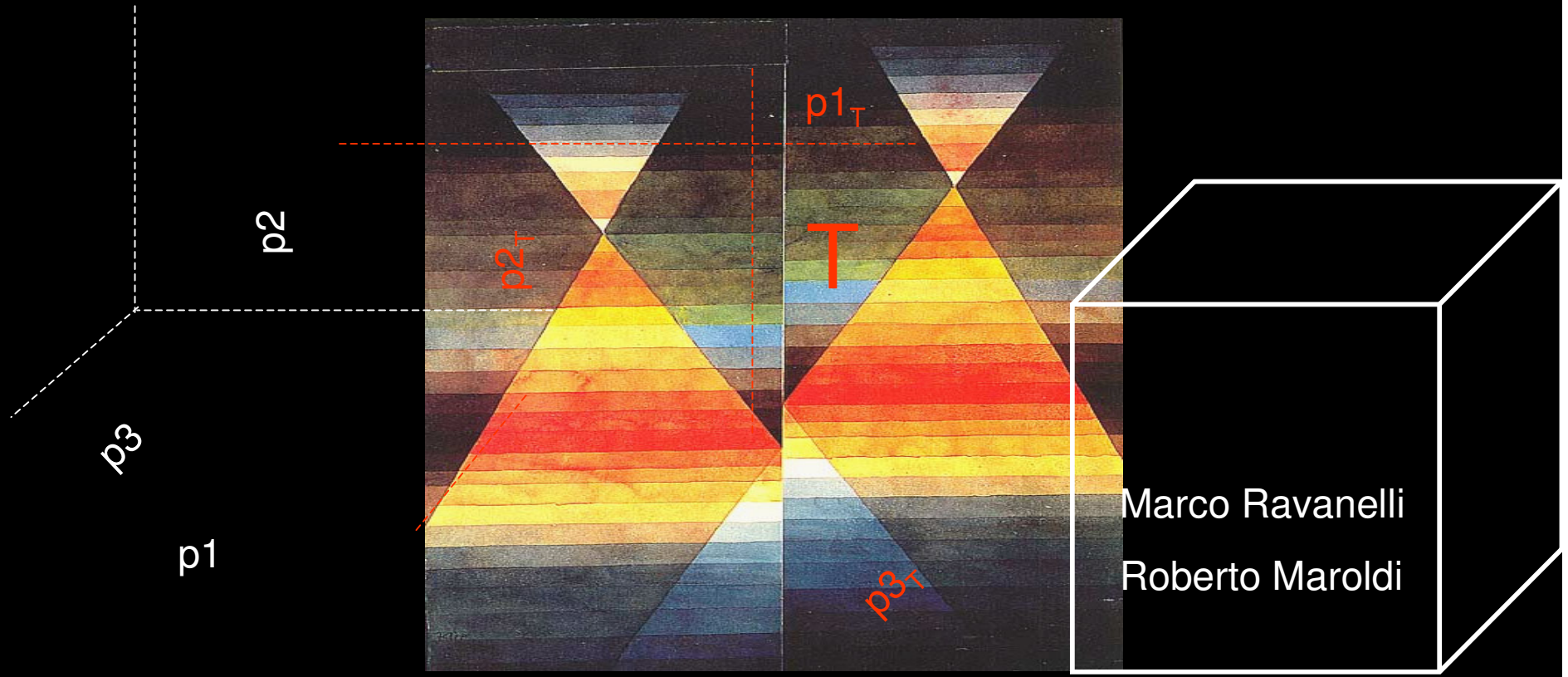
Multiparametric imaging in oncology



Marco Ravanelli

Roberto Maroldi

- The goal of traditional imaging is high spatial and contrast resolution → diagnosis, tumor extent → treatment planning, surgery.

- When a non-surgical treatment is planned, other questions raise: will it work? Which is the best treatment option?

- Traditional imaging is not able to provide adequate answers. Multiparametric imaging constitutes an attempt to respond these questions, especially.

Multimodal vs multiparametric

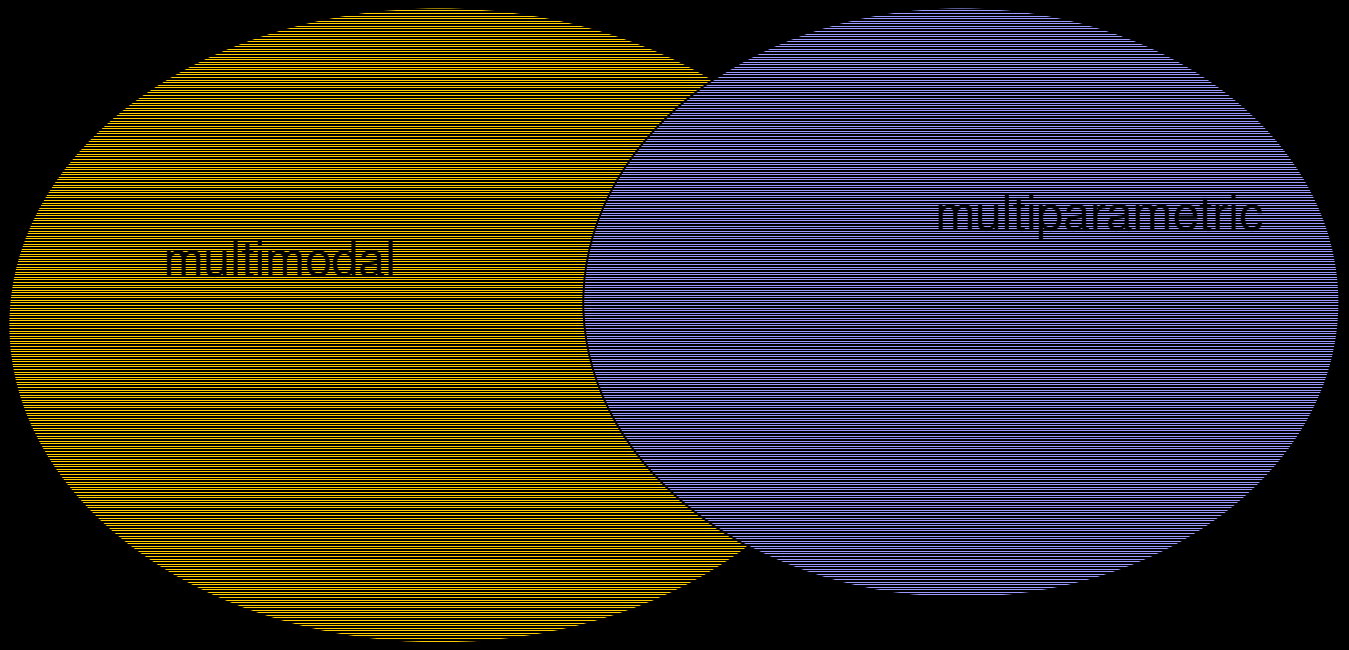
1) Multimodal: combine different imaging techniques to work out uncertain findings

