

Photodynamic Therapy in Gynecology

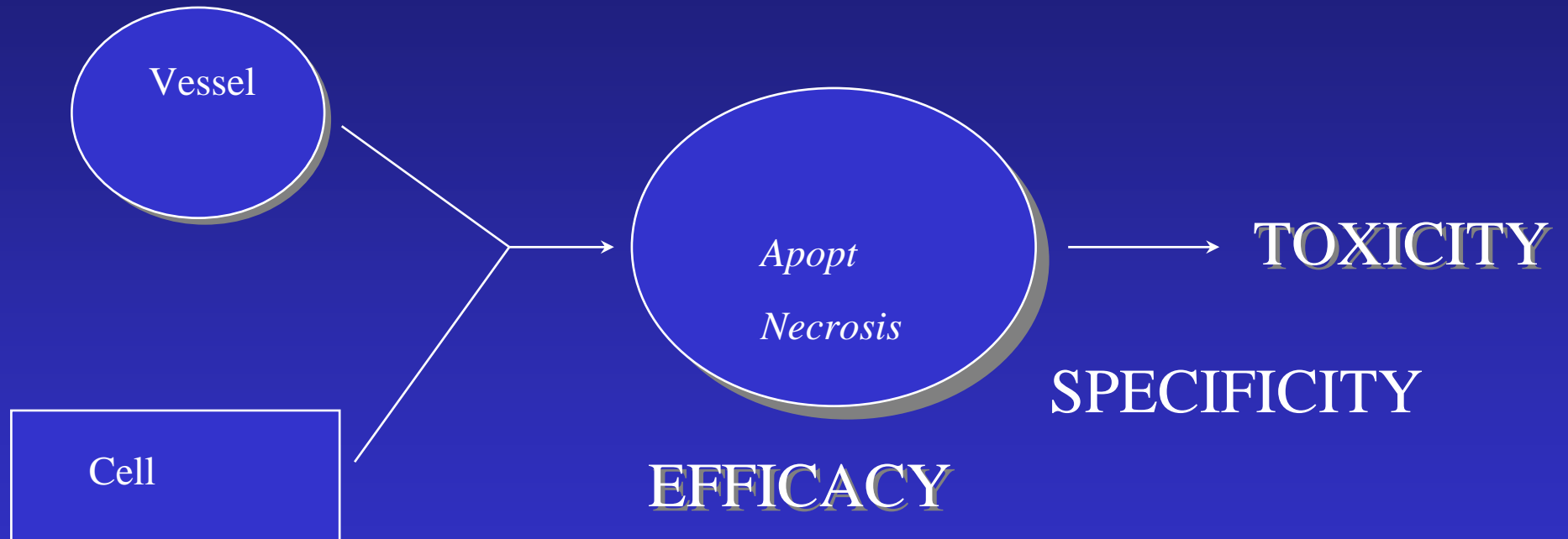
Attila L Major

Clinical Studies in Gynecology

- Peritoneal cavity
(Ovarian Cancer, Endometriosis)
- Breast cancer
- Cervical and Vulvar Precancer and Cancer
- Condyloma
- Endometrial Destruction

Photodynamic therapy targeting vasculature

Photodynamic Therapy



Presentation Plan

- Microvascular Photodynamic Effects Determined In Vivo Optical Doppler/Coherence Tomography
- Photodynamic Therapy of the Rat Endometrium by Systemic and Topical Administration of Tin Ethyl Etiopurpurin (SnET2)
- High Efficacy of Photodynamic Therapy on Rat Endometrium after Systemic Administration of Benzoporphyrin Derivative Monoacid Ring A (BPD)
- Meta-tetrahydroxyphenylchlorin (mTHPC) uptake and tissue distribution in relation to photodynamic efficacy
- Light Device (Balloon) for Patients
- Proposition

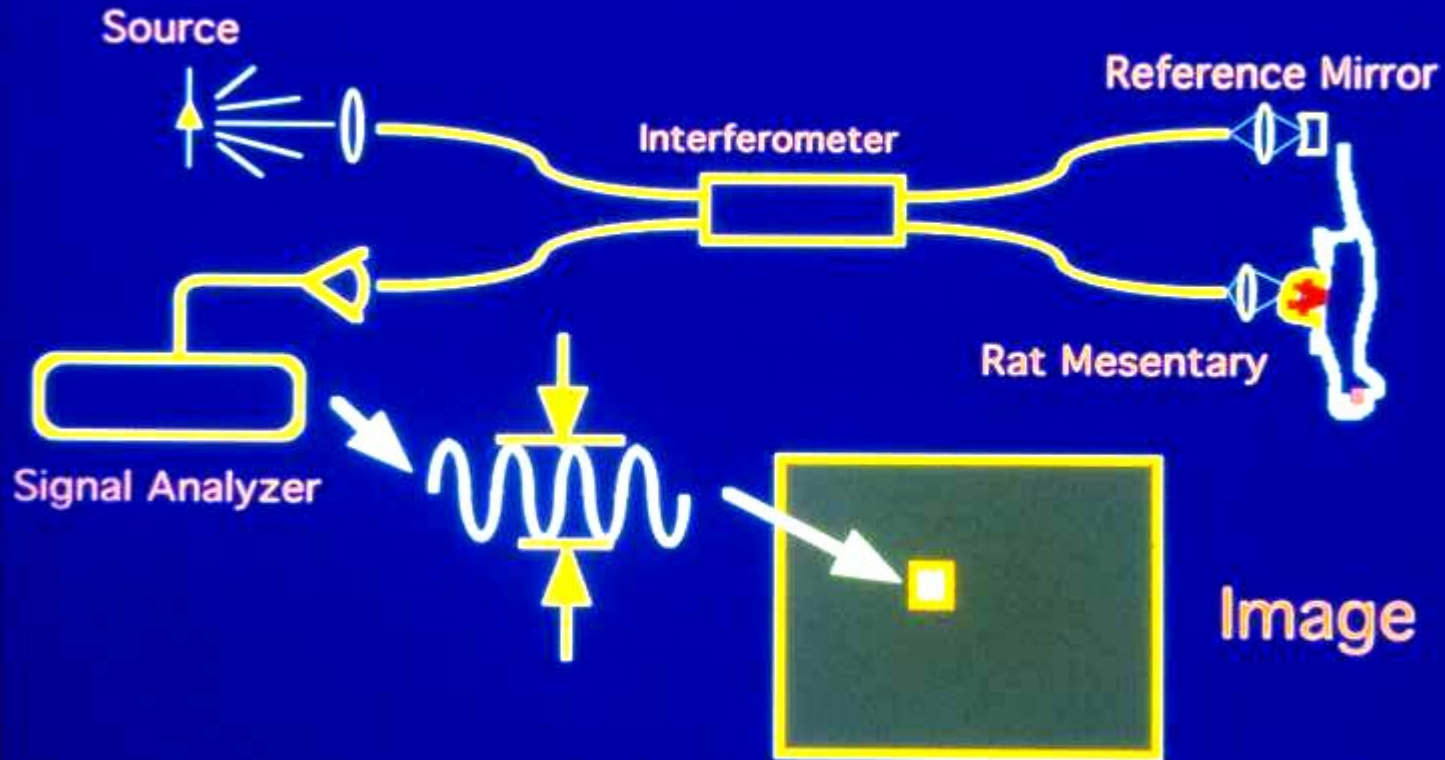
AIMS

- *In Vivo* determination of vessel diameters (artery and vein) and blood flow velocity profiles following laser irradiation in PDT
- Determine efficacy of short and long drug-light intervals with ODT/OCT
- Determine efficacy of ODT/OCT to monitor different PDT (light dose) regimens

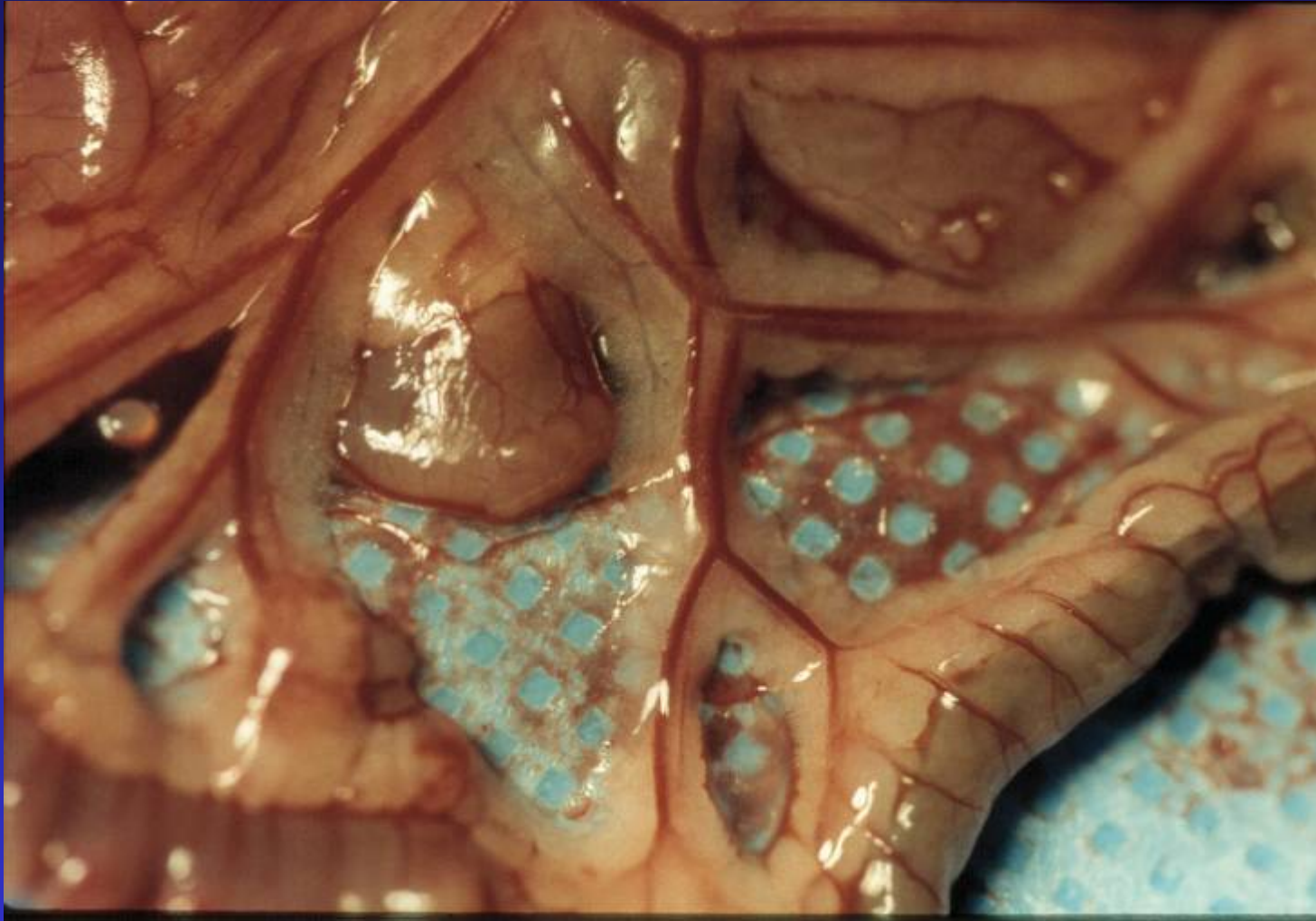
Material & Methods

- Rodent jejunal mesentery
- I.V. (tail vein injection) of photosensitizers (BPD and Photofrin)
- Midline laparotomy
- Laser irradiation (690 nm, 630 nm) with a microlens (2 cm diameter spot) after different drug-light time intervals (20 min to 8 hours)
- ODT/OCT measurements during 1 hour post-PDT

