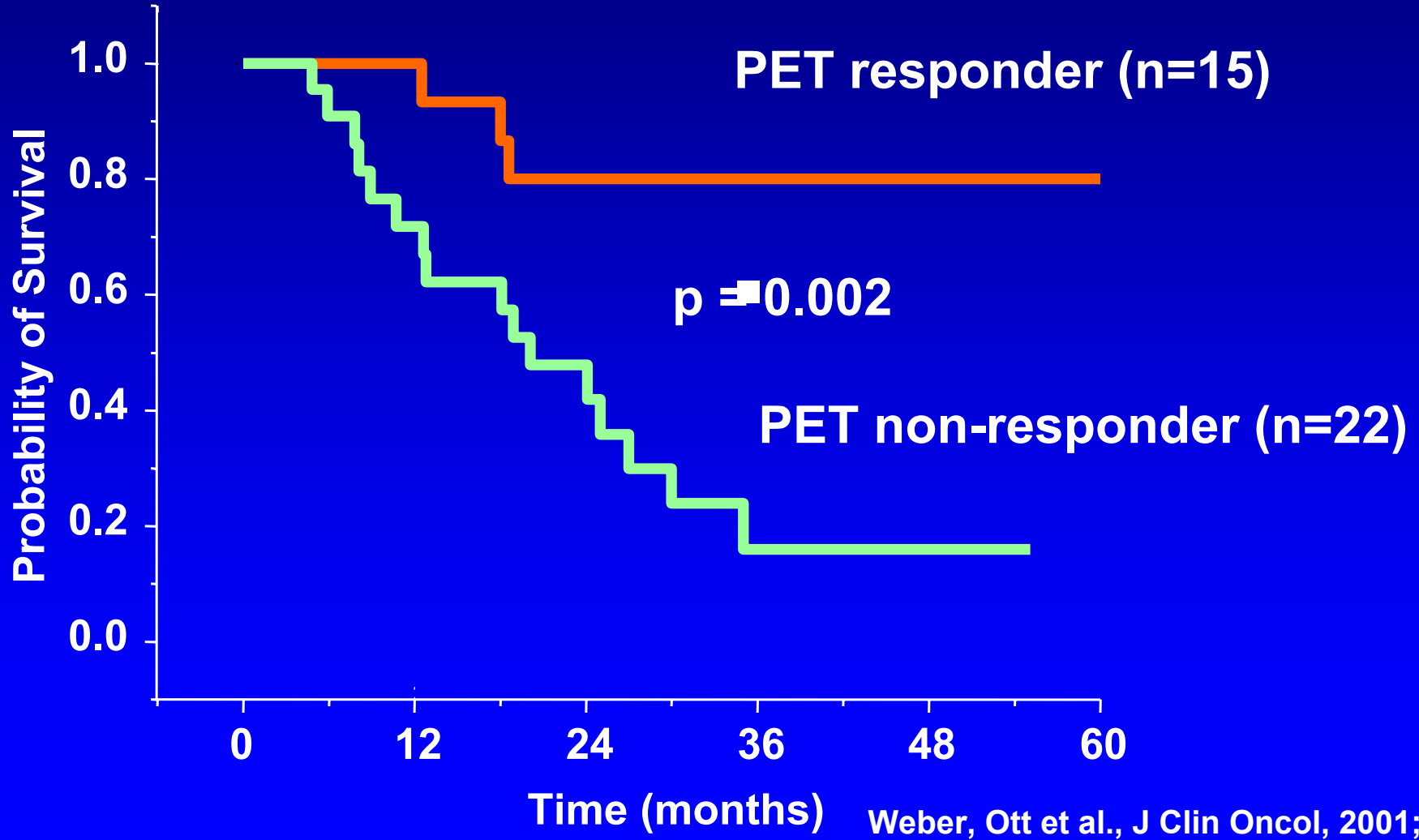
Treatment Non-Responder



Prediction of histopathologic response in patients with esophageal cancer



Survival Prediction in Esophageal Cancer

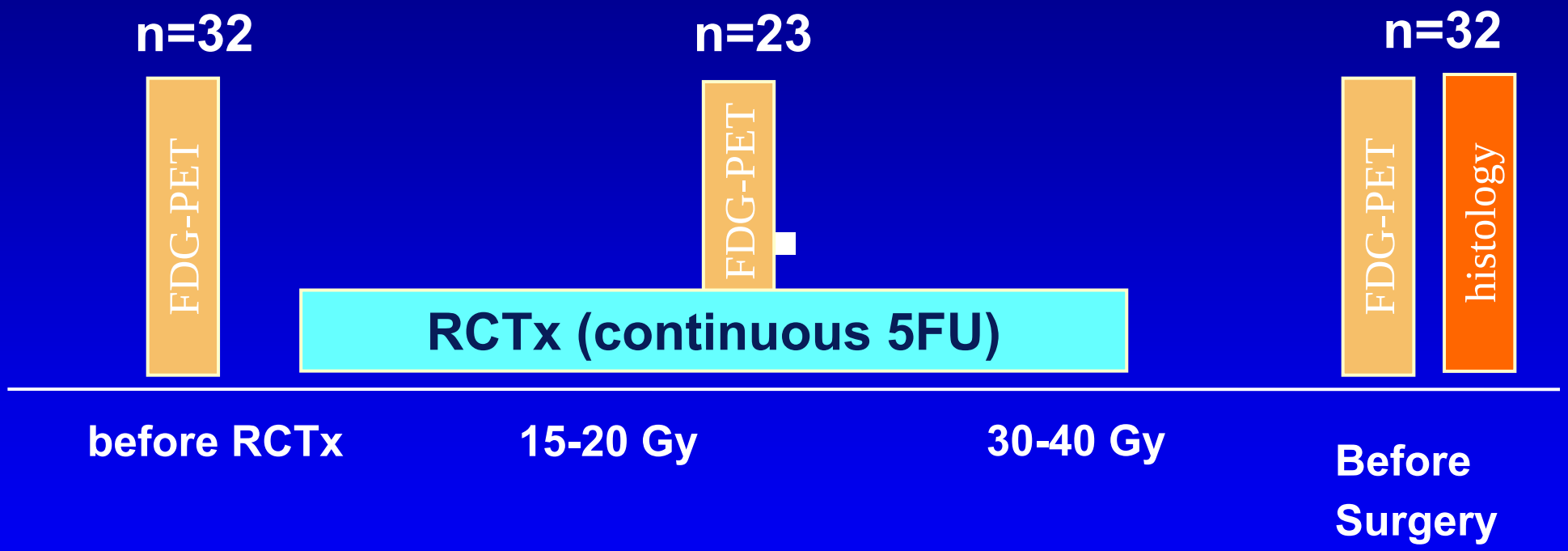


Weber, Ott et al., J Clin Oncol, 2001; 19:3058-3065

FDG-PET for monitoring (chemo)radiotherapy

- Inflammatory reactions during radiotherapy can potentially limit the accuracy of FDG-PET immediately following chemoradiotherapy
- It has been recommended that FDG-PET should be performed only several months after completion of radiotherapy
- There are relatively few systematic data on the time course of radiation induced inflammation and its intensity