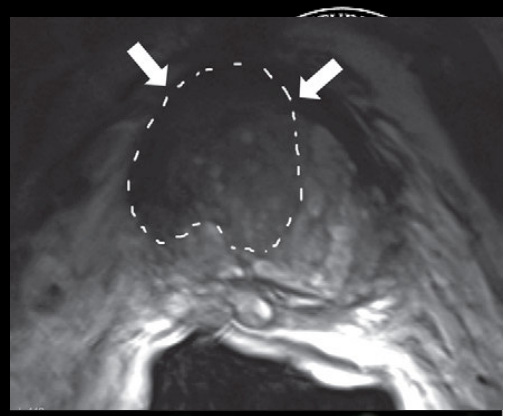
From screening to tumor diagnosis; recurrence identification

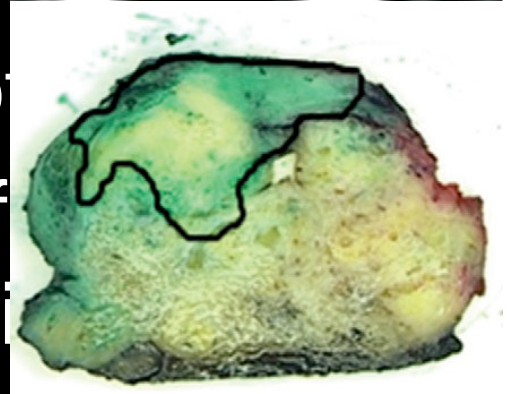
2) Multiparametric: combine information about tumor to understand more about it.

a) quantitative

b) the same information can be provided by different imaging techniques (i.e. blood flow ← pCT, pMR,CEUS, PET).







- Different but not exclusive concep
- Prostate imaging is an example of intersection: multiparametric imag to T2W imaging (central and trans cancer)

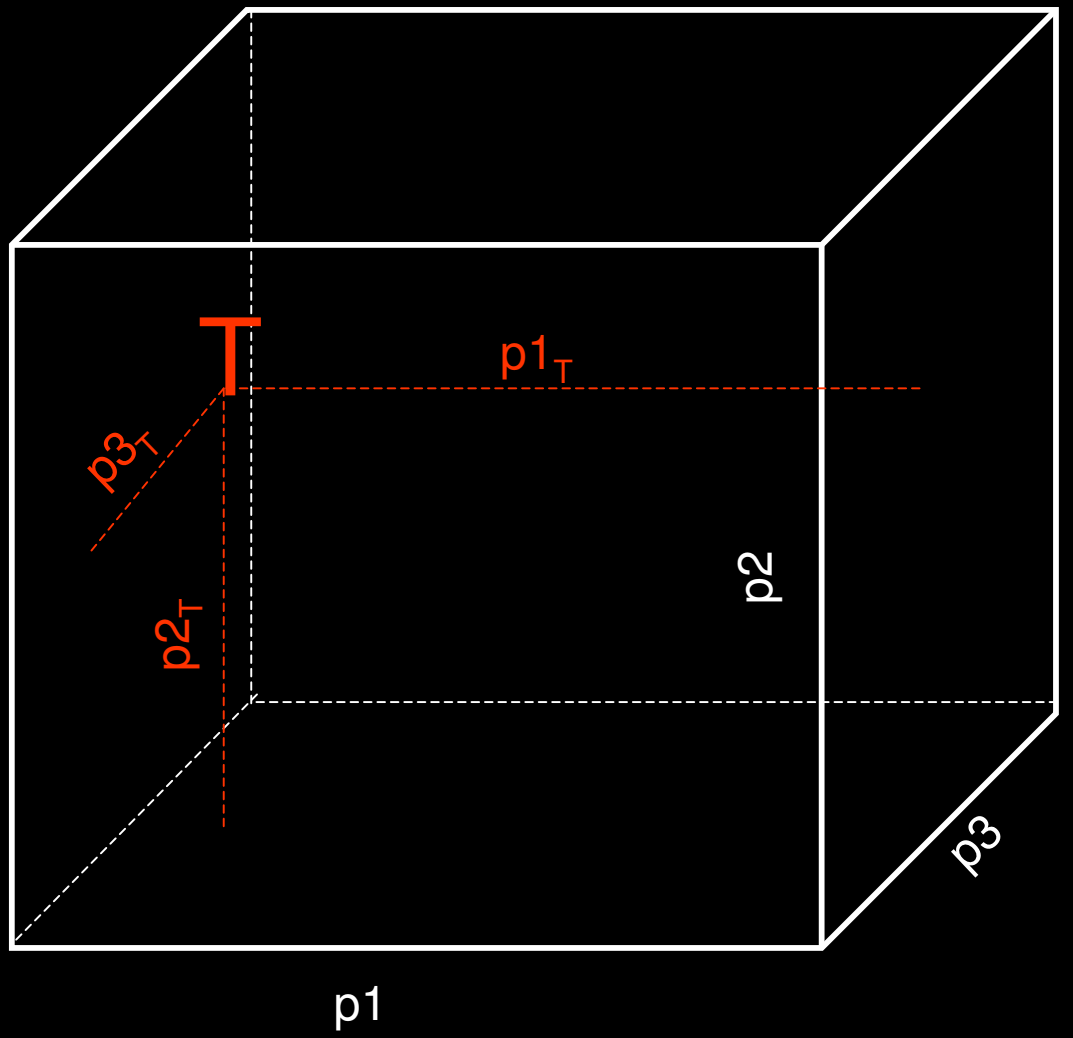
Hoeks CM et al. Radiology 2011;261:46-66