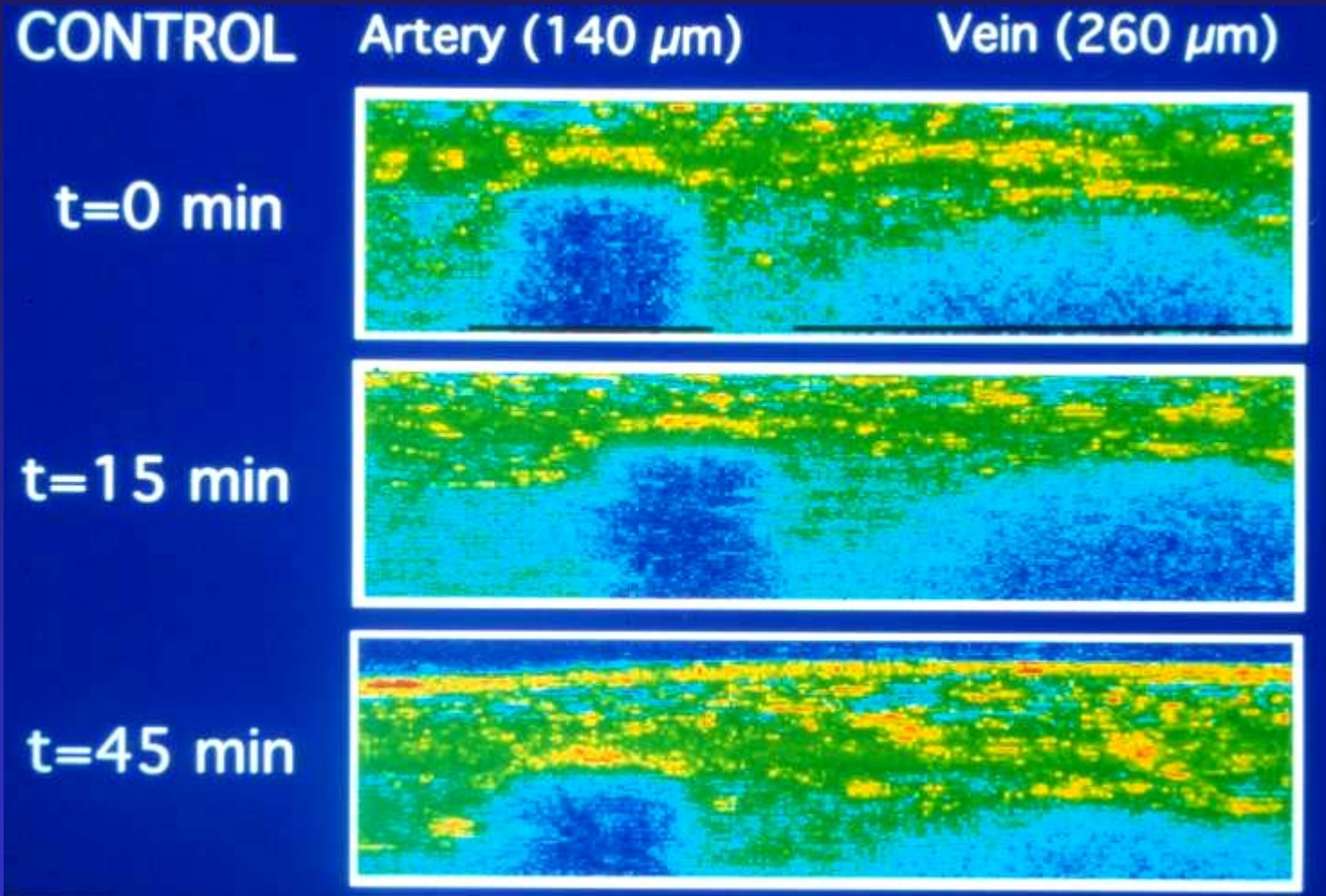
ODT Tomographic Image



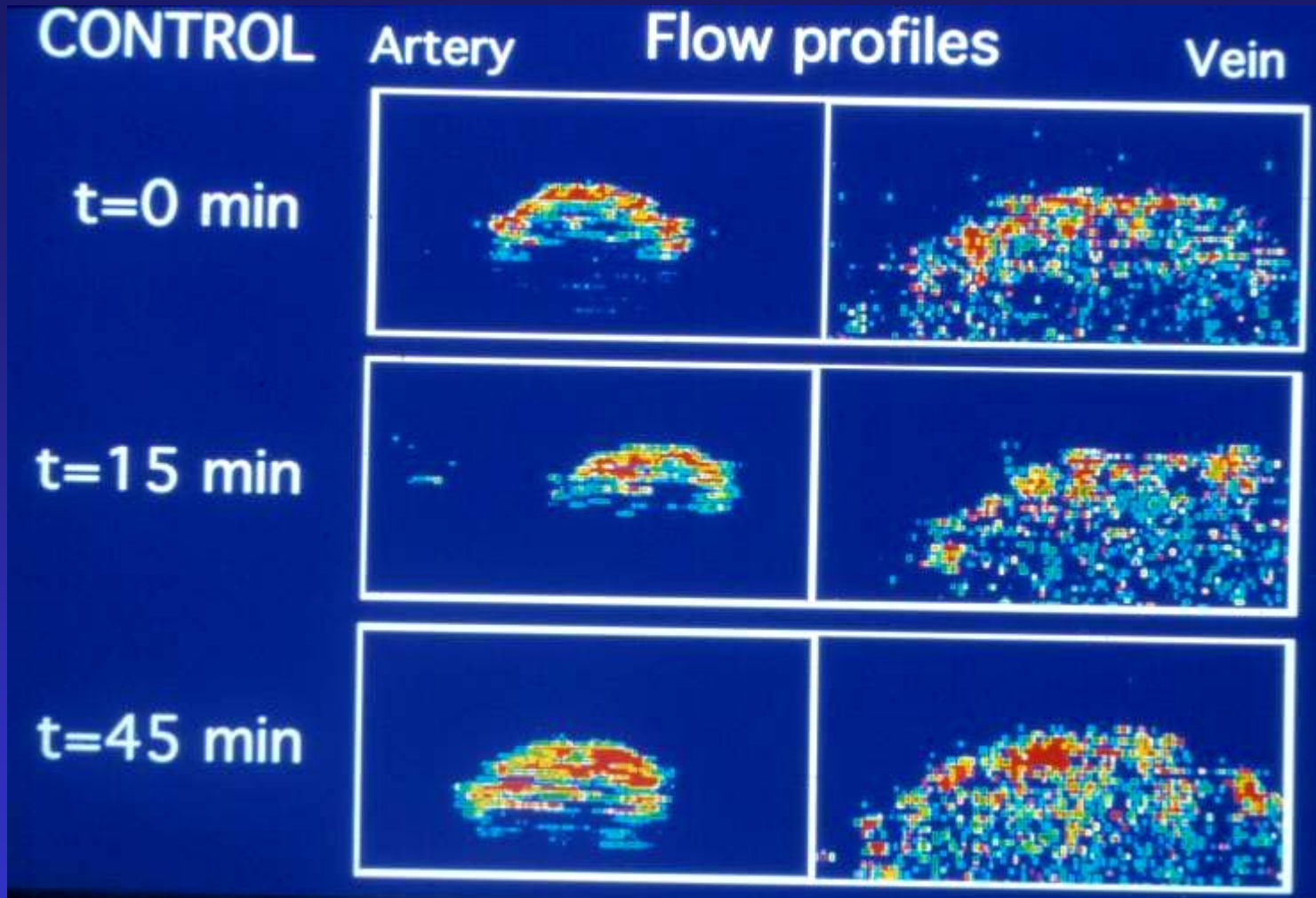
Schematic of Optical Doppler/Coherence Tomography



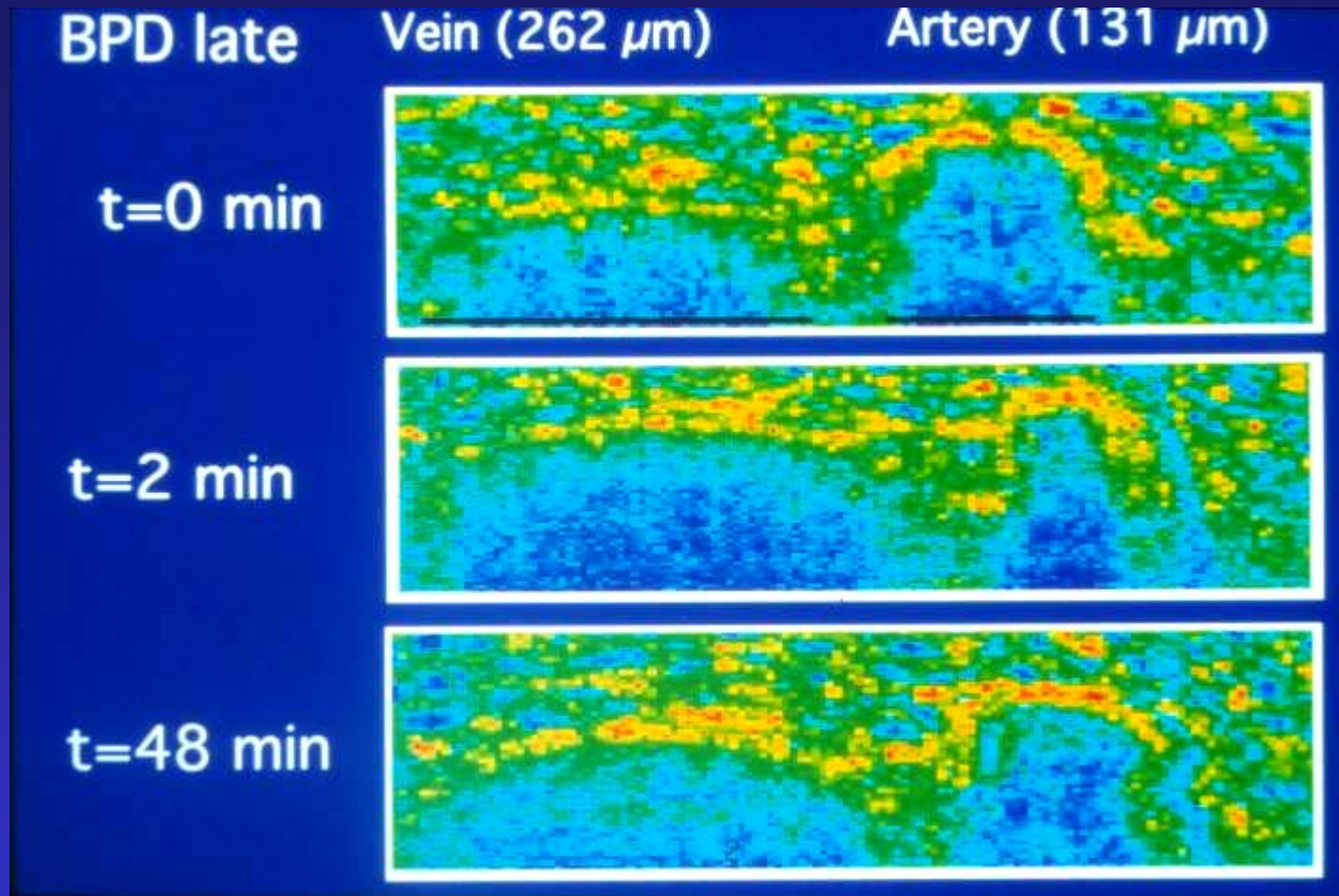
Sprague-Dawley Rat Mesentery



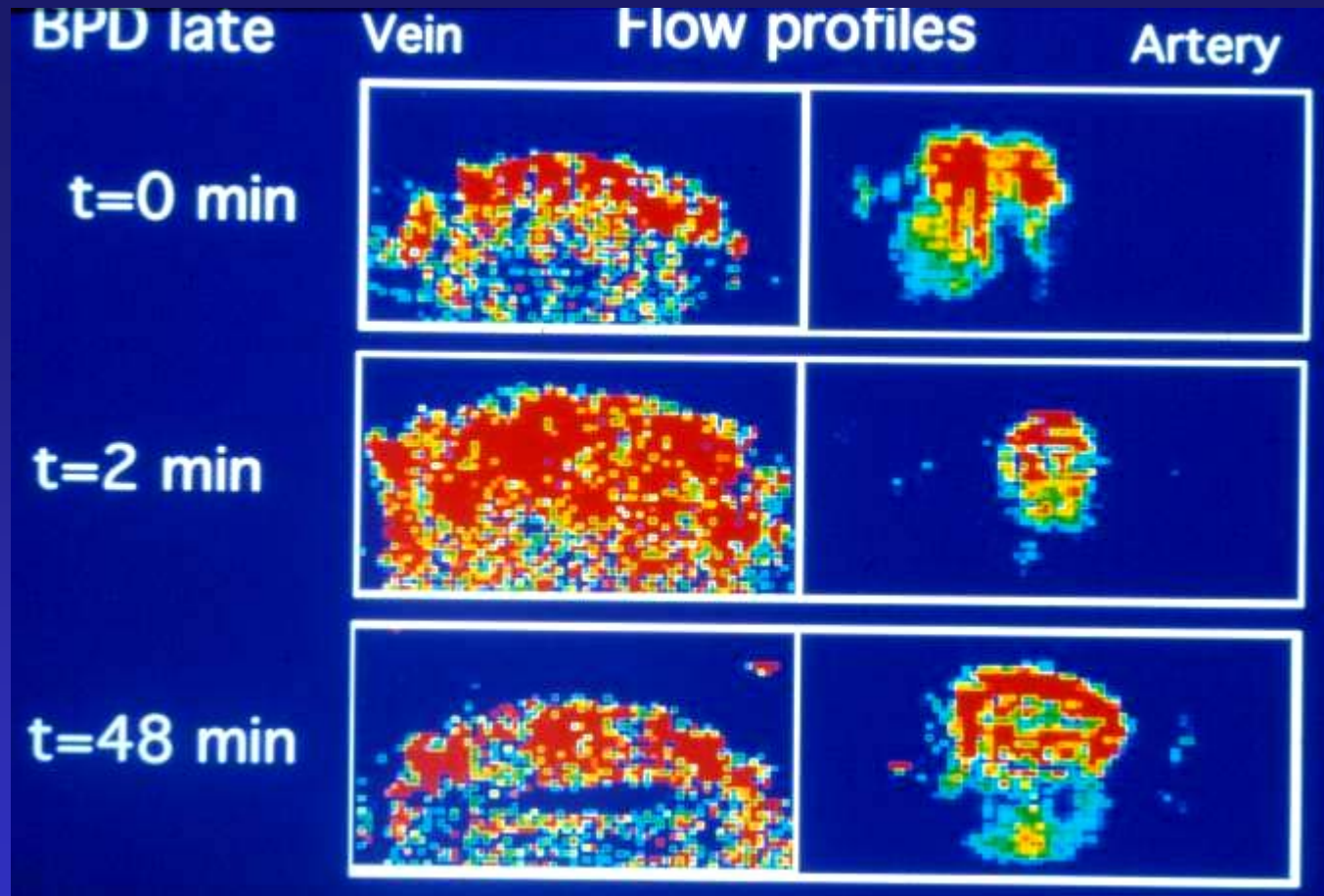
OCT of Control Mesentery (0.9% NaCl, 12J/cm²)