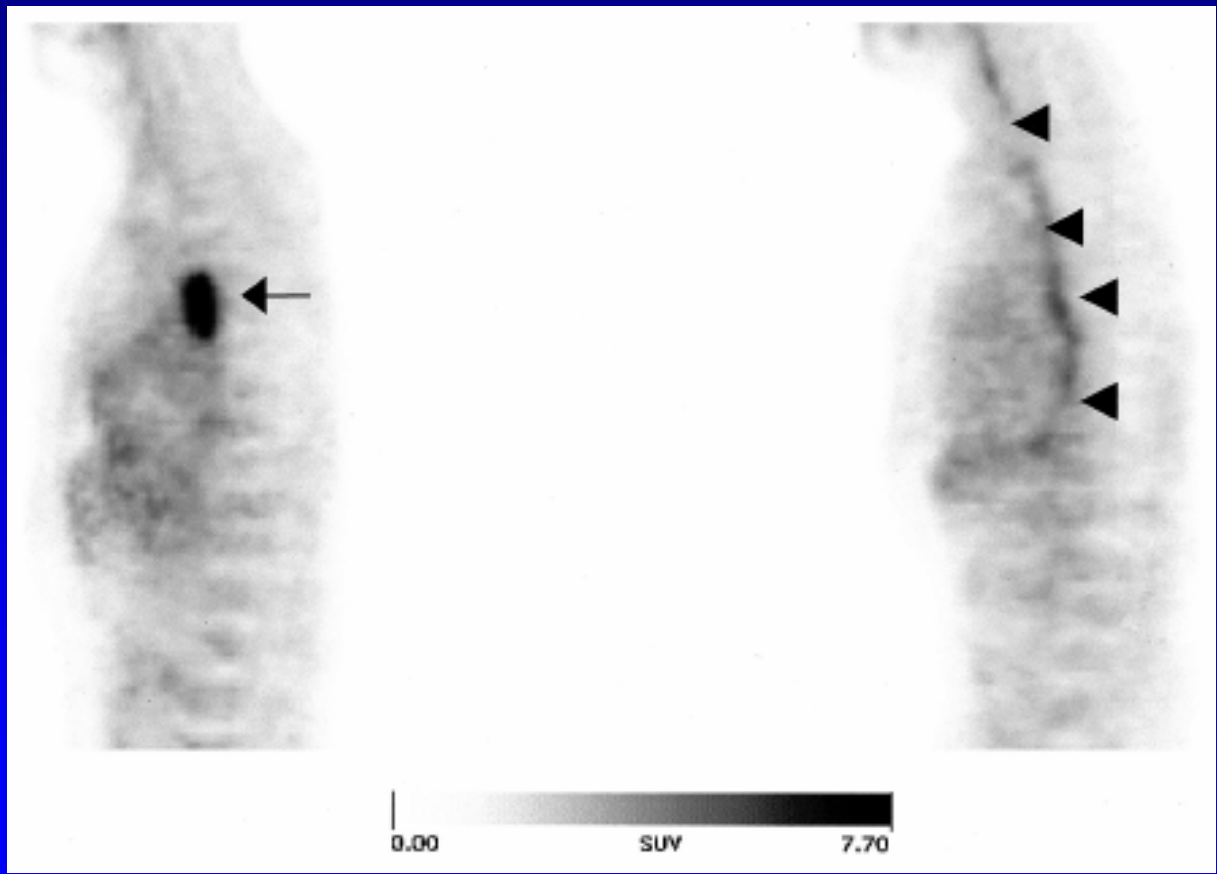
FDG-PET for Monitoring Chemoradiotherapy of Esophageal Squamous Cell Carcinoma



