**Modélisation biostatistique et biomathématique des données d'imagerie en cancérologie - 2016**

# Expectations in oncologic imaging :

## *Tumor dynamics during treatment response*

*N. Grenier, Université de Bordeaux*

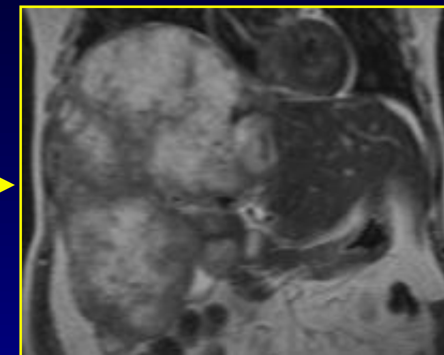
université de BORDEAUX

10 octobre 2012 - Montpellier

CHU Hôpitaux de Bordeaux

Hanahan & Weinberg
Cell 2011

**Normal** → **Atypia** →

*Altered oxygenation, pH & metabolism*

*Dysregulated angiogenesis & erratic perfusion*

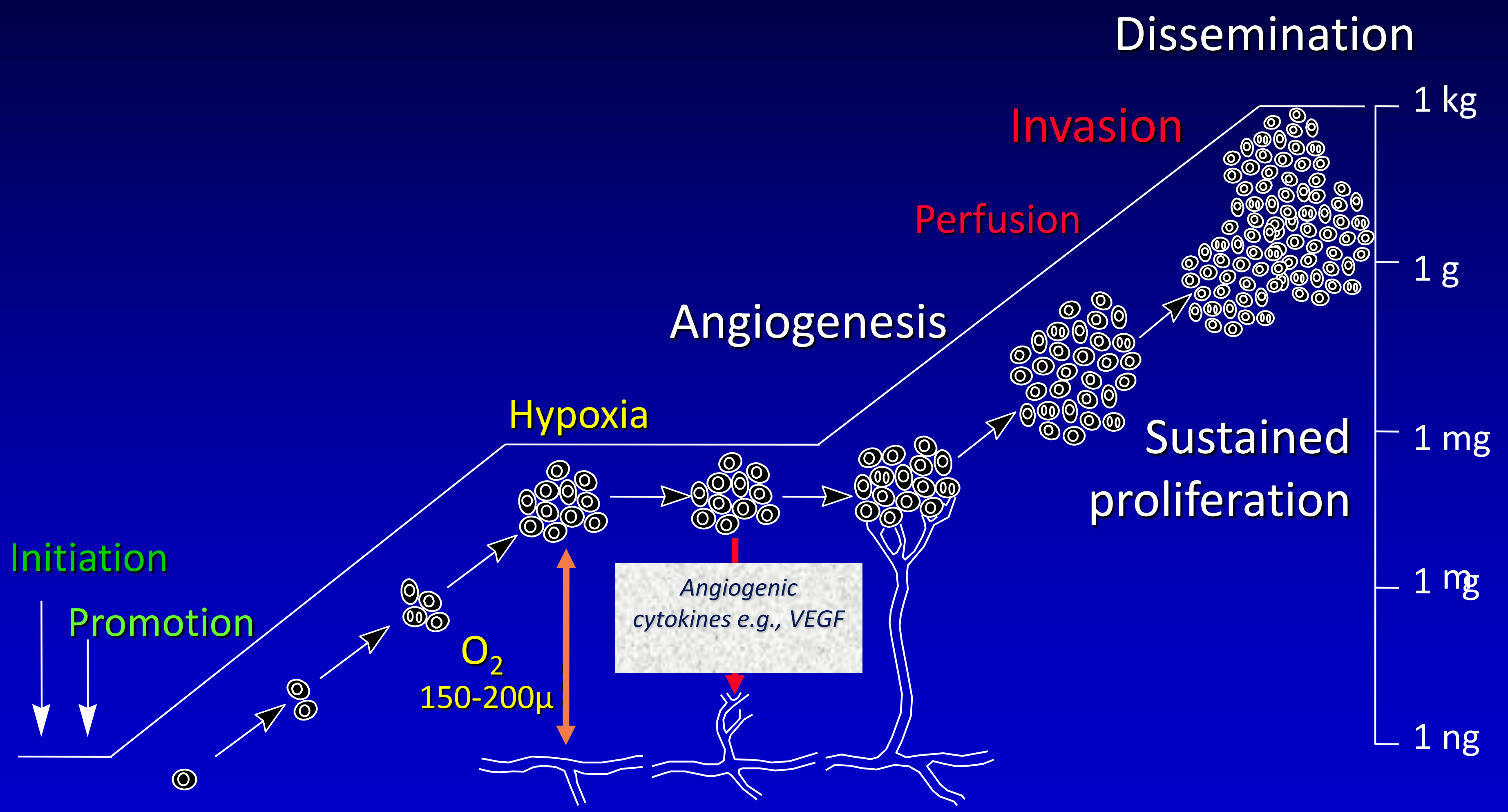
*Proliferation & invasion*

*Cell death & necrosis*

*Metastasis*

## Depictable in clinical practice

# Key biological hallmarks



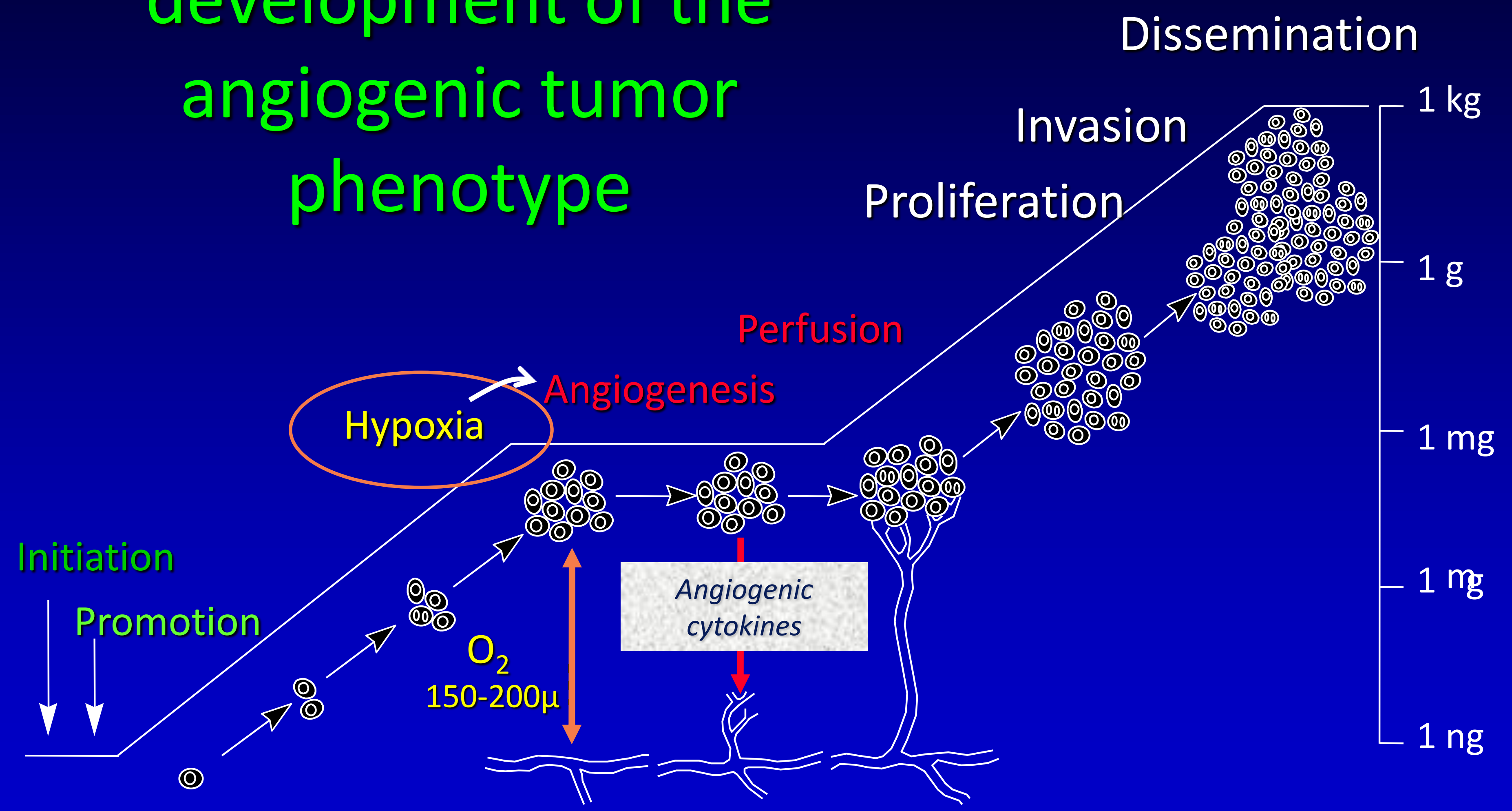

*Fidler IJ. Differentiation 2002; 70:498-505*
*Cairns R, et al. Mol Cancer Res 2006; 4:61-70*

*Courtesy of P Choyke, NIH, USA*

| TECHNIQUE | BIOLOGICAL PROPERTY ON WHICH IMAGING IS BASED | COMMONLY DERIVED BIOMARKERS | PATHOPHYSIOLOGICAL CORRELATES |
|---|---|---|---|
| Dynamic contrast-enhanced MRI (DCE-MRI) | Contrast medium uptake rates<br>Transfer rates<br>Extra-cellular volume<br>Plasma volume fraction | Initial area under gadolinium curve (IAUGC)<br>Transfer and rate constants ($K^{trans}$, $k_{ep}$)<br>Leakage space fraction ($v_e$)<br>Fractional plasma volume ($v_p$)<br>Non-enhancing fraction | Vessel density<br>Vascular permeability<br>Perfusion<br>Extravascular space<br>Plasma volume |
| Dynamic susceptibility contrast MRI (DSC-MRI) | Blood volume and blood flow | relative blood volume/flow (rBV/rBF)<br>Transit times (MTT) | Vessel density<br>Blood flow<br>Vessel diameter<br>Tumour grade |
| Intrinsic susceptibility weighted MRI (ISW-MRI or BOLD-MRI) | Balance between red blood cell oxyhaemoglobin & deoxyhaemoglobin<br>Tissue blood volume & perfusion<br>Intrinsic composition of tissues | Intrinsic tissue relaxation rates ($R2^* = 1/T2^*$) | Ferromagnetic properties of tissues<br>Level of tissue oxygenation – some tumors (prostate ca)<br>Level of blood volume/flow (breast ca) |
| Diffusion weighted MRI (DW-MRI) | Diffusivity of water | Apparent diffusion coefficient (ADC)<br>Perfusion fraction (f)<br>Diffusion (D) | Tissue architecture: cell density & size, extracellular space tortuosity, gland formation, cell membrane integrity, necrosis. Microvessel perfusion. |
| Dynamic contrast enhanced (perfusion) CT (DCE-CT) | Contrast medium uptake rate in tissues, which is influenced by:<br>• Perfusion & transfer rates<br>• Extra-cellular volume<br>• Plasma volume fraction | • Tissue perfusion<br>• Blood volume<br>• Transit time<br>• permeability | Vessel density<br>Vascular permeability<br>Perfusion<br>Tissue cell fraction<br>Plasma volume |
| Dynamic contrast enhanced ultrasound (DCE-US) | Microbubbles reside within the intravascular space. Perfusion indices are derived from model fitting of time-intensity curves | • Microbubble velocity, Fractional BV<br>• Peak intensity and time to peak intensity<br>• Mean transit time, coefficient of washin (ascending slope)<br>• Areas under the entire curve, washin hemicurve and washout hemicurve | Tissue blood flow<br>Transit time<br>Tissue blood volume<br>Microvessel density |

Padhani AR, Miles KA. Multiparametric imaging of tumor response to therapy. Radiology 2010; 256(2):348-64

# Low $pO_2$ is the key to the development of the angiogenic tumor phenotype




*Fidler IJ. Differentiation 2002; 70:498-505*
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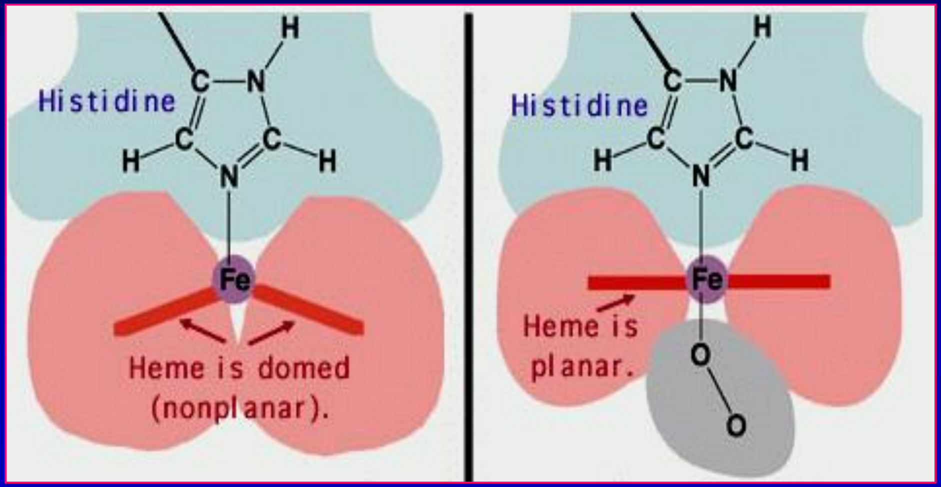
*Courtesy of P Choyke, NIH, USA*

# Imaging the tumor microenvironment

| | | Oxygenation | Glycolysis | Acidification | Angiogenesis | Perfusion | Proliferation | Cell density | Apoptosis | Necrosis |
|---|---|---|---|---|---|---|---|---|---|---|
| PET | Nitroimidazoles (FAZA, FMISO), Cu-ATSM | + | | | | | | | | + |
| | RDG | | | | + | | | | | |
| | FLT | | | | | | + | | | |
| | Annexin V | | | | | | | | + | |
| | FDG | | + | | | | | + | | |
| | Water, Inert gas | | | | | + | | | | |
| | Dynamic modelling | | | | | + | | | | |
| MRI | DCE-MRI (CT/US) | + | | | | + | | | | |
| | BOLD-MRI | + | | | + | | | | | |
| | Diffusion | | | | | + | + | + | + | + |
| | $^{1}$H & $^{31}$P-MRS | | | + | | | + | | | |