Cultural switch:

from image interpretation

to parameter interpretation;
develop multidimensional and more abstract thinking

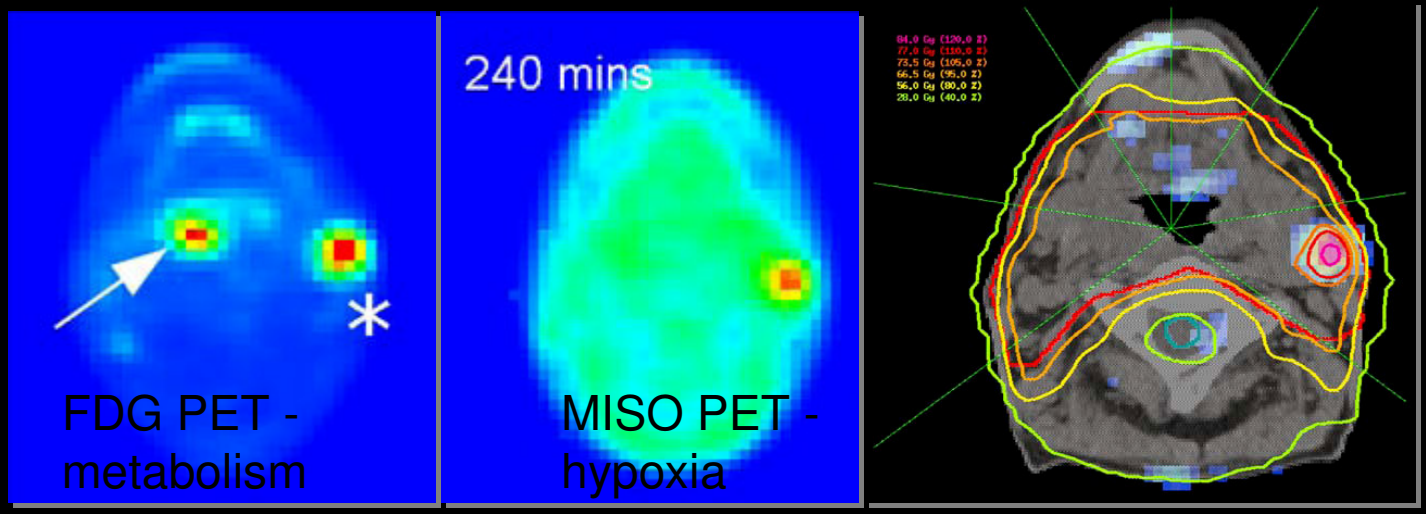
Prediction/early assessment of response to treatment



morphology parameters function

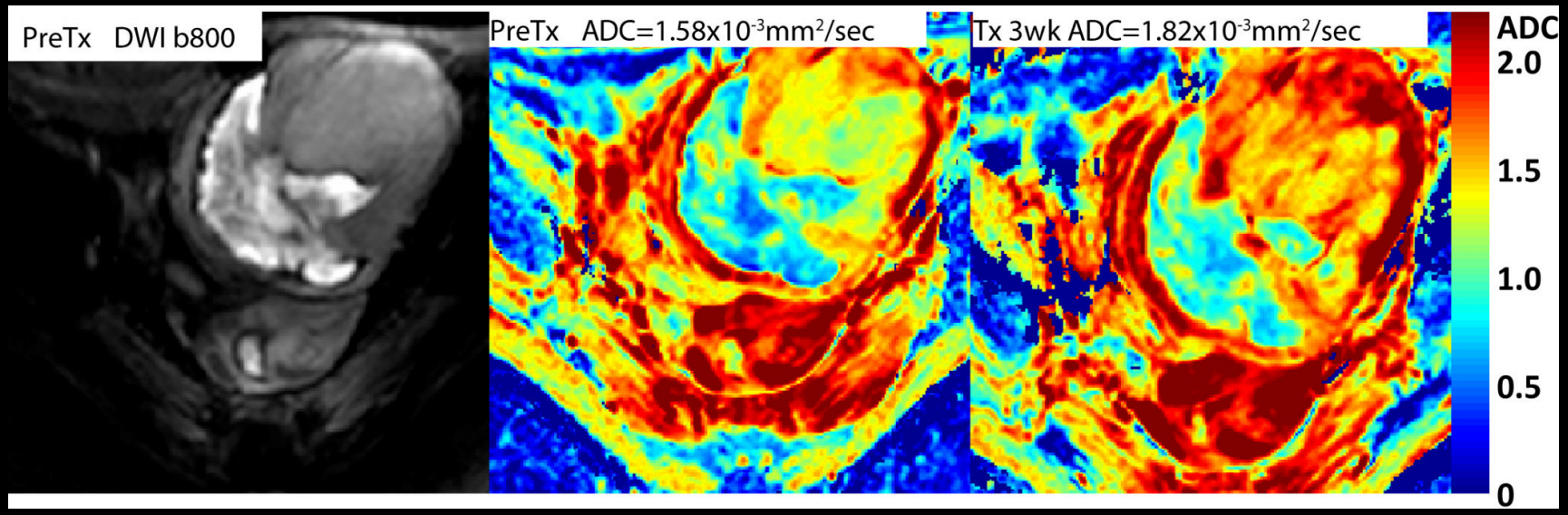
Why function?

- angiogenesis, hypoxia → biologic characteristics → aggressiveness → prediction of disease control and/or → target-therapy;
- → towards individual-targeted therapy



morphology parameters function

- Functional changes during treatment predict earlier than morphological changes the response to treatment.



Thoeny H and Ross BD, J Magn Reson Imaging 2010; 32:2-16.

morphology parameters function

- Volume is not an indicator of response to treatment for cytostatic drugs (antiangiogenesis, metastatic renal cell cancer, GIST etc.) and other treatments (i.e. TACE)→ inadequacy of RECIST criteria.

MRI

- Dynamic contrast enhanced (DCE MRI): angiogenesis. Tumor perfusion, vascular permeability, extracellular space. Limitations: reproducibility.
- Dynamic susceptibility contrast (DSC MRI): perfusion. Blood flow, blood volume. No information about permeability.
- Diffusion weighted (DWI MR): cellularity, necrosis. Limitations: difficult reproducibility, artifacts.

MRI

- Spectroscopy (MRS): metabolism, proliferation. Limitations: low spatial resolution, time demanding, technically challenging.
- Blood oxygenation level dependent (BOLD MRI): tissue oxygenation. Limitations: reflects acute more than chronic hypoxia, time and technically demanding, difficult post-processing.