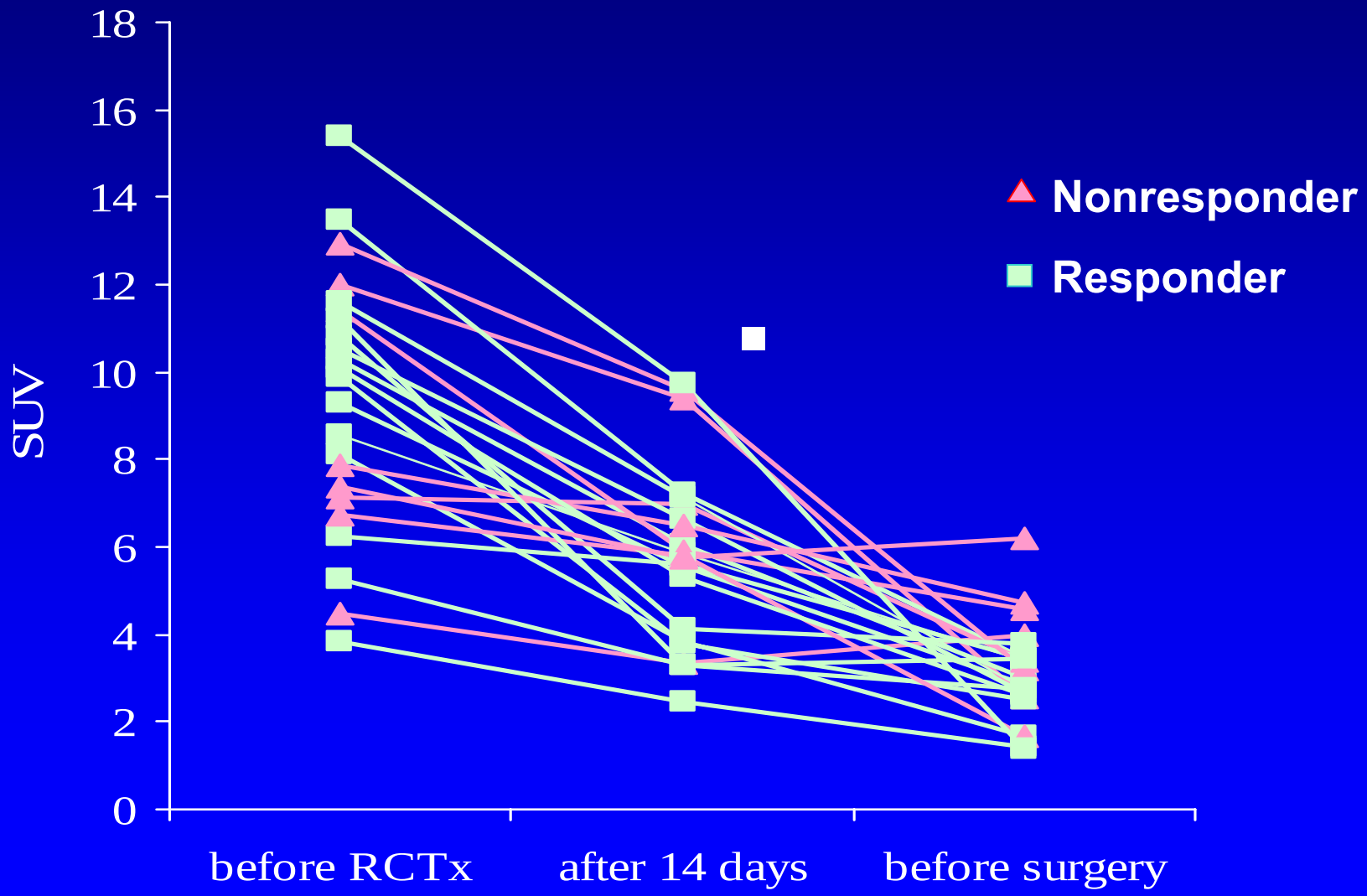
N=23: during treatment

Wieder, Weber J Clin Oncol (2004) 22:900-908

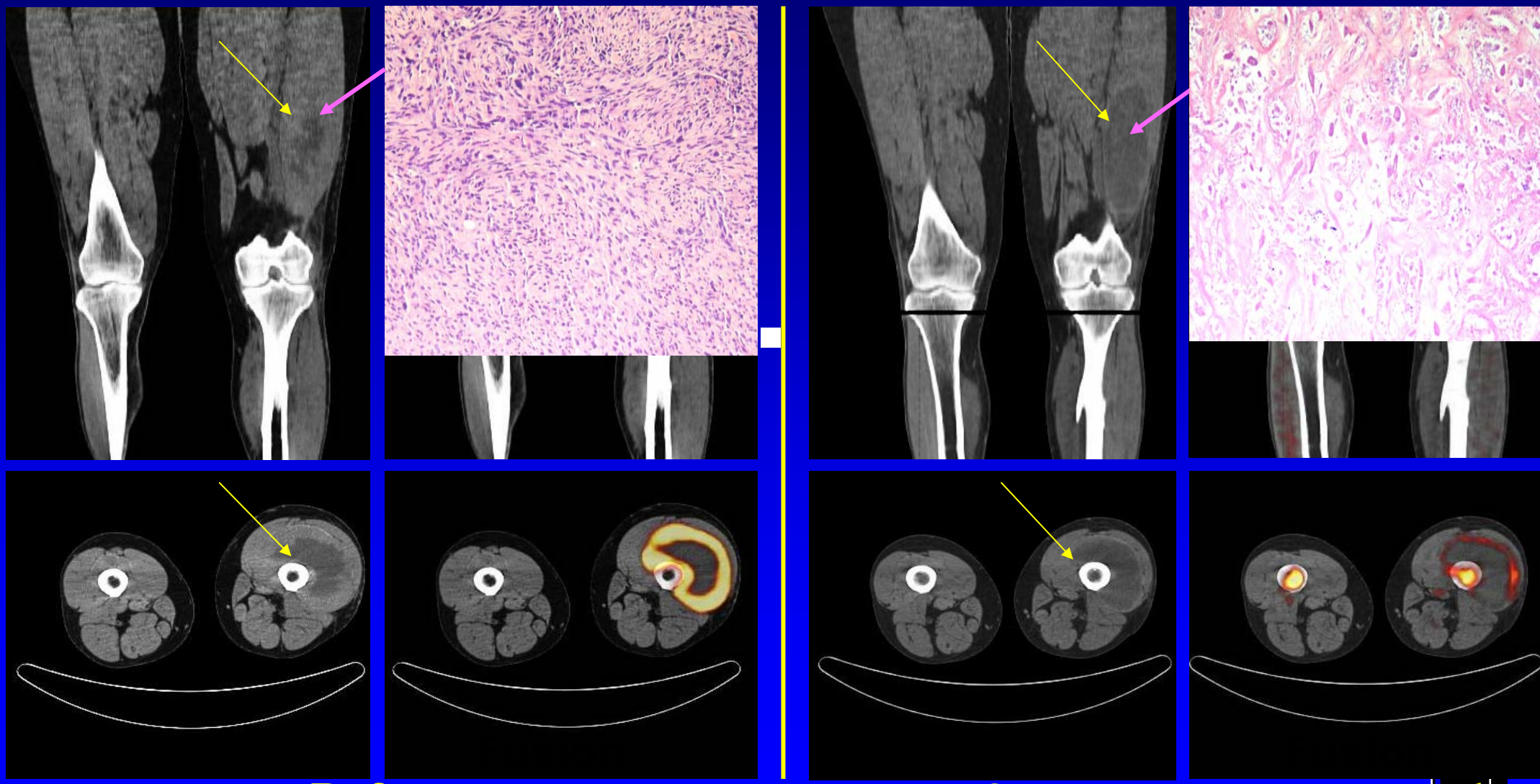
Radiation induced esophagitis



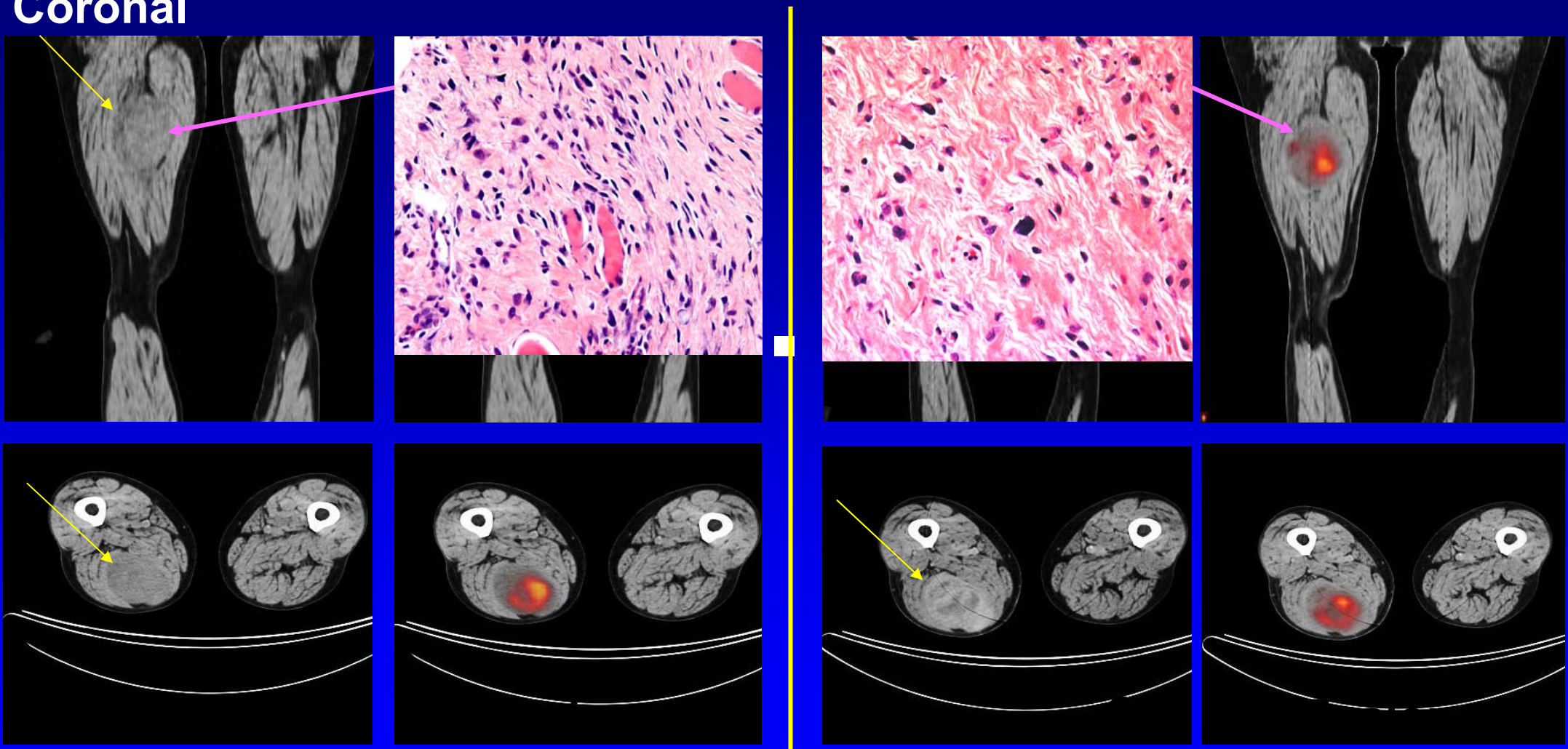
Time course of tumor FDG-uptake



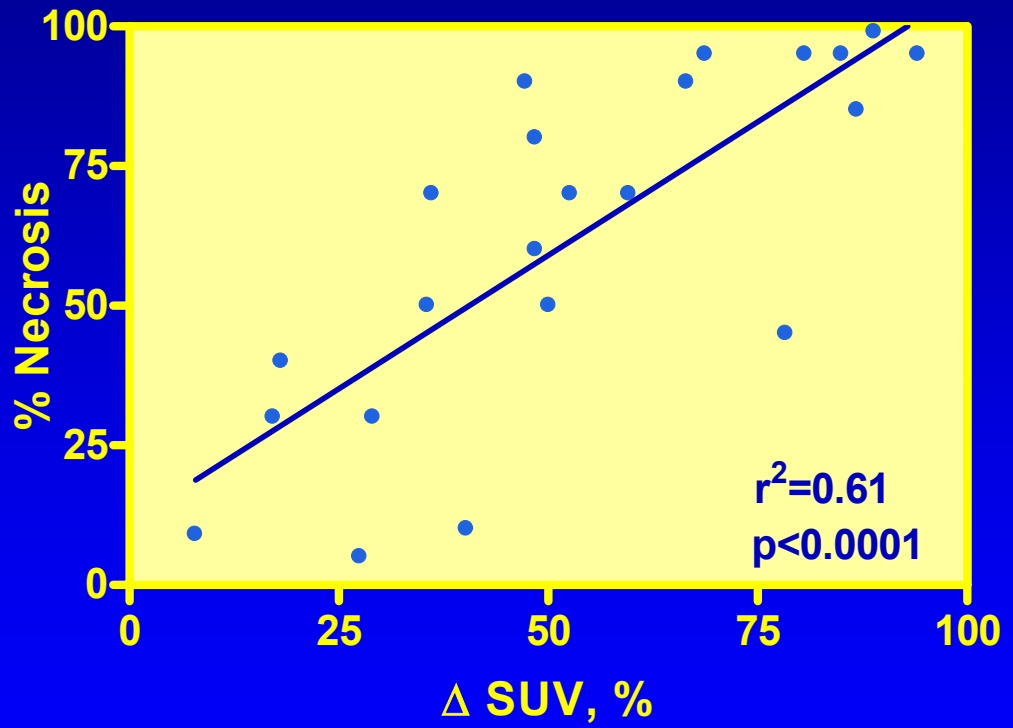