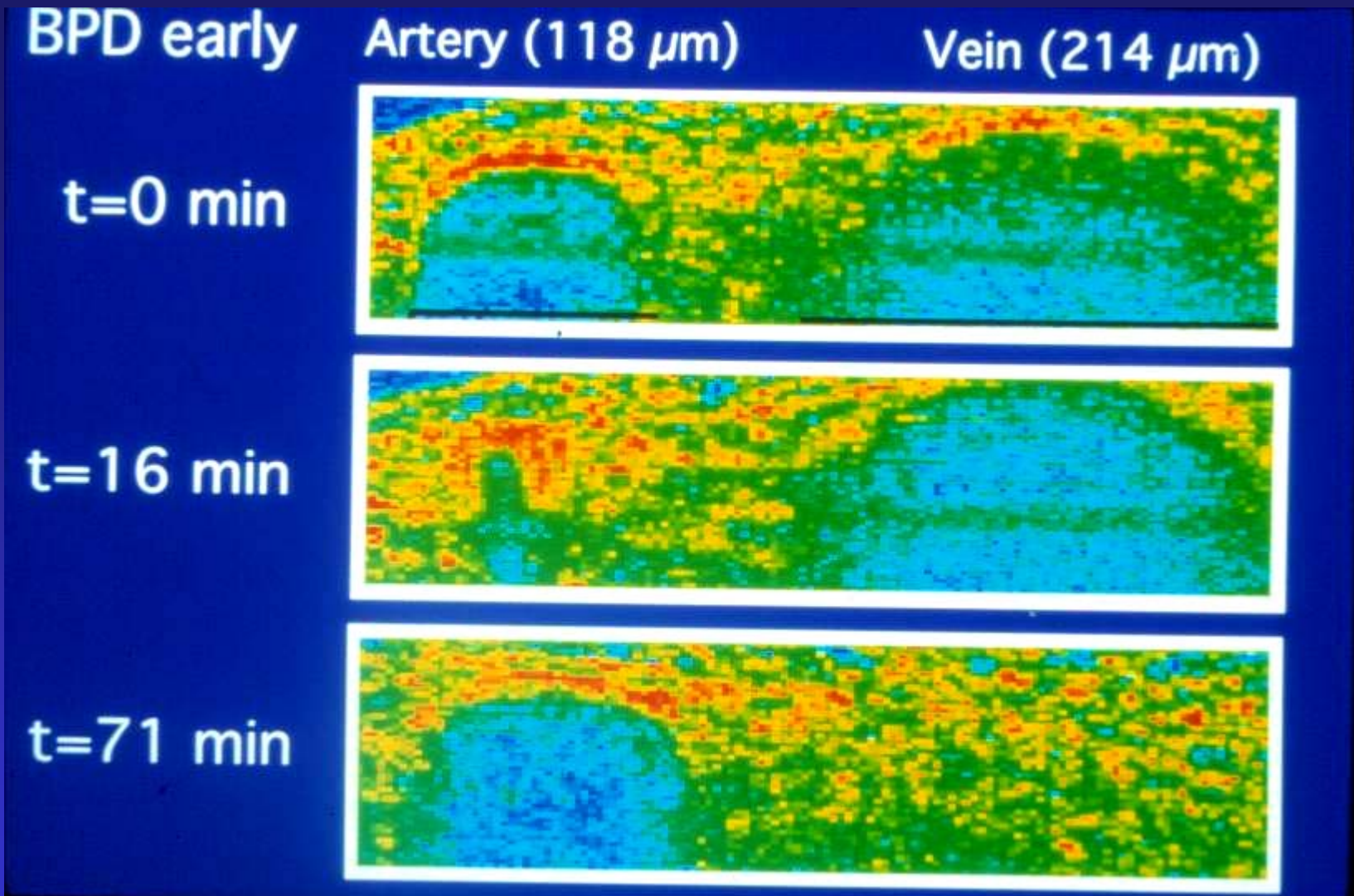
ODT of Control Mesentery (0.9% NaCl, 12 J/cm²)



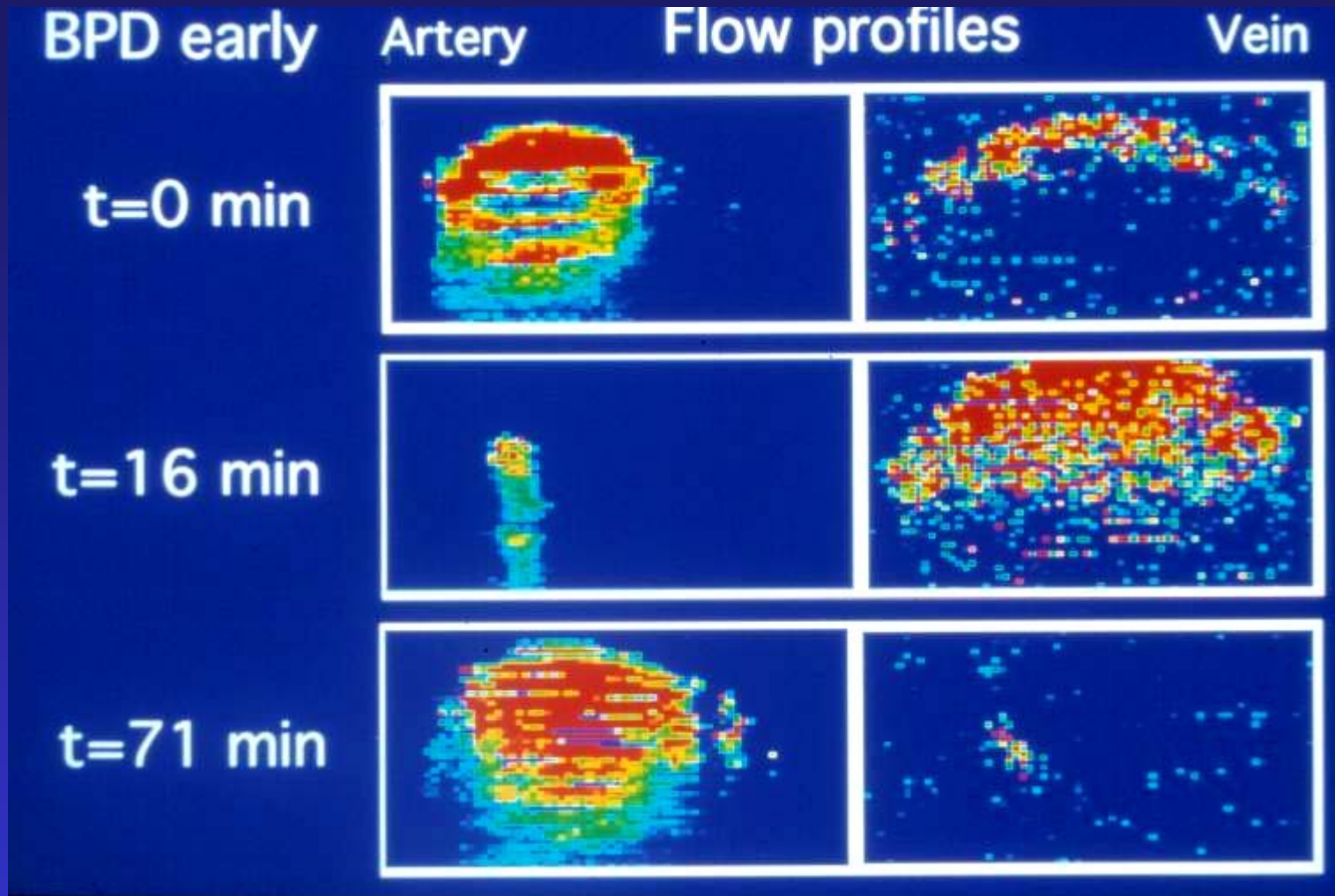
BPD 2mg/kg, 12 J/cm², 7 hours (OCT)



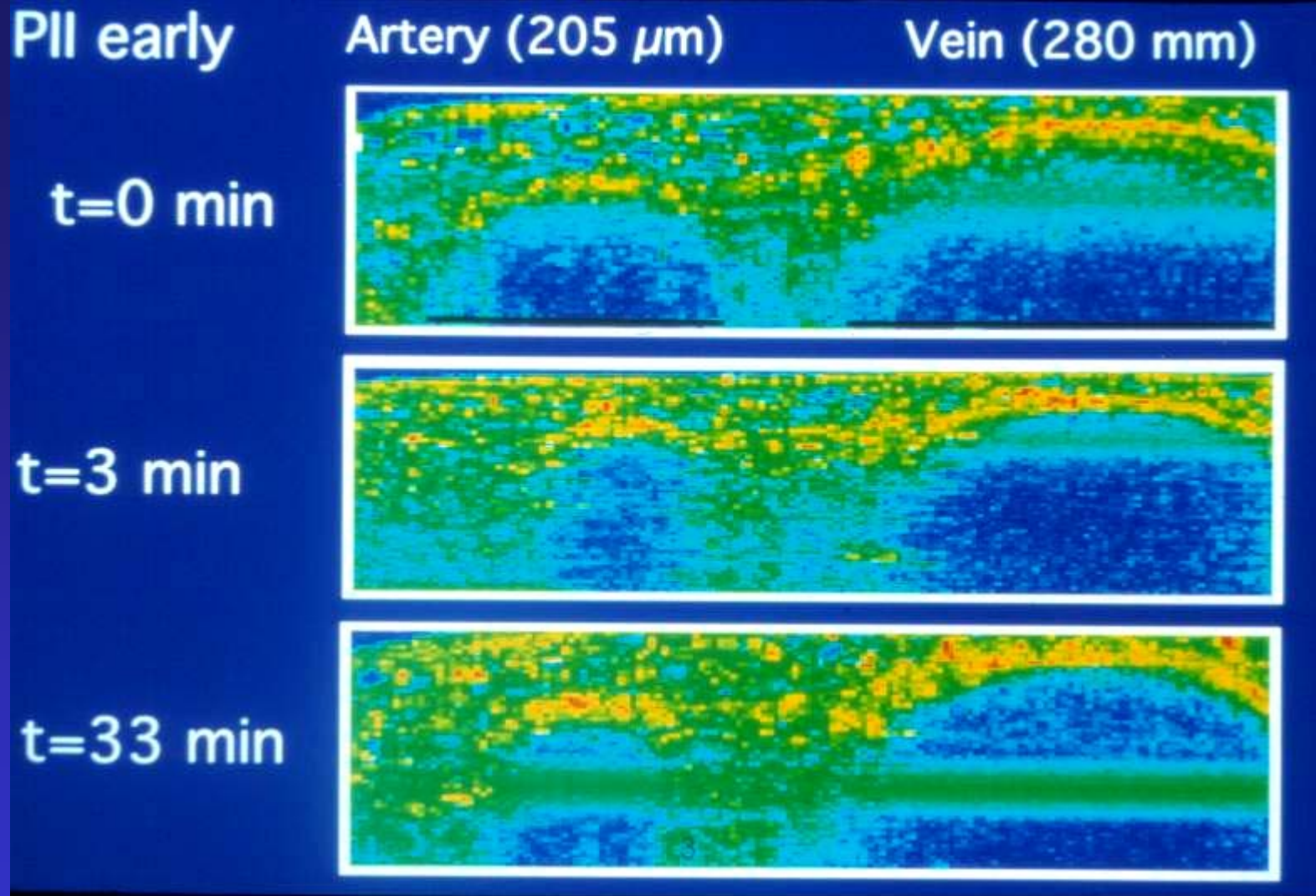
BPD 2mg/kg i.v., 12 J/cm², 7 hours (ODT)



