ECHODOPPLER AS A CARCINOMATOSIS PROGNOSIS MARKER – PREDICTIVE MARKER OF HIGH TUMOR PROLIFERATION OR ANGIOGENESIS

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PLAN

1. Assessment of tumor response
2. Functional anatomy
3. Hemodynamics
4. Application to peritoneal carcinomatosis (PC)
    1. Pseudomyxoma peritonii (PMP)
    2. Ovarian cancer PC

1. ASSESSMENT OF TUMOR RESPONSE

ASSESSMENT OF TUMOR RESPONSE

RECIST 1.1 criteria is recommended for the monitoring of the tumor response of solid tumors

Response	Definition
Complete Response (CR)	All non-nodal TLs disappeared; all lymph nodes short axis <10 mm
Partial Response (PR)	SOD decreased ≥ 30% from baseline
Progressive Disease (PD)	SOD increased ≥ 20% from nadir and the 20% has absolute increase ≥ 5 mm
Stable Disease (SD)	Not PR nor PD
Not Evaluable (NE)	Cannot determine target lesion response

ASSESSMENT OF TUMOR RESPONSE

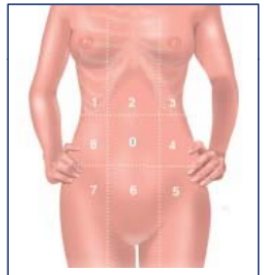
- RECIST 1.1 criteria are limited in the setting of PC
  - By the size of the implants
  - Almost exclusive peritoneal location
  - Do not take into account the resectability
  - Do not take into account the functional / scar appearance of the implants

- Peritoneal Carcinomatosis Index (PCI)
  - No size limit
  - Resectability
  - **No functional criteria**

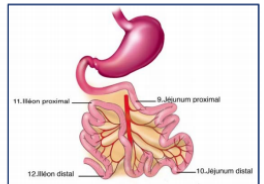
Régions abdomino-pelviennes prises en compte pour le calcul du score PCI [1,2]

0 - Central	Incision médiane, grand épiploon, côlon transverse
1 - Hypochondre droit	Glisson du lobe droit, péritoine diaphragmatique de la coupole droite, espace rétro-hépatique droit
2 - Épigastre	Graisse épigastrique, lobe gauche du foie, petit épiploon, ligament falciforme
3 - Hypochondre gauche	Péritoine diaphragmatique de la coupole gauche, rate, queue du pancréas, faces antérieure et postérieure de l'estomac
4 - Flanc gauche	Côlon gauche, gouttière pariéto-colique gauche
5 - Fosse iliaque gauche	Côlon sigmoïde, paroi pelvienne gauche en dehors du sigmoïde
6 - Pelvis	Utérus, trompes, ovaires, vessie, cul de sac de Douglas, recto-sigmoïde
7 - Fosse iliaque droite	Paroi pelvienne droite, cæcum, appendice
8 - Flanc droit	Côlon ascendant, paroi pelvienne et abdominale droite

1. Sugarbaker. 1995 ; 2. Chéreau. 2010.



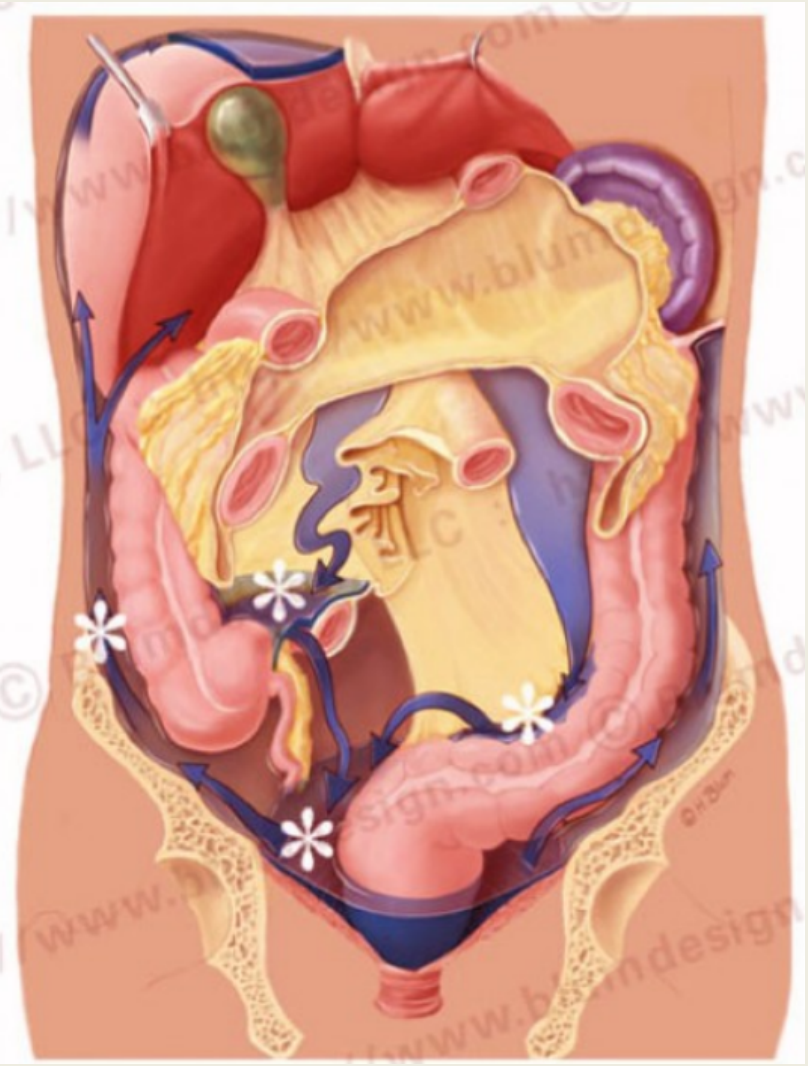
9 quadrants abdomino-pelviens
numérotés de 0 à 8 dans le sens des aiguilles d'une montre en partant de la zone contenant le nombril

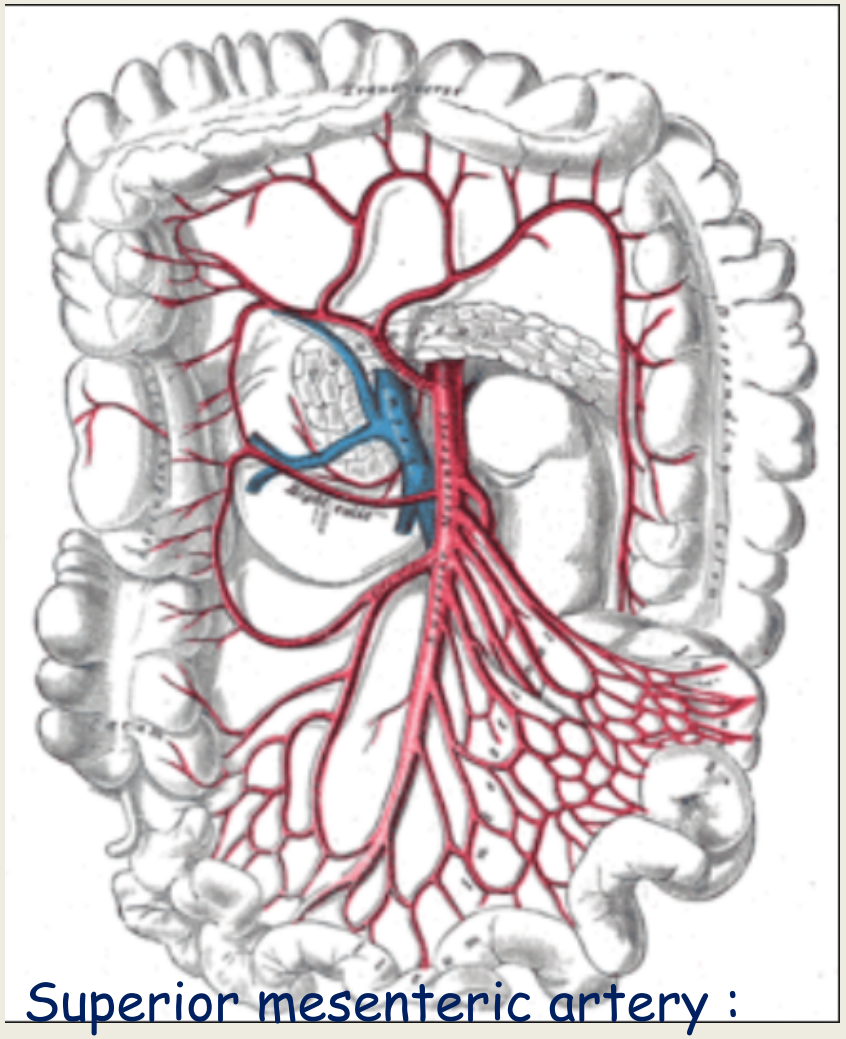


4 segments de l'intestin grêle

2. FUNCTIONAL ANATOMY

FUNCTIONAL ANATOMY

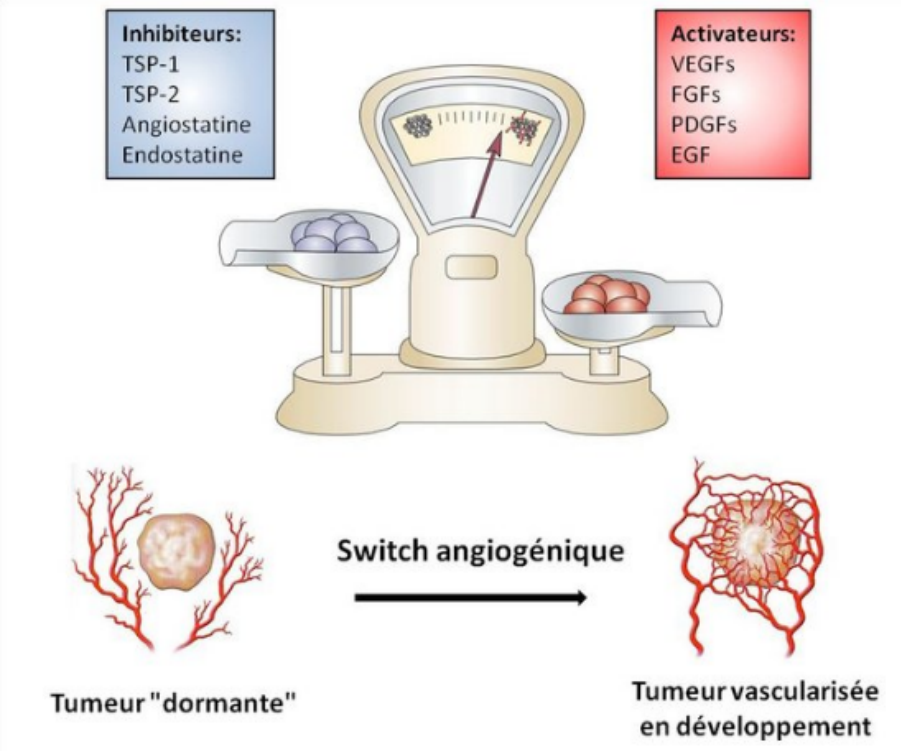




Superior mesenteric artery : (SMA)