# BOLD MR imaging

## «Blood Oxygenation Level Dependent »

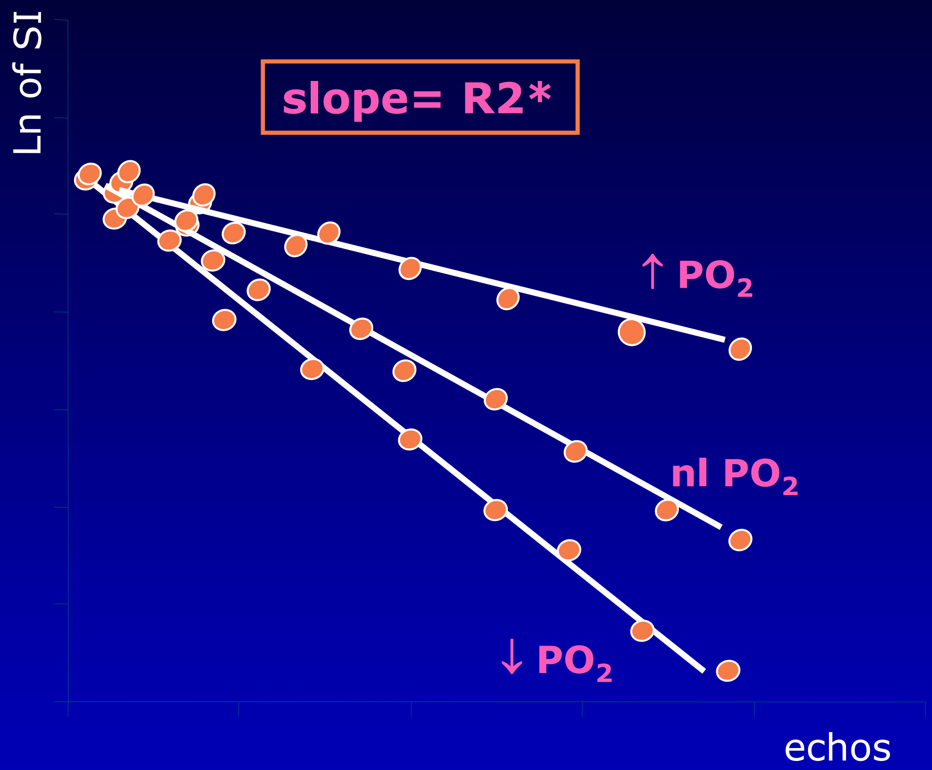



**DEOXY-HB**
**Paramagnetic**

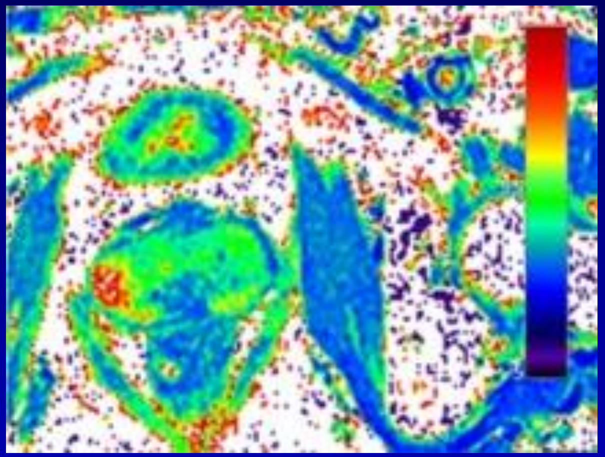
**OXY-HB**
**Diamagnetic**

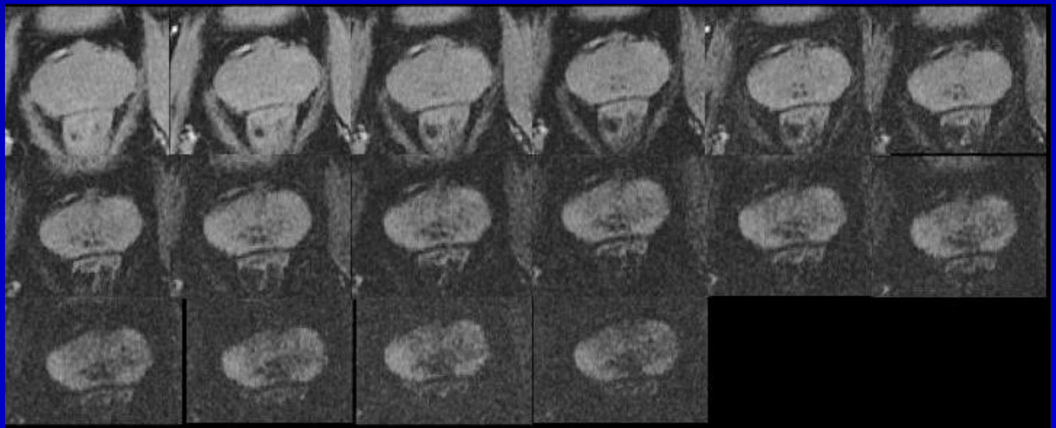
- <u>MR effect</u> : increase of deoxyhemoglobin production induces an increase of R2* relaxivity (decrease of signal)

# BOLD MR imaging

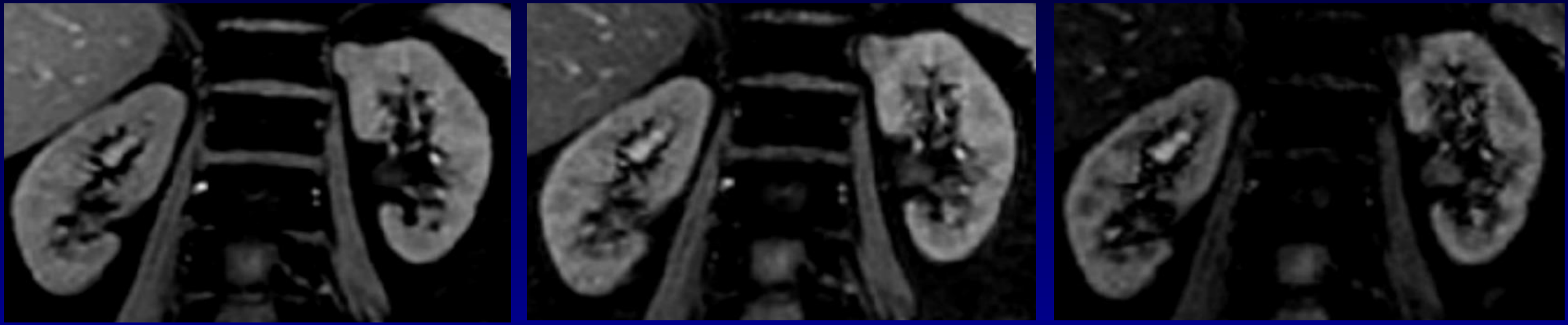


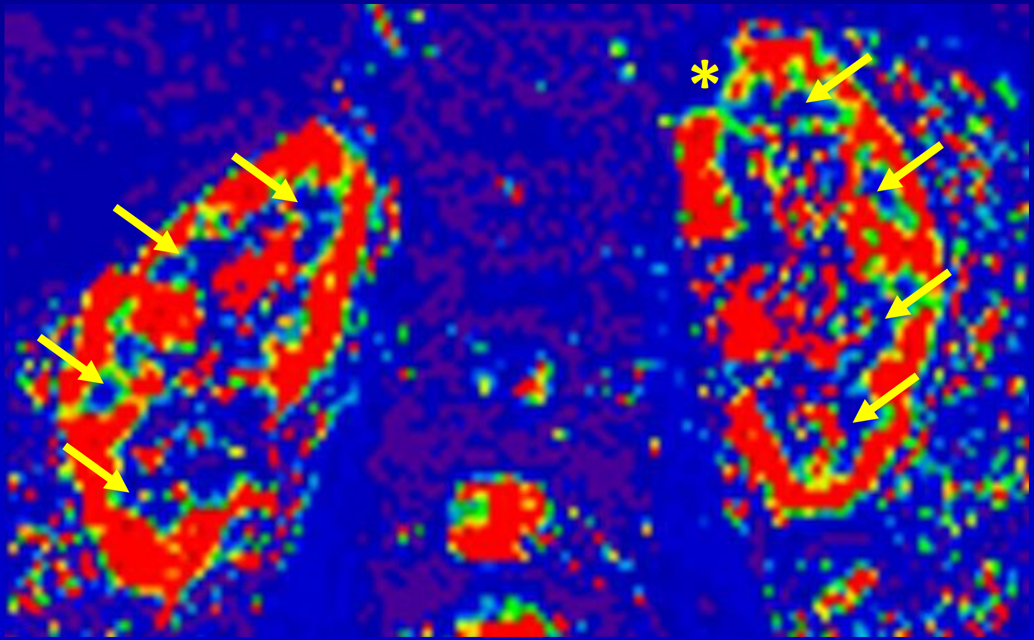

R2* map





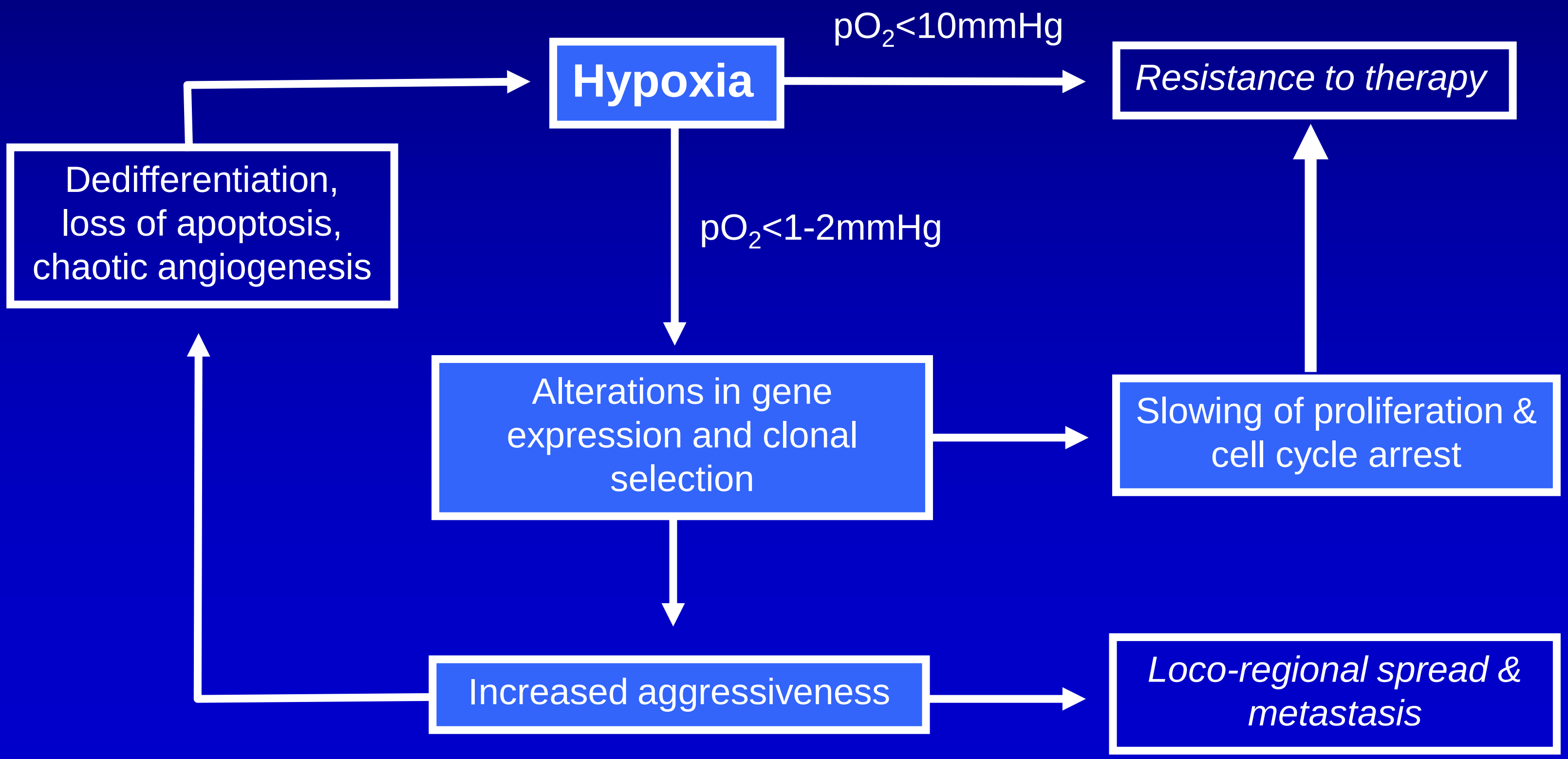
# BOLD MR imaging





# BOLD MR imaging

- **Why is tumor hypoxia important to identify?**
  - Resistance to radiotherapy & PDT (also chemo)
  - Development of aggressive clones → poor local control, ↓disease free intervals and ↓overall survival times

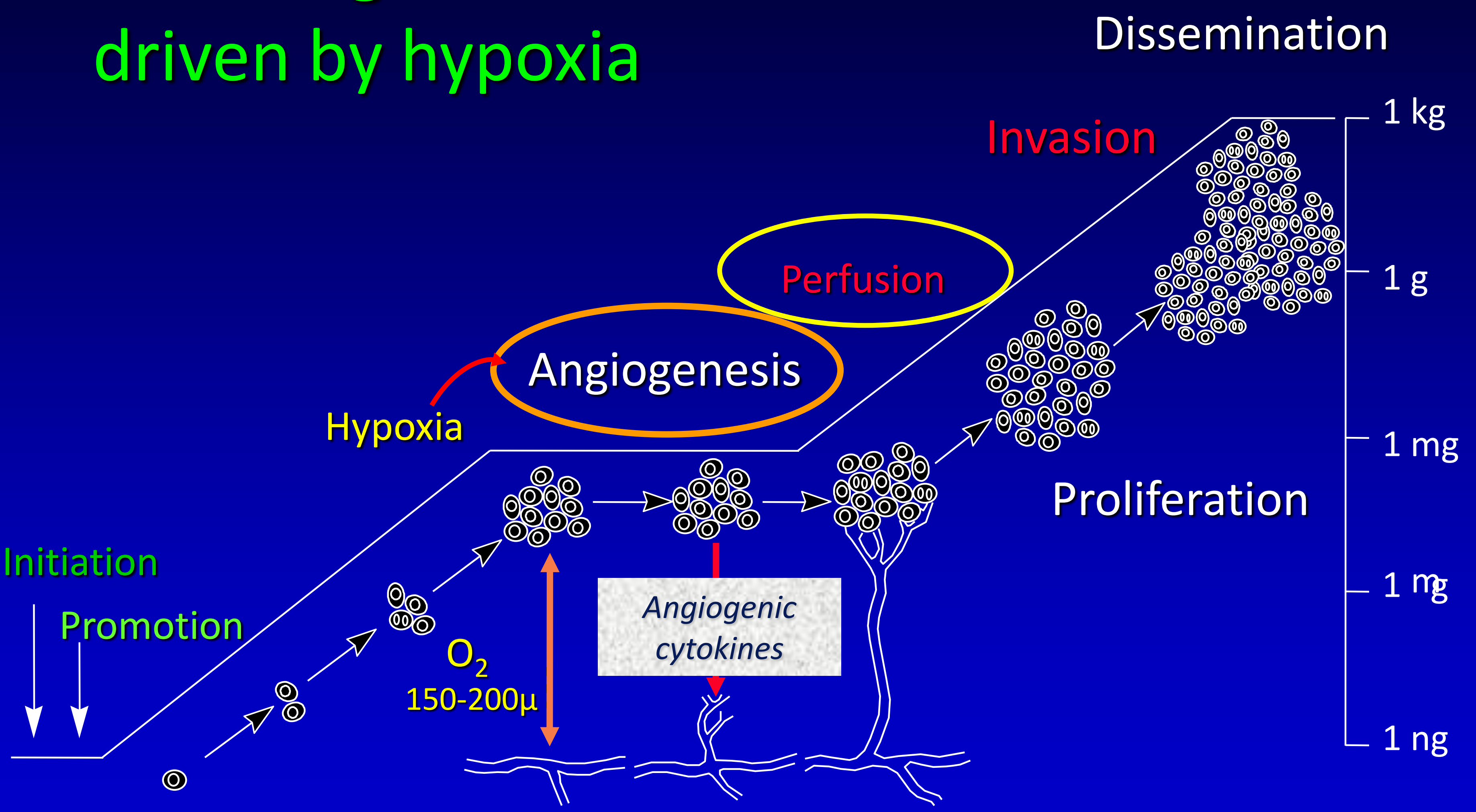


# BOLD MR imaging for tumor response

- In preclinical studies in animals, it has been shown that the R2* value of tumours decreases dose-dependently with anti-vascular treatment in prolactinoma and fibrosarcoma models.
- There have not yet been any studies analysing the usefulness of BOLD MRI in the response to anti-angiogenic treatment in humans.