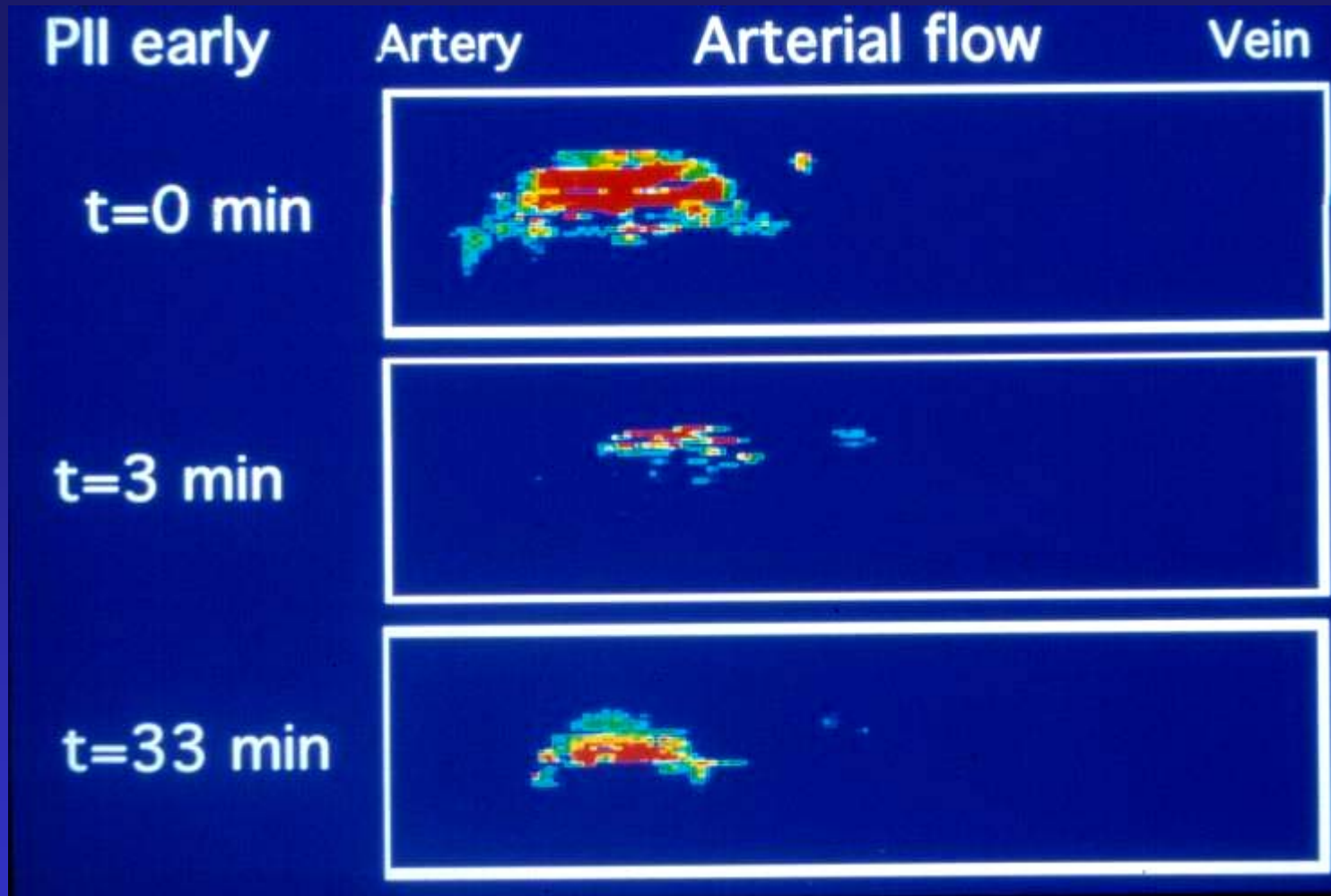
BPD 2mg/kg, 12 J/cm², 20 min (OCT)



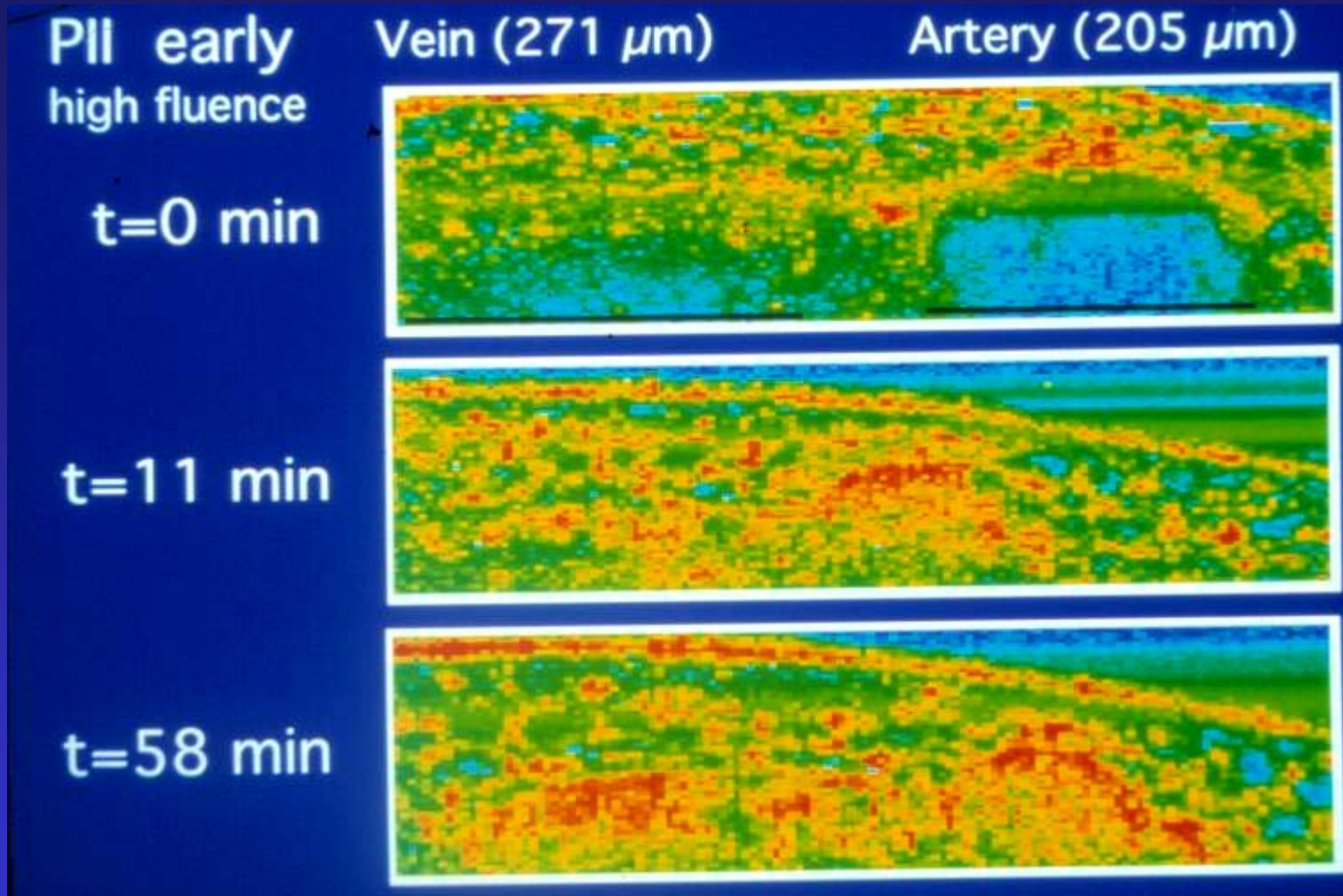
BPD 2mg/kg, 12 J/cm², 20 min (ODT)



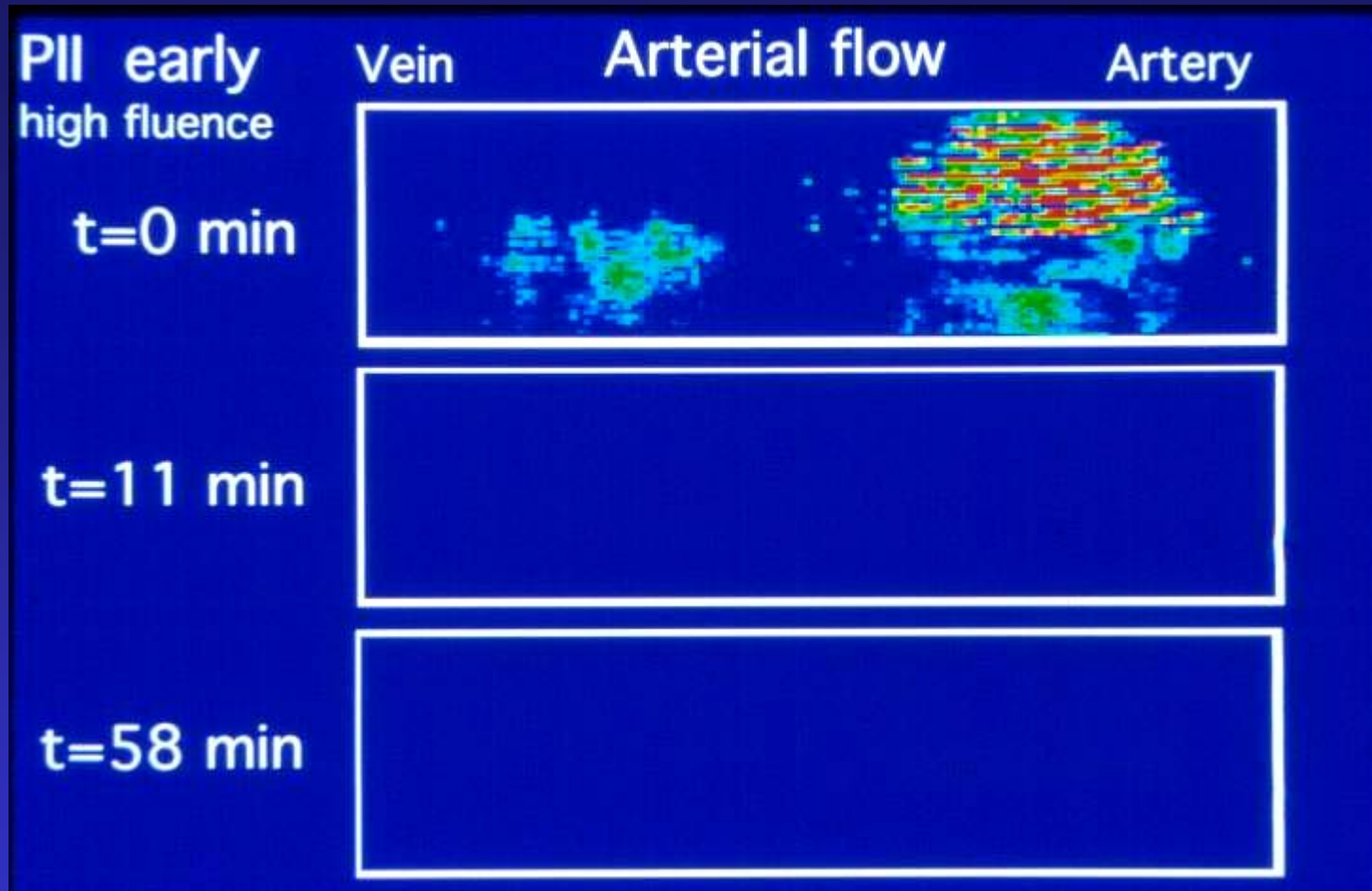
Photofrin 10mg/kg, 12 J/cm², 20 min (OCT)



Photofrin 10mg/kg, 12 J/cm², 20 min (ODT)



Photofrin 10mg/kg, 48 J/cm², 20 min (OCT)



Photofrin 10mg/kg, 48 J/cm², 20 min (ODT)

CONCLUSIONS

- BPD-PDT with short drug-light time interval is more effective than long interval
- First event by increasing the dose of PDT is reversible vasoconstriction of the artery, second event is the shut-down of the vein and third the shut-down of the artery
- ODT/OCT is an ideal technique for real-time imaging, with high spatial resolution, of structures as well as flow velocity in PDT

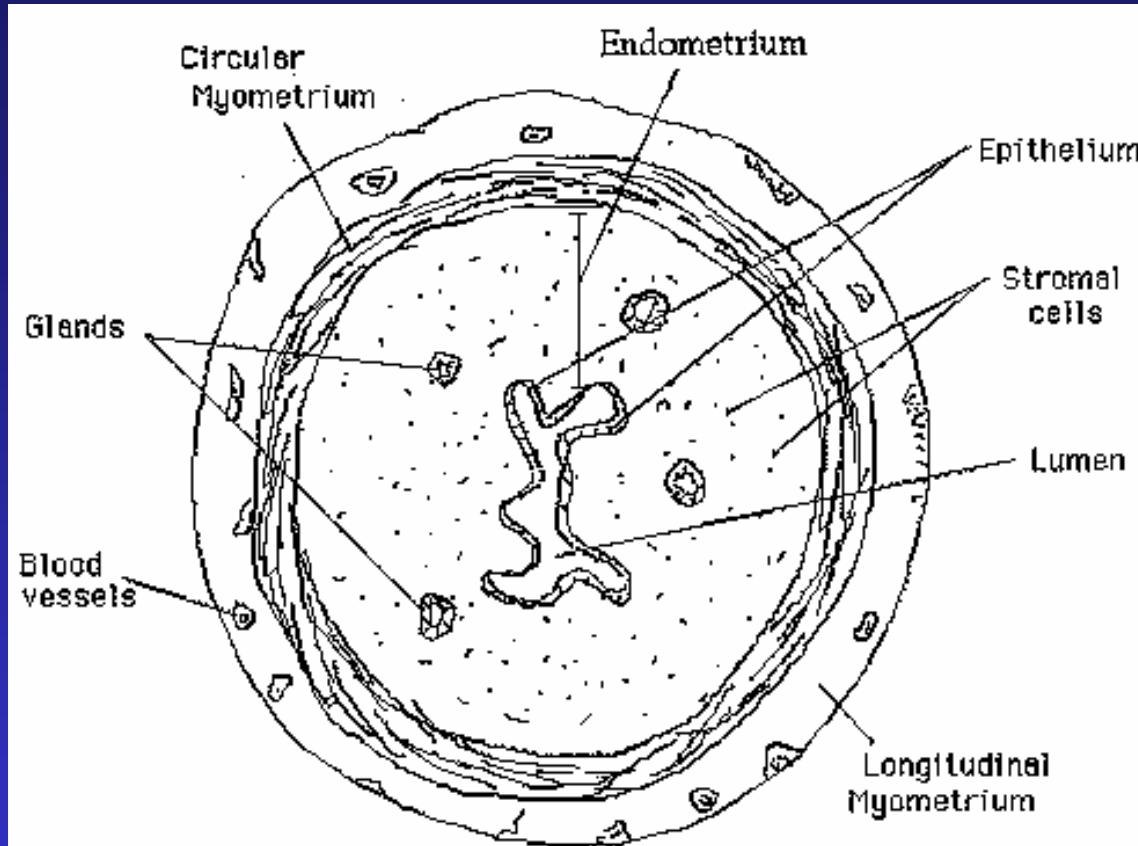
Photodynamic Therapy of the Rat Endometrium by
Systemic and Topical Administration of Tin Ethyl
Etiopurpurin (SnET2)