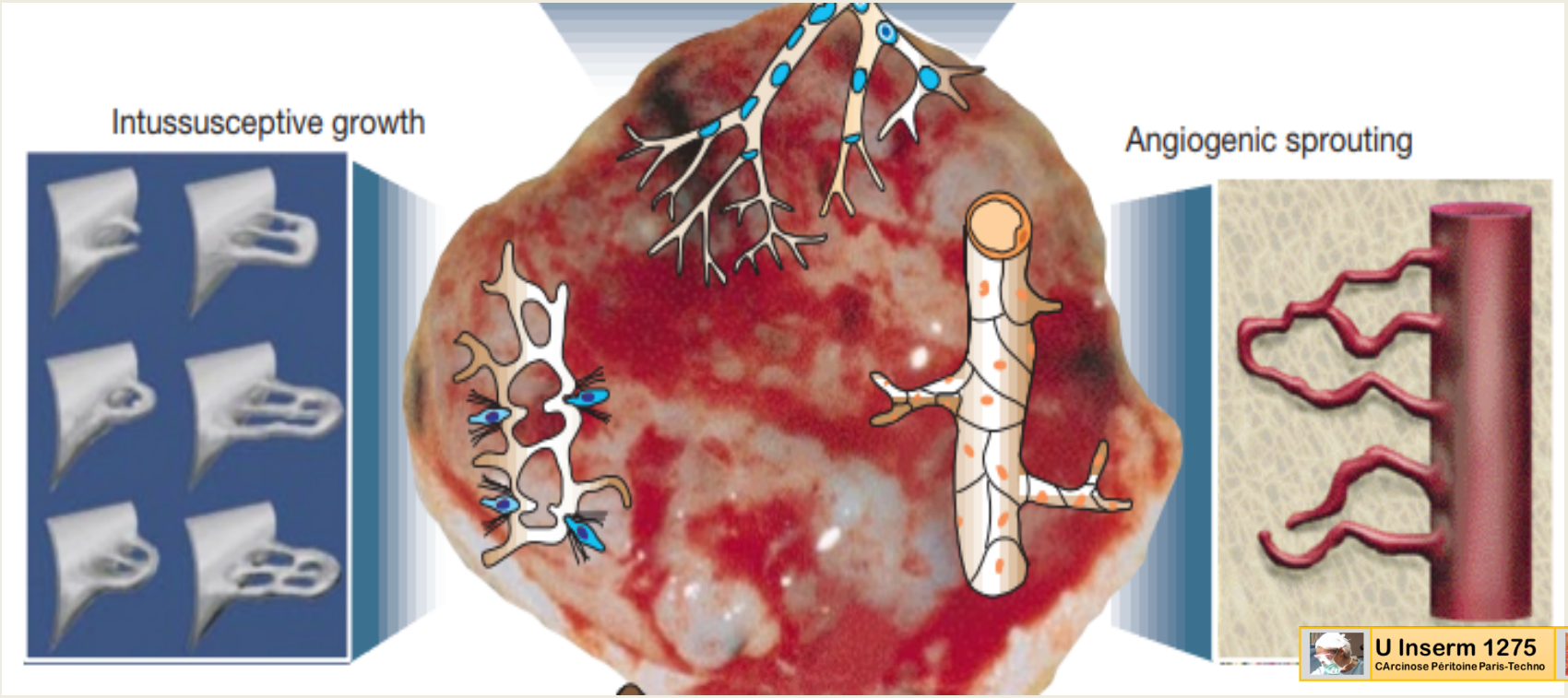
FUNCTIONAL ANATOMY

Critical mass (> 2mm^3): stimulation of the secretion of pro-angiogenic factors = "angiogenic switch"



FUNCTIONAL ANATOMY

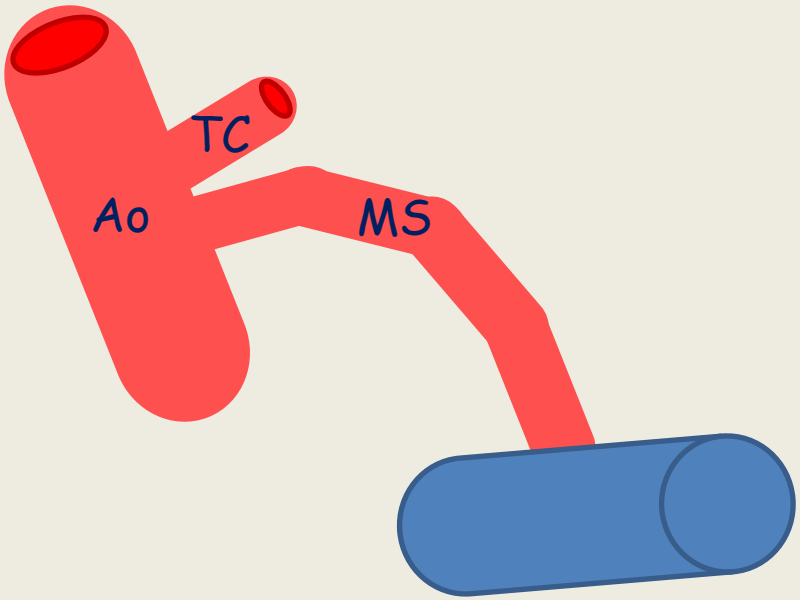
Angiogenesis by sprouting or by intussusception contributes to the creation of a neo-formed vascular network



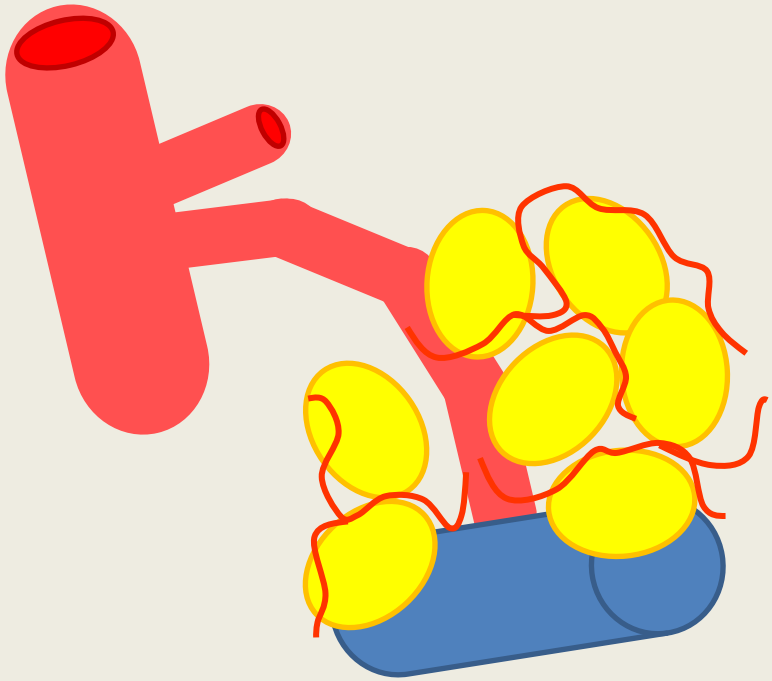
FUNCTIONAL ANATOMY

Poor quality tumor neoangiogenesis, hyperpermeable and made of arteriovenous shunts.

Healthy subjects



PC implants



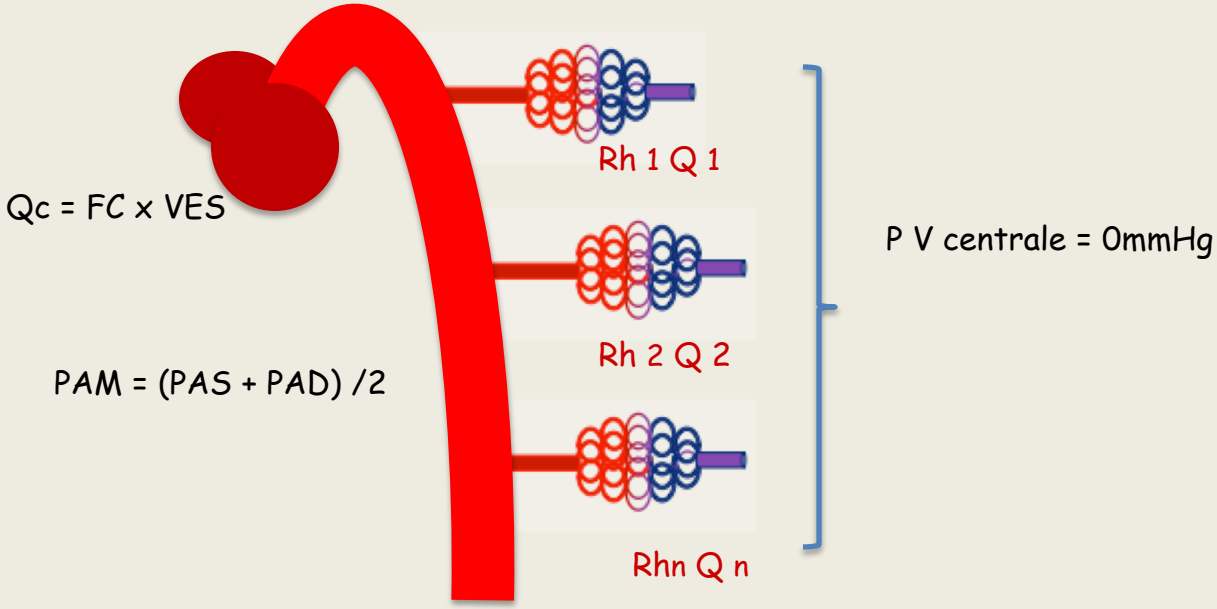
Angiogenesis is associated to tumor growth and is responsible for an **expansion of its microvascular bed**.