PET

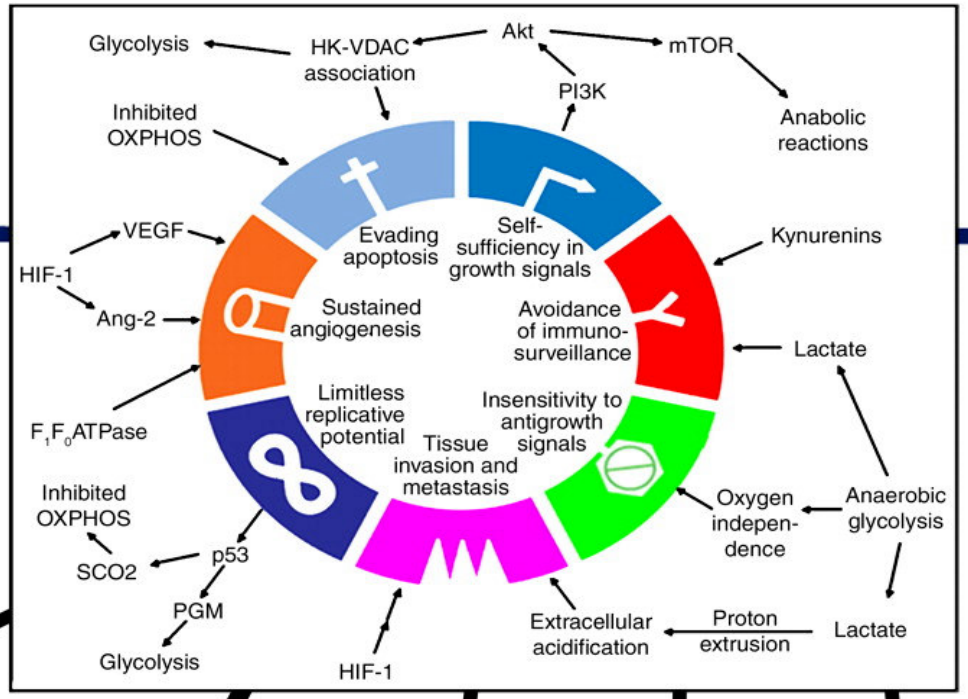
- FDG PET: glucose metabolism.
- Labeled water PET: perfusion.
- Fluorothymidine PET: cellular proliferation.
- Fluoromisonidazole (MISO) PET: hypoxia.
- Iodine annexin V: apoptosis.
- Choline PET: cellular proliferation.
- Methoxyisobutyl-isonitrile PET: multidrug resistance.

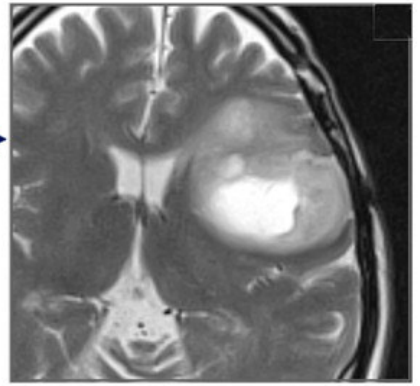
First… Biology

- The choice of imaging techniques is dictated by the functional parameters needed to describe biological characteristics of the tumor or expected effects of specific therapies.

- The interpretation of imaging results is guided by the knowledge of tumor's (disregulated) biology.

Normal





Altered metabolism & hypoxia

^{18}FDG-PET
^{1}H and ^{13}C MRS
BOLD-MRI
^{18}F-MISO PET

Angiogenesis

H_2 ^{15}O-PET
DCE-CT
DCE-MRI
DCE-US

Proliferation

^{18}FLT-PET
^{1}H-MRS
Diffusion MRI

Apoptosis

^{99m}Tc-Annexin V
Diffusion MRI

Metastasis

Lymphography
Whole body
DW-MRI
Bone scan
^{18}FDG-PET
CT etc

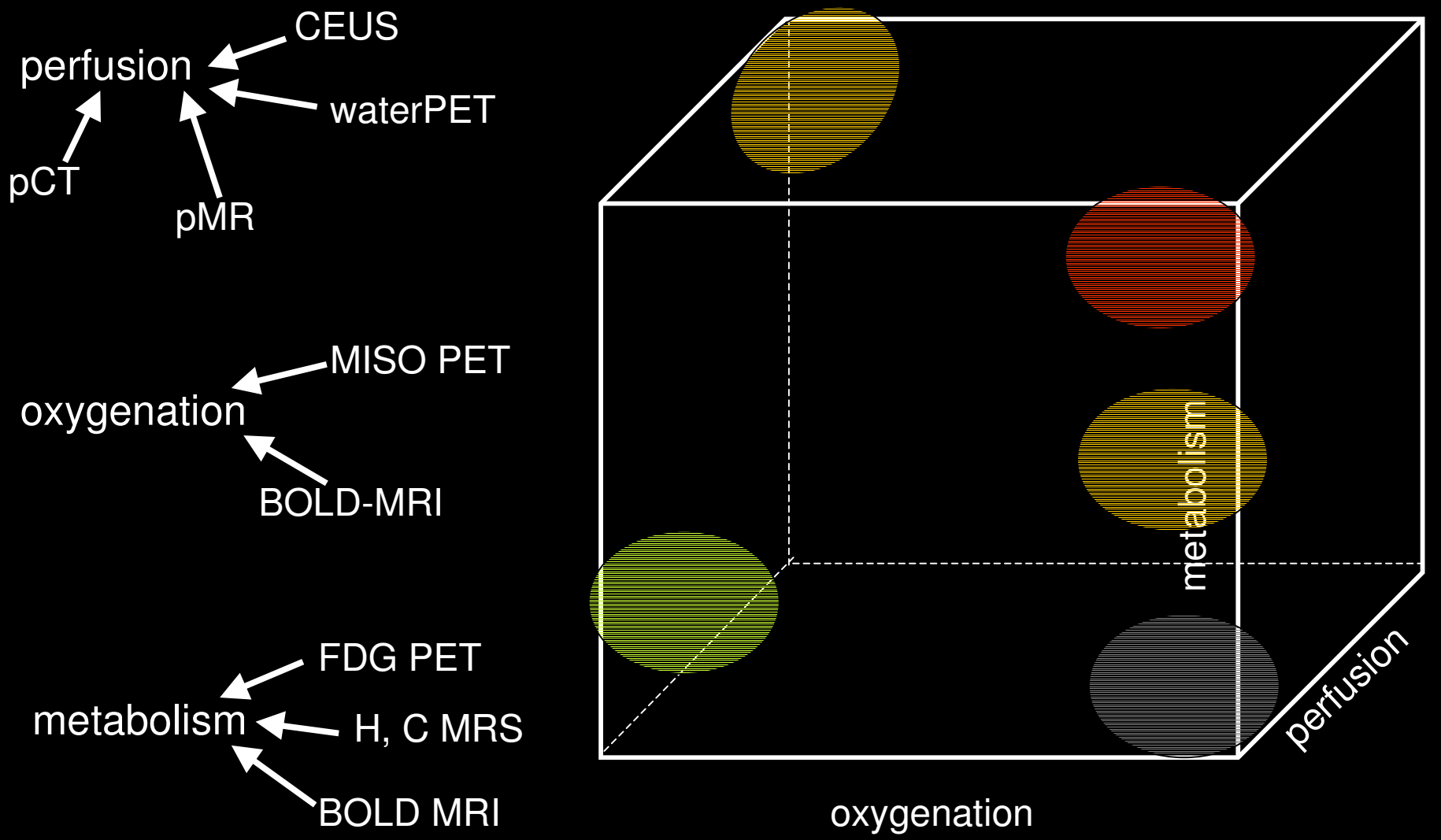
- Evading apoptosis
- Self sufficiency in growth signals
- Insensitivity to anti-growth signals
- Limitless replication potential
- Abnormal glucose uptake & metabolism
- Resistance to acid-mediated toxicity
- Tissue invasion and metastasis
- Sustained angiogenesis
- Avoidance of immune surveillance