AIMS

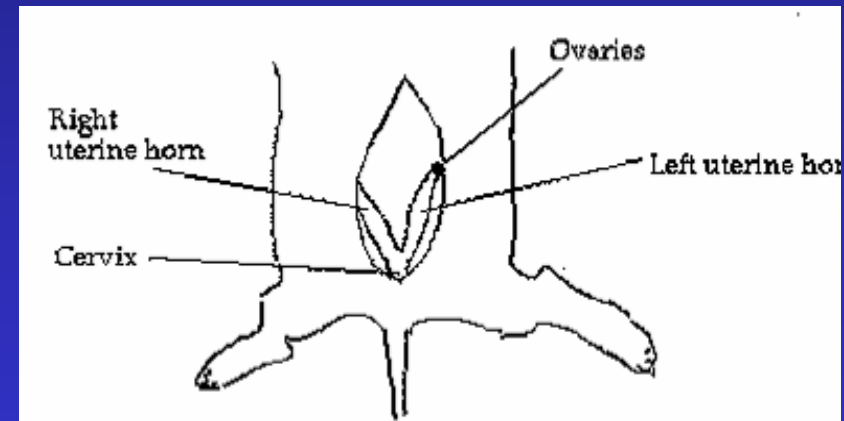
- Evaluate PDT effects on the rat uterine tissue comparing:
- Different routes of administration
- Different time intervals after drug administration
- Different light doses at 1.5 h after I.V. injection of SnEt₂

Material & Methods

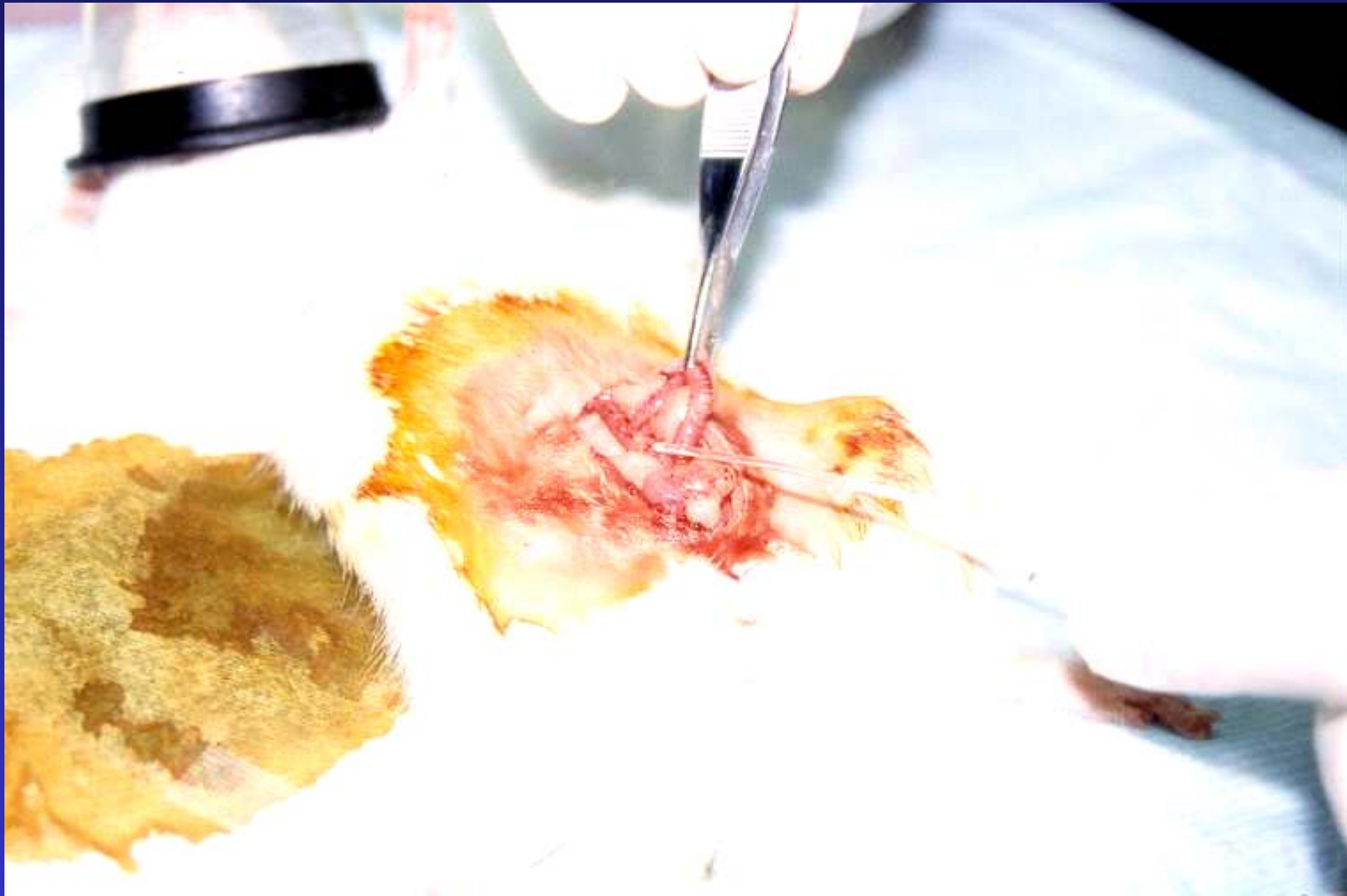
- Rodent uterine horn
- IV (tail vein injection) of SnET2 (2 mg/kg) or IU (0.15 ml of 1 mg/ml)
- Midline laparotomy
- Laser irradiation (665 nm) with a cylindrical diffusing fiber (3 cm long, 1.2 mm diameter) after different drug-light time intervals (1.5 h – 24 h) and different light doses (6.25 – 375 J/cm²)
- Sacrifice of the rats 48 h after light treatment for histology



The didelphic uterine horns
in the rat

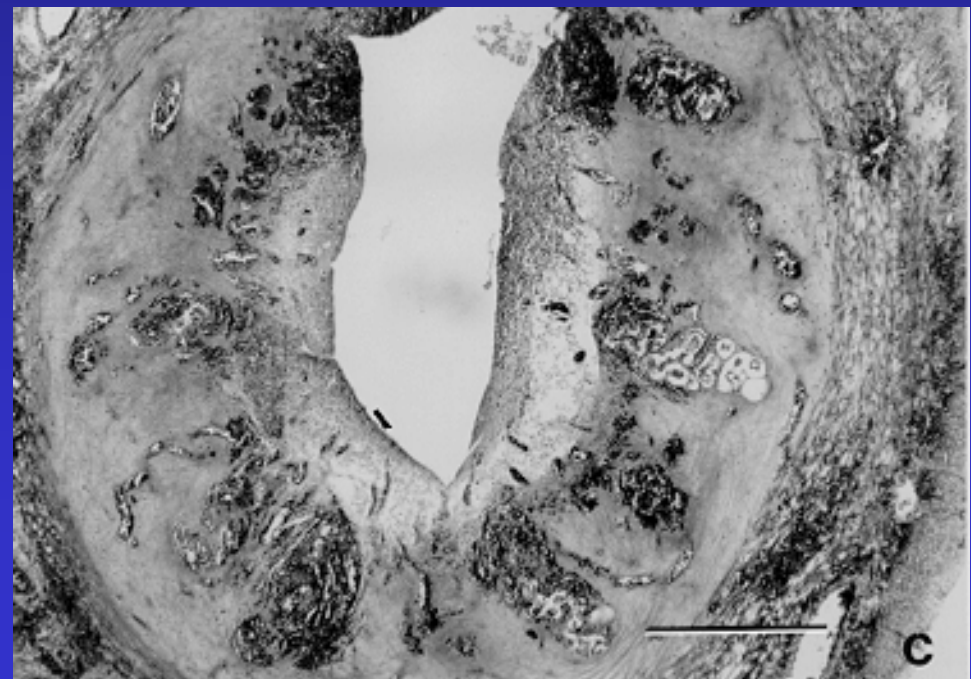
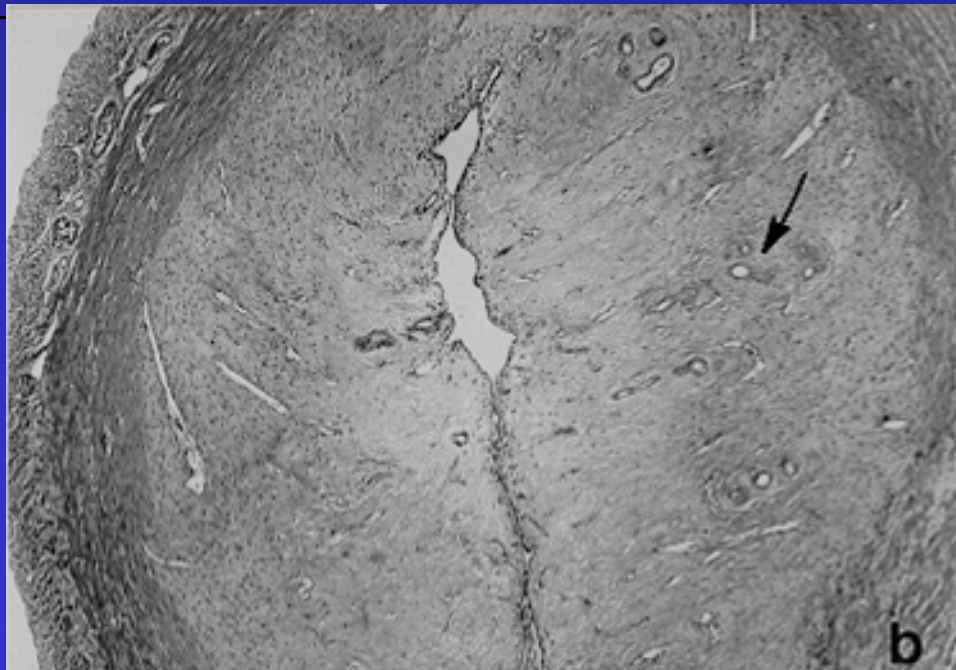


Structure of the rat uterus



Insertion of cylindrical diffusing fiber (3 cm, 1.2 mm diameter)

Hematoxylin and eosin stained sections of left uterine horn 2 days after illumination (375 J/cm²): Control uterine horn (a), 3 h after IU (b), 1.5h after 2 mg/kg IV (c). Length scale represents 0.5 mm .



CONCLUSIONS

- SnET2-PDT IV is more effective than topical administration
- SnET2-PDT with short drug-light time interval (1.5 h) is more effective than long interval (24 h)
- At short time interval (1.5 h) 30 times less light dose (12.5 J/cm²) is more effective than long time interval (24 h) with a high light dose (375 J/cm²)