3. HEMODYNAMICS

HEMODYNAMICS

- The perfusion pressure (ΔP mmHg) of organs connected in parallel is identical to the BP and kept constant
  - Blood flow: Q (ml / s)
  - The level of local hemodynamic resistance: Rh
- Interact to keep it constant

$$\Delta P = Q.Rh$$



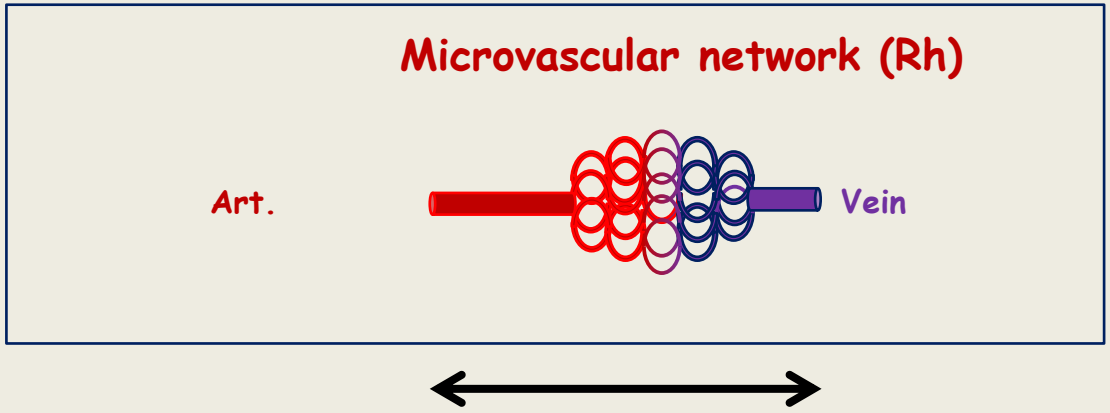
HEMODYNAMICS

The **hydraulic resistance** (Rh) (Poiseuille's law) depends from

- Length of vessel (L)
- Liquid viscosity (η)
- The radius of the vessel (R)

$$Rh = \frac{8\eta L}{\pi R^{\wedge}4}$$

Normal vascular bed



 = constant

L = constant

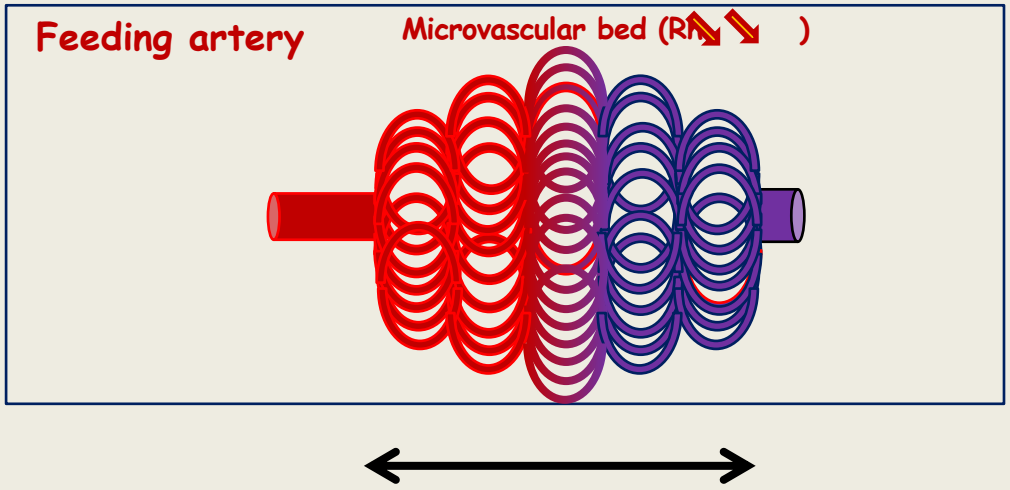
HEMODYNAMICS

The **hydraulic resistance** (Rh) (Poiseuille's law) depends from

- Length of vessel (L)
- Liquid viscosity (η)
- The radius of the tube considered (R)

$$Rh = \frac{8\eta L}{\pi R^{\wedge}4}$$

Neoangiogenesis



 = constant

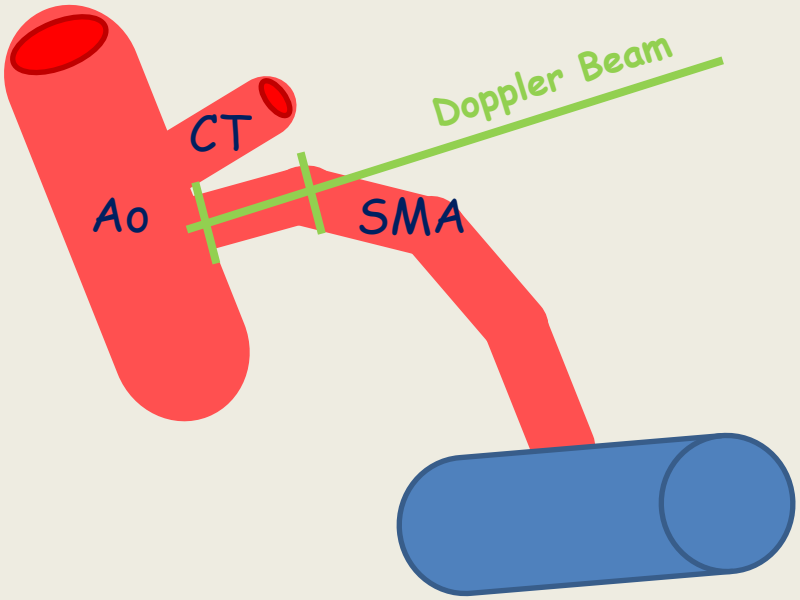
R =

L = constant

Rh =

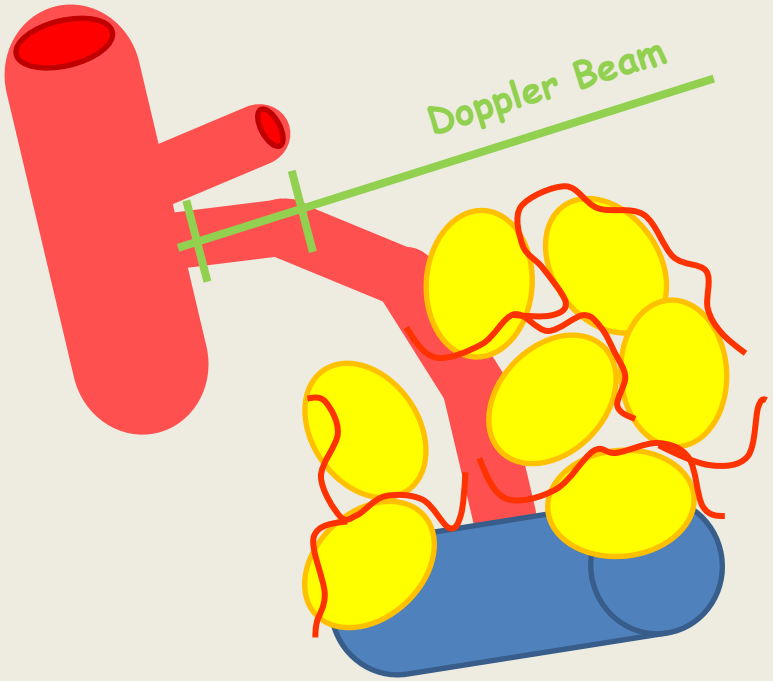
HEMODYNAMICS

Healthy subjects



$$\Delta P = Q.Rh$$

PC implants



$$\Delta P_{tumor} = Q_{tumor}.Rh_{tumor}$$

HEMODYNAMICS

- To increase BFVol, the system must either increase the **BFVel** or the **diameter** of the feeding vessel (vascular remodeling)

$$Q = \pi \left(\frac{D}{2}\right)^2 . V$$

↑ or ↑

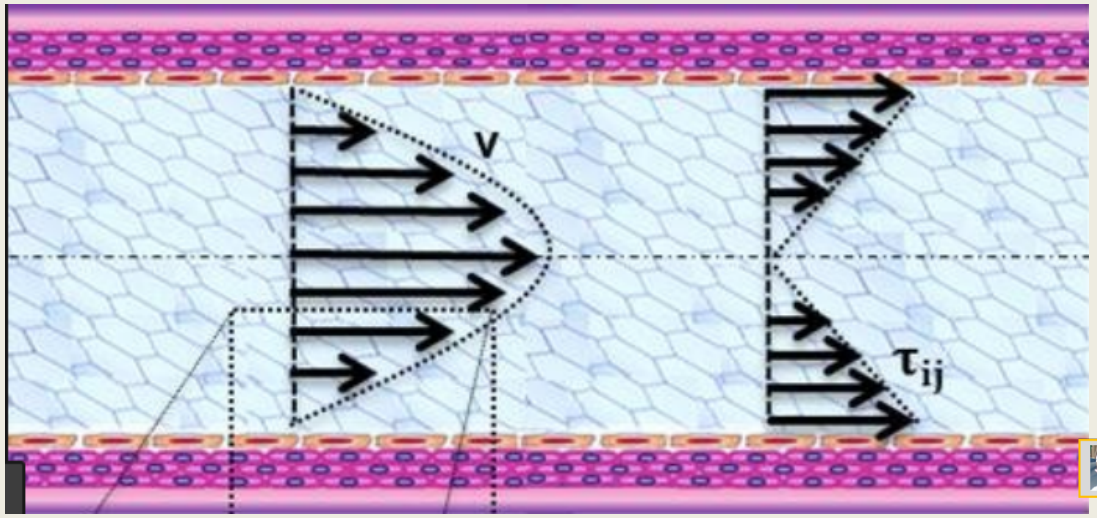
HEMODYNAMICS

- At first, the diameter does not have time to change.
- There is therefore an **increase** in **BFVel**

$$Q = \pi \left(\frac{D}{2}\right)^2 . V$$

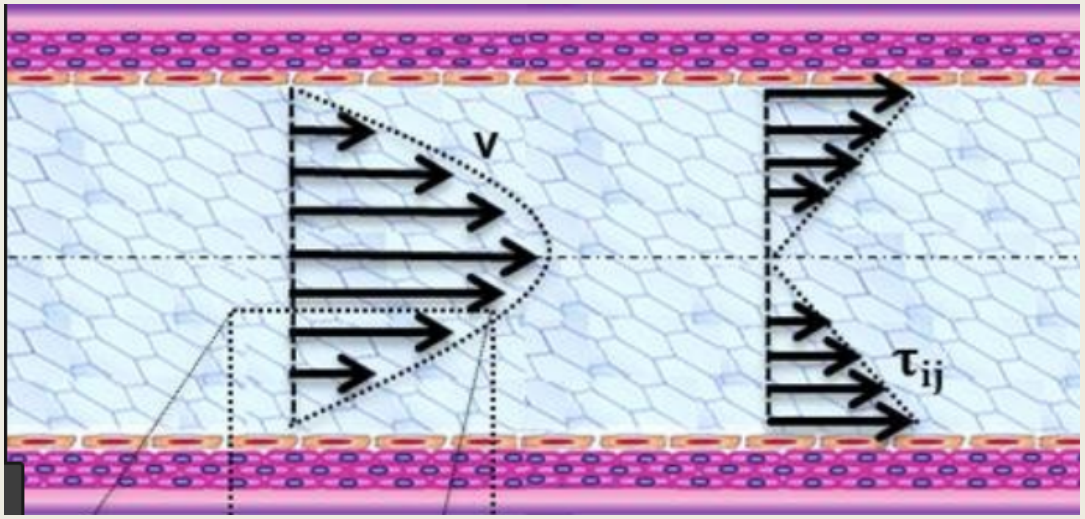
HEMODYNAMICS

The increase in BFVel is responsible for increasing shear forces (**wall shear stress**) at the interface blood / vascular endothelium