Padhani A R , Miles K A Radiology 2010;256:348-364

The HIF-1 pathway example

- HIF-1 (hypoxia inducible factor) activates a cascade of events that lead to hypoxia adaptation:
  - ? Metabolism: Warburg effect (? GLUT1 and hexokinase→ ? glycolisis, lactate production and extrusion, resistance to acid environment).
  - ? Angiogenesis (via VEGF).
  - ? Chemotherapy resistance (p-glycoprotein upregulation)
- HIF-1 can be actually induced by hypoxia (RT resistance) or constitutionally up-regulated (p53 mutation)
- HIF activation by hypoxia > HIF activation by gene mutation

Naming and filling the cube



Prediction of treatment response

Hypoxia	Perfusion	Glucose Metabolism	Significance
Absent	Low	Moderate	No constitutive upregulation of angiogenesis or metabolism
			Query low tumor aggression/low grade neoplasm
			Query low treatment resistance
Absent	High	High	Probable constitutive upregulation of angiogenesis and metabolism
			Query moderate tumor aggression
			Query moderate treatment resistance
Present	Low	Low	Necrosis
Present	Low	Moderate	Failure of adaptation to hypoxia
			Query tumor aggression
			Query moderate treatment resistance
Present	Low	High	Adaptation to hypoxia
			High tumor aggression
			Likely treatment resistance

- Mismatch between perfusion (low) and metabolism (high)→poor prognosis

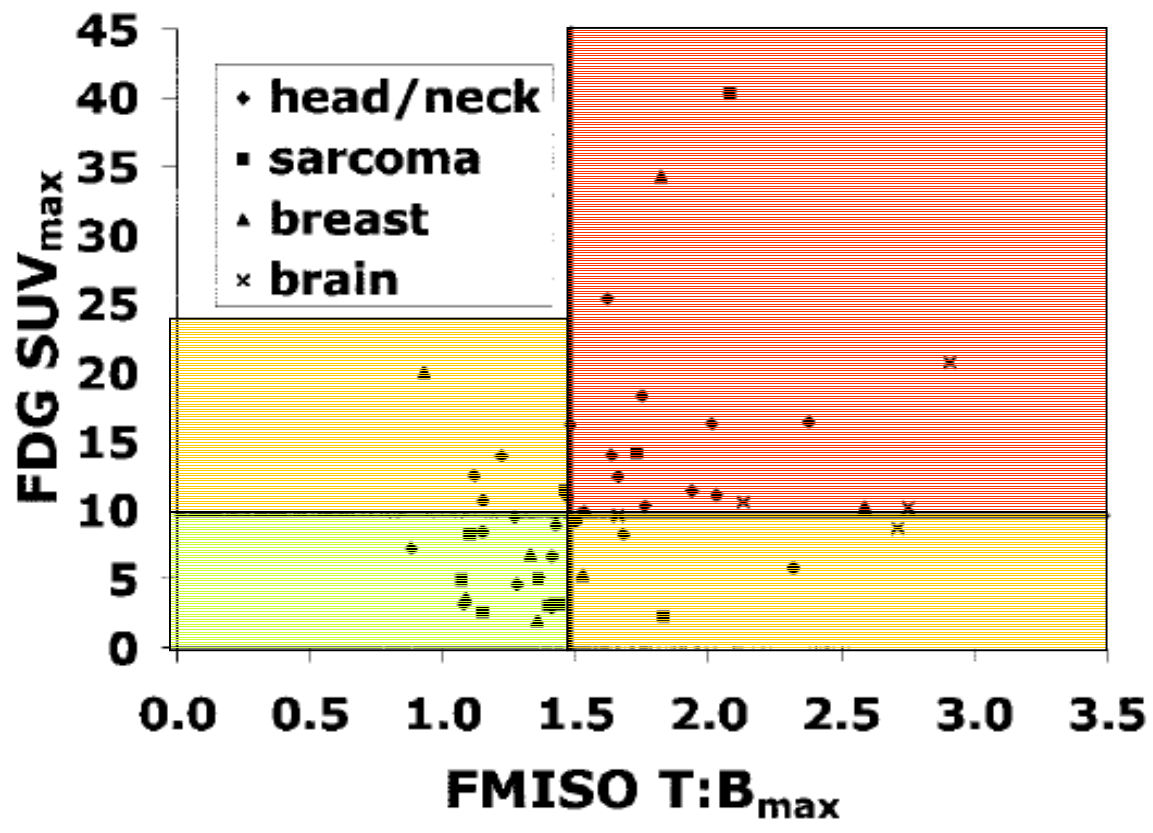
Padhani A R , Miles K A Radiology 2010;256:348-364; Mankoff et al. Clin Cancer Res 2009; 43:500-509.