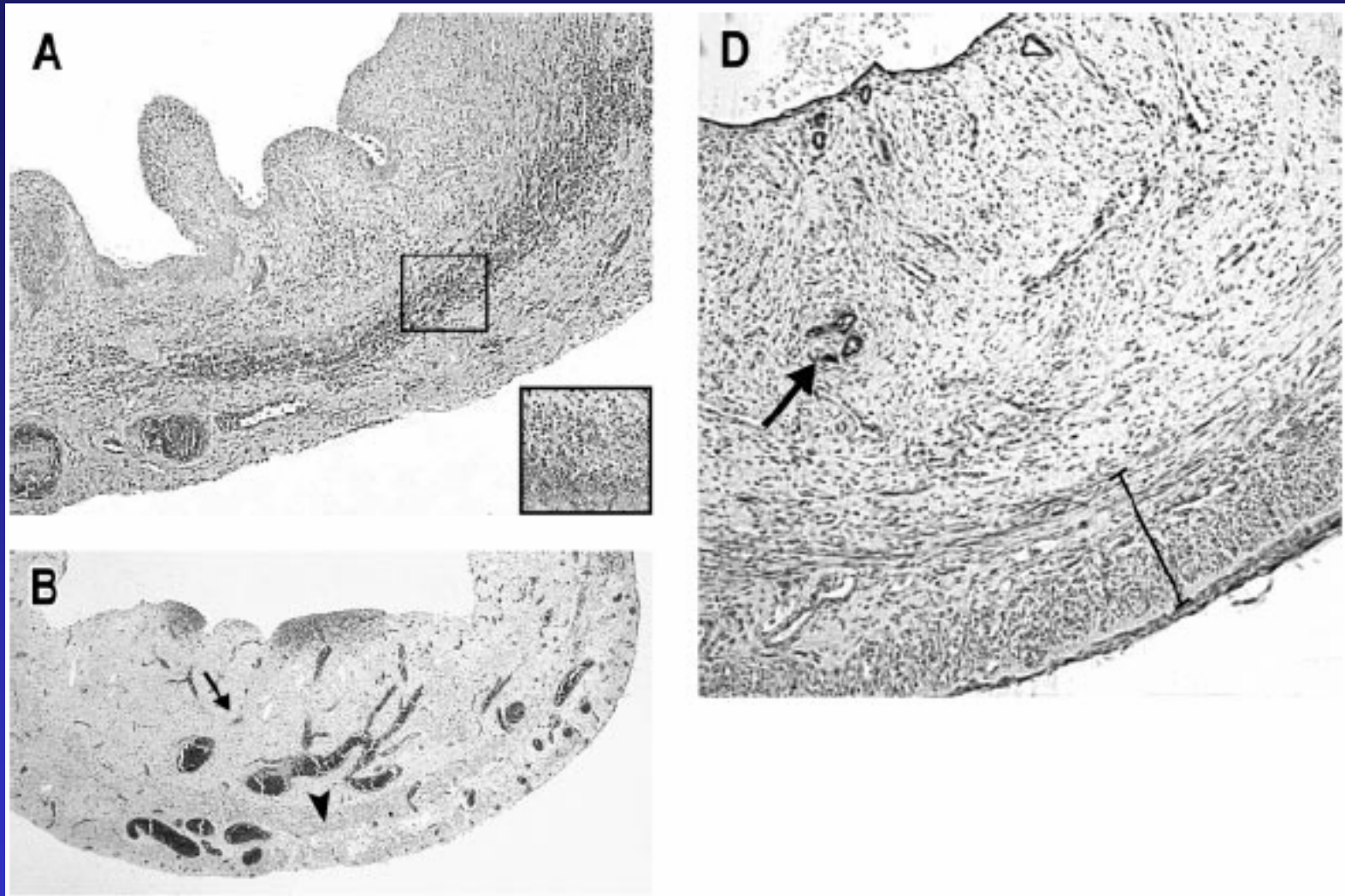
High Efficacy of Photodynamic Therapy on Rat
Endometrium after Systemic Administration of
Benzoporphyrin Derivative Monoacid Ring A
(BPD)

AIMS

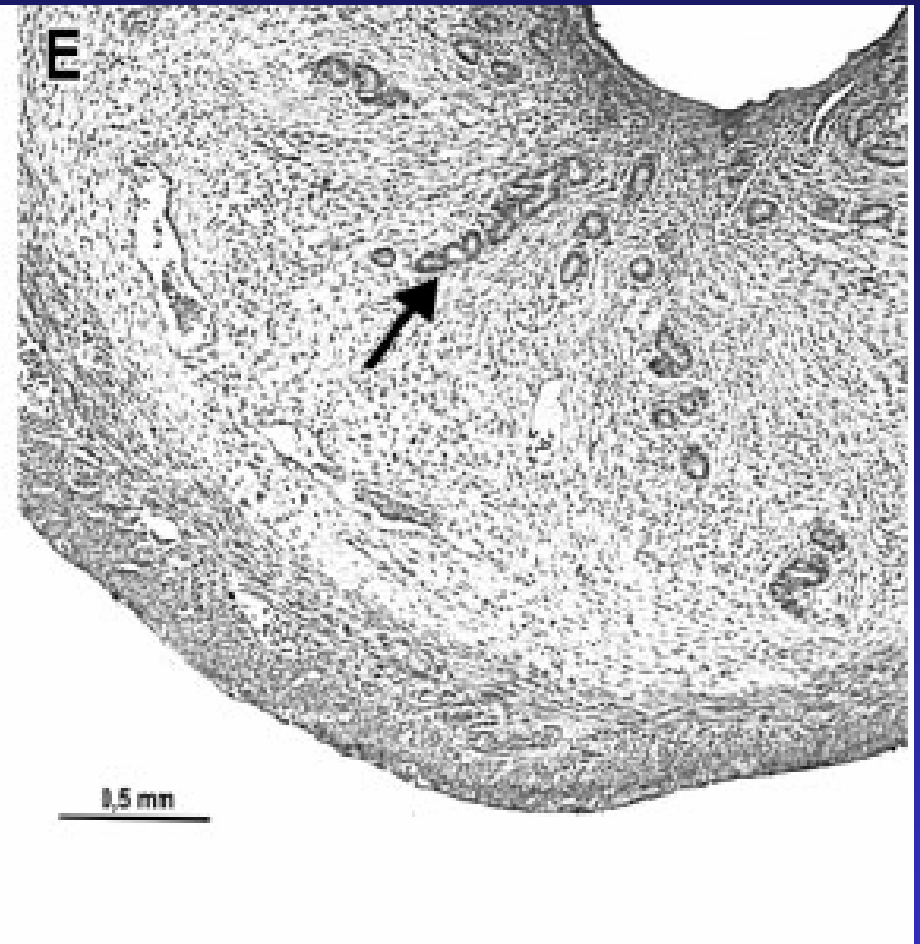
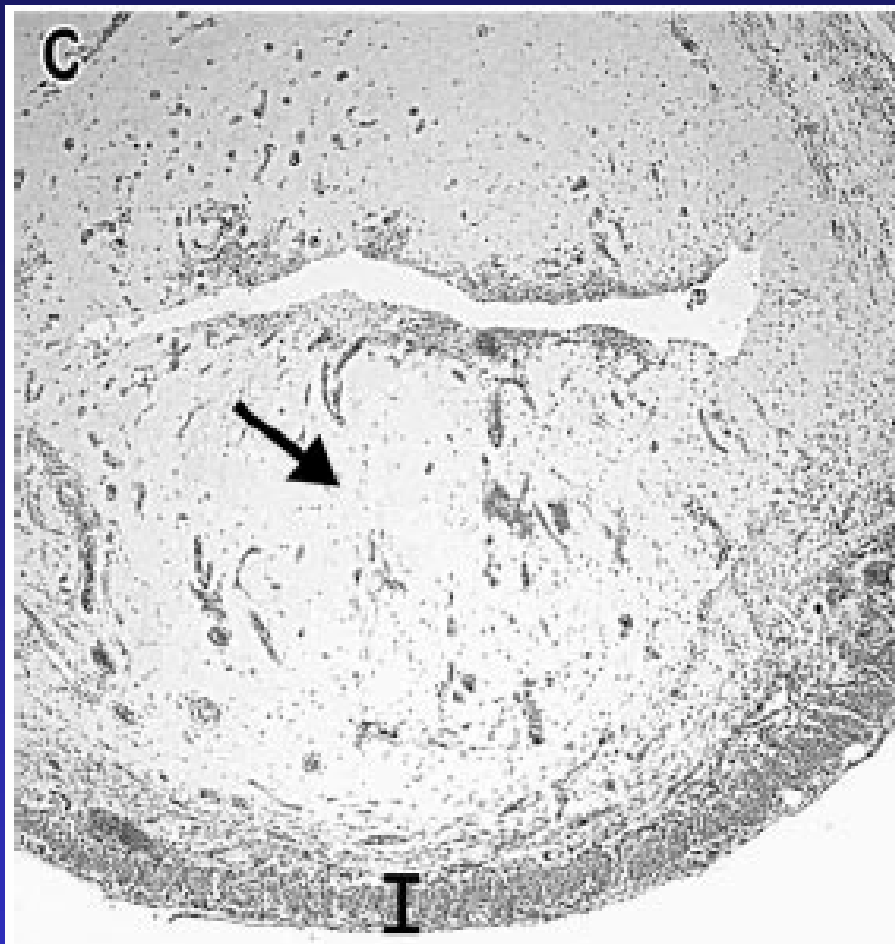
- Evaluate the structural effect of PDT with BPD on the rat uterus by using it in an IV injection and with a short drug-light interval
- Determine the optimal concentration of BPD required for selective endometrial tissue destruction

Material & Methods

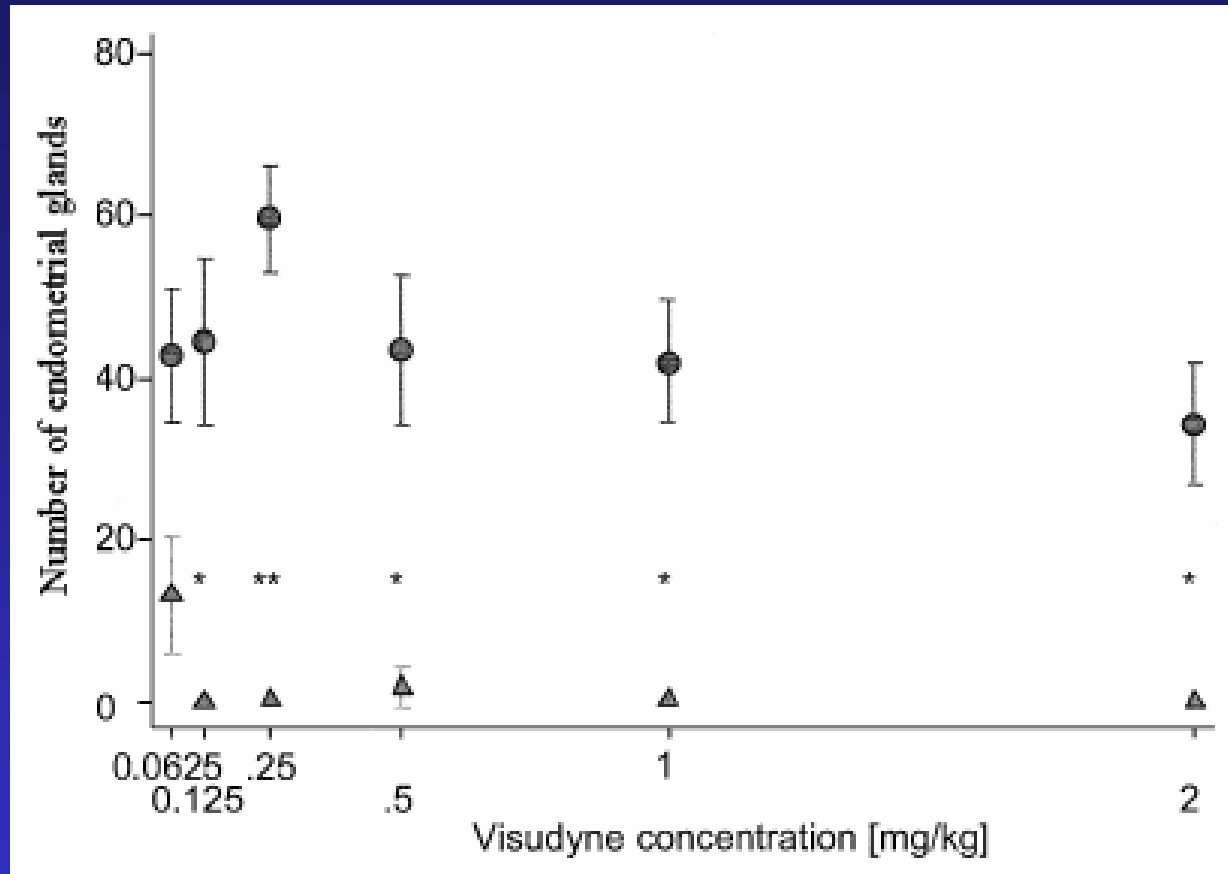
- Rodent uterine horn
- IV (jugular vein injection) of BPD in a liposomal formulation (2 mg/kg, 1 mg/kg, 0.5 mg/kg, 0.25 mg/kg, 0.125 mg/kg and 0.0625 mg/kg)
- Midline laparotomy
- Laser irradiation (630 nm) with a cylindrical diffusing fiber (3 cm long, 1.2 mm diameter) after 5 minutes and 120 J/cm² light dose (100 mW/cm, 500 s)
- Sacrifice of the rats 4 days after light treatment for histology