Sarcoma: PET/CT Responder



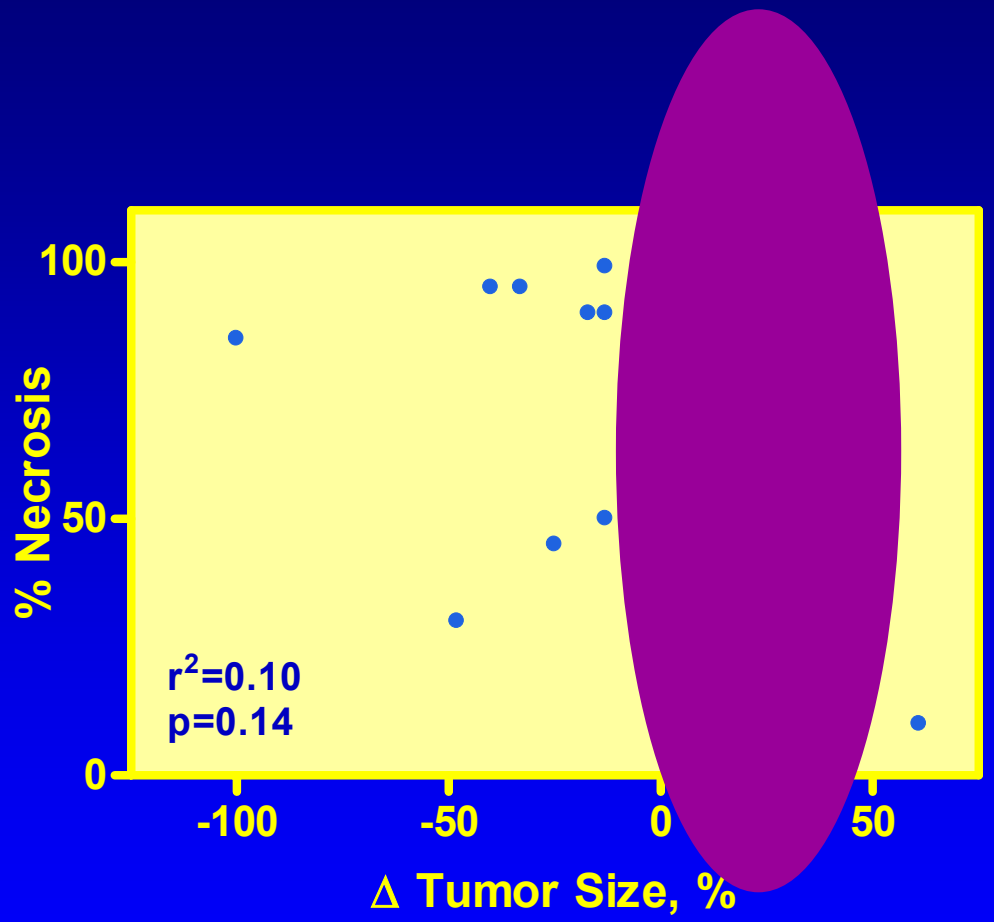
PET/CT Non-Responder



% Necrosis versus Δ SUV

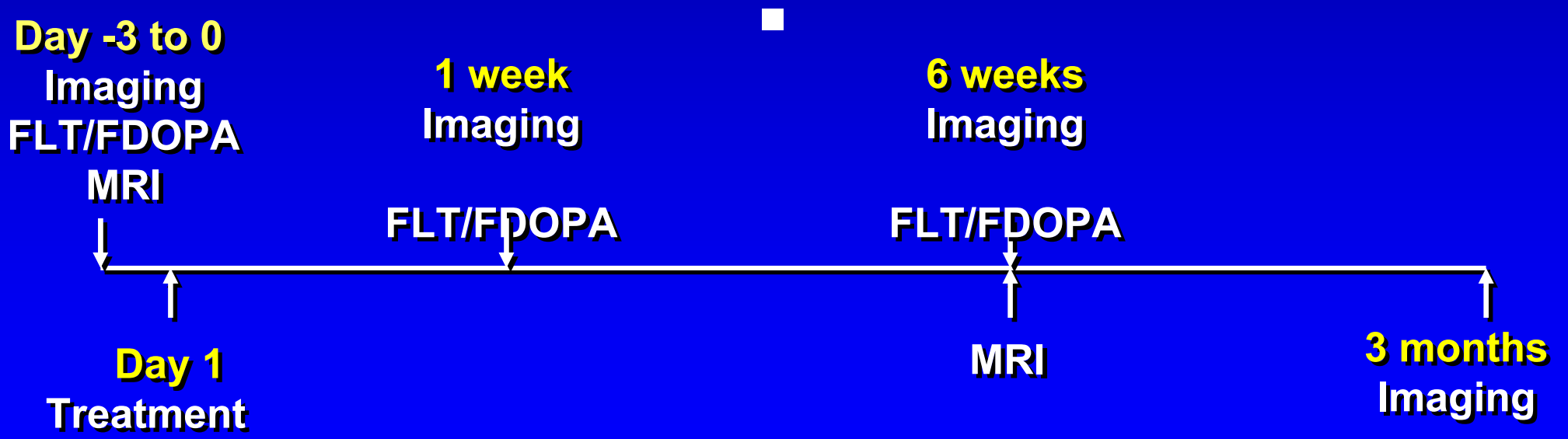


Necrosis versus Changes in Tumor Size



Effects of Bevacizumab and Irinotecan on malignant gliomas monitored with ^{18}F-FLT and ^{18}F-FDOPA PET