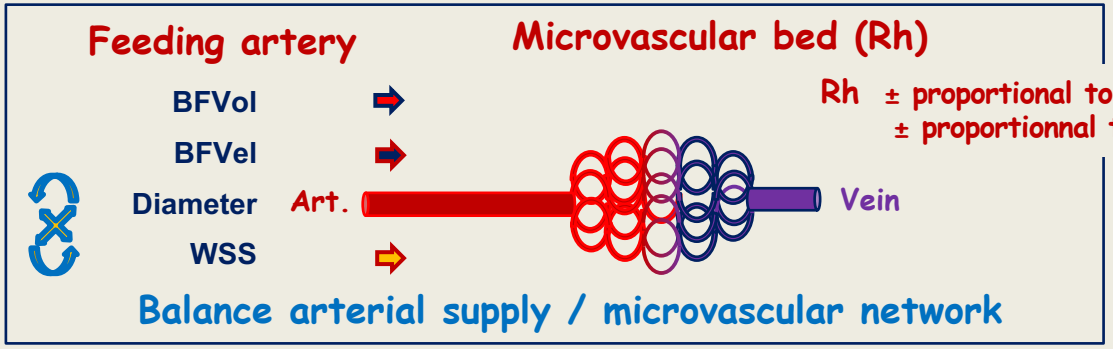
HEMODYNAMICS

Increasing the WSS stimulates cell proliferation (NO pathway) resulting in the **increase in diameter of the feeding vessel**



WSS = 8.μ. V / D

Normal vascular bed



Rh ± proportional to microvascular density
± proportionnal to arterial tone

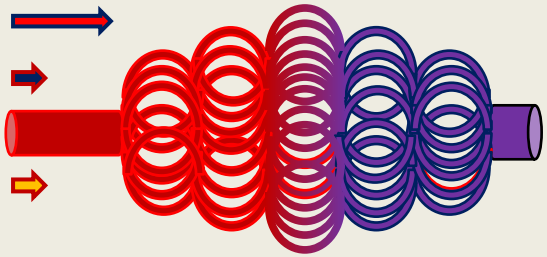
Rh = local hemodynamic resistance

Neoangiogenesis
Stable disease

Feeding artery — Microvasculaire network (Rh ↗↘)

- ↗ BFVol
- = BFVel
- ↗ Diameter
- WSS

(adapted NO pathway)



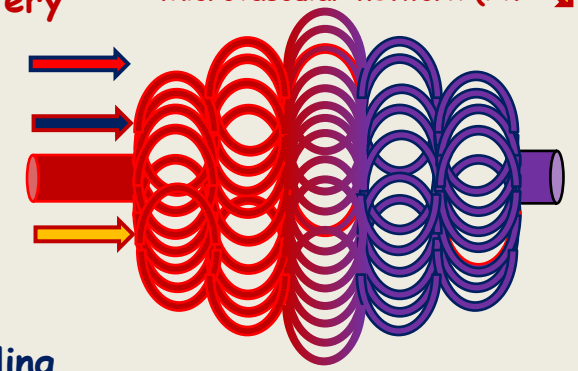
Feeding artery remodeling:
Balance arterial input / microvascular network

Neoangiogenesis
Progressive expansion of the vascular bed

Feeding artery — Microvascular network (Rh ↘↘)

- ↗ BFVol
- ↗ BFVel
- = Diameter
- ↗ WSS

(increasing)



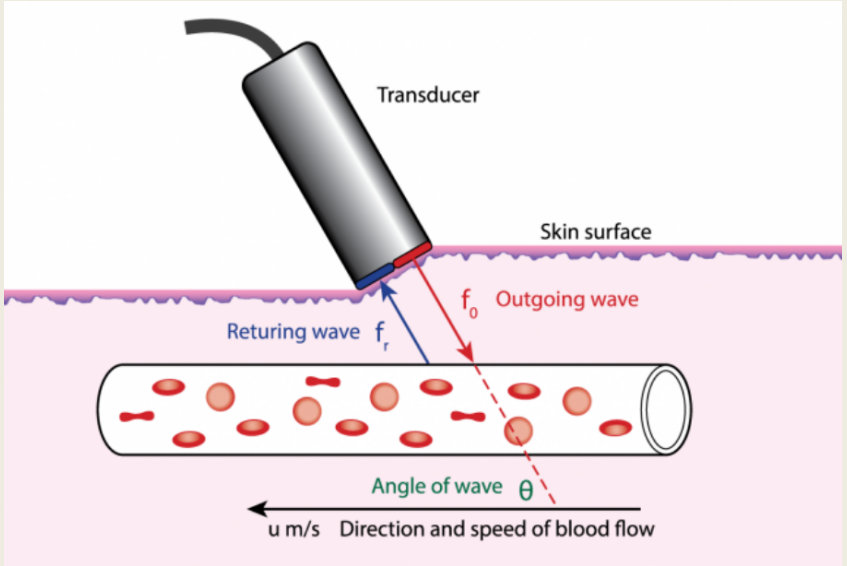
No remodeling
(Offset, a few weeks / months):
Imbalance arterial input / microvascular network

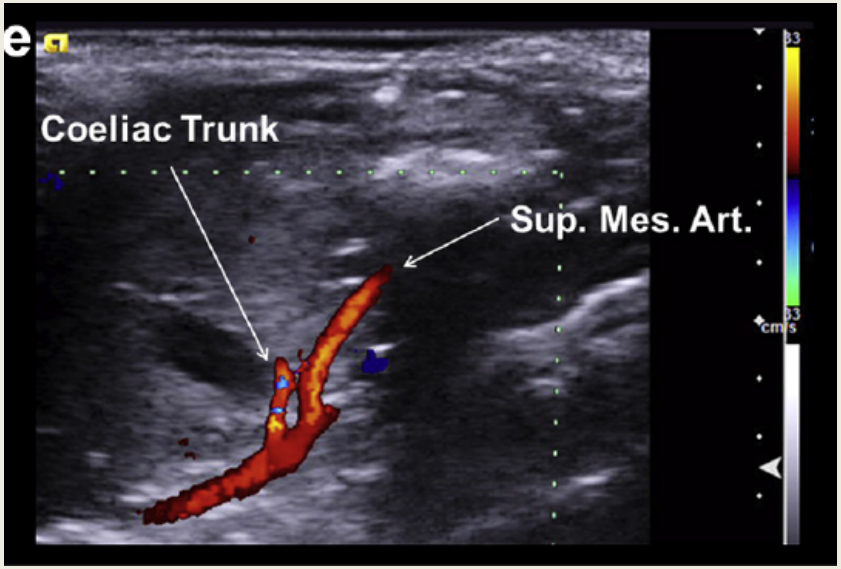
Rh = local hemodynamic resistance

HEMODYNAMICS

Doppler ultrasound is a non-invasive US imaging that allows

- **Identification of vascular structures** in ultrasound and color Doppler





HEMODYNAMICS

- Measurement of **blood flow velocity** (BFVel)

V *(cm / s)*

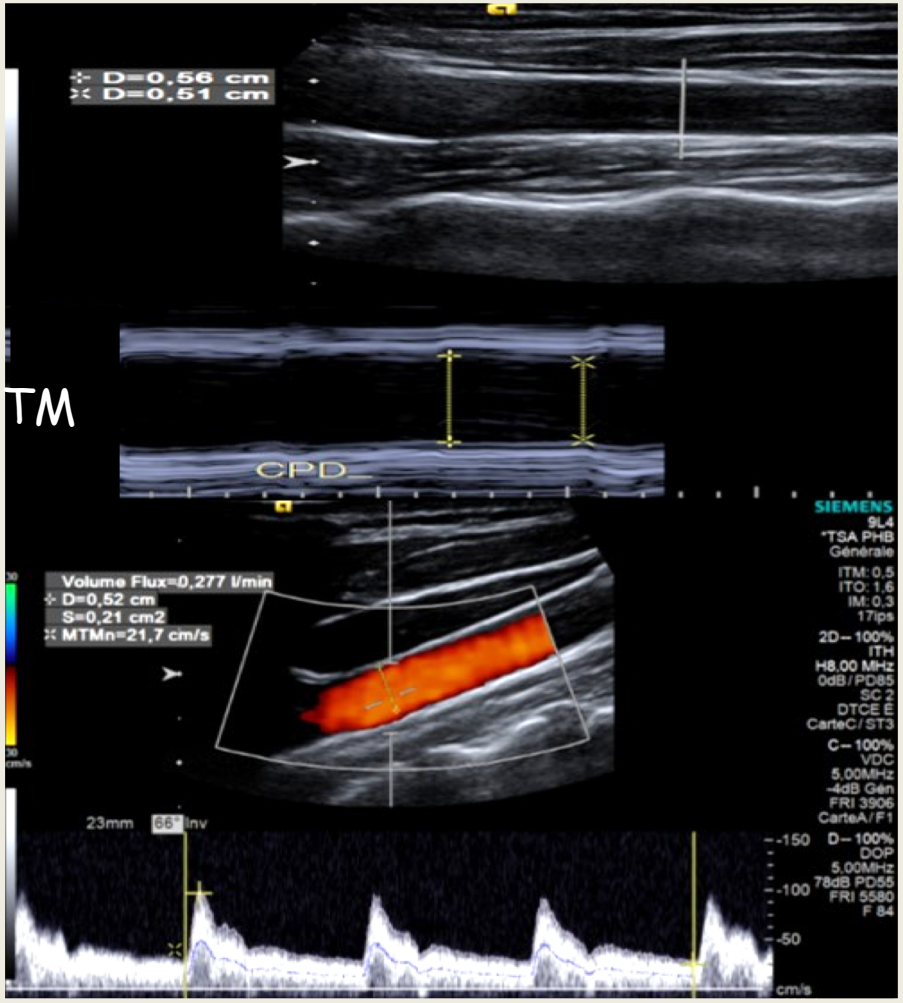
- Measurement of the **diameter** of the section slice of the vessel:

D *(mm)*

- **Blood flow volume** (BFVol):

Q *(ml / s)*

$$Q = \pi \left(\frac{D}{2}\right)^2 . V$$

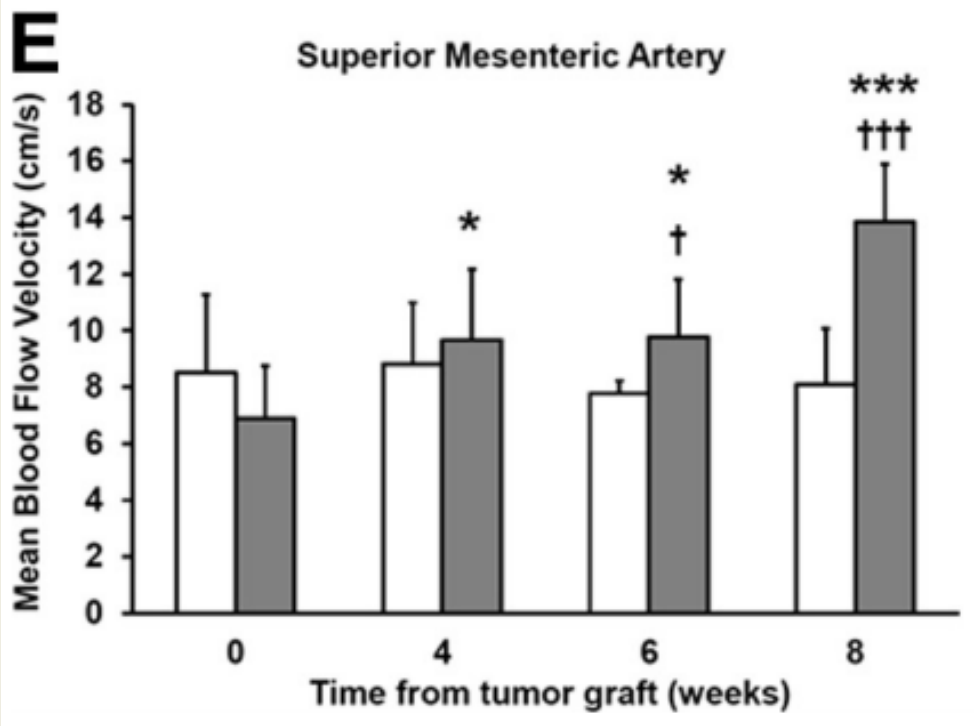


4. APPLICATION TO PERITONEAL CARCINOMATOSIS

4.1. Pseudomyxoma peritonii (preclinical & clinical studies)

APPLICATION TO PC: PRECLINICAL STUDY ON PMP

BFVel are **increased** in SMA of *Nude* mice with PMP orthotopic grafting.

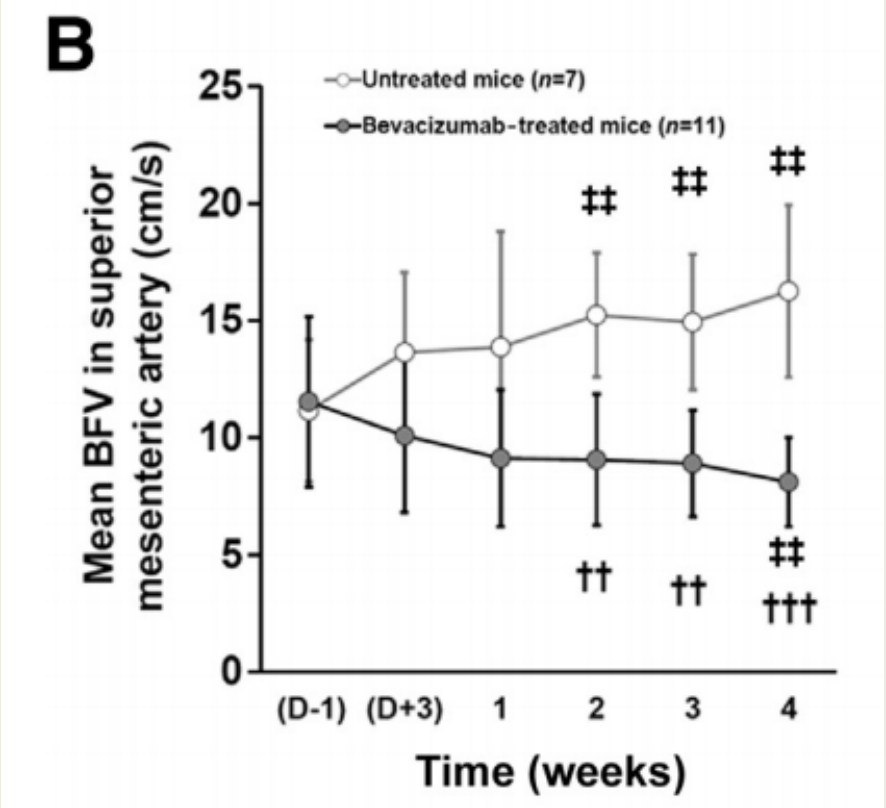


Dohan et al. Am J Pathol 2014

APPLICATION TO PC: PRECLINICAL STUDY ON PMP

Nude mice with orthotopic **PMP** implants treated with **bevacizumab** had a **decrease** in SMA **BFVel** correlated with a decrease in the vascular bed

(CD31, vascular endothelial cadherin, and desmine)

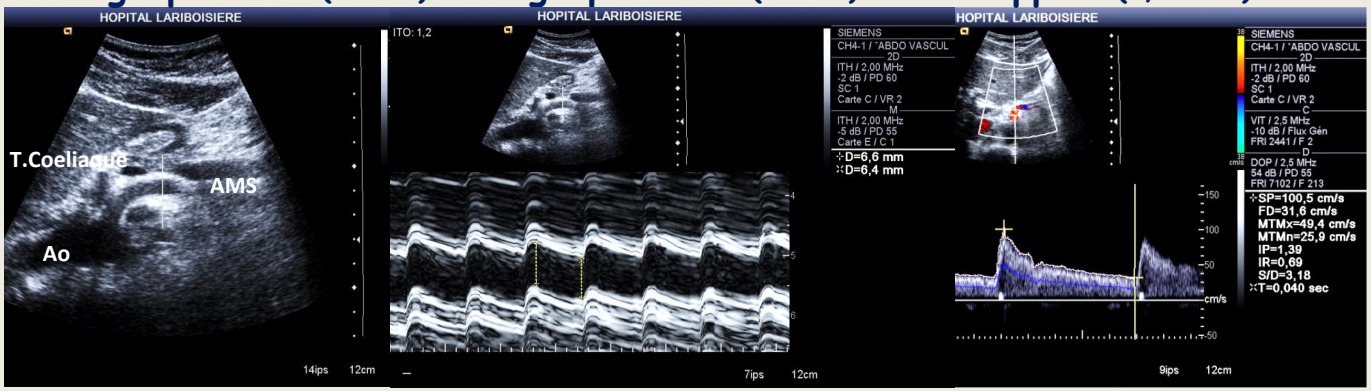


Dohan et al. Am J Pathol 2014

APPLICATION TO PC: PRECLINICAL STUDY ON PMP

- 52 patients
- BFVol & WSS before / after surgery
- 3 groups :
  - Group 1 : CCR 0-1, no relapse
  - Group 2 : CCR 2-3, alive > 2y postoperative, PFS 0-1
  - Group 3 : CCR 2-3, dead < 2y or PFS > 1

Échographie 2D (2 MHz) **Échographie TM** (2 MHz) **Doppler** (2,5 MHz)



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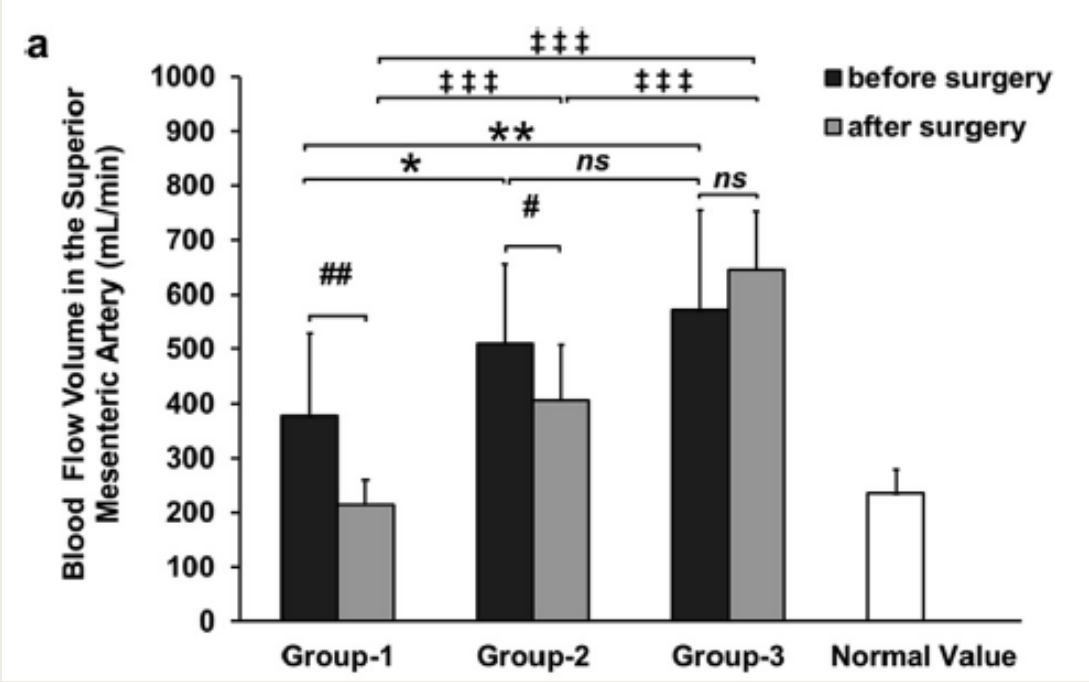
Dohan et al. EJSO 2018

APPLICATION TO PC: PRECLINICAL STUDY ON PMP

BFVel and **BFVol** in the SMA were **increased** in patients with PMP



Group 1 : CCR 0-1 (PCI 16)
Group 2 : CCR 2-3 slow progessor (PCI 31)
Group 3 : CCR 2-3 rapid progressor (PCI 33)