fg

# Angiogenesis is critical for tumor growth and driven by hypoxia




Fidler IJ. Differentiation 2002; 70:498-505

Courtesy of P Choyke, NIH, USA

# Imaging the tumor microenvironment

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|---|---|---|---|---|---|---|---|---|---|---|
| PET | Nitroimidazoles (FAZA, FMISO…) | + | | | | | | | | + |
| | RDG | | | | + | | | | | |
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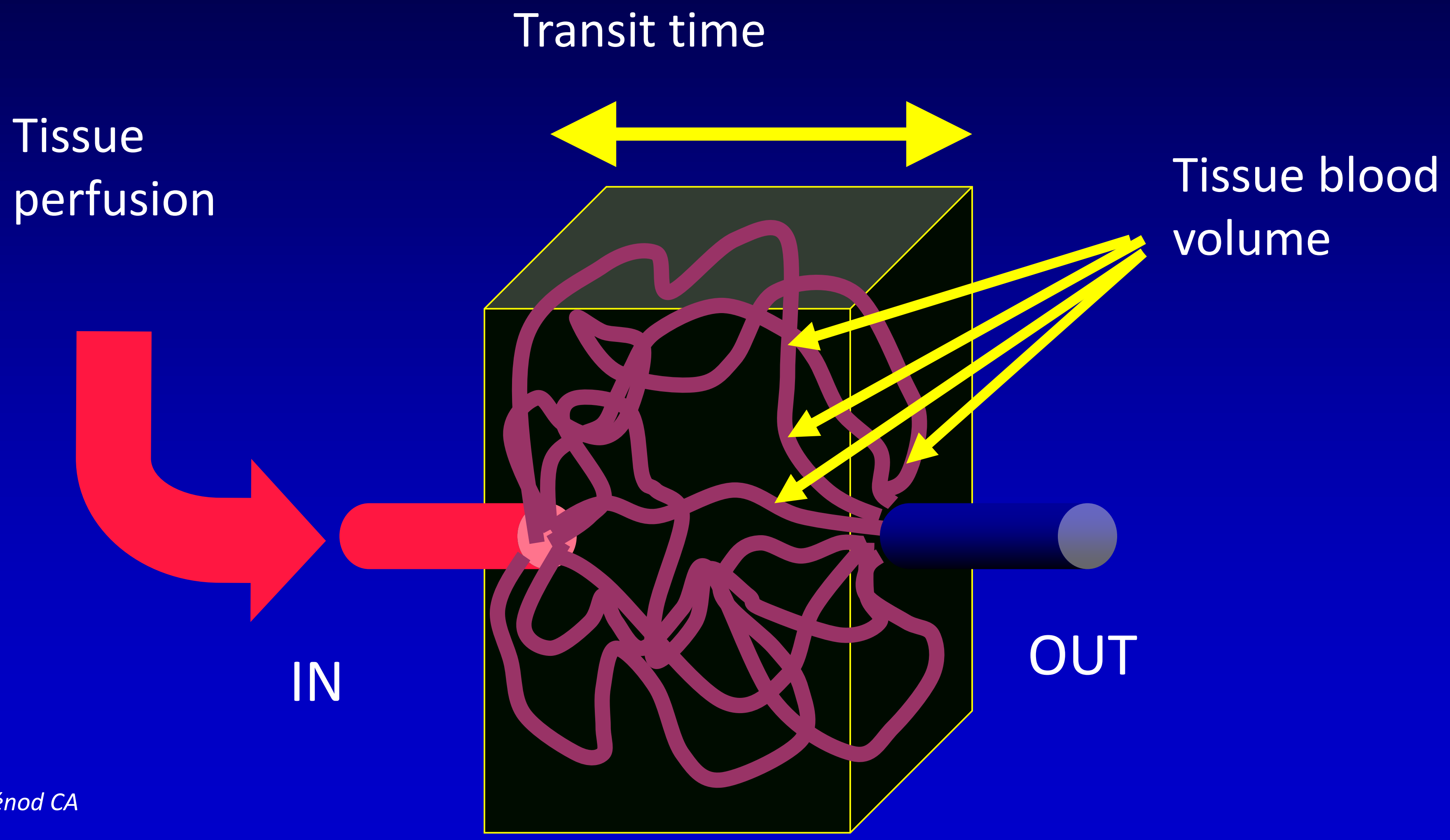
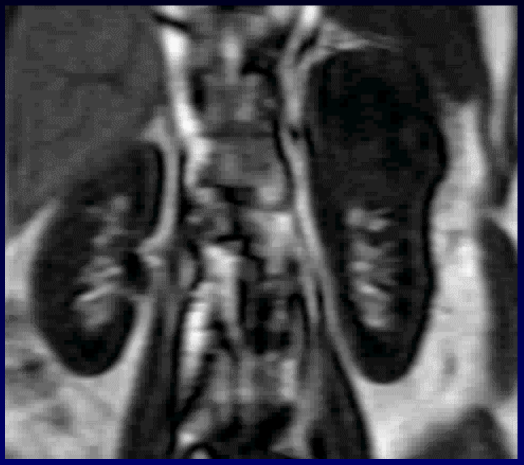
| | Annexin V | | | | | | | | + | |
| | FDG | | + | | | | | + | | |
| | Water, Inert gas | | | | | + | | | | |
| | Dynamic modelling | | | | | + | | | | |
| Non-PET | DCE-MRI (CT/US) | + | | | | + | | | | |
| | BOLD-MRI | + | | | + | | | | | |
| | Diffusion | | | | | + | + | + | + | + |
| | $^{1}H$ & $^{31}P$-MRS | | | + | | | + | | | |

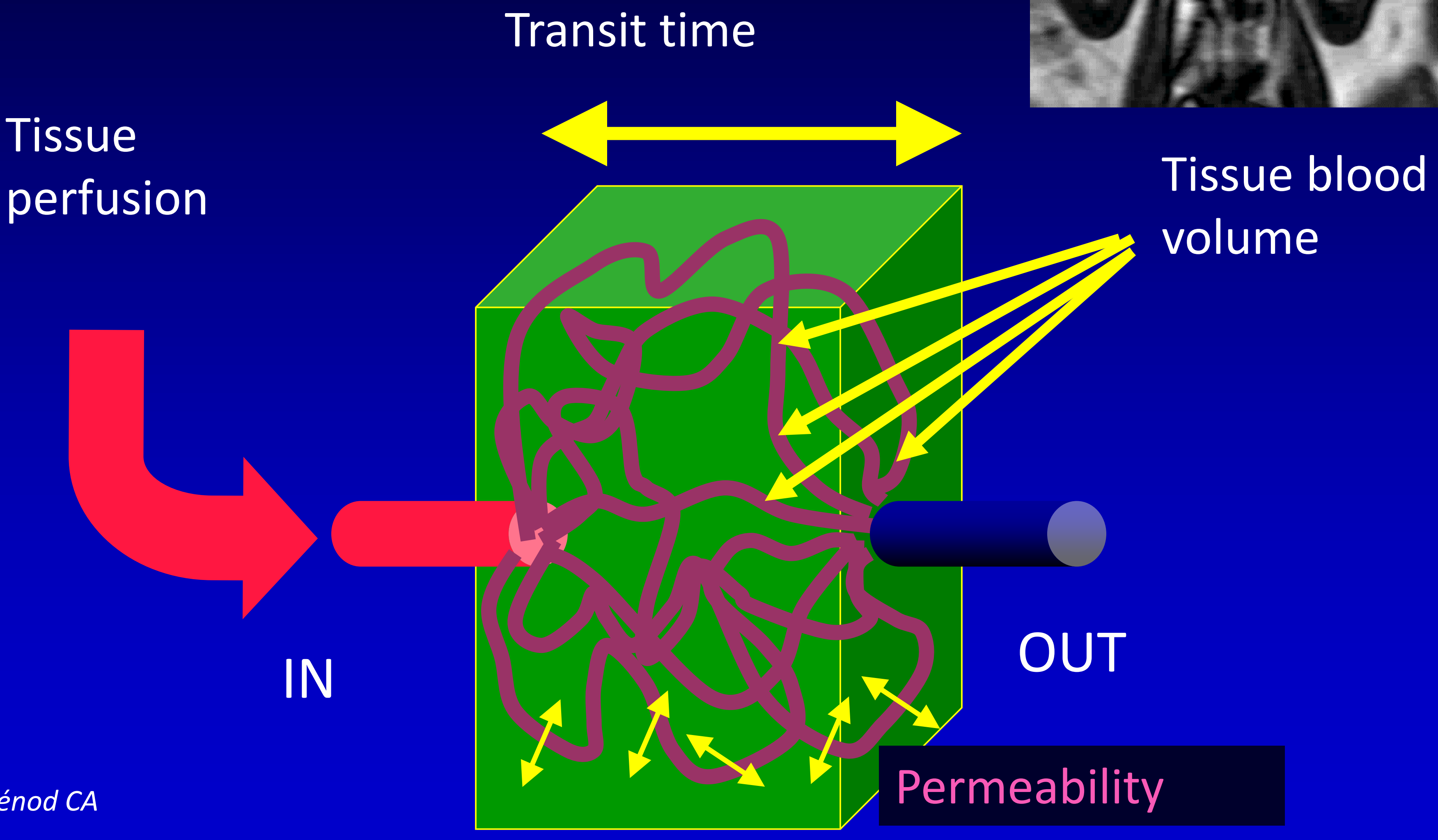
# DCE-MRI or CT : principles




*Cuénod CA*

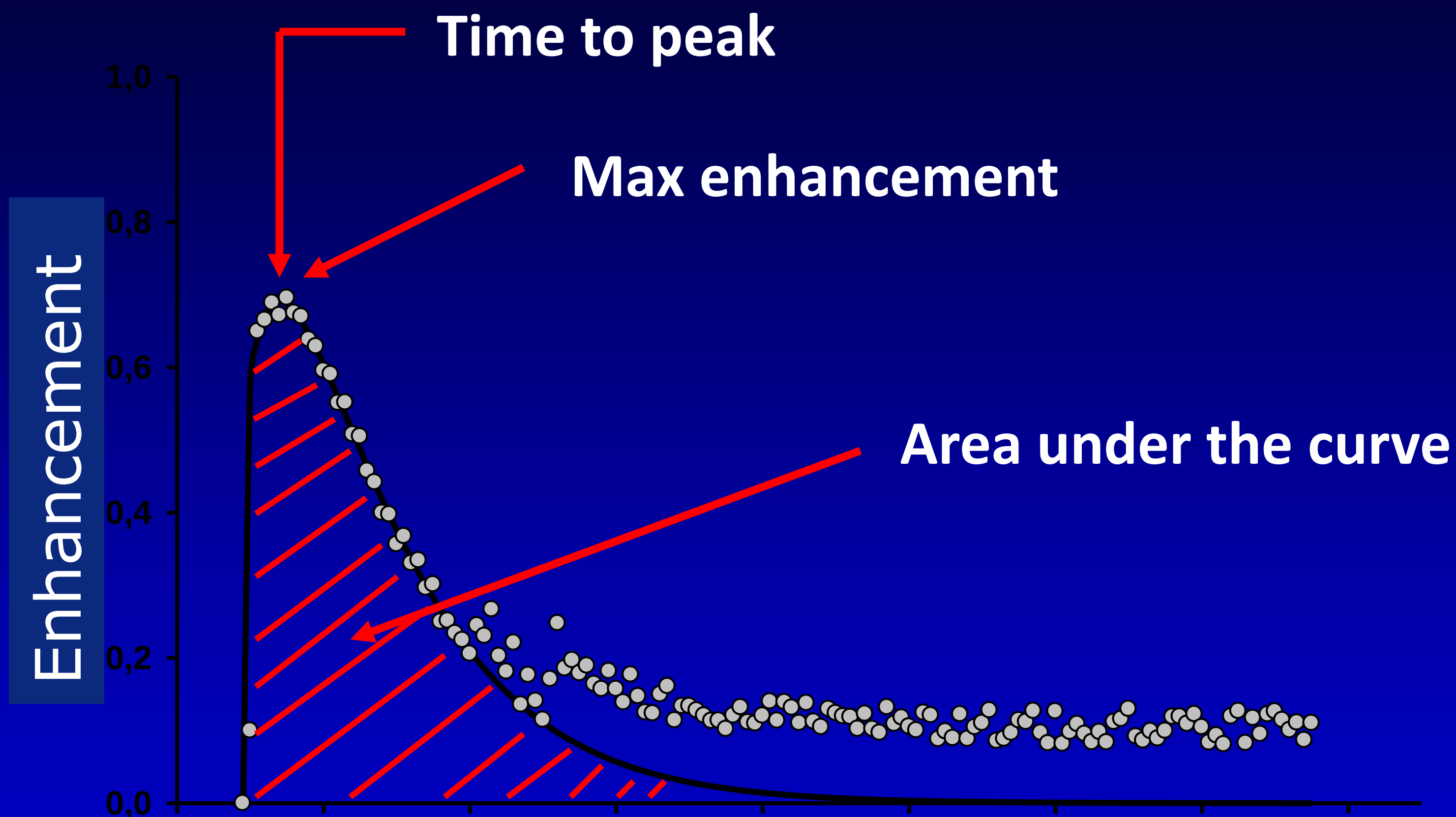
# DCE-MRI or CT : principles





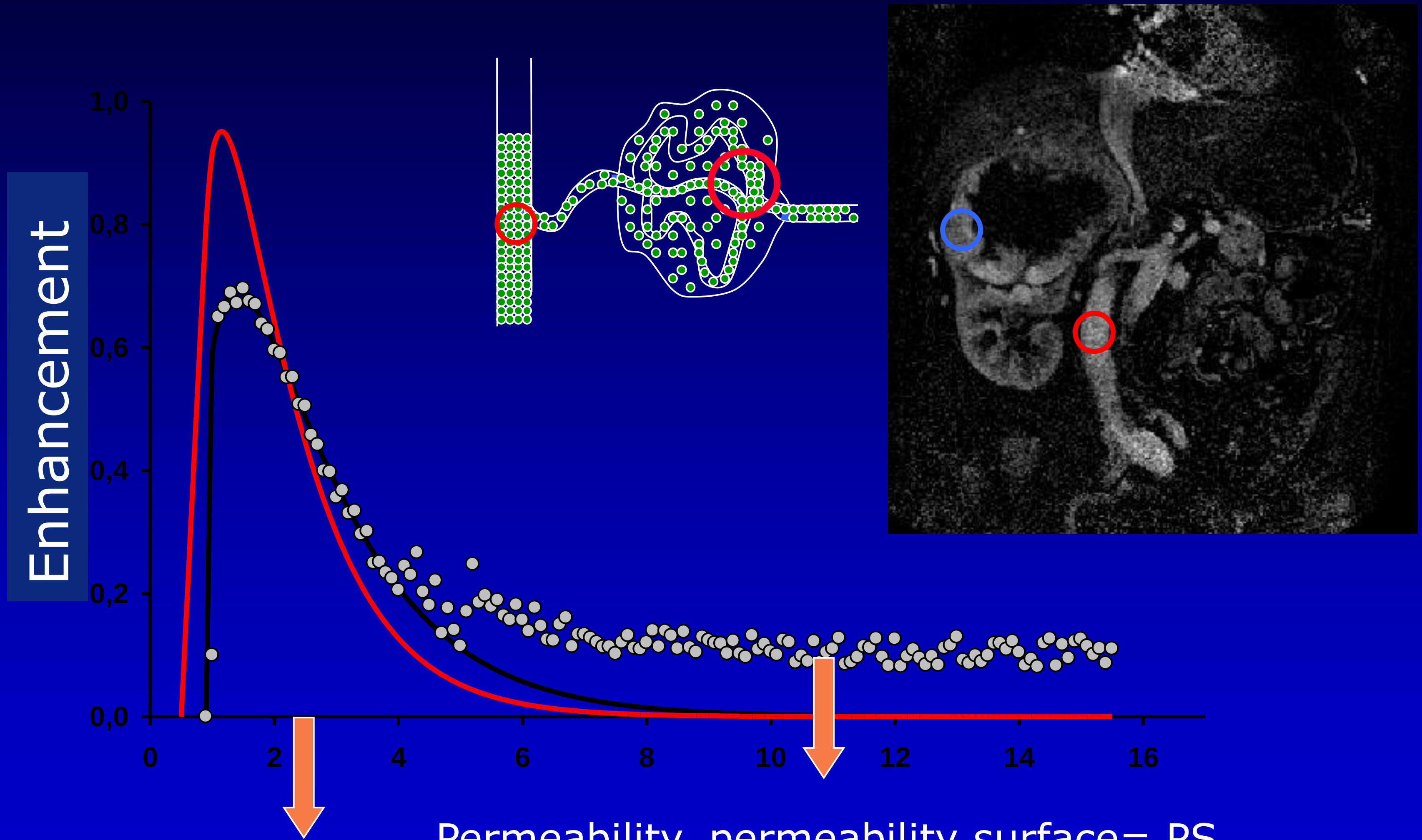

*Cuénod CA*

# DCE-MRI or CT : Semi-quantitative analysis



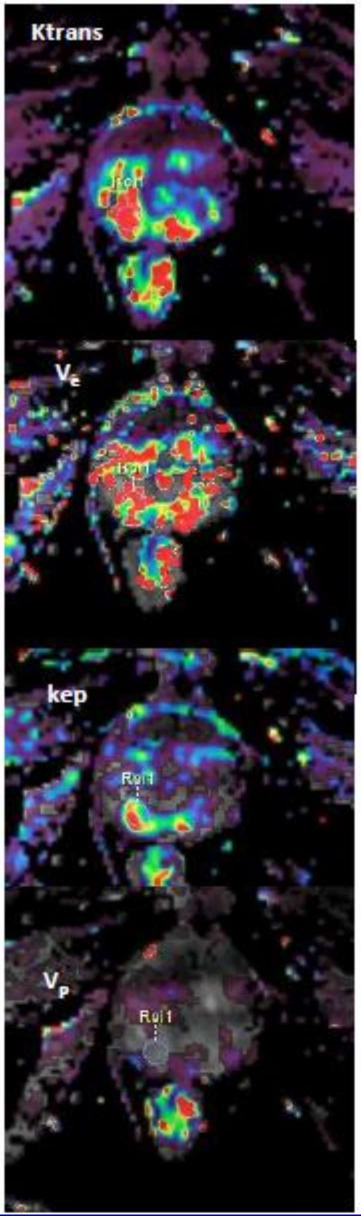

- no kinetic models
- links with physiologic parameters uncertain
- low reproducibility between imaging systems