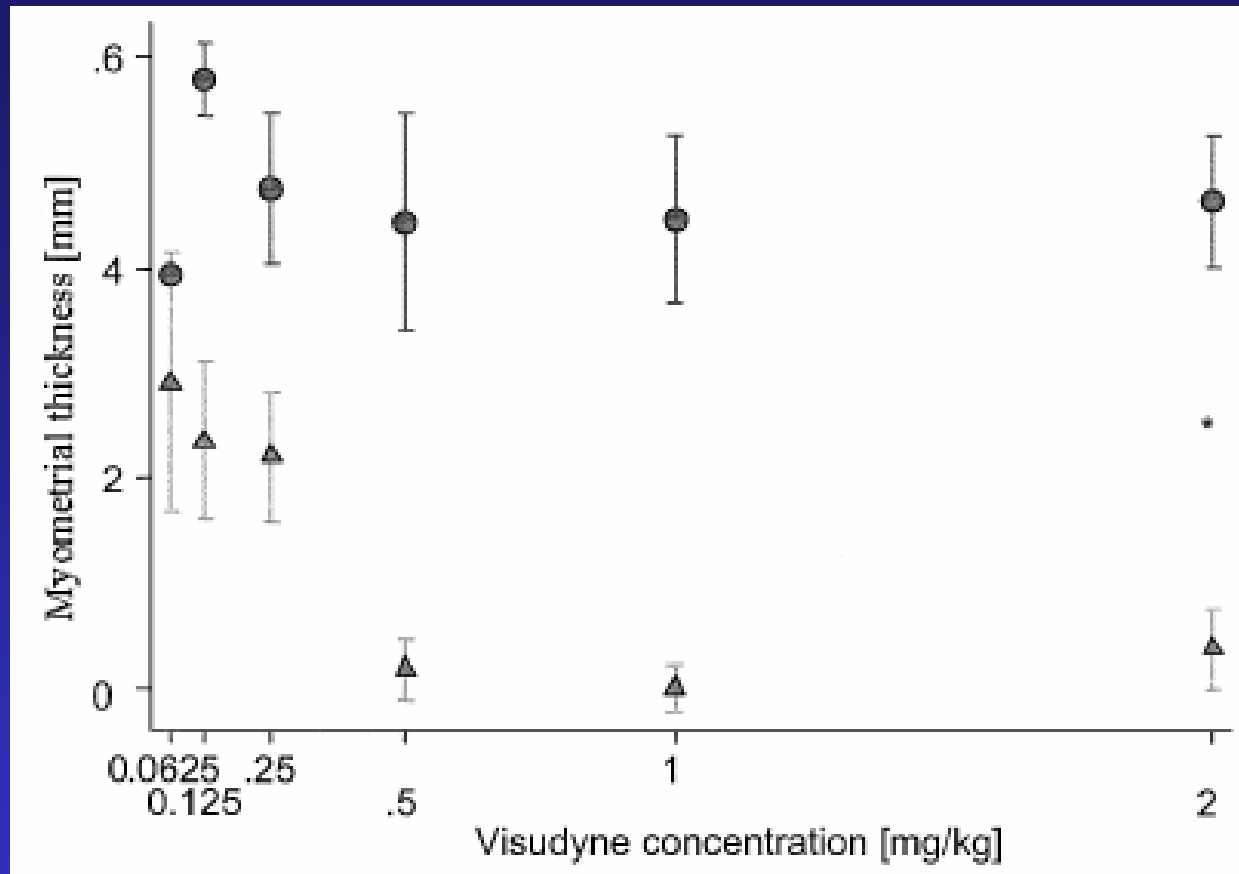
(A) BPD 2mg/kg i.v., (B) 1mg/kg, (D) 0.0625 mg/kg



(C) BPD 0.25 mg/kg i.v., (E) Control (0.9% NaCl)



Median and interquartile range for the number of glands between the untreated uterine horn and treated horn in each of the six treatment groups. *P* values after Bonferroni's correction: **P* < 0.008; ***P* < 0.001. Circles represents the untreated horn and triangles the treated horn.



Median and interquartile range for the myometrium thickness measured in the untreated and treated horn in each of the six treatment groups. *P* values after Bonferroni's correction: **P* < 0.008. Circles represents the untreated horn and triangles the treated horn.

CONCLUSIONS

- BPD-PDT with short drug-light time interval (5 min) is very effective at all concentrations
- The optimal drug concentration, defined as that which causes total glandular destruction with minimal loss of the myometrial thickness and minimal inflammatory reaction, ranged from 0.25 to 0.125 mg/kg
- With the highest concentration (2 and 1 mg/kg) a significant loss of myometrial thickness, severe inflammatory reaction and adherence of the adjacent organ to the uterus was recorded

Meta-tetrahydroxyphenylchlorin (mTHPC) uptake
and tissue distribution in relation to photodynamic
efficacy

AIMS

- Evaluate the PDT response of the tumour with mTHPC by using different drug-light intervals after IV injection
- Compare long with short drug-light interval

Material & Methods

- Female nude BalbC mice with H-MESO1 (human mesothelioma xenograft)
- IV (tail vein injection) of mTHPC (0.3 mg/kg) dissolved in ethanol, polyethylene glycol 400 (PEG) and water
- Laser irradiation (652 nm) with a microlens applicator (12 mm diameter light spot) at 5 min to 72 h after drug administration and different light doses (5, 10 or 30 J/cm²) to the tumour surface
- Measurement of tumour size and tumour-free survival of maximum 120 days

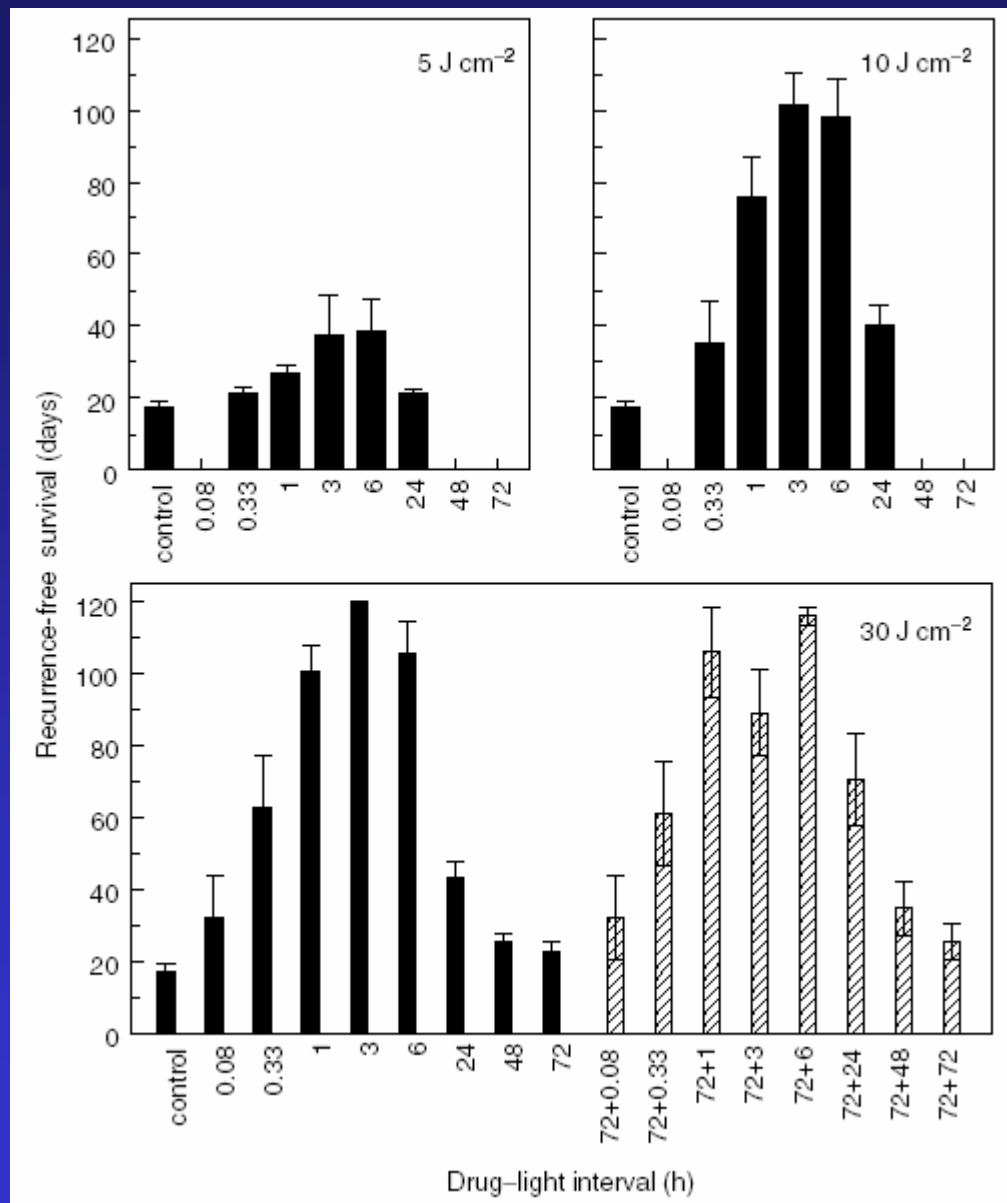
Drug dose (mgkg ⁻¹)	Light dose (J cm ⁻²)	Drug-light interval							
		5 min	20 min	1 h	3 h	6 h	24 h	48 h	72 h
1 × 0.3	5		0/8	0/8	1/8	0/8	0/8		
1 × 0.3	10		1/8	1/8	4/8	4/8	0/8		
1 × 0.3	30	1/8	2/8	3/7 [†]	8/8	5/8	0/8	0/8	0/8
2 × 0.3	30	1/8	1/8	5/7	3/8	5/7	1/7	0/8	0/8

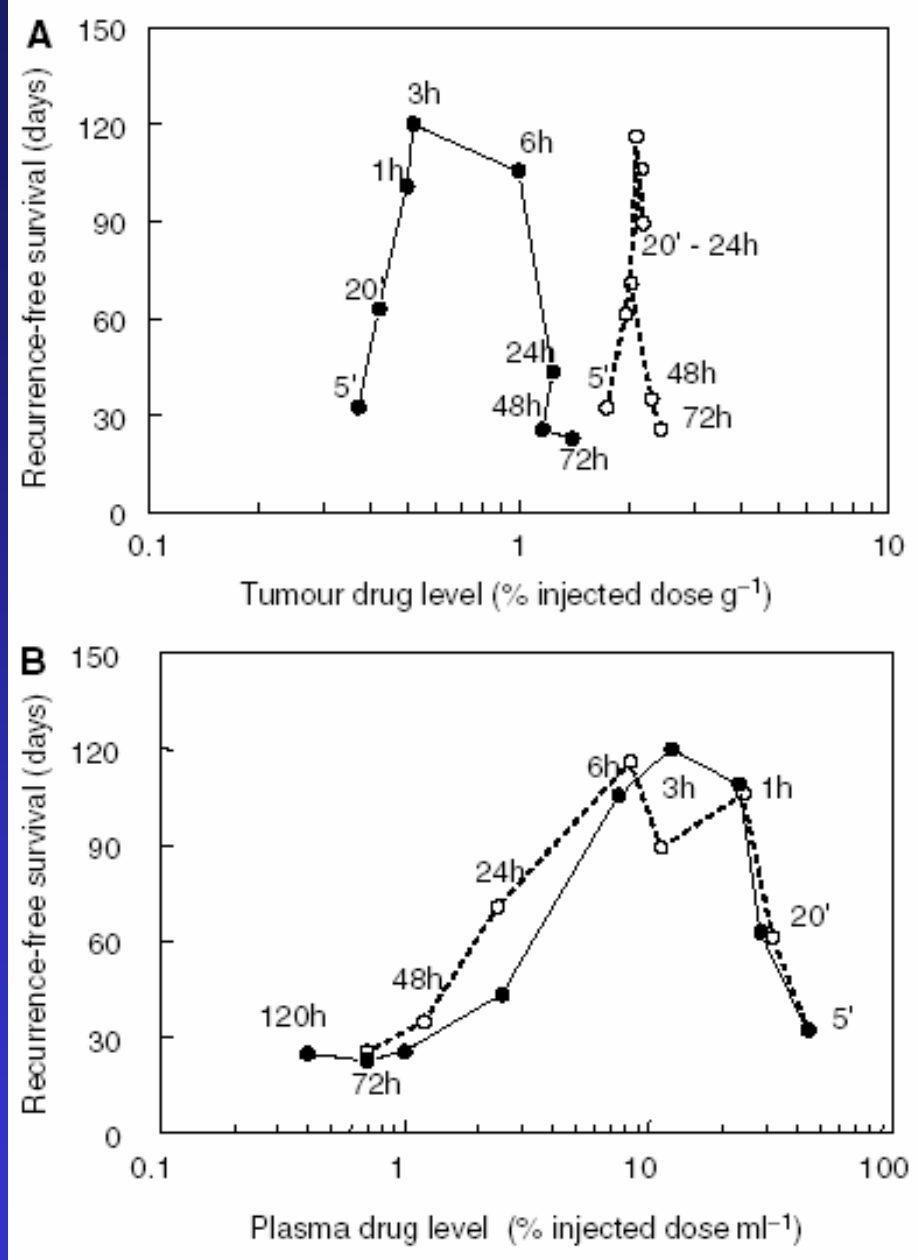
[†]No palpable tumour at 20 days after treatment time.

[†]This group also included three tumours that did not regrow, but mice were sacrificed with lung metastases before the cure end point time of 20 days.

Number of cured (a) tumours per treatment group for light doses 5-30 J/cm² applied at various intervals after one or two doses of mTHPC (0.3 mg/kg)

Mean recurrence-free survival (\pm s.d.) for groups of mice ($n=8$) illuminated with 5 or 10 J/cm² at different intervals after a single mTHPC dose (top panels), or with 30 J/cm² after a single drug dose (solid bars, bottom panel) or two doses separated by 72 h (hatched bars, bottom panel). Cured tumours were assigned a tumour-free survival of 120 days and were included in the calculation of mean-recurrence-free survival.