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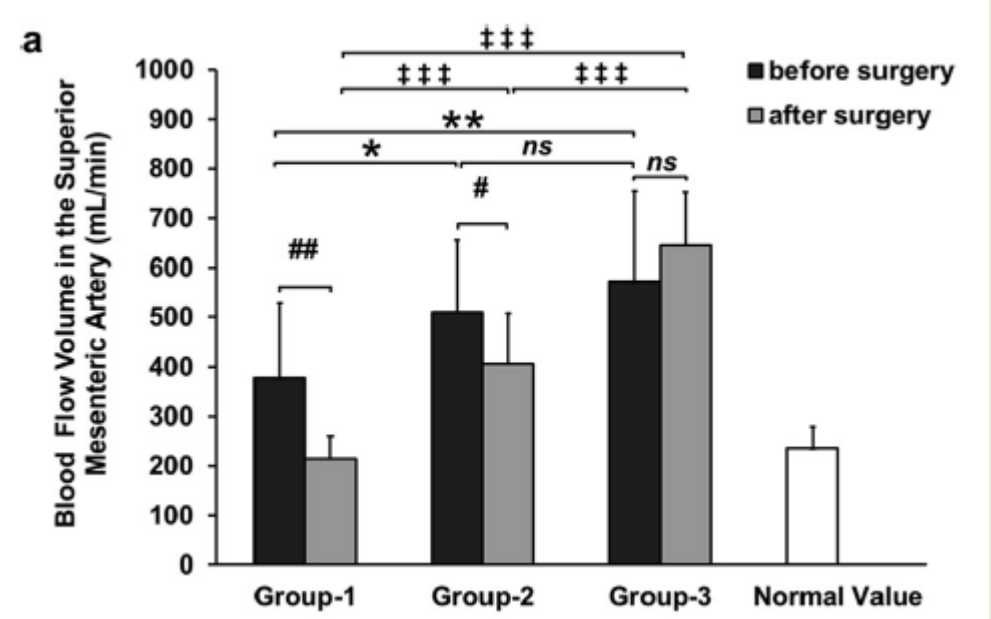
APPLICATION TO PC: PRECLINICAL STUDY ON PMP

- **BFVol dropped**
  - Group 1 & 2
- No BFVol change in group 3
- Postoperative BFVol > 530mL

AUC=0.827 **se 80% spe 93.3%**
diagnostic group 3 *(rapid progressor)*



Group 1 : CCR 0-1
Group 2 : CCR 2-3 *slow progessor*
Group 3 : CCR 2-3 *rapid progressor*

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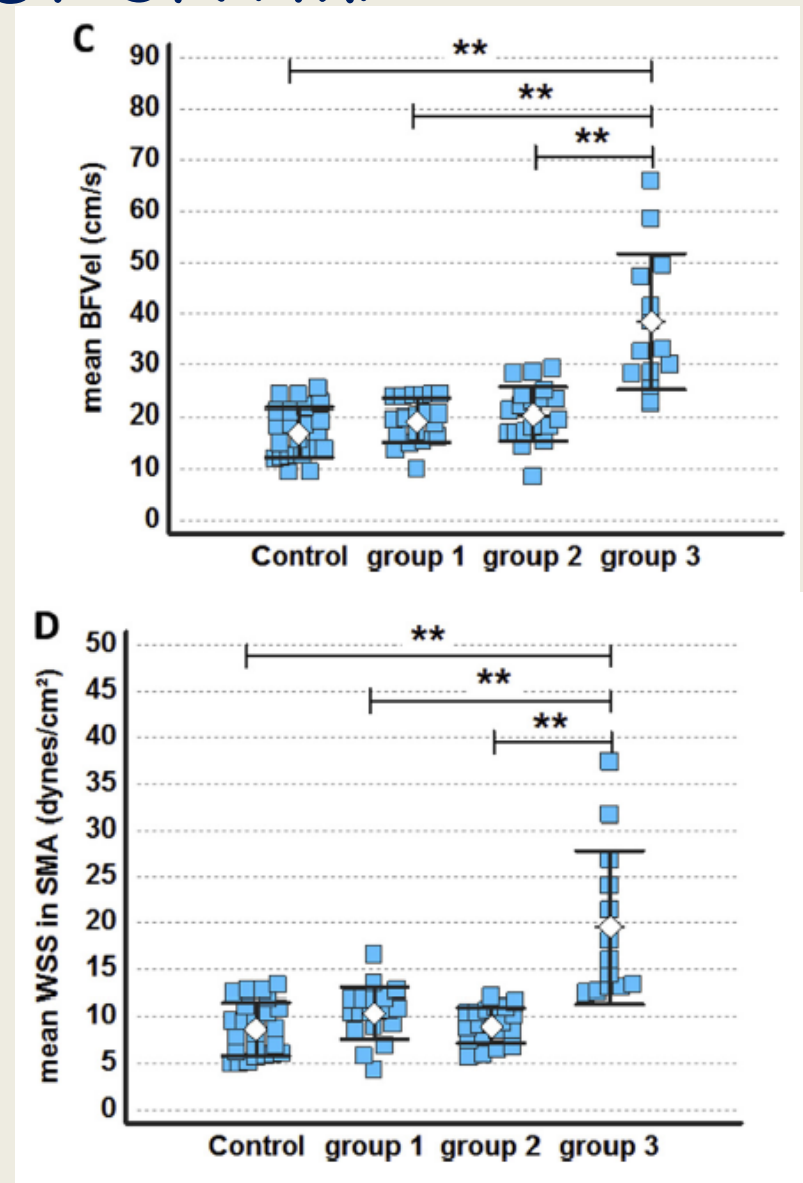
APPLICATION TO PC: PRECLINICAL STUDY ON PMP

- **BFVel** were **normal** in group 2 (*slow progressor*)
- **WSS** was **normal** in groups 1, 2 and control
- **WSS** was **increased** in group 3 (*rapid progressor*)

Cut off : 12,1 dynes/cm²

AUC=1,00 **se 100% spe 100%**

diagnosis group 3 *(rapid progressor)*



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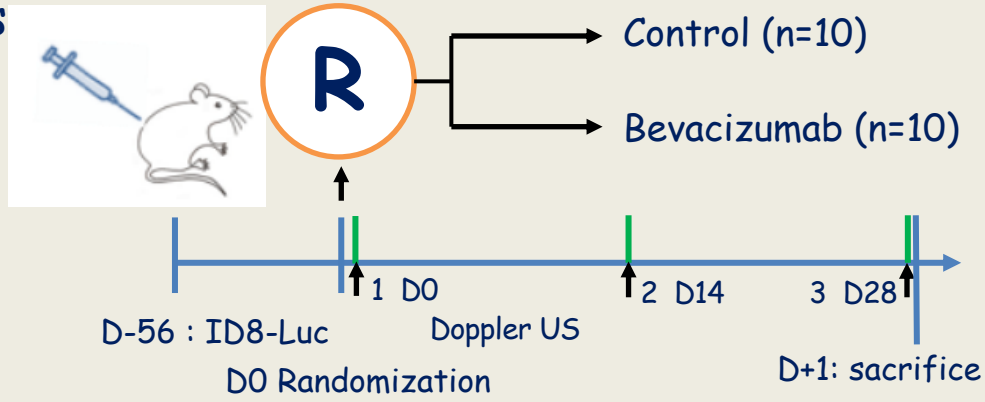
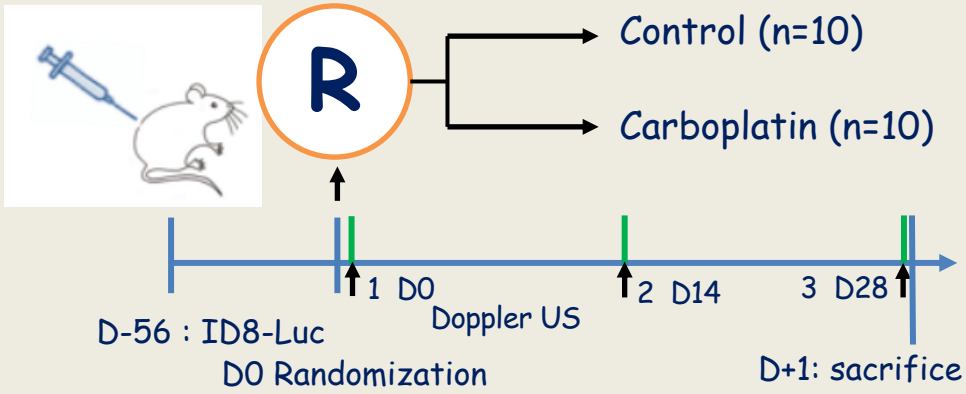
4.2. OVARIAN PERITONEAL CARCINOMATOSIS (OPC) : PRECLINICAL STUDY

APPLICATION TO PC: PRECLINICAL STUDY ON OPC

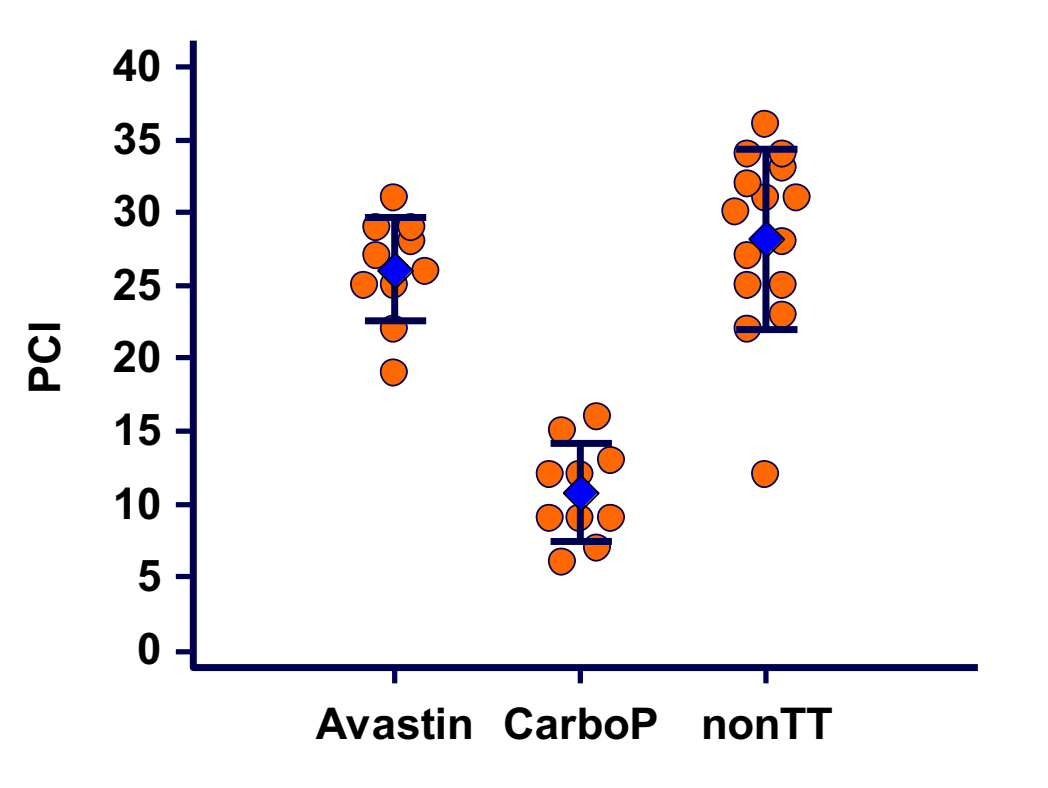
Mice were divided into 2 homogeneous groups with regard to fluorescence intensity at W8 of the IP injection of ID8-Luc cells