# DCE-MRI or CT : quantitative analysis

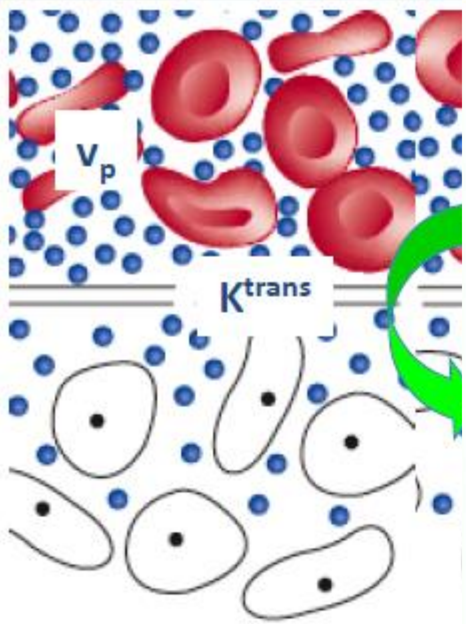


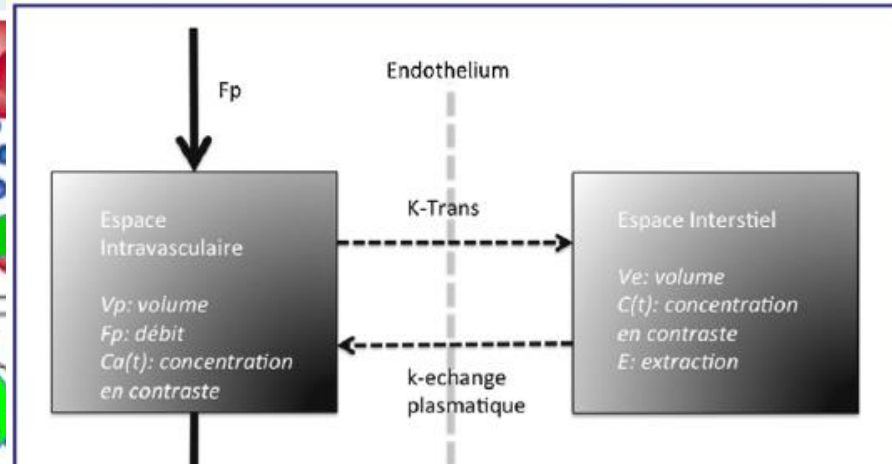

Permeability, permeability surface= PS

Blood volume, perfusion




| PARAMETER | INTERPRETATION | MARKER |
|---|---|---|
| $K^{trans}$ | Constant Transfer = Flow of tracer from plasma to EES across the capillary endothelium<br>Rapid enhancement = high $K^{trans}$ | PERFUSION<br>PERMEABILITY |
| $v_e$ | Extravascular extracellular (EEE)<br>High $v_e$ lesions take longer to reach peak | EXTRAVASCULAR EXTRACELLULAR VOLUME |
| $k_{ep}$ | Rate constant. Flow of tracer from EEE to plasma. Easier to measure than $K^{trans}$ and $v_e$, but less physiological; determines shape of response | PERMEABILITY related |
| $v_p$ | Plasma volume ($v_p$) describes intravascular contribution | PERFUSION |



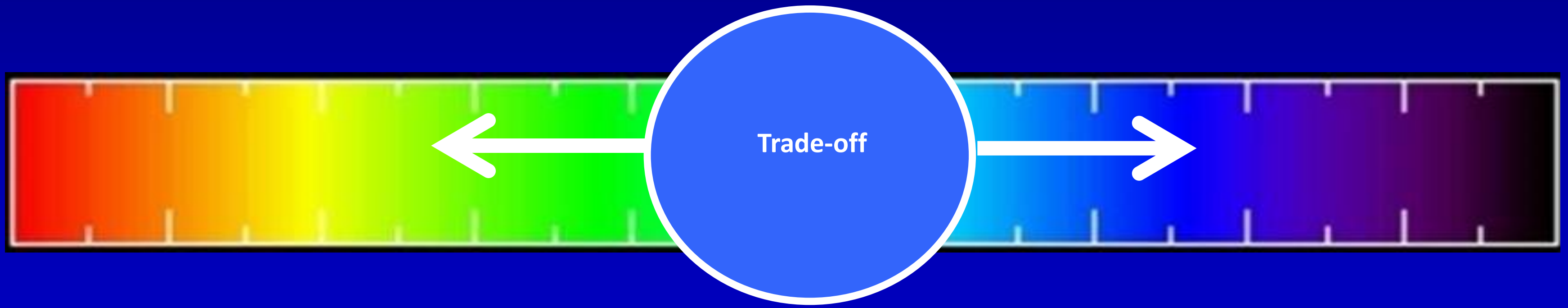




$$C(t) = v_p\, C_a(t) + K^{trans}\, e^{-tk_{ep}} * C_a(t)$$
$$K^{trans} = EF_p$$
$$k_{ep} = EF_p/v_e$$

# Range of endpoints

**Quantitative**
Perfusion *measurement*
Permeability *measurement*
Function *measurement*

**Descriptive**
Perfusion-*weighted*
Permeability-*weighted*
Function-*weighted*




More specific/reproducible (*)
Less practical/cost-effective

Less specific/reproducible
More practical/cost-effective

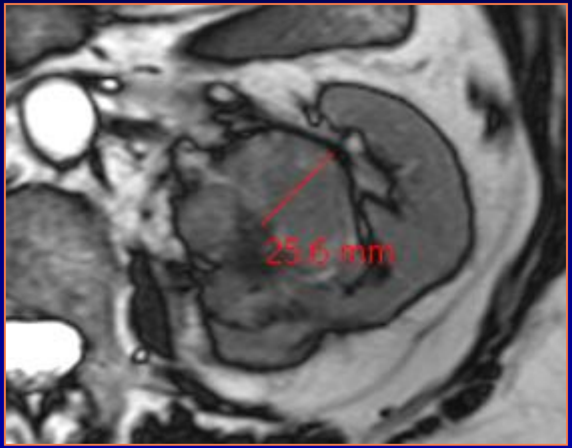
(*) **IF** the measurement is sufficiently *accurate* **AND** *precise*