Prediction of treatment response

To correlate or not to correlate? – The patient level

Trying to understand the mixed correlations at the patient level.

→ Need to match the individual results with the individual biology and/or the response to treatment



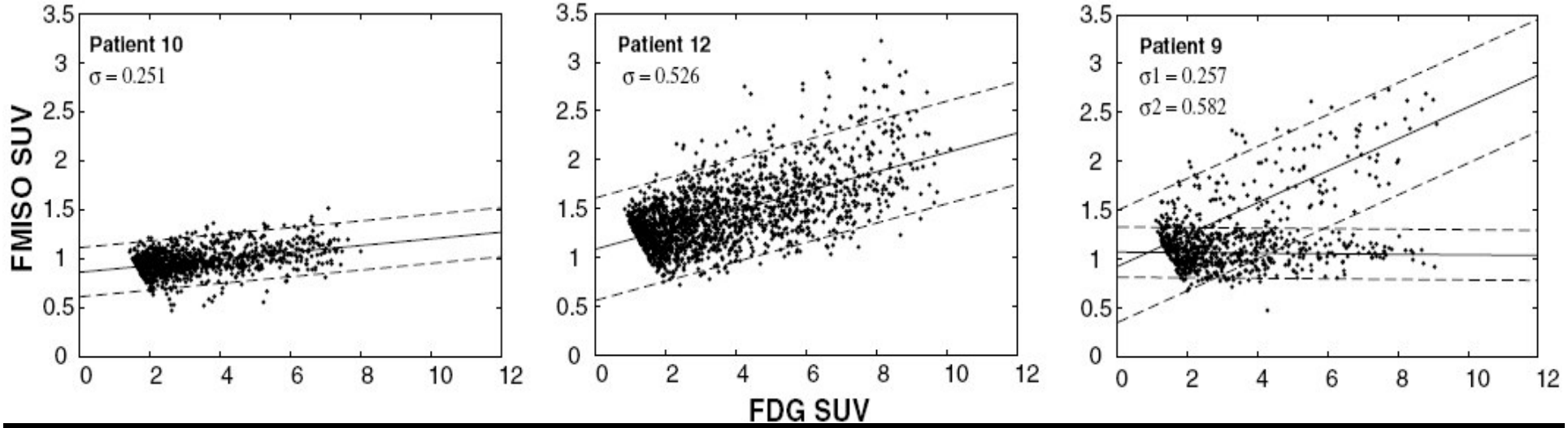
Rajendran et al Clin Cancer Res 2004; 10:2245-52.

Prediction of treatment response

To correlate or not to correlate? – The voxel level and the tumor heterogeneity.

Trying to understand the correlations at the voxel level.

→ Need to match the results with the biological heterogeneity within the tumor and/or the response to treatment.

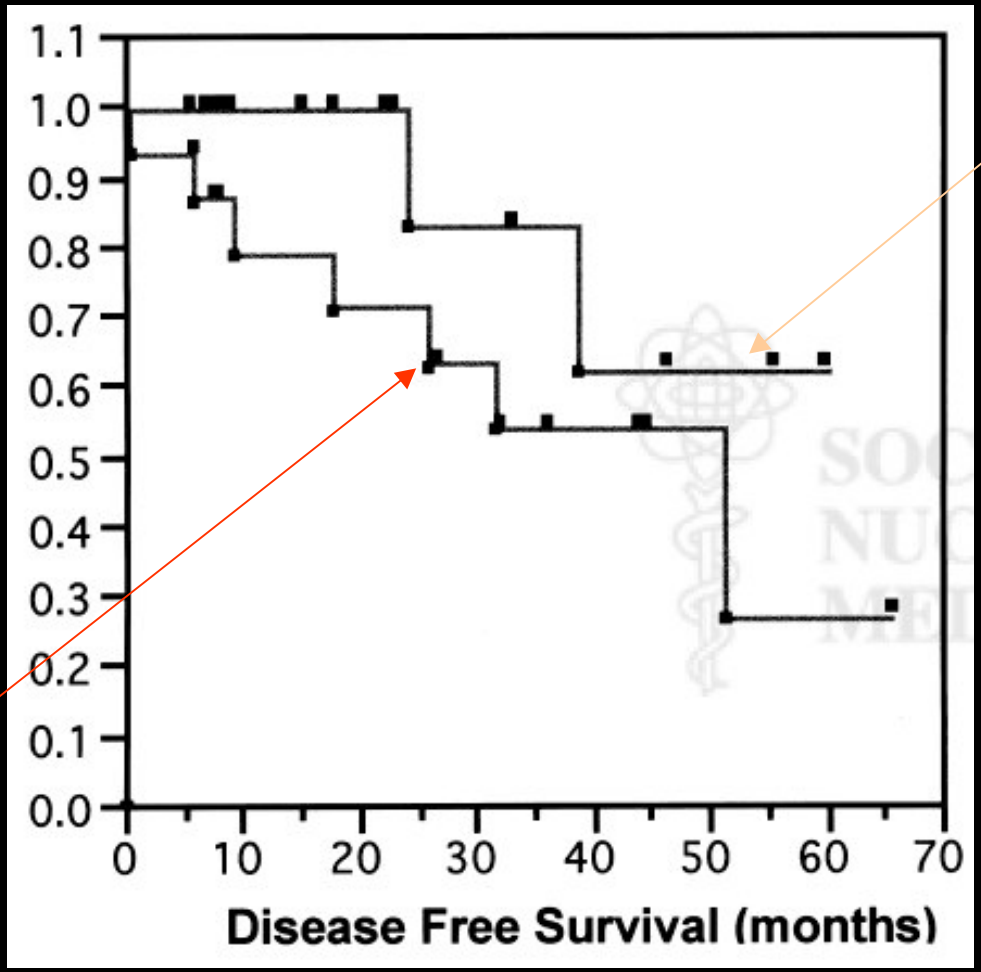


Scatter width (σ) correlates with outcome (local relapse + or -) in head and neck cancers.

Thorwarth et al. Radiother and Oncol 2006; 80:151-156.