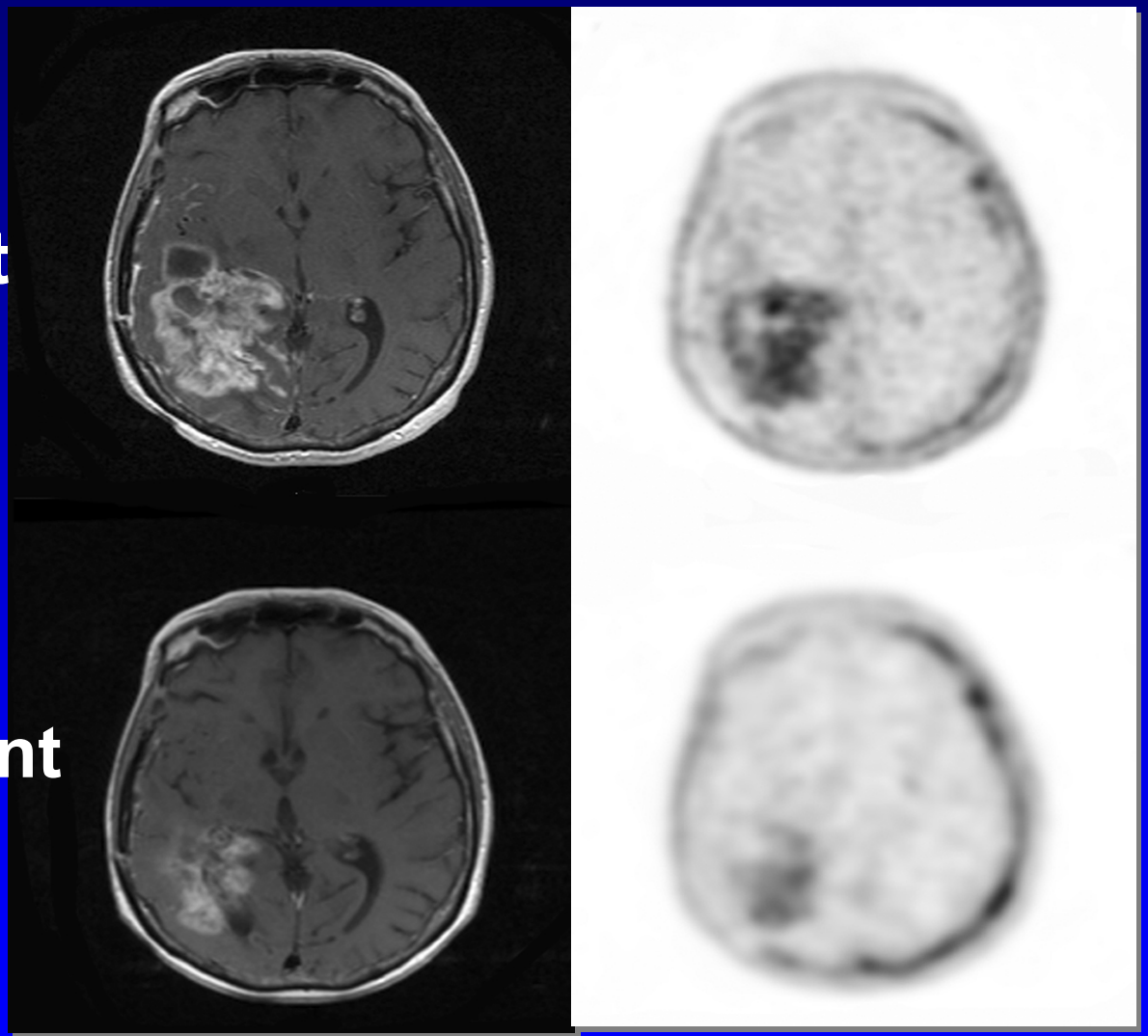
20 patients with tumor progression by MRI after prior surgery and radiation therapy



MRI and FLT scans in a GBM before and after treatment with Bevacizumab and Irinotecan

Pre-treatment

After-treatment

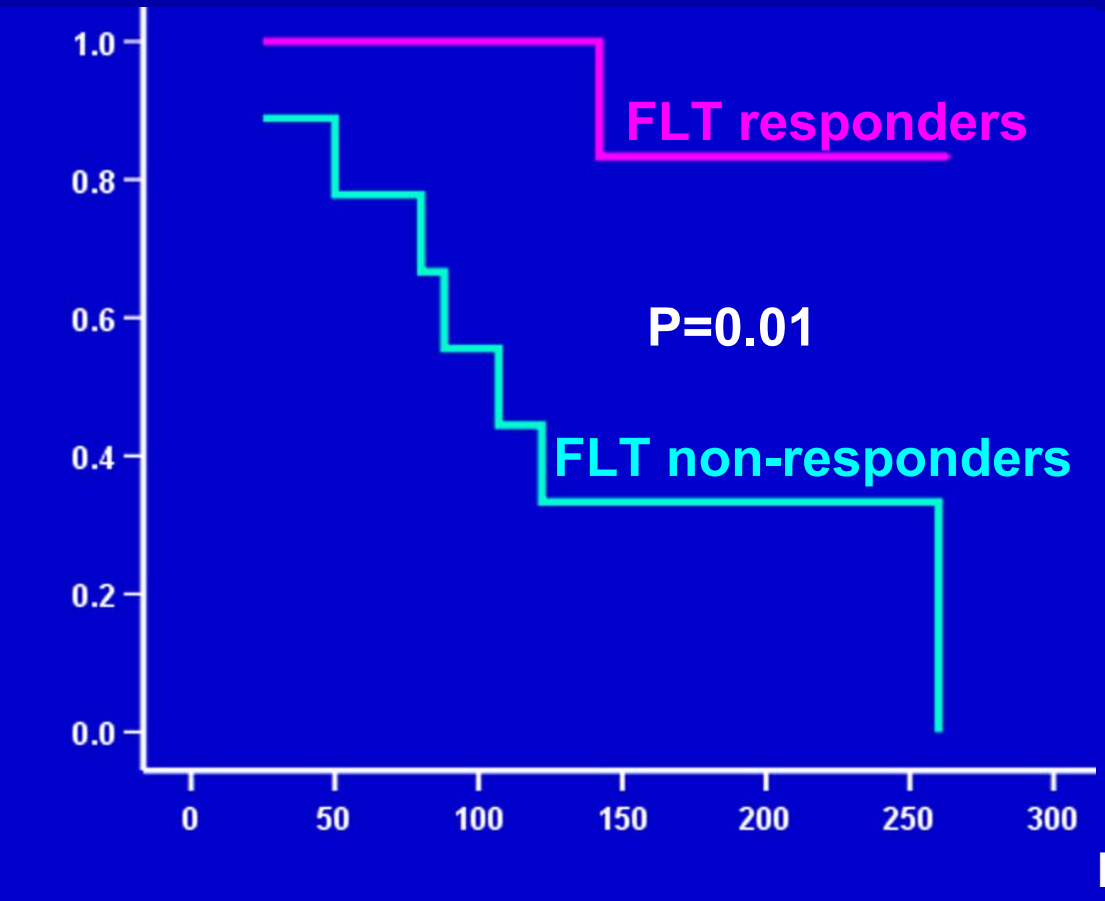


MRI- 3 months

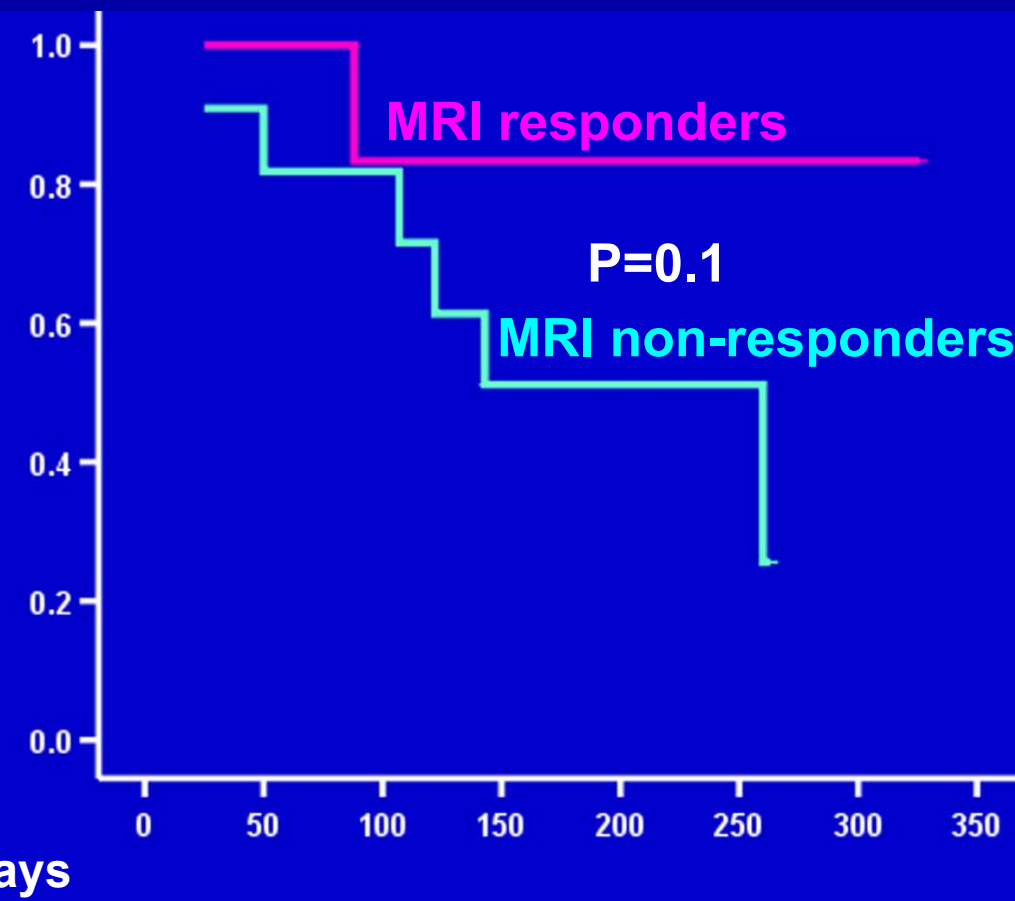
FLT- 1 week

FLT PET and MRI Prediction of Survival in Glioma Patients

FLT at 1 week (n=19)



MRI at 3 months (n=19)



Days

Treatment Monitoring: When and How Frequently?