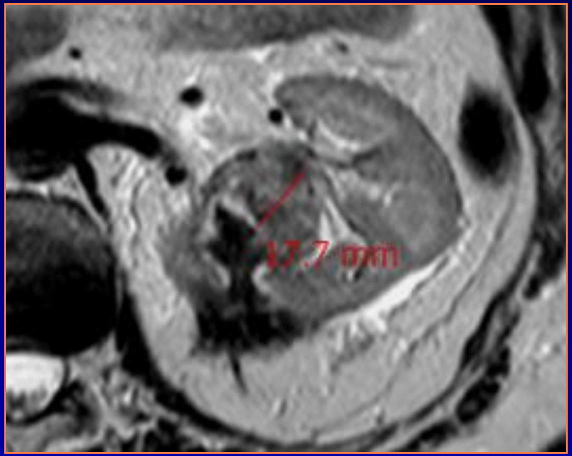
From S. Sourbron, Leeds

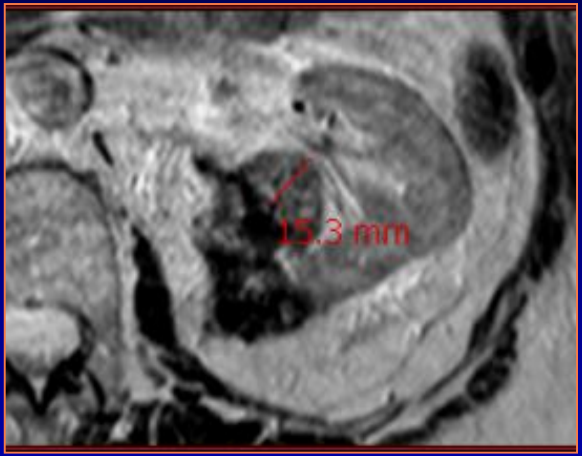
# Perfusion changes induced by therapy

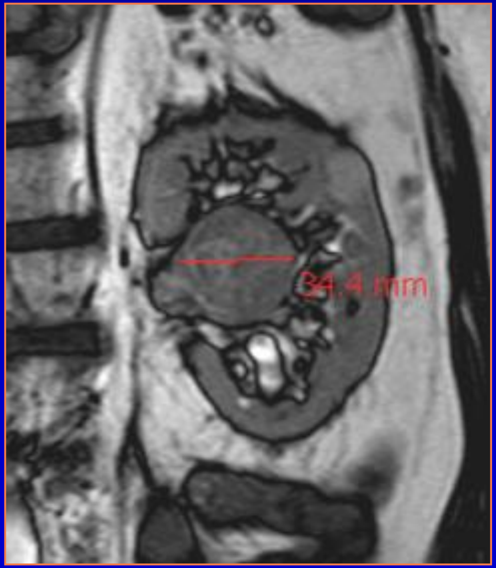
Renal cell carcinoma under sunitinib

**29-01-08** | **25-04-08** | **25-07-08**



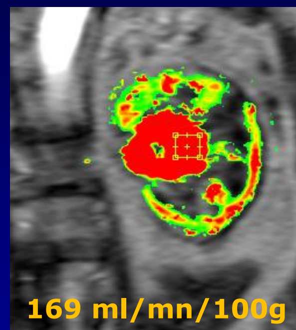



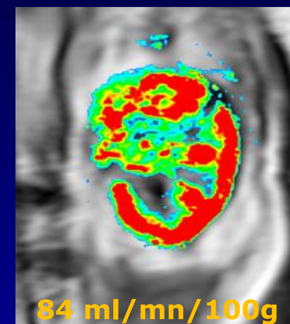


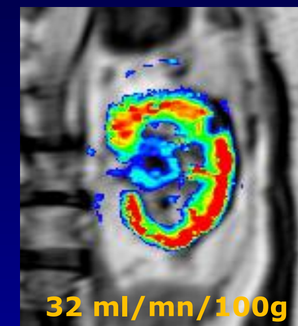
# Perfusion changes induced by therapy

29-01-08 | 25-04-08 | 25-07-08

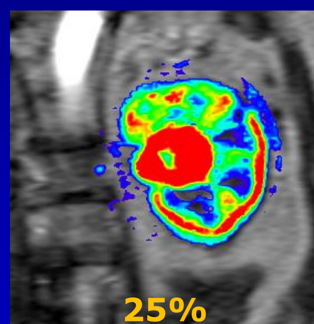
**Blood flow**

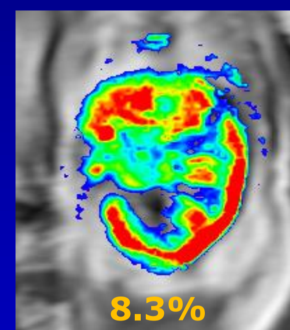


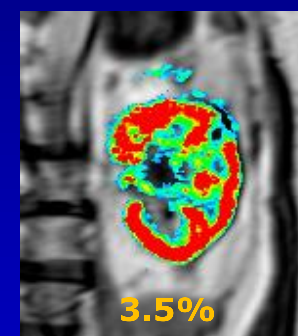



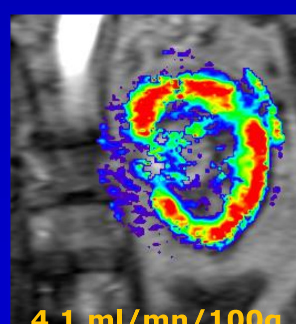

**Blood volume**

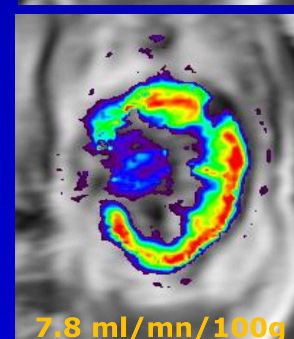


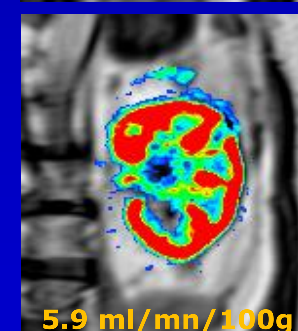




**K-trans**

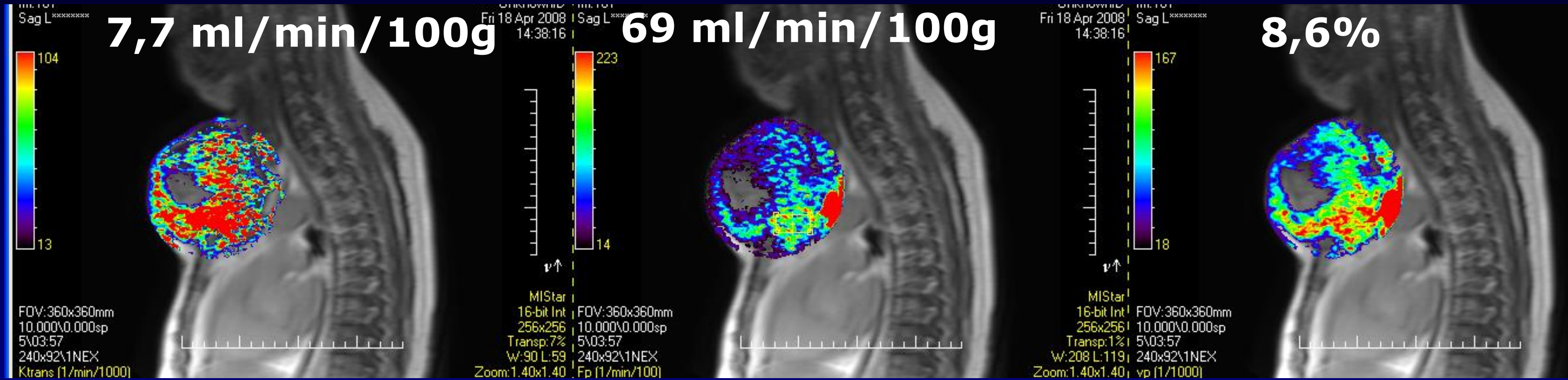


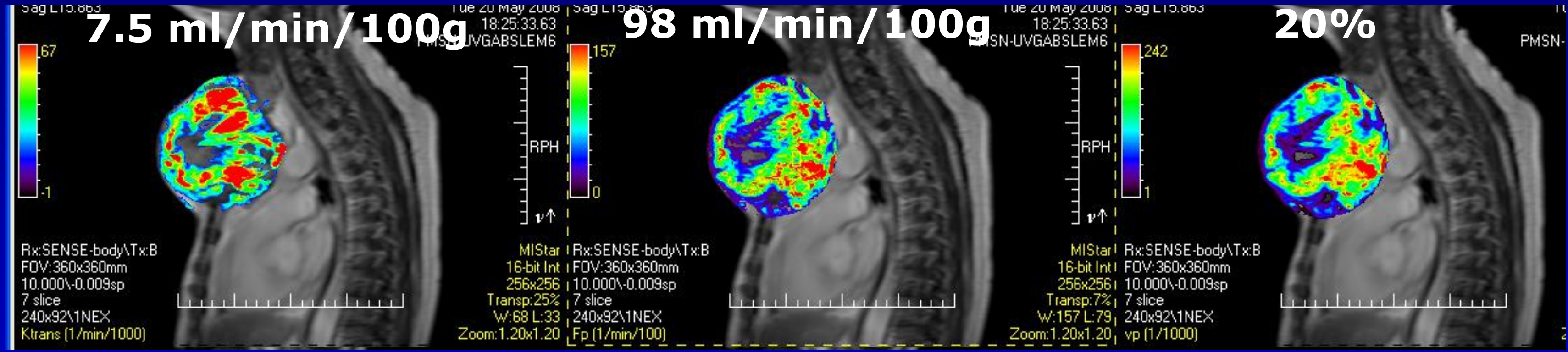



| | K-trans | Blood flow | Blood volume |
|---|---|---|---|

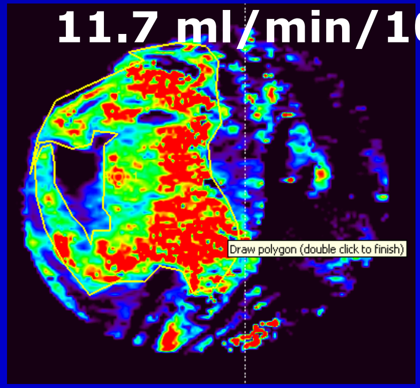
18-04

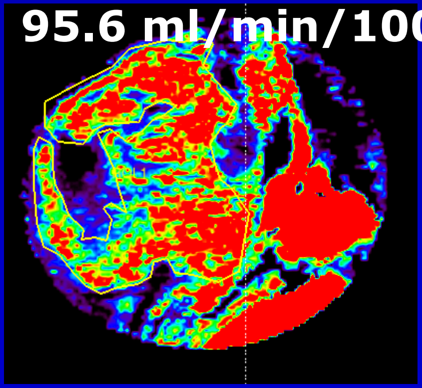


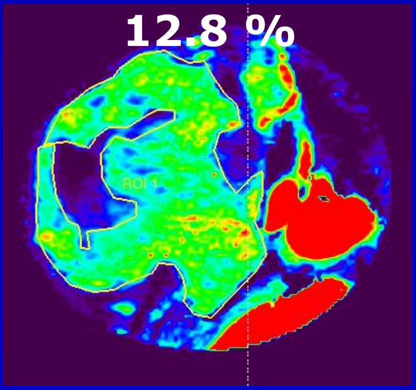

06-05




17-06

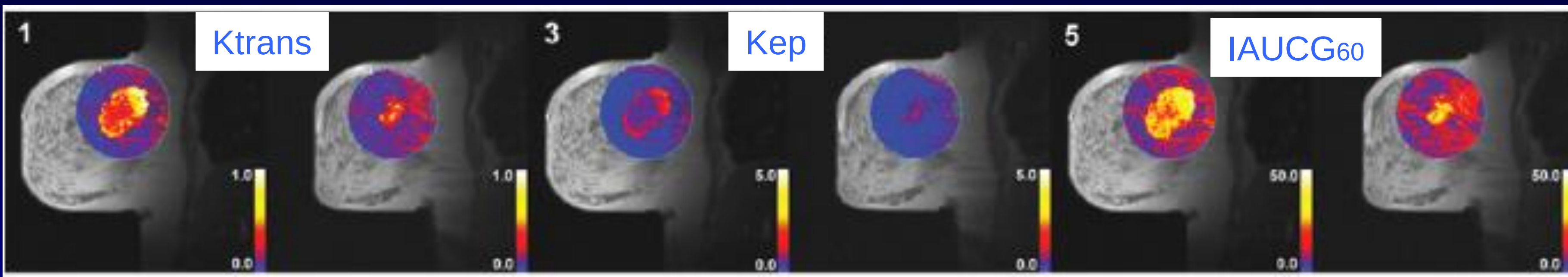


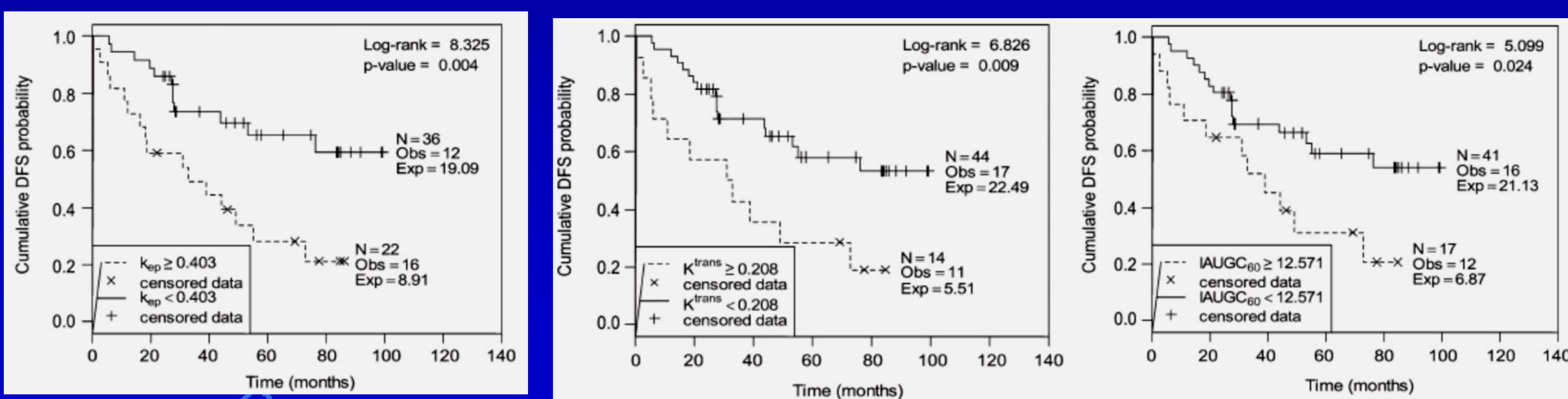



# Prediction of tumor response after 2 cycles

Breast cancer : DCE before and after 2 cycles neoadjuvant chemotherapy




- Higher posttreatment *K* trans (*P* = .048), and IAUGC 60 (*P* = .035) were significant predictors of worse disease-free survival.
- Higher posttreatment *K* trans ( *P* = .043), and IAUGC 60 ( *P* = .029), were predictive of worse overall survival ( *P* = .018).
- *K* trans remained an independent indicator of overall survival ( *P* = .038).




*Li SP et al, Radiology 2011;260:68*

# Prediction of tumor response after 1 cycle

- Phase-III randomized controlled trial (51pts) : sunitinib compared with interferon and sorafenib

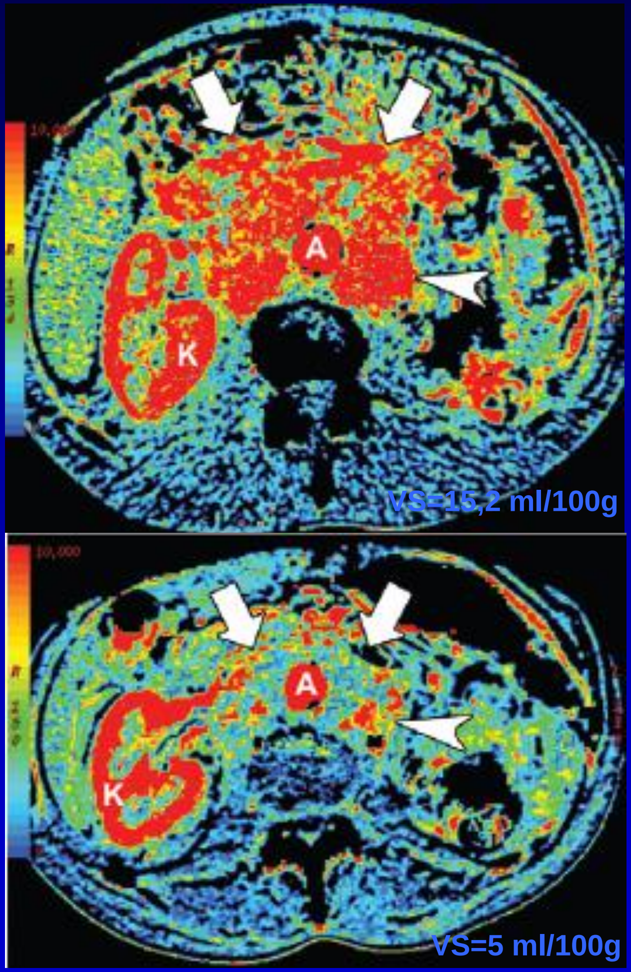
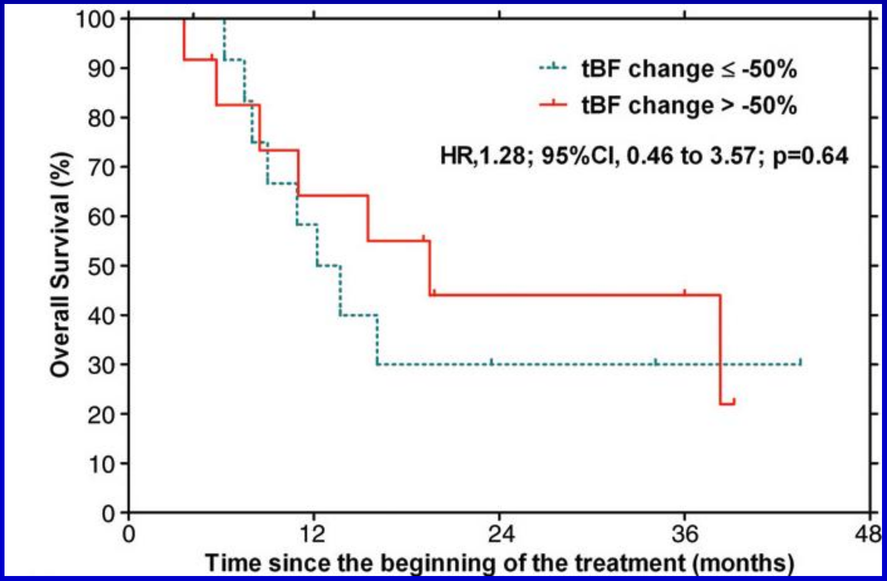



**Table 3**

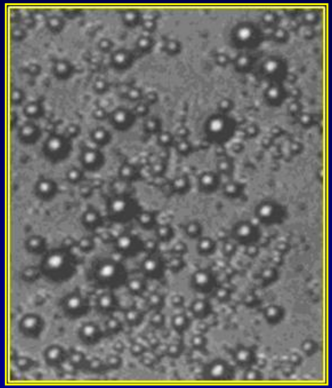
**Baseline Parameters in Patients Treated with Antiangiogenic Drugs according to Their Best Overall Response**

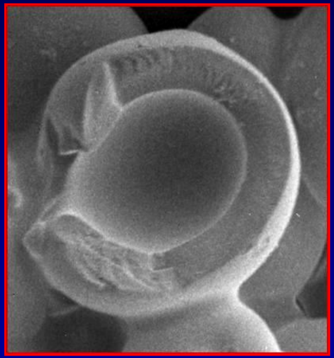
| Parameter | Responder (*n* = 10) | Stable (*n* = 20) | Nonresponder (*n* = 2)* | *P* Value† |
|---|---|---|---|---|
| TBF (mL/min/100 mL) | 245.3 (130.3, 453.5) | 119.5 (74.1, 224.3) | 162.5, 218.5 | .04 |
| TBV (mL/100 mL) | 15.5 (9.0, 24.5) | 8.2 (5.6, 14.9) | 9.2, 10.1 | .02 |
| Mean transit time (sec) | 5.6 (3.5, 9.5) | 9.0 (5.0, 13.6) | 5.1, 5.7 | .07 |
| Sum of longest diameters (mm) | 104.0 (76.0, 252.0) | 155.0 (91.0, 198.5) | 50.0, 96.0 | .18 |



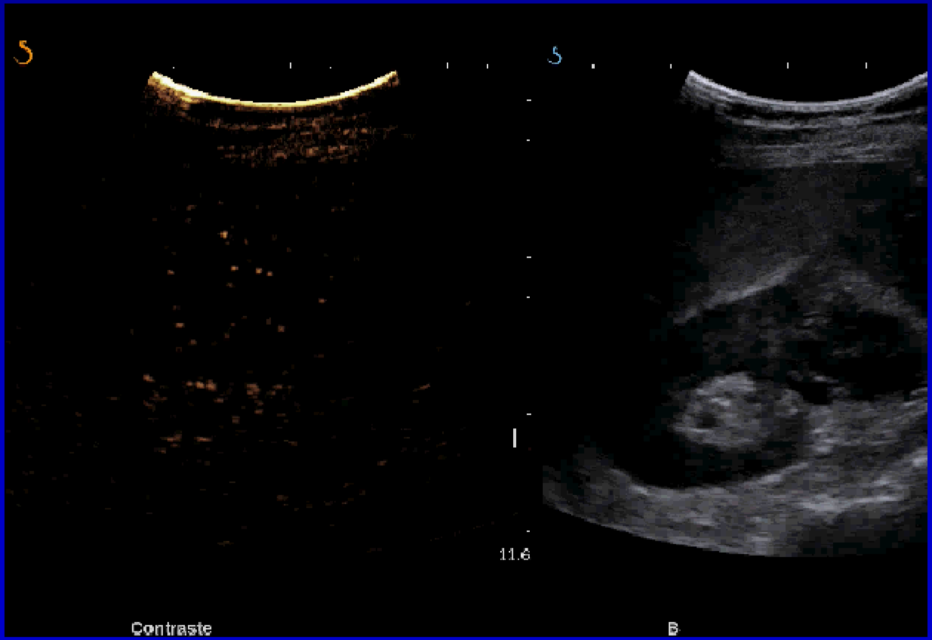

Fournier C, Radiology 2010;256:511

# DCE-US : principle



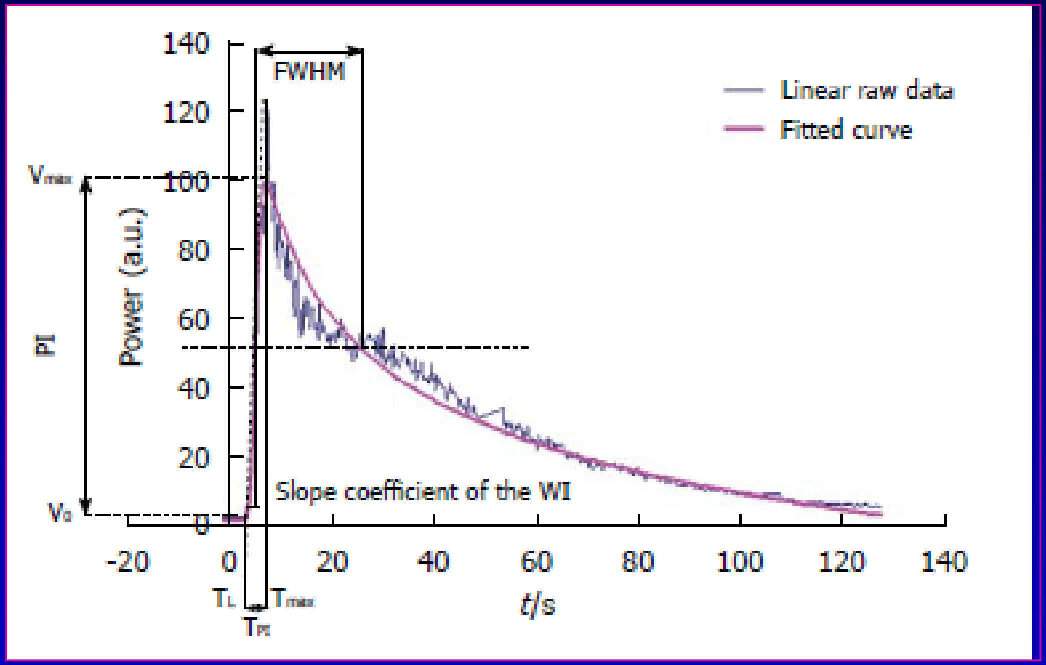


- Microbubbles (diameter 2-15 µm)
- Low density gas
- Intravascular distribution
- No linearity signal-[C]
- Attenuation with depth