Prediction of treatment response

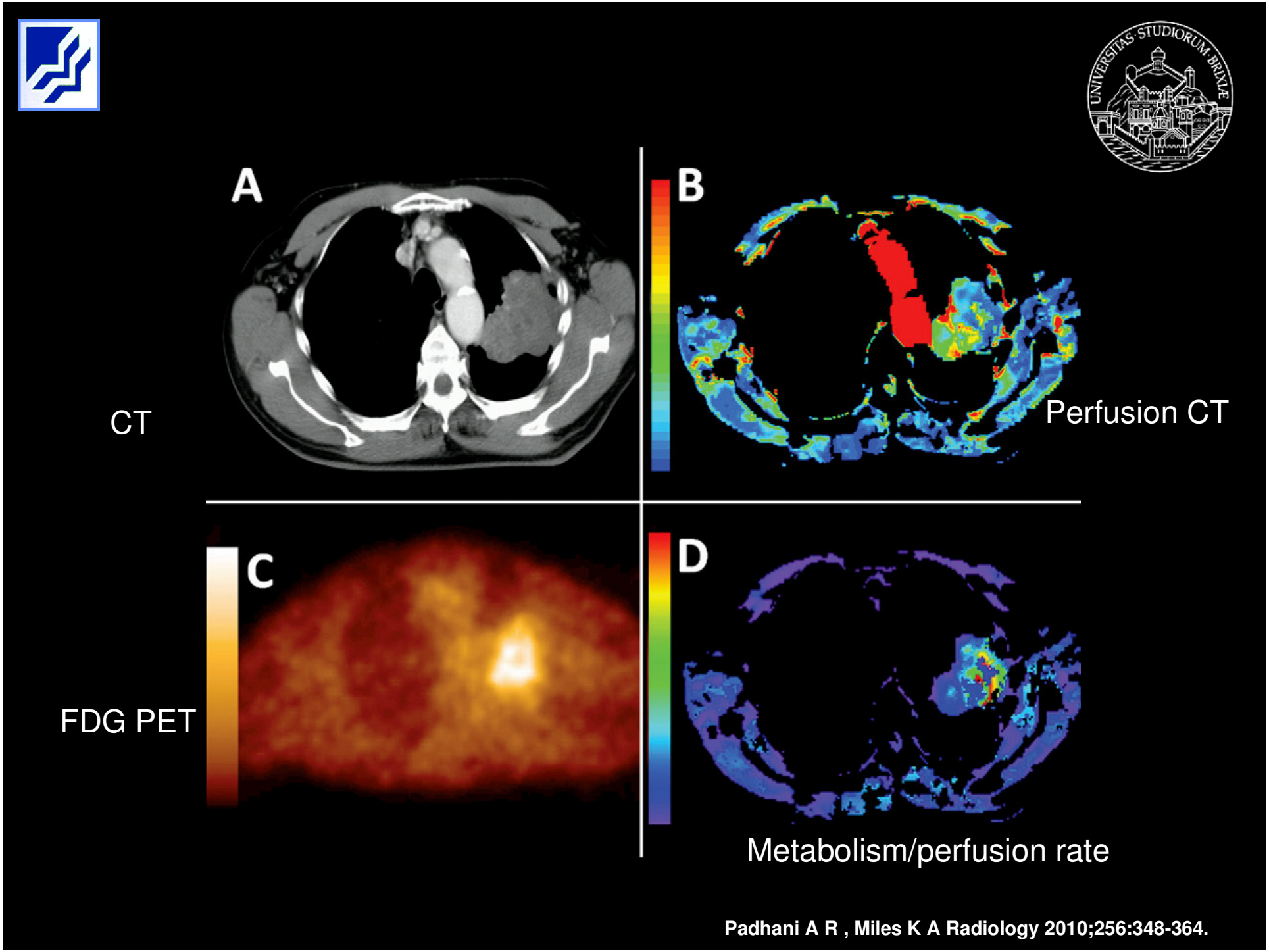
Advanced breast cancer – PET, 37 patients



↓ metabolism/flow

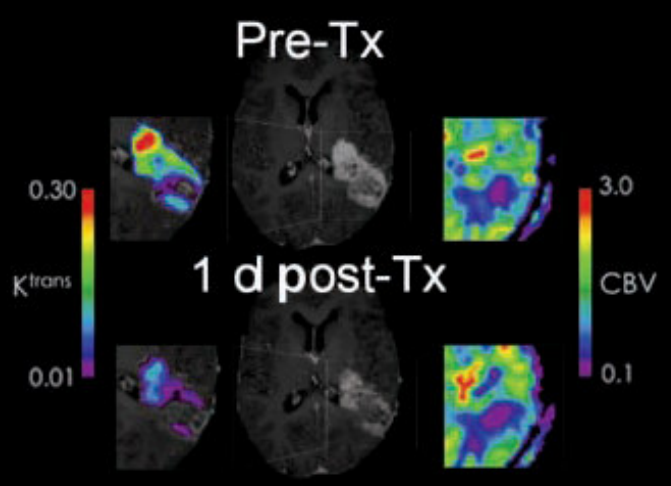
↑ metabolism/flow

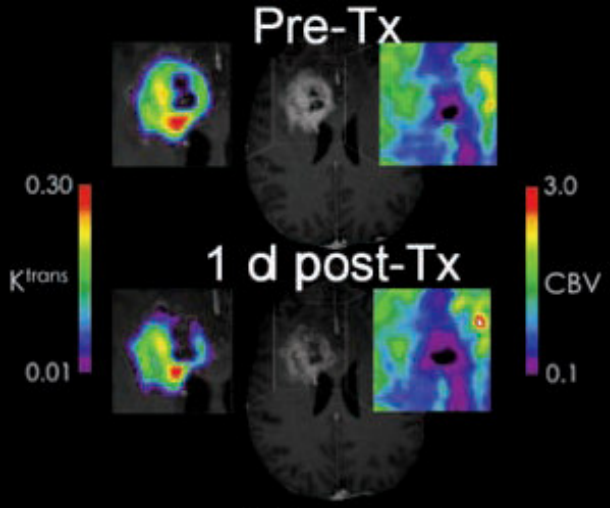
Mankoff et al J Nucl Med 2002; 43:500-9.