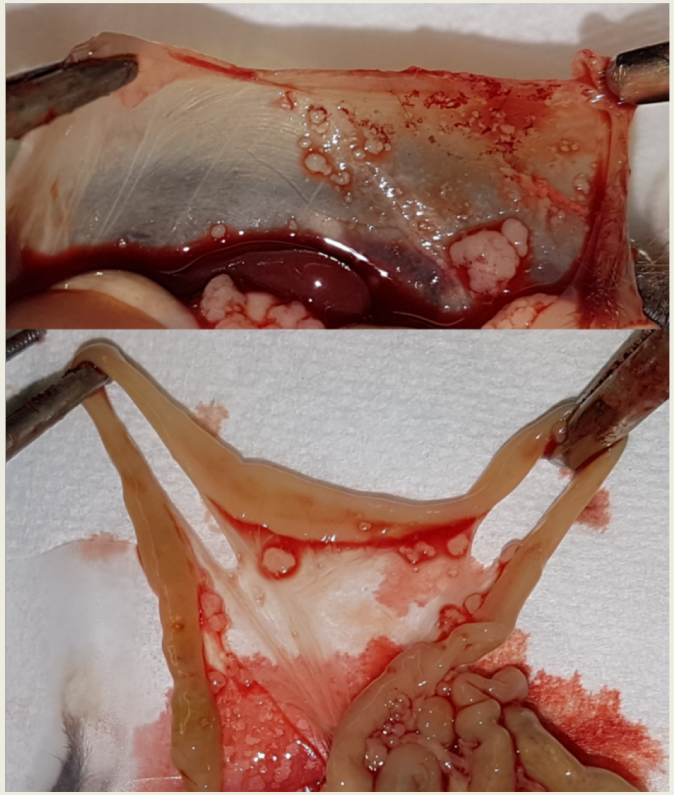
- A control group (n = 10)
- A treated group
  - **Bevacizumab** IP (5 mg / kg twice / wk) (n = 10)
  - **Carboplatin** IP (n = 10) (16 mg / kg every 4 days)





APPLICATION TO PC: PRECLINICAL STUDY ON OPC





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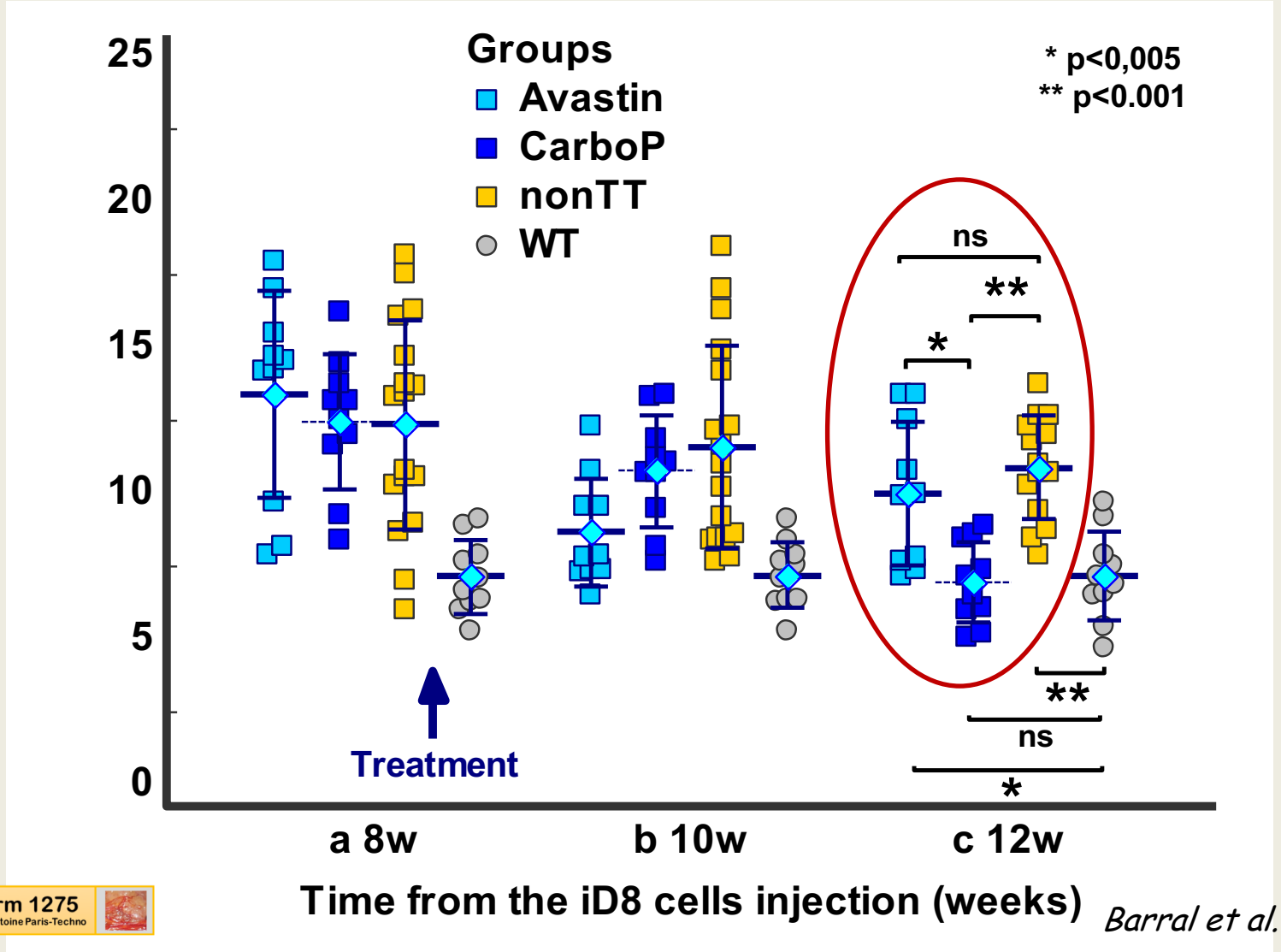
APPLICATION TO PC: PRECLINICAL STUDY ON OPC



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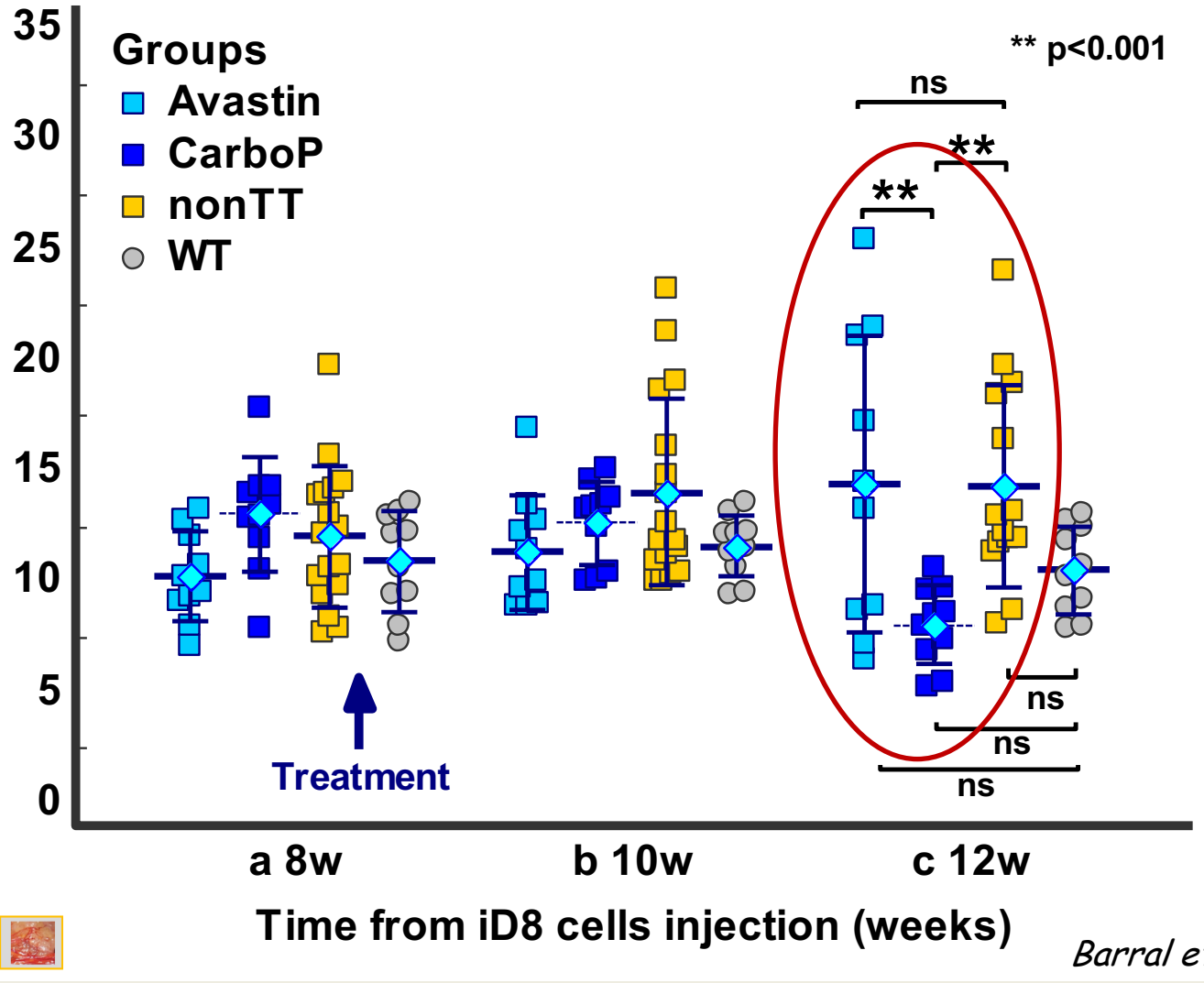