# DCE-US : principle

- **Semi-quantitative analysis:** ***from « raw data »***




Parameters:

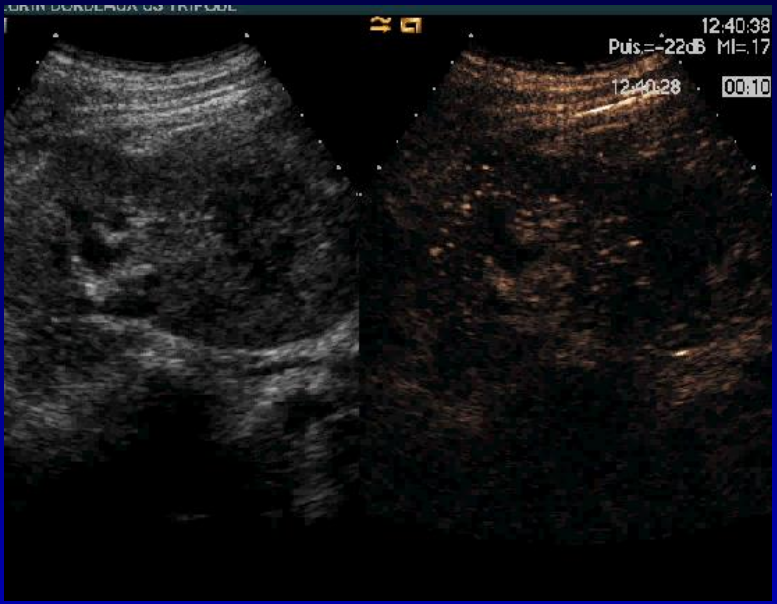
- Peak intensity
- Slope of wash-in
- Mean transit time
- Time to peak intensity
- Area under the curve
- Area under the wash-in
- Area under the wash-out

« The tumor perfusion quantification obtained from the raw linear data is different from that derived from the image data obtained after data compression. In the latter case, the quantification is derived from a sum of logarithms, which is different from the arithmetic mean and thus completely falsifies the results because the operation is nonlinear. »