TABLE 2
Recommendations of Workshop Panel

Parameter	Recommendation
Patient preparation	Patients fast overnight for morning scan or 4 h for afternoon scan. Venous serum glucose concentration is measured before injection (<120 mg/dL for nondiabetic patients and 150–200 mg/dL for diabetic patients). Diabetic patients are scanned in morning after overnight fast and before first use of medication. Patients are well hydrated and, if possible, drink 500 mL of water after injection and before scanning. For renal/pelvic imaging, furosemide (20–40 mg) may be given 10–15 min after ^{18}F-FDG injection, or urinary catheter may be used. All medications being taken by patients are recorded. Diazepam or other mild sedative may be used at clinician's discretion to decrease uptake in muscle.
PET timing	Pretreatment and posttreatment scans are acquired. Pretreatment scans are acquired as close to start of therapy as possible (preferably <2 wk). Posttreatment scans are acquired no sooner than 2 wk after end of chemotherapy to avoid transient increases or decreases. Timing is determined by endpoint being assessed. Timing of scans after changes due to radiotherapy needs further investigation. Whole-body imaging begins 60 ± 10 min after injection of ^{18}F-FDG.
Attenuation correction	Attenuation correction is used. No standard procedure has yet been recommended. Procedure chosen is documented.
^{18}F-FDG dose	No standard dose has yet been recommended. Doses of 370–740 MBq (10–20 mCi) are appropriate. Dose injected is documented.

Image Analysis

- **SUV for all target lesions**
- **SUV calculated based on LBM or BSA**
- **SUV of a reference organ/tissue**
- **Target lesion should be the most visible and easily defined lesion**

- ***When: 6 weeks after start of chemotherapy, end of radiation, surgery***

:

Conclusion

- **PET can be used**

in preclinical studies

To determine whether drug hits its target

To study biodistribution of drug analogues in humans (excluding drugs with unfavorable distribution)

In clinical studies

To predict treatment responses

To monitor treatment responses early

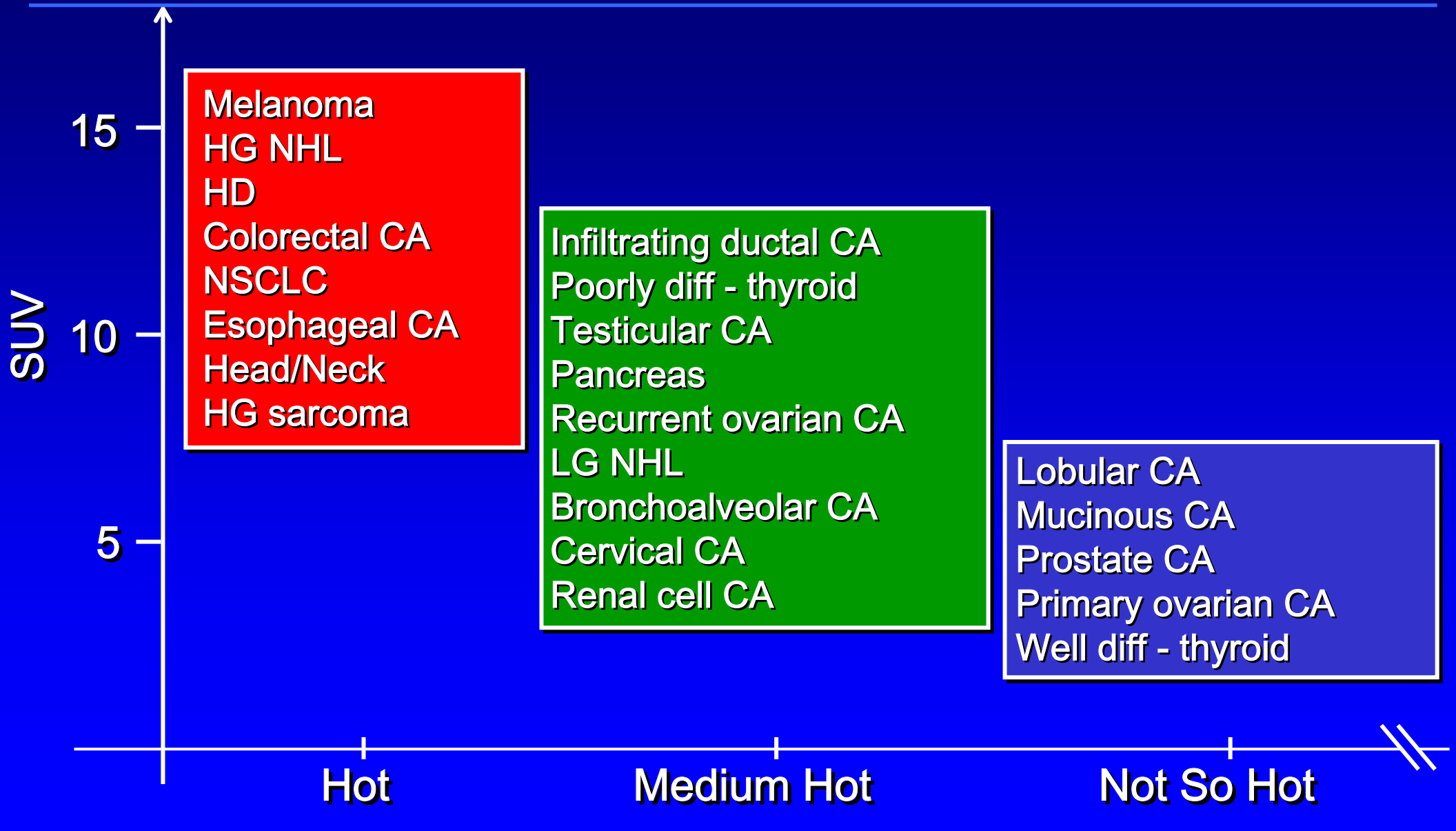
To abbreviate phase III clinical trials

Warburg, Posener and Naegelein: The Metabolism of the Carcinoma Cells; Biochemische Zeitschrift; 1924; 152; p309