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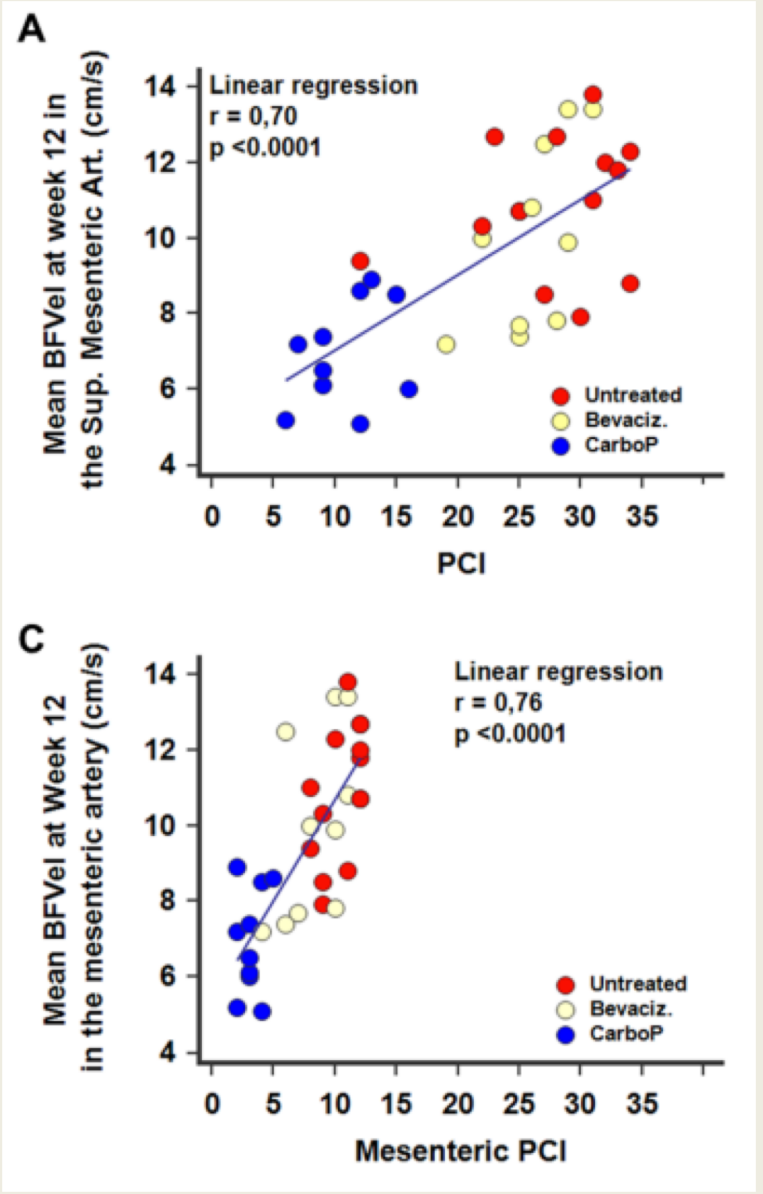
APPLICATION TO PC: PRECLINICAL STUDY ON OPC

- mBFVels in the SMA and CT were correlated with the PCI:
  - R=0.70 and R=0.65
- mBFVel in the SMA was highly correlated with the PCI within the mesentery R=0.76



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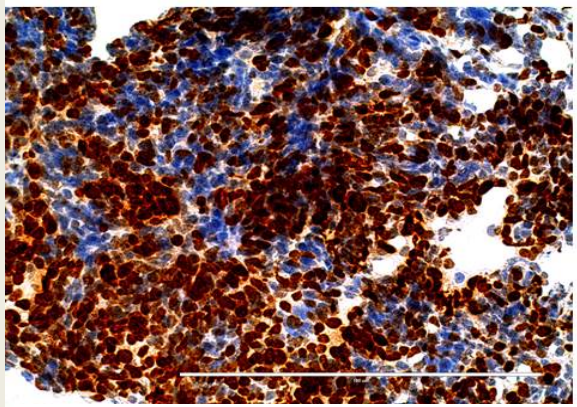
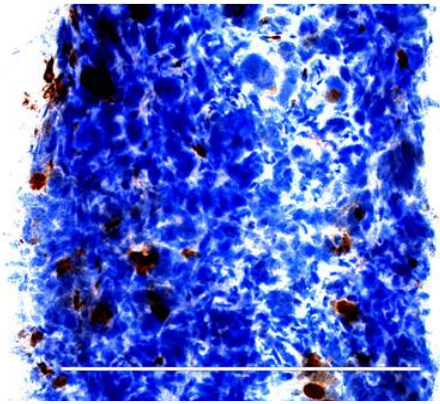
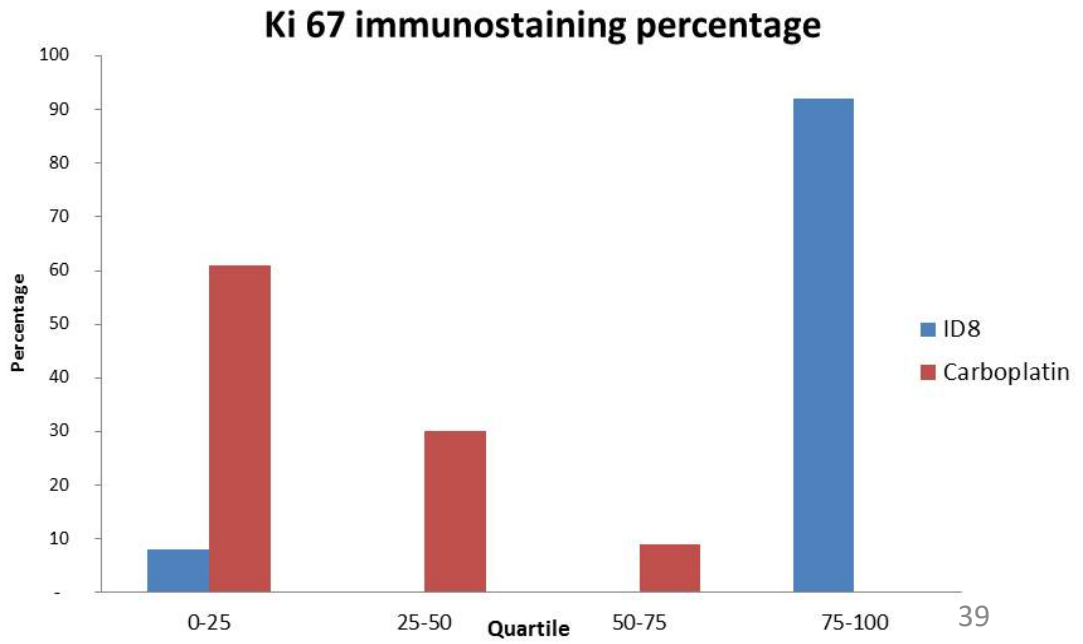
APPLICATION TO PC: PRECLINICAL STUDY ON OPC

Carboplatin decreases cell proliferation

1. In mice treated with **carboplatin**, **61%** had <25% Ki 67 vs. 25% in **untreated** mice.
2. Conversely, **92%** of **untreated** mice **> 75% Ki 67** and none in mice treated with carboplatin.







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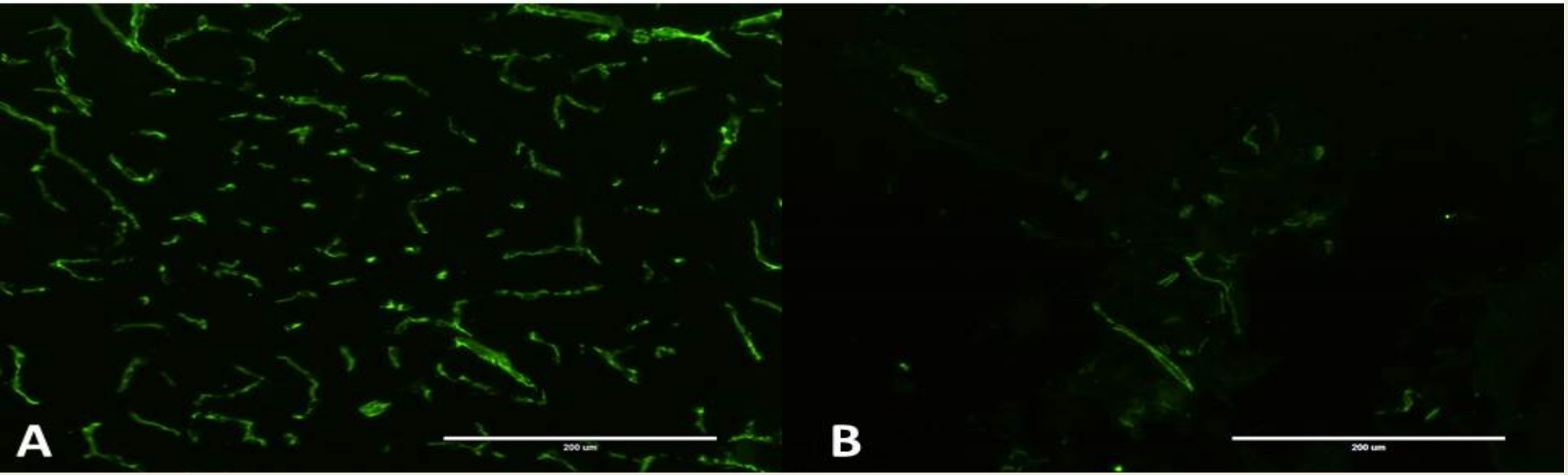
APPLICATION TO PC: PRECLINICAL STUDY ON OPC

Carboplatin decreased the vessels' density.

1. The **mean vascular density** was 34% in **untreated** vs. 21% in mice treated with **carboplatin** ($p < 0.001$)
2. The **mean vascular length density** was 3.2% in **untreated** vs. 2.1% in mice treated with **carboplatin** ($p < 0.001$)



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CONCLUSION

- **Upstream vascular remodeling** is a macroscopic expression of intra-tumoral microvascular phenomena
- Provides information on the current tumor dynamics
- Easily detectable and measurable in vivo

CONCLUSION

- **BFVol** in the SMA **rather** reflects tumor mass

- **BFVel** and **WSS** **rather** reflect the **activity** of the neoformed downstream vascular network