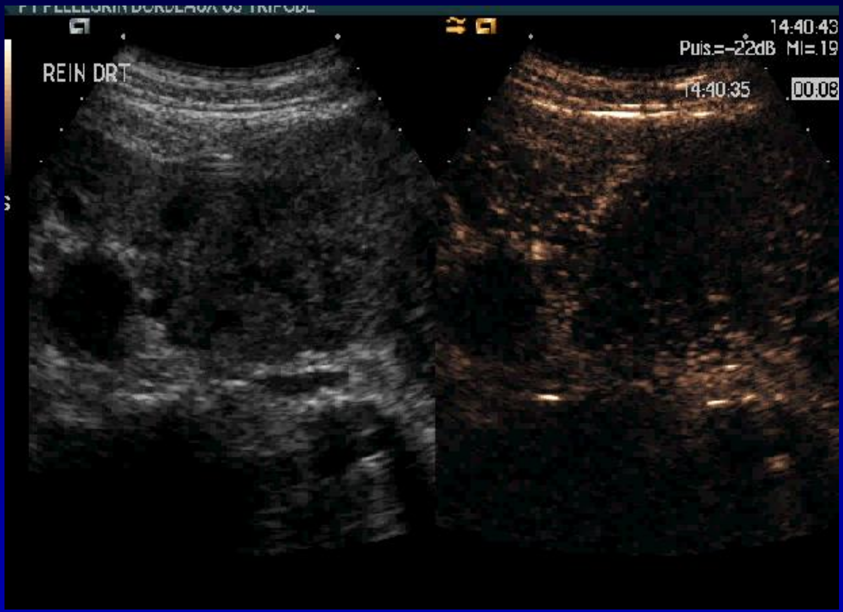
*Lassau N et al, Radiology 2010*

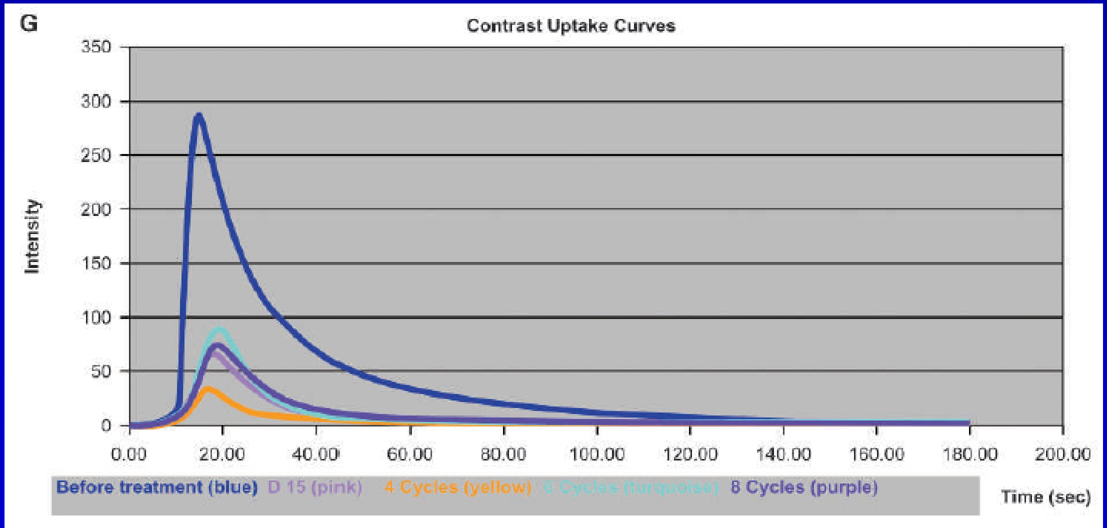
# DCE-US : tumor response

25-02-09




17-03-09

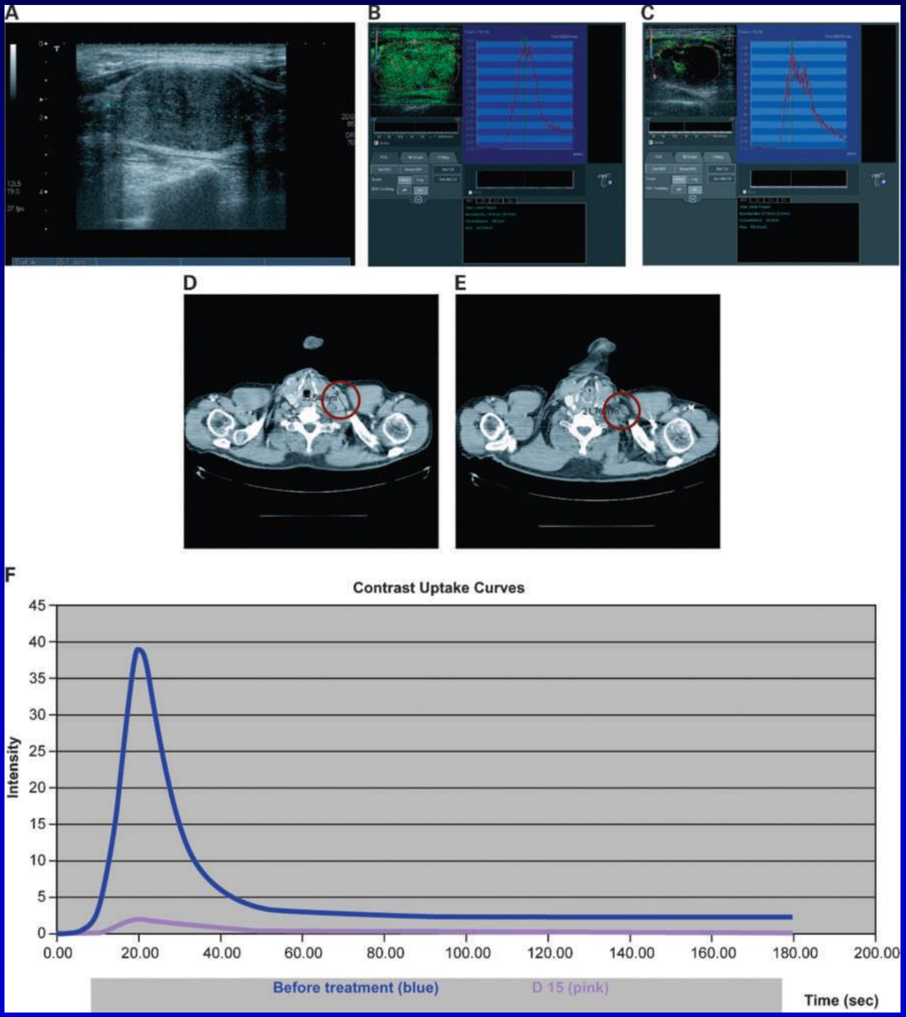


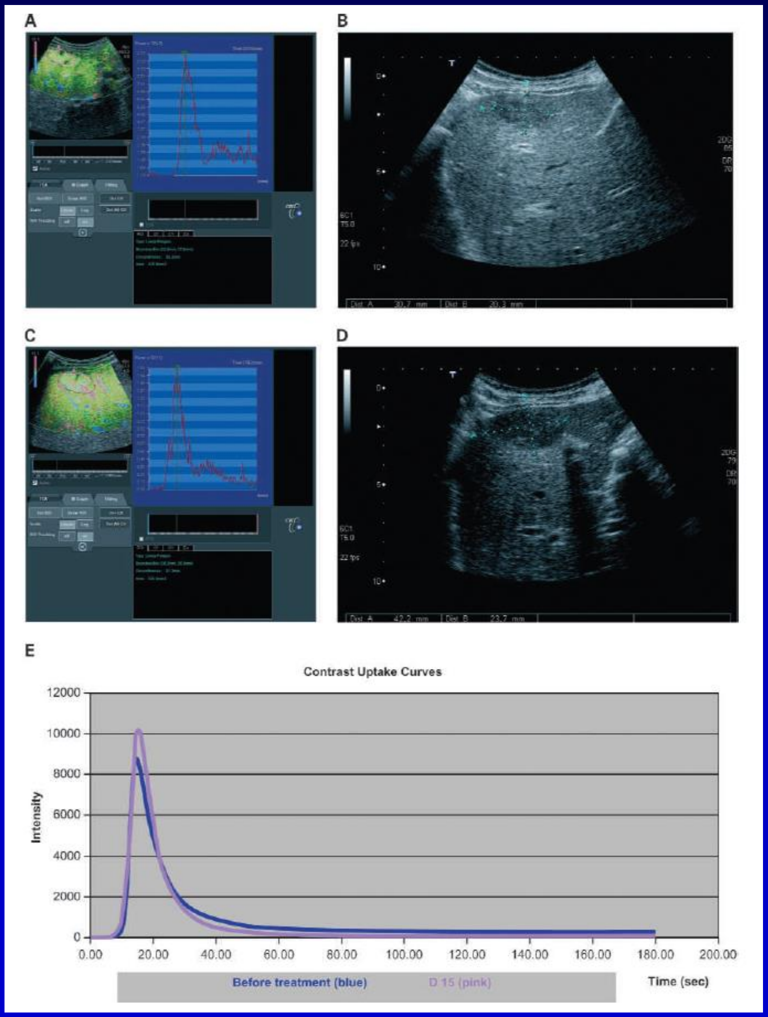
# DCE-US : tumor response

38 patients with sunitinib for metastatic renal cancer : **US between D0 & D15**

Responder



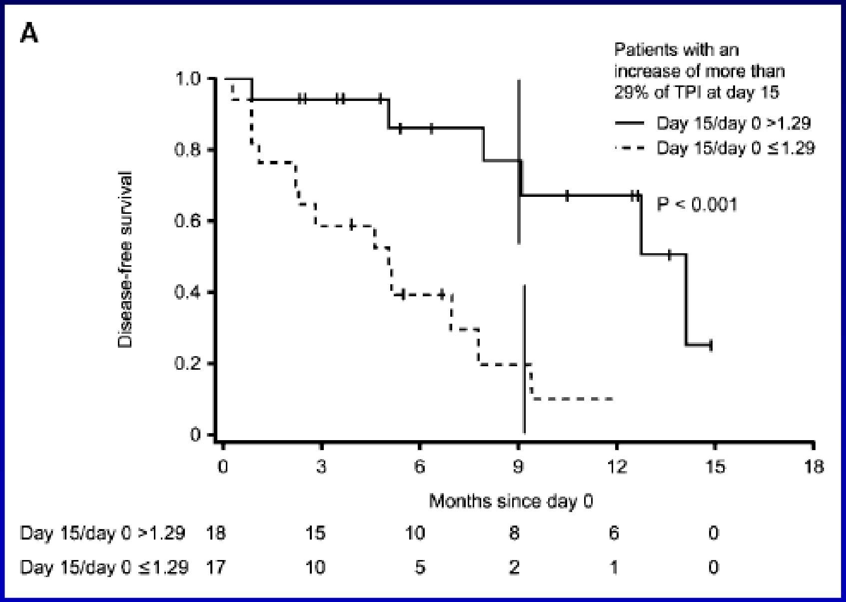

Non responder

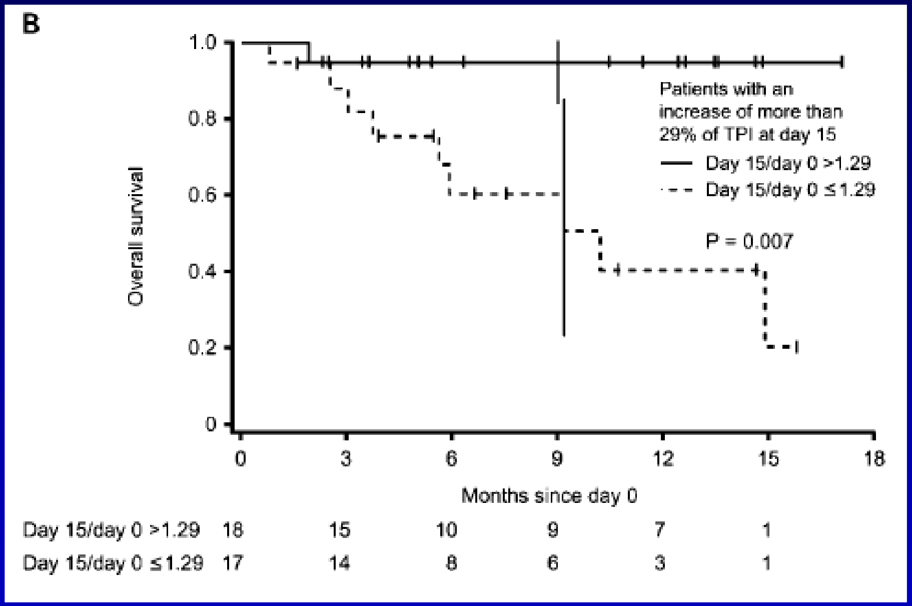



*Lassau N et al, Clin Cancer Res 2010*

# DCE-US : tumor response

38 patients with sunitinib for metastatic renal cancer : **US between D0 & D15**

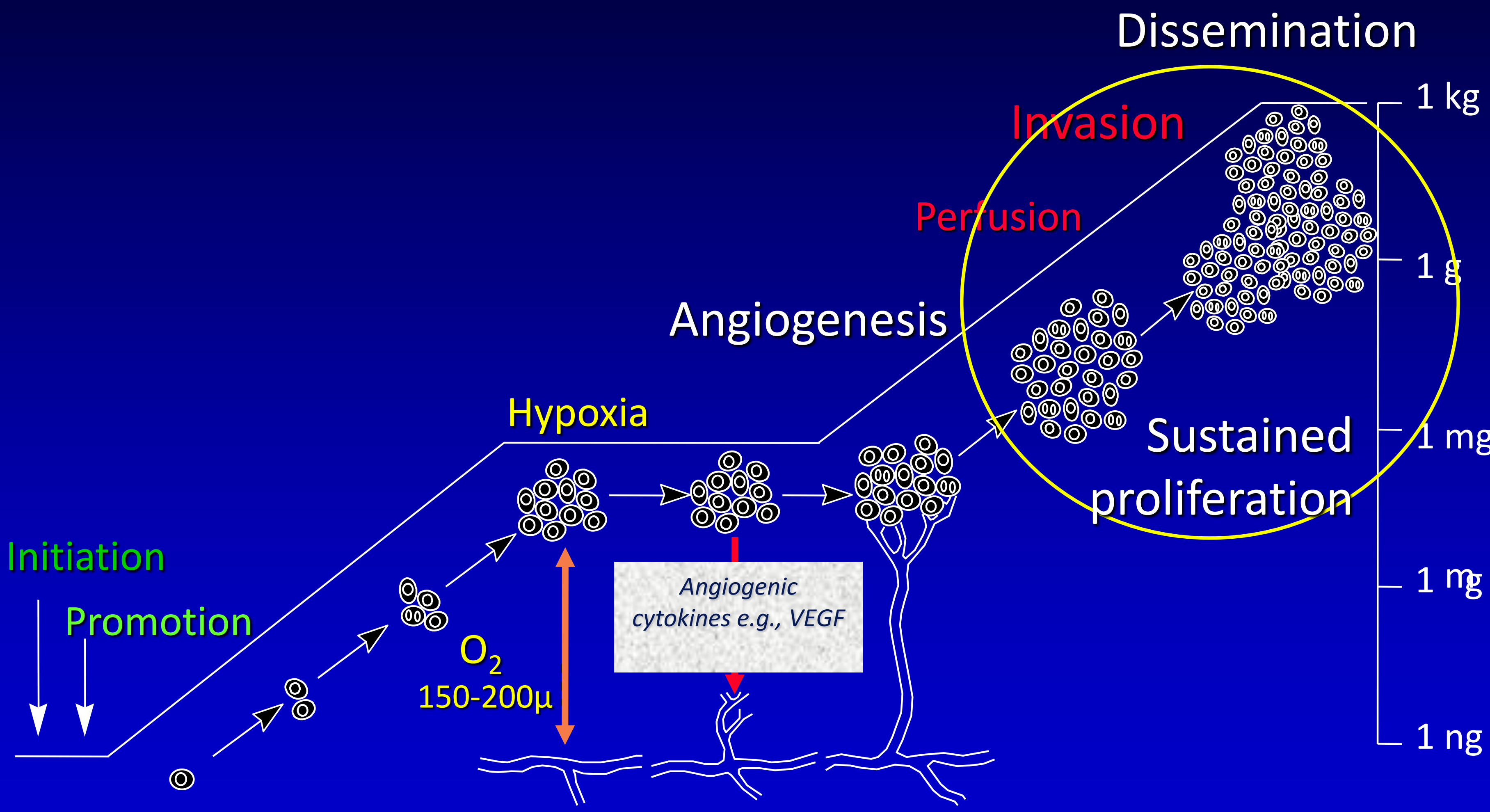



There is a correlation between functional parameters at D15 and RECIST criteria at 3 months

*Lassau N et al, Clin Cancer Res 2010*

# Key biological hallmarks




*Fidler IJ. Differentiation 2002; 70:498-505*
*Cairns R, et al. Mol Cancer Res 2006; 4:61-70*

*Courtesy of P Choyke, NIH, USA*

# Imaging the tumor microenvironment

| | | Oxygenation | Glycolysis | Acidification | Angiogenesis | Perfusion | Proliferation | Cell density | Apoptosis | Necrosis |
|---|---|---|---|---|---|---|---|---|---|---|
| PET | Nitroimidazoles (FAZA, FMISO…) | + | | | | | | | | + |
| | RDG | | | | + | | | | | |
| | FLT | | | | | | + | | | |
| | Annexin V | | | | | | | | + | |
| | FDG | | + | | | | | + | | |
| | Water, Inert gas | | | | | + | | | | |
| | Dynamic modelling | | | | | + | | | | |
| Non-PET | DCE-MRI (CT/US) | + | | | | + | | | | |
| | BOLD-MRI | + | | | + | | | | | |
| | Diffusion | | | | | + | + | + | + | + |
| | $^{1}$H & $^{31}$P-MRS | | | + | | | + | | | |

# Diffusion MRI – principle

Monoexponential fit

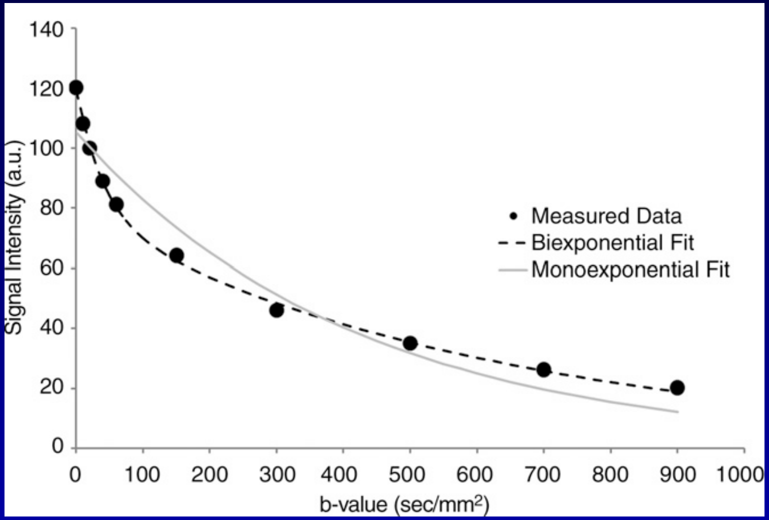
$$S_i = S_0 \times e^{-b_i \times \mathrm{ADC}_{tot}}$$

at least 2 b-values

Biexponential fit

$$S_i = S_0 \times \left[ (1 - F_P) \times e^{-b_i \times \mathrm{ADC}_D} + F_P \times e^{-b_i \times \mathrm{ADC}_P} \right]$$

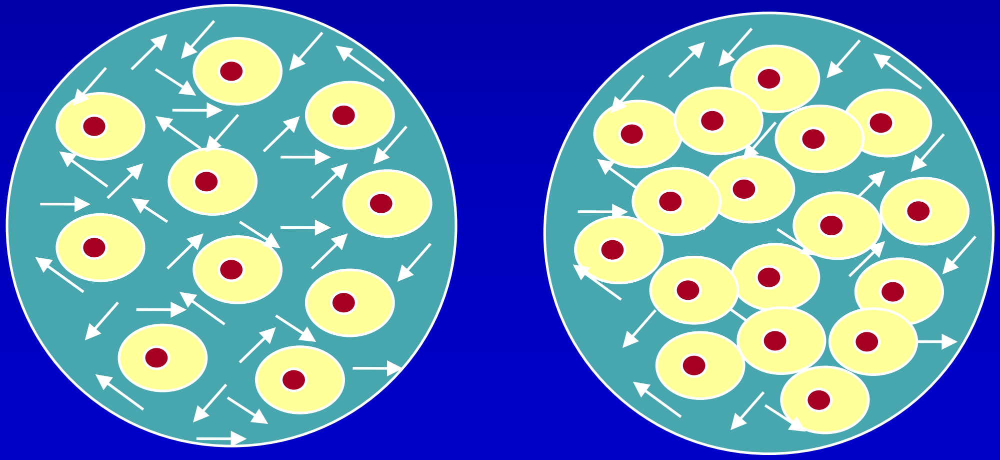
at least 4 b-values, best 10 : 0,10,20,40,60,150,300,500,700,900

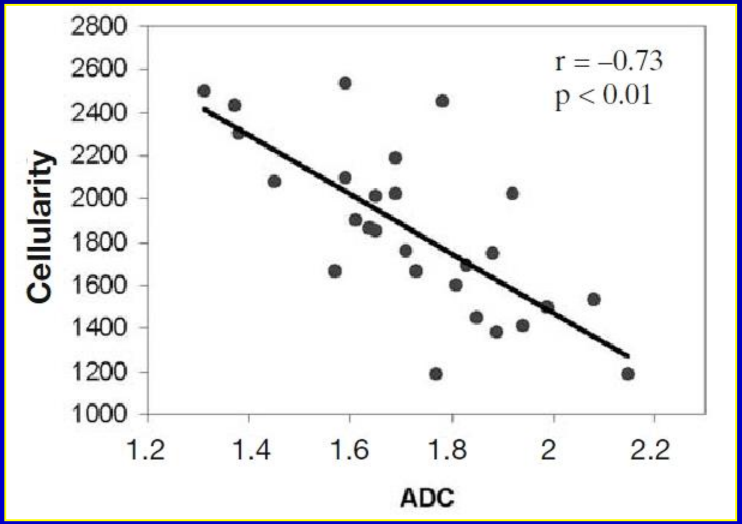



- Parameters with Mo-exp fit : $\mathrm{ADC}_{trace}$
- Parameters with Bi-exp fit :
  - $\mathrm{ADC}_D$ or $\mathrm{ADC}_{high}$ or Dt = pure or slow diffusion (with b>200 sec/mm$^2$)
  - $\mathrm{ADC}_{D*}$ ou $\mathrm{ADC}_{low}$ = perfusion-dependent or fast diffusion or pseudodiffusion
  - Fp = perfusion fraction

# Diffusion MRI – biological basis

- DW-MRI reflects on tissue architectural properties including cell size distributions & density, extracellular space tortuosity, nucleus-cytoplasm ratio, integrity of cellular membranes, extent of glandular tissues, fluid viscosity & perfusion
- ADC ( $x10^{-3}$ $mm^2/s$ or $\mu m^2/s$)

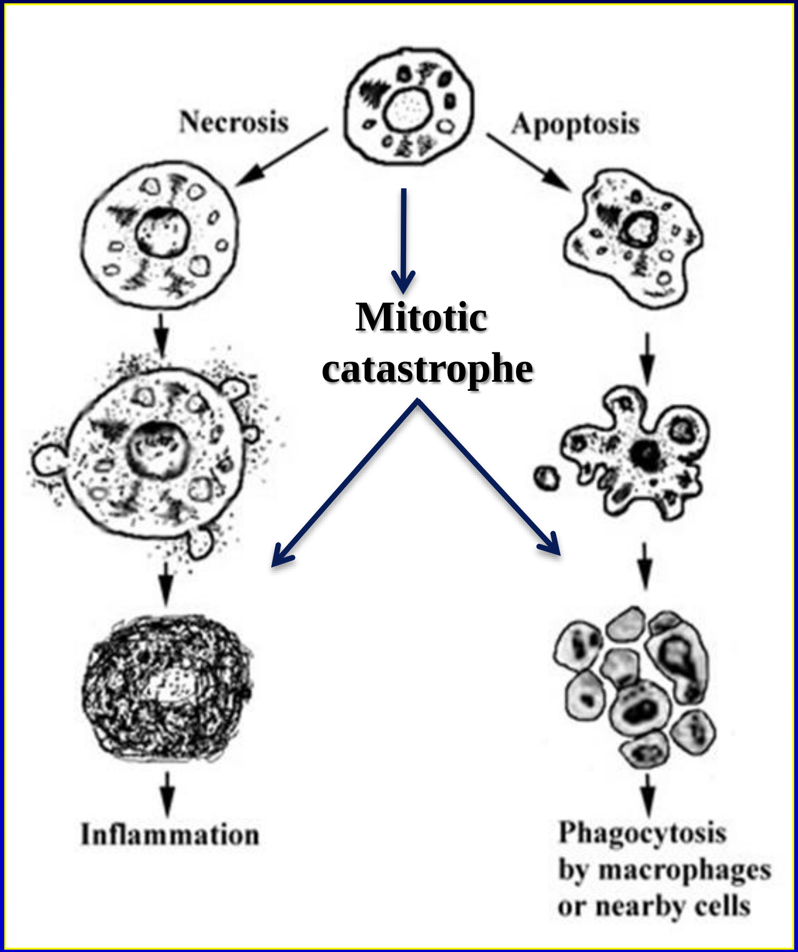





G. Manenti, et al. Malignant renal neoplasms: correlation between ADC values and cellularity at 3T. Radiol med (2008) 113:199–213.

# Diffusion changes induced by therapy

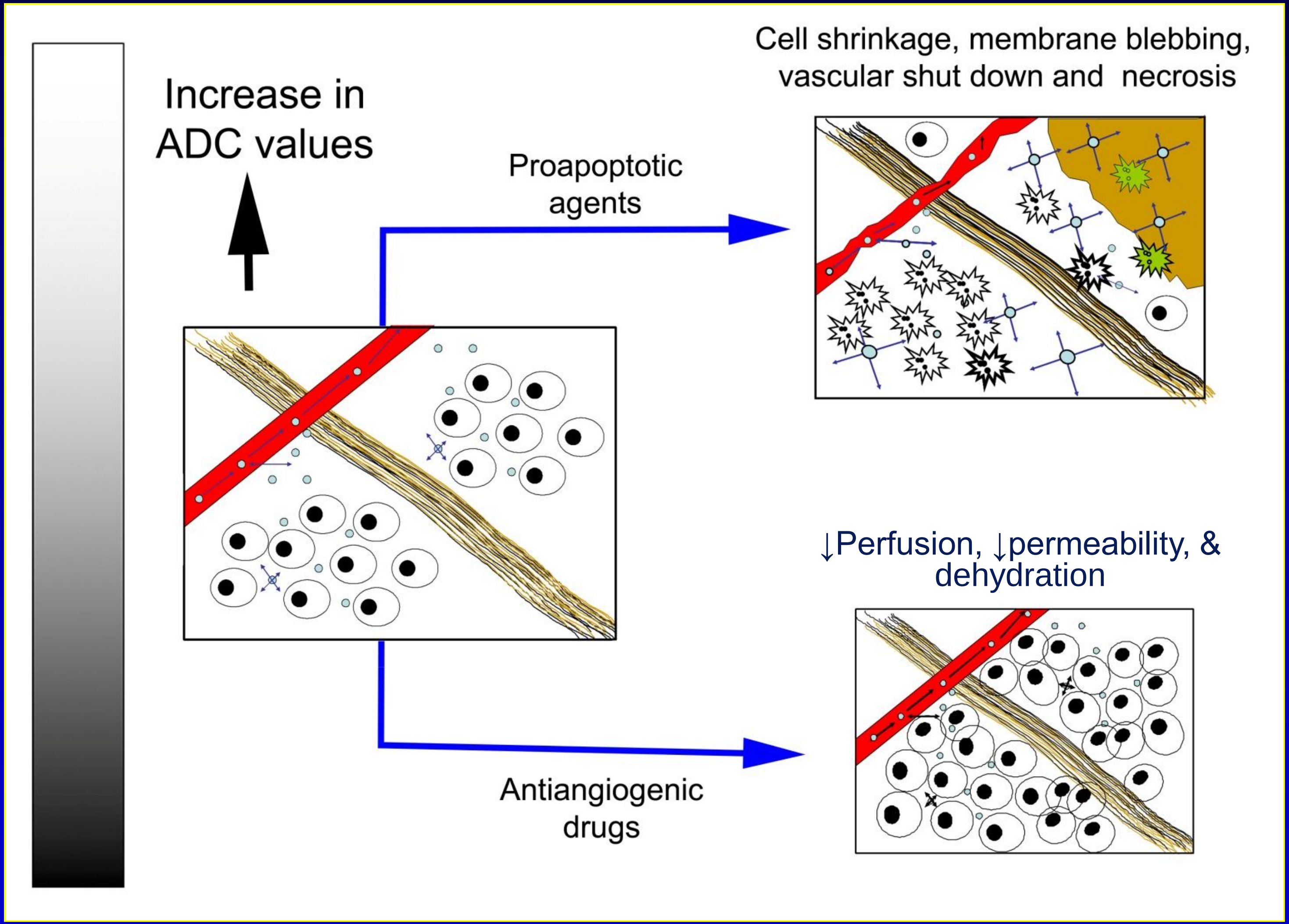
- Cancer cell death :
  - Necrosis
  - Apoptosis
  - The degree of ADC change depends on the balance between tumor cell killing, inflammation and proliferation




- Perfusion inhibition

Edinger AL, Thompson CB. Death by design: apoptosis, necrosis and autophagy. Curr Opin Cell Biol. 2004 Dec;16(6):663-9.