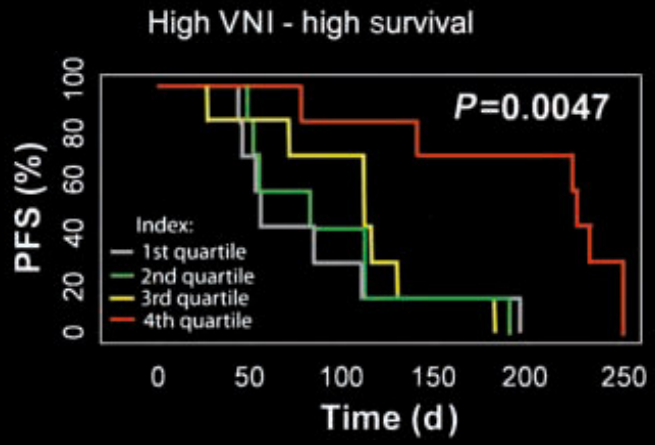

A
B
CT
Perfusion CT
C
D
FDG PET
Metabolism/perfusion rate
Padhani A R , Miles K A Radiology 2010;256:348-364.

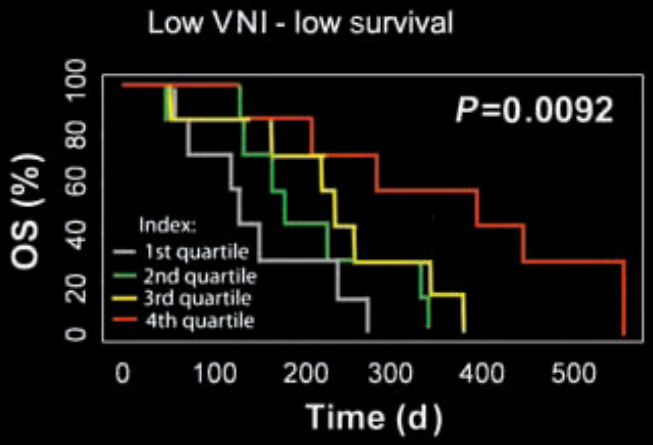
Early assessment during therapy

- Adding two variables: treatment effects and time → complexity increase
- Numerous studies about single functional techniques. Very few studies about multiparametric imaging.









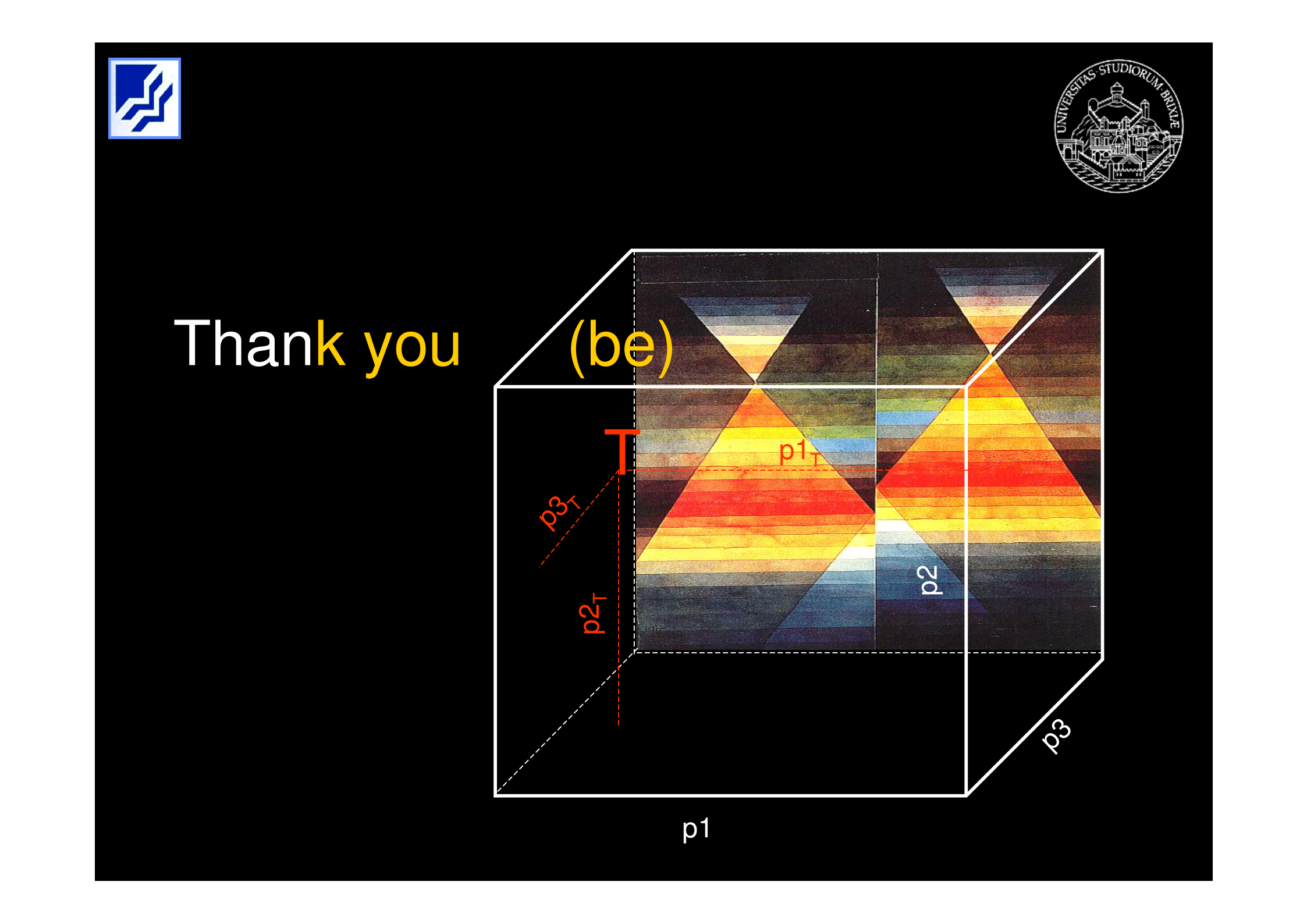
Vascular normalization index (VNI) unifies in a single parameter: ΔK^{trans}, ΔCBV, ΔCoII-IV.

It well predicted FPS and OS in glioblastoma multiforme after a single dose of anti-VEGFR.

Sorensen AG et al. Cancer Res 2009;69:5296-300.

Future: when and how

- Multiparametric imaging is already future
- Need of multicentric prospective studies.
- Need of technical standardization (MRI)
- Need of new-concept informatic platforms to analyse, visualize and interpolate functional data.


Thank you (be)
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