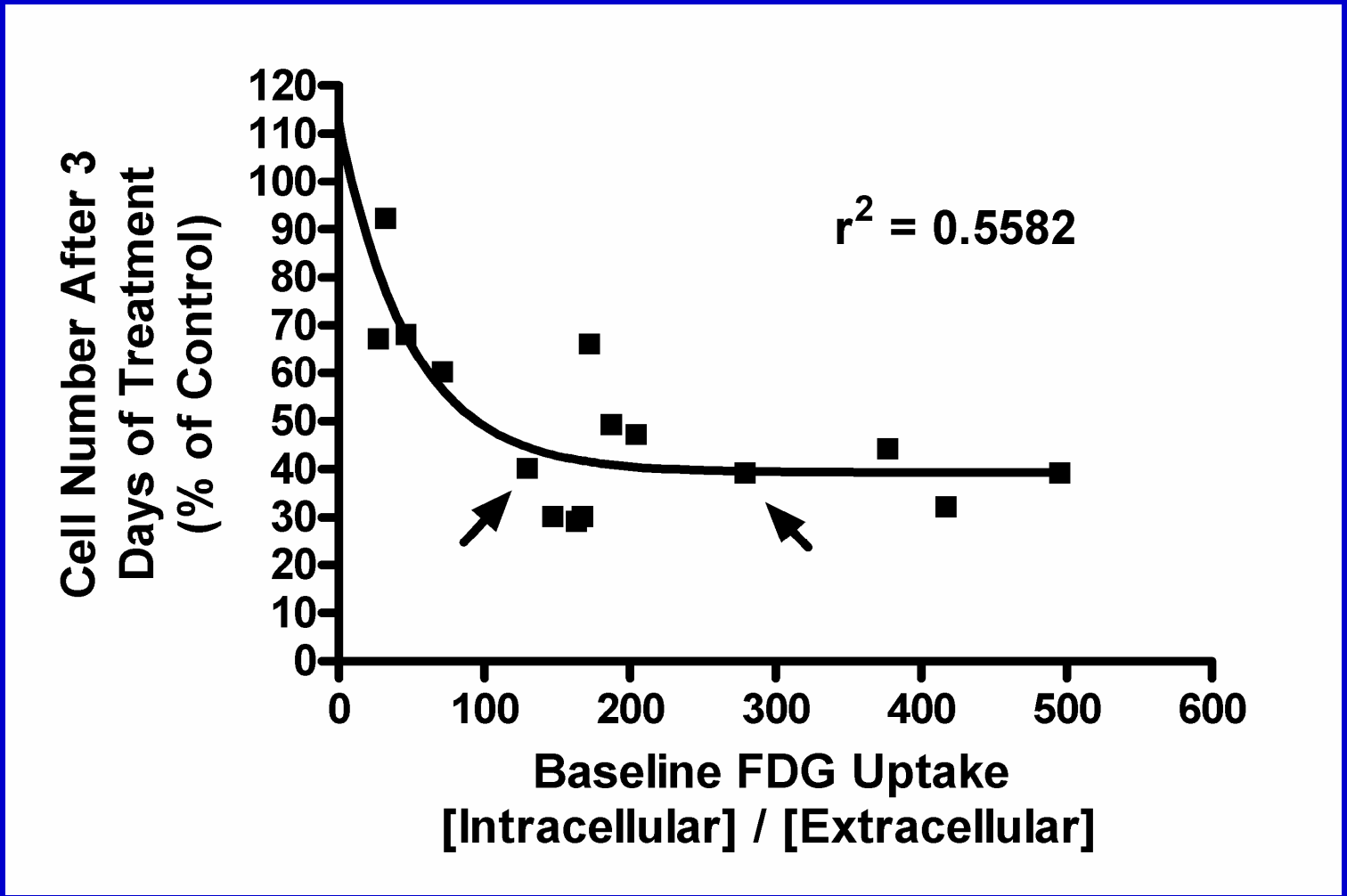
If the carcinoma problem is attacked in its relation to the physiology of metabolism the first question is: In what way does the metabolism of growing tissue differ from the metabolism of resting tissue? The prospects of finding and answer are good.

- **Tumor metabolism is predominantly one of glycolysis**
- **Glucose metabolism is predominantly anaerobic**
- **Benign tumors can also exhibit increased glucose metabolism**

Glycolysis: a Therapeutic Target?

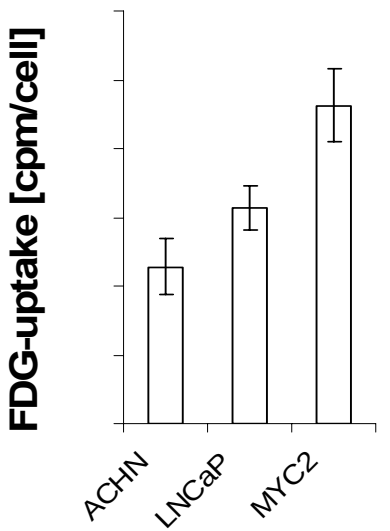


Treatment Effects of Deoxyglucose as a Function of FDG Uptake in Cell Lines

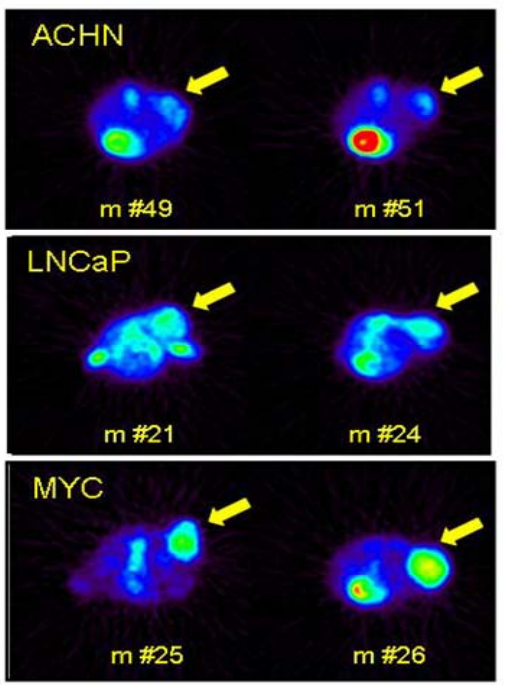


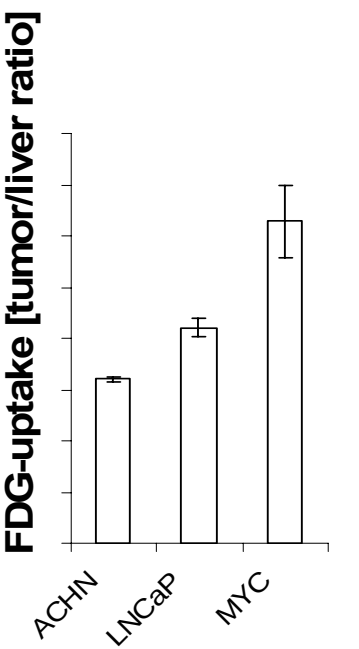
in vitro *versus* in vivo tracer retention (FDG)