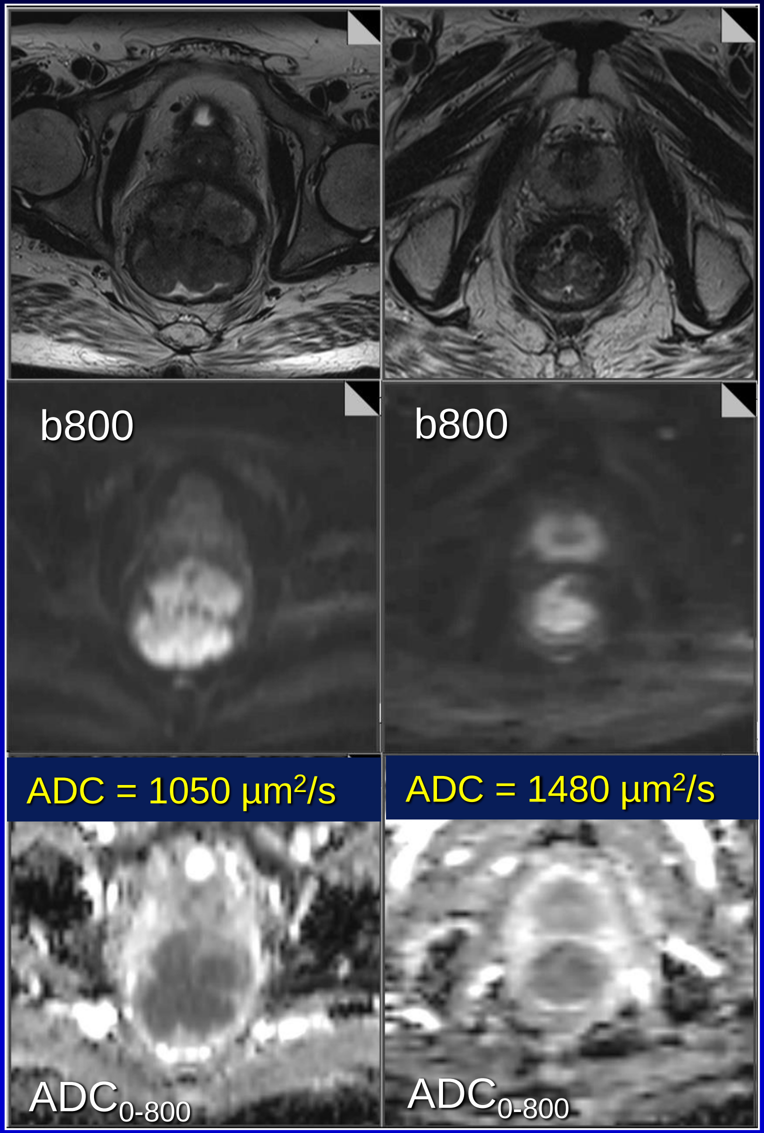
# Diffusion changes induced by therapy




Patterson DM, et al. Nat Clin Pract Oncol. 2008; 5(4):220-33.

# Diffusion changes induced by therapy

Rectal cancer response chemotherapy + RT (6/52) – increase in ADC values



Eur Radiol (2009) 19: 2728–2738
DOI 10.1007/s00330-009-1469-4

ONCOLOGY

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Rajesh Sinha
Pat Walicke
Martin O. Leach
Ian Judson
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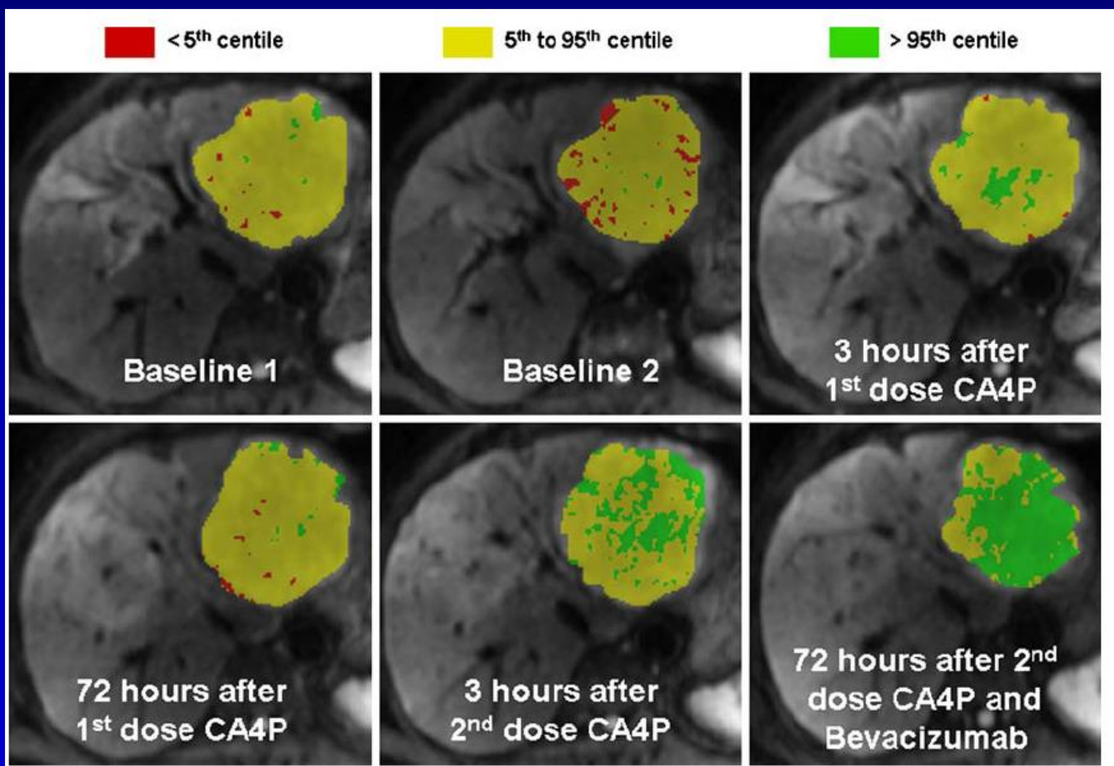
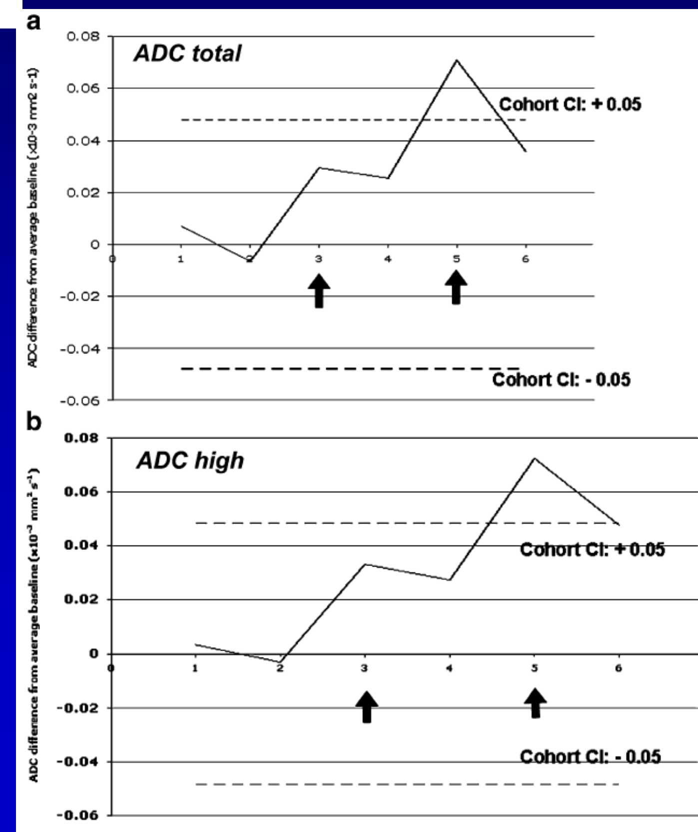
# Reproducibility and changes in the apparent diffusion coefficients of solid tumours treated with combretastatin A4 phosphate and bevacizumab in a two-centre phase I clinical trial



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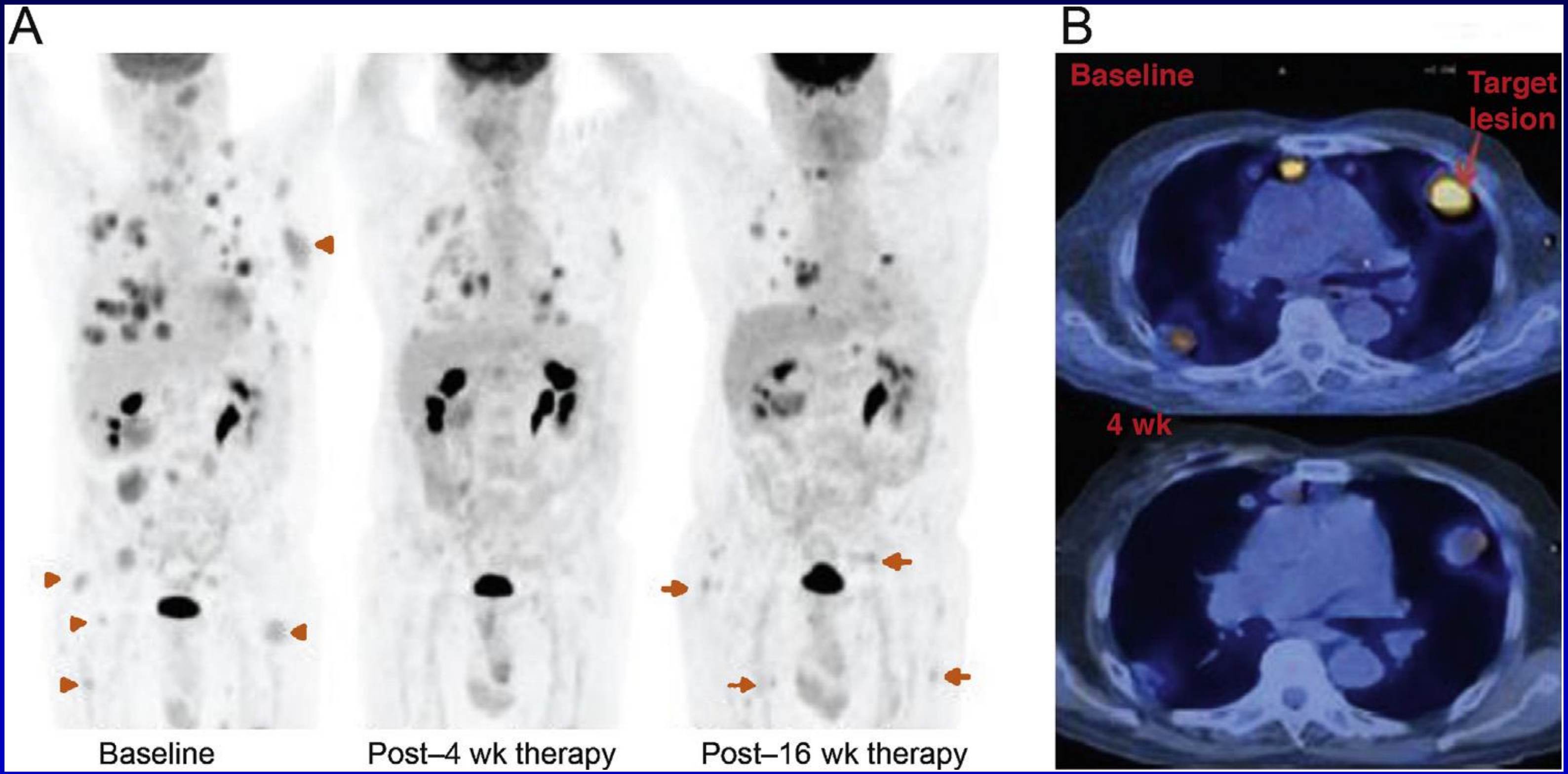
| | Dynamic modelling | | | | | + | | | | |
| **Non-PET** | DCE-MRI (CT/US) | + | | | | + | | | | |
| | BOLD-MRI | + | | | + | | | | | |
| | Diffusion | | | | | + | **+** | **+** | + | + |
| | $^{1}$H & $^{31}$P-MRS | | | + | | | + | | | |

# TEP-FDG




Primary clear cell RCC (ccRCC) tumours with lower SUV at baseline were more likely to respond to therapy

Khandani et al. Nucl Med Commun 2012, 33:967

**Table 2 – A clinician's viewpoint of the practical considerations of currently available imaging methods for response assessment to targeted agents in renal cell carcinoma**

| | CT | DCE-CT | DCE-MRI | DCE-US | PET |
|---|---|---|---|---|---|
| Advantages* | • Availability<br>• Straightforward quantification<br>• Long-term experience | • Availability<br>• Straightforward quantification<br>• Predictive of early response | • No radiation<br>• Can be done without contrast agent injection (ASL)<br>• Multiparametric evaluation (DCE, DWI)<br>• Predictive of early response<br>• Potentially predictive of OS | • Cost<br>• No radiation<br>• Simple standardised quantification using bolus injection<br>• Largest clinical data set of functional imaging with strong evidence<br>• No renal failure contraindication because of elimination by lung<br>• Up to six injections feasible if necessary at each examination | Imaging of metabolic activity |
| Disadvantages* | • Radiation dose<br>• Limited in patients with renal insufficiency<br>• Not predictive for early response | • Radiation dose 10–20% higher than standard CT<br>• Limited in patients with renal insufficiency<br>• Predictive value for OS not yet established | • No standardised acquisition<br>• Quantification more complex<br>• Cost<br>• Availability<br>• Predictive value for OS not yet validated in larger studies<br>• Limited experience | • Limited availability<br>• Acquisition window restricted to 10 cm × 15 cm during wash-in and wash-out<br>• Not a whole-body technique<br>• Bone, lung, and brain not evaluable | • Availability<br>• Cost<br>• Radiation dose<br>• Low sensitivity<br>• Very limited experience<br>• Data not validated |

ASL = arterial spin labelling; CT = computed tomography; DCE = dynamic contrast-enhanced; DWI = diffusion-weighted imaging; MRI = magnetic resonance imaging; OS = overall survival; PET = positron emission tomography; US = ultrasound.

* Methodology, ease of use, availability of equipment, experience to date, and costs were considered.

Bex et al. Eur Urol 2014, 65:766

# Conclusion

- For prediction and follow-up of tumor response, we need to take into account the physiologic characteristics of the tumors and the type of therapy
- The link between functional imaging techniques and these physiologic parameters is sometimes intuitive
- Mathematical models do not always reflect physiology
- Harmonization of protocols and validation of these biomarkers is essential
- Integration of these criteria into biostatistical and biomathematical models is also essential