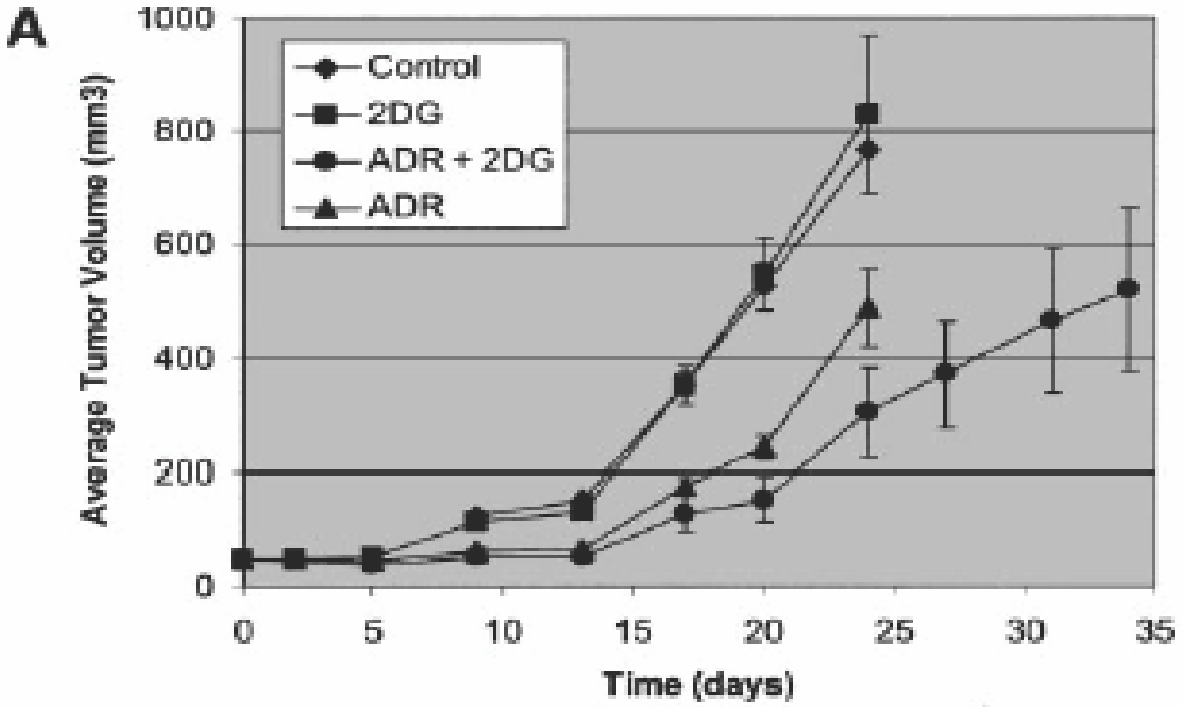
in vitro

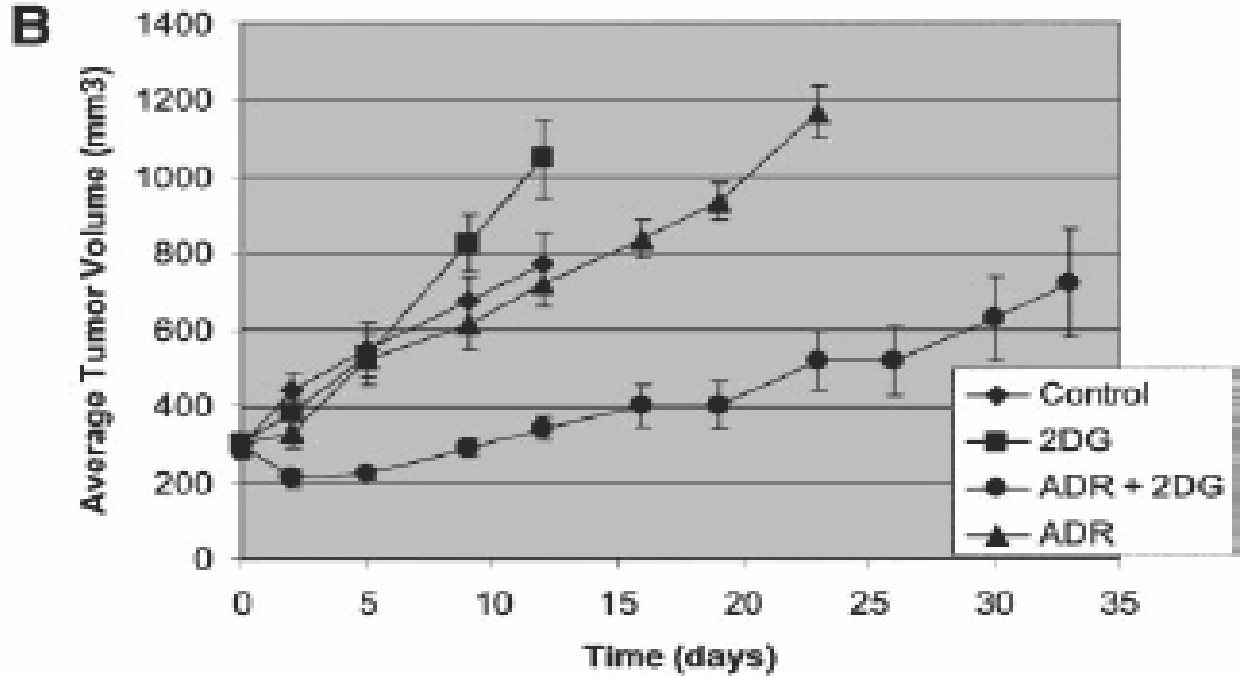


in vivo







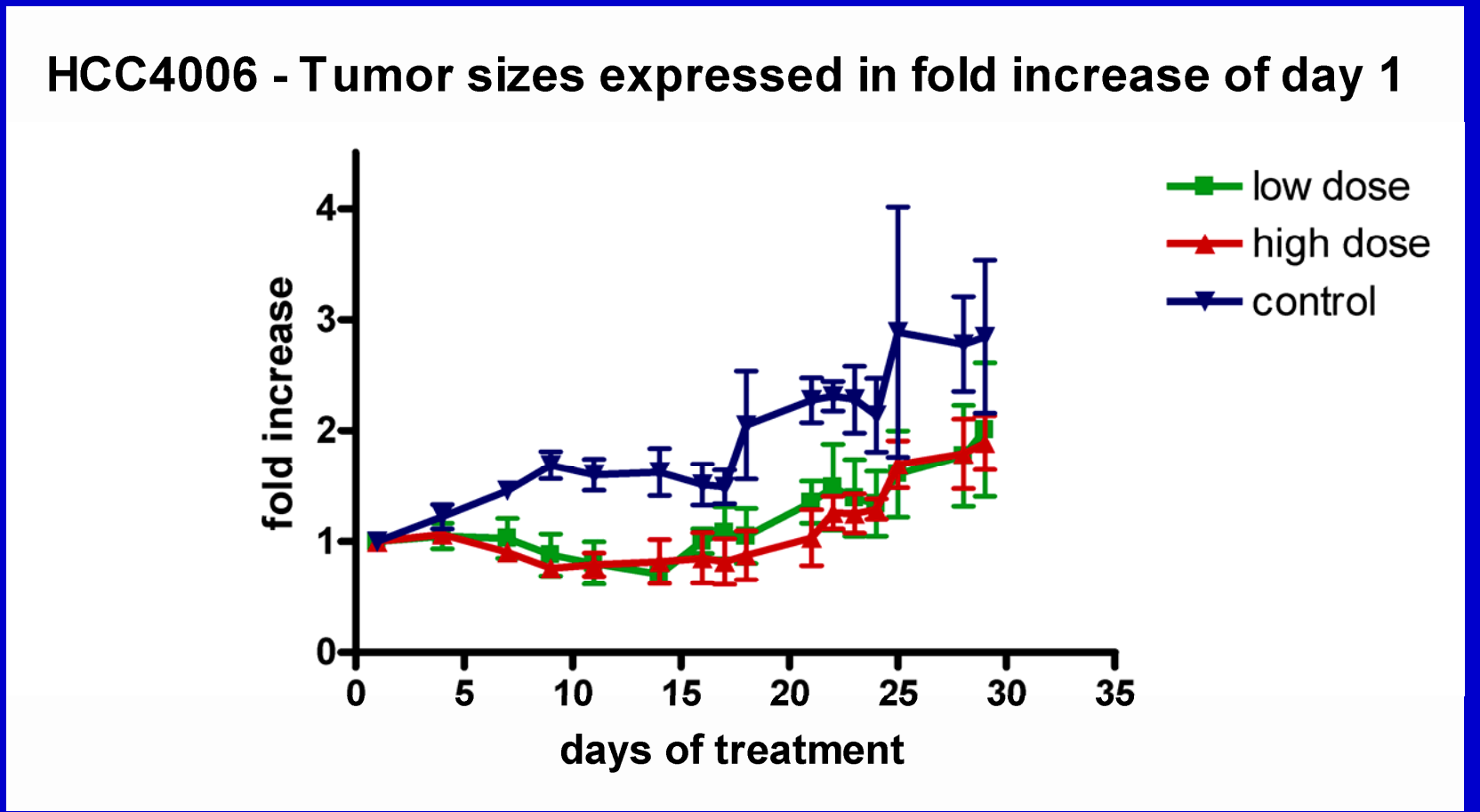


Treating Cancer with Deoxyglucose?

G. Maschek et al. Cancer Research 64, 31–34,

Synergistic Effects of DG and Adriamycin

Treating Tumors with Deoxyglucose



History of RECIST Criteria

- Sixteen oncologists determined the diameter of 12 spheres (∅ 1.8-14.5 cm)
- Due to measurement errors the measured size (area) of identical spheres differed ■
  - by at least 25% in 25% of the measurements
  - by at least 50% in 6.8% of the measurements

  („false-positive rate for response“; this error was deemed acceptable; hence we use 50% reduction in size)

Moertel and Hanley, Cancer (1976) 38:388-394