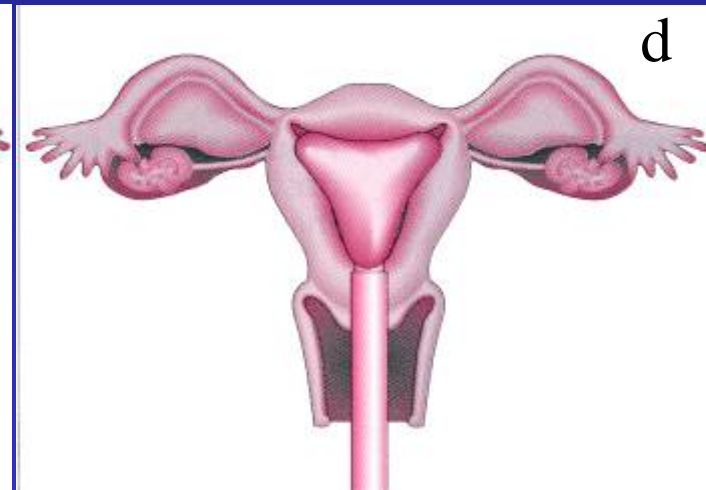
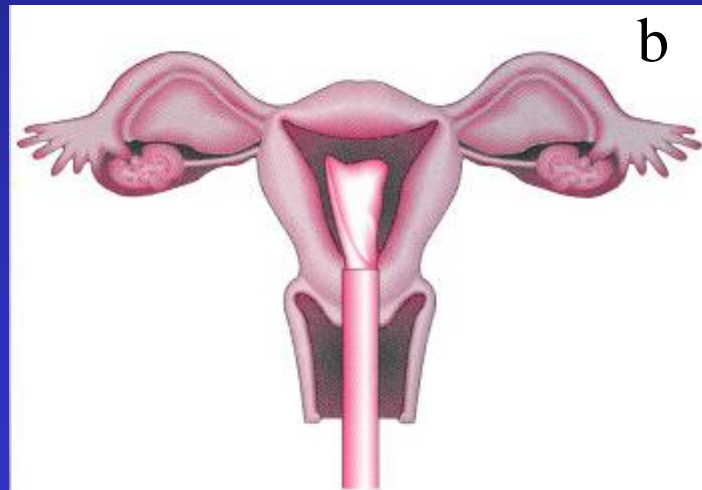


Mean recurrence-free survival for groups of mice

CONCLUSIONS

- mTHPC-PDT with short drug-light time interval (3 h) is more effective than long drug-time interval as long as 72 h
- No correlation between PDT response of the tumour and tumour drug level or plasma drug level
- A second injection of a same dose of mTHPC didn't increase the effect
- mTHPC-PDT is largely mediated via vascular damage and that selectivity of the treatment is based on other than differential tumour drug uptake

Light Device (Balloon) for Patients



Reflective elastic balloon shaped like the cavity of the uterus

H. van den Bergh, Endoscopy 1998, 30 p392-407

Perspective

- Photodynamic therapy of the endometrium in the animal model after IV administration of mTHPC
- Determine optimal drug, light doses and drug-light interval
- Pilot study in patients



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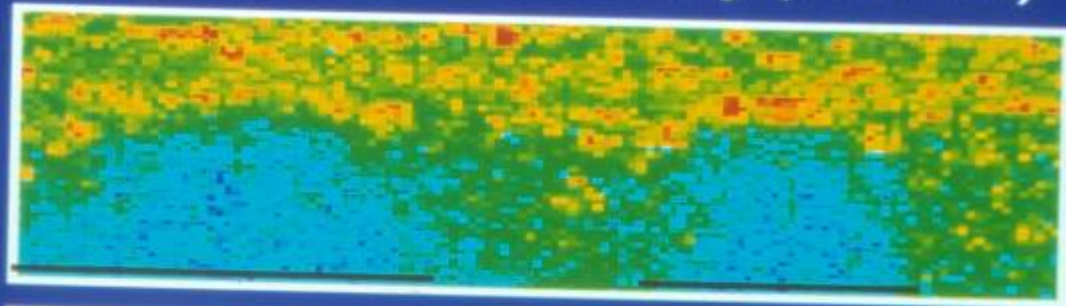
Werner Marie-Laure

PII late

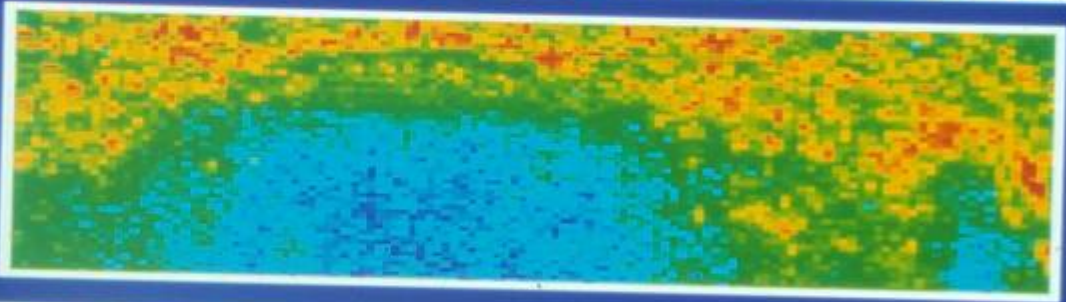
Vein (231mm)

Artery (140 mm)

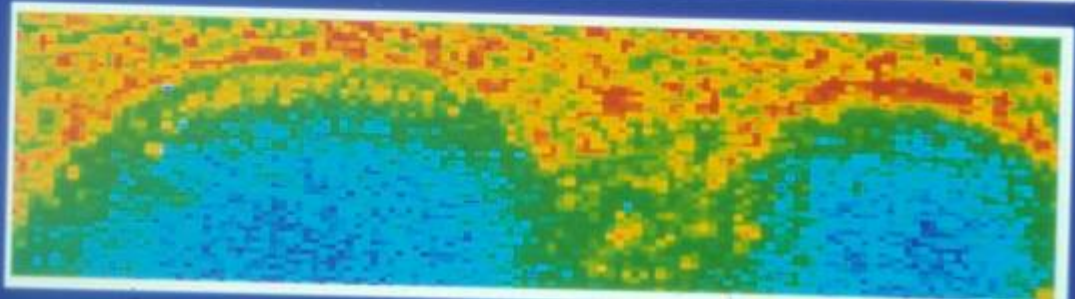
t=0 min



t=11 min



t=51 min



PII late

Vein

Arterial flow

Artery

t=0 min



t=11 min

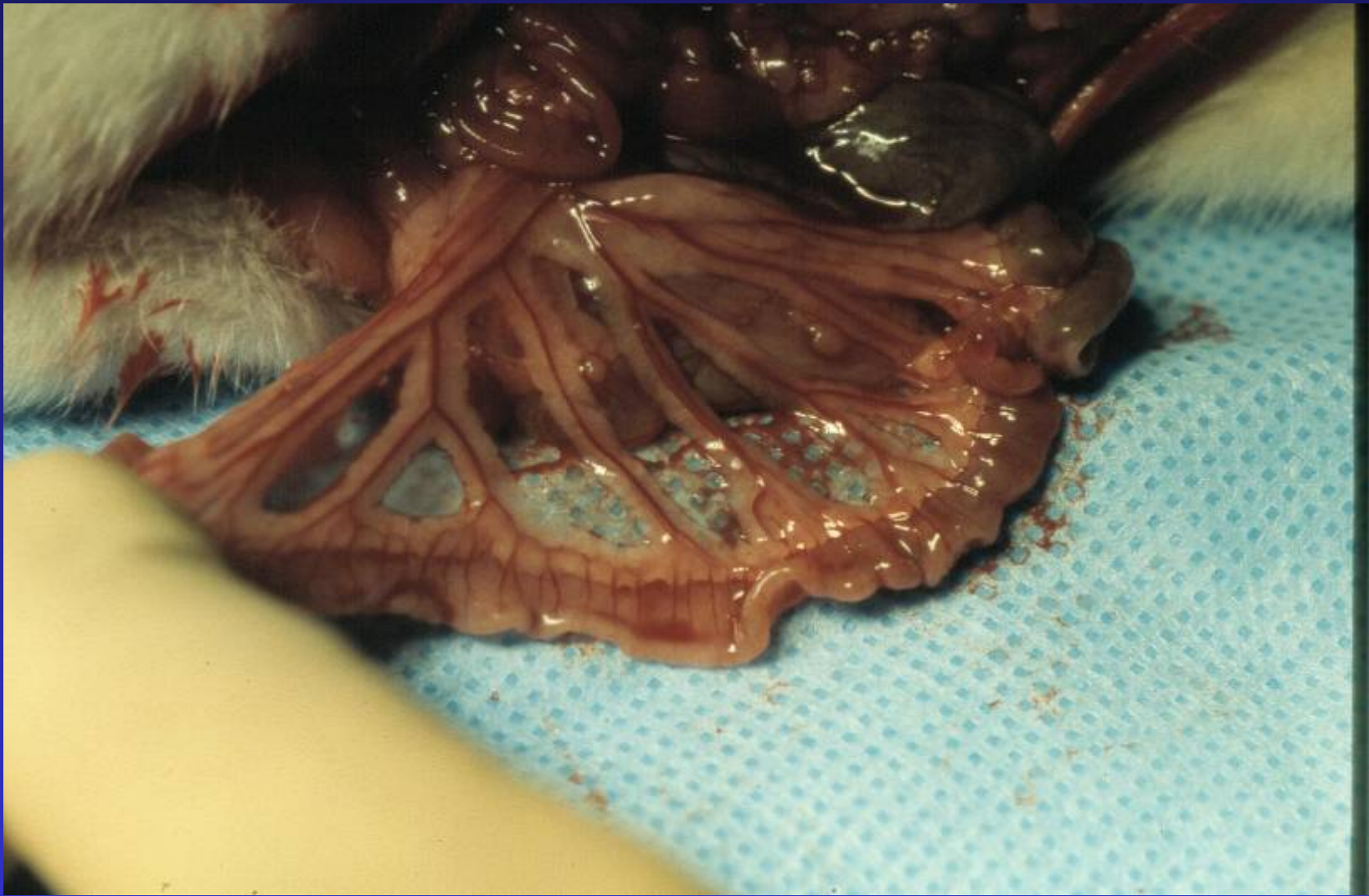


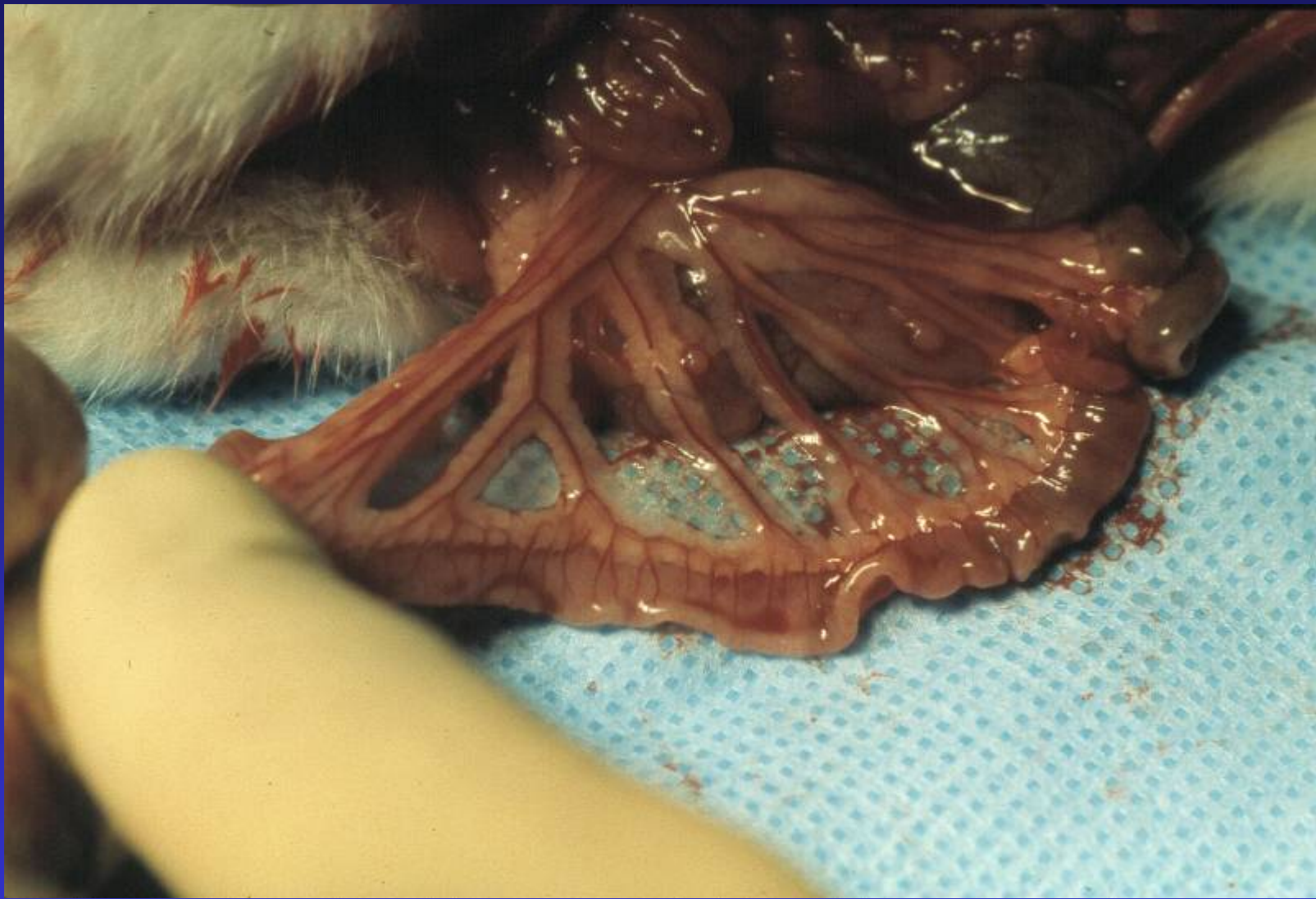
t=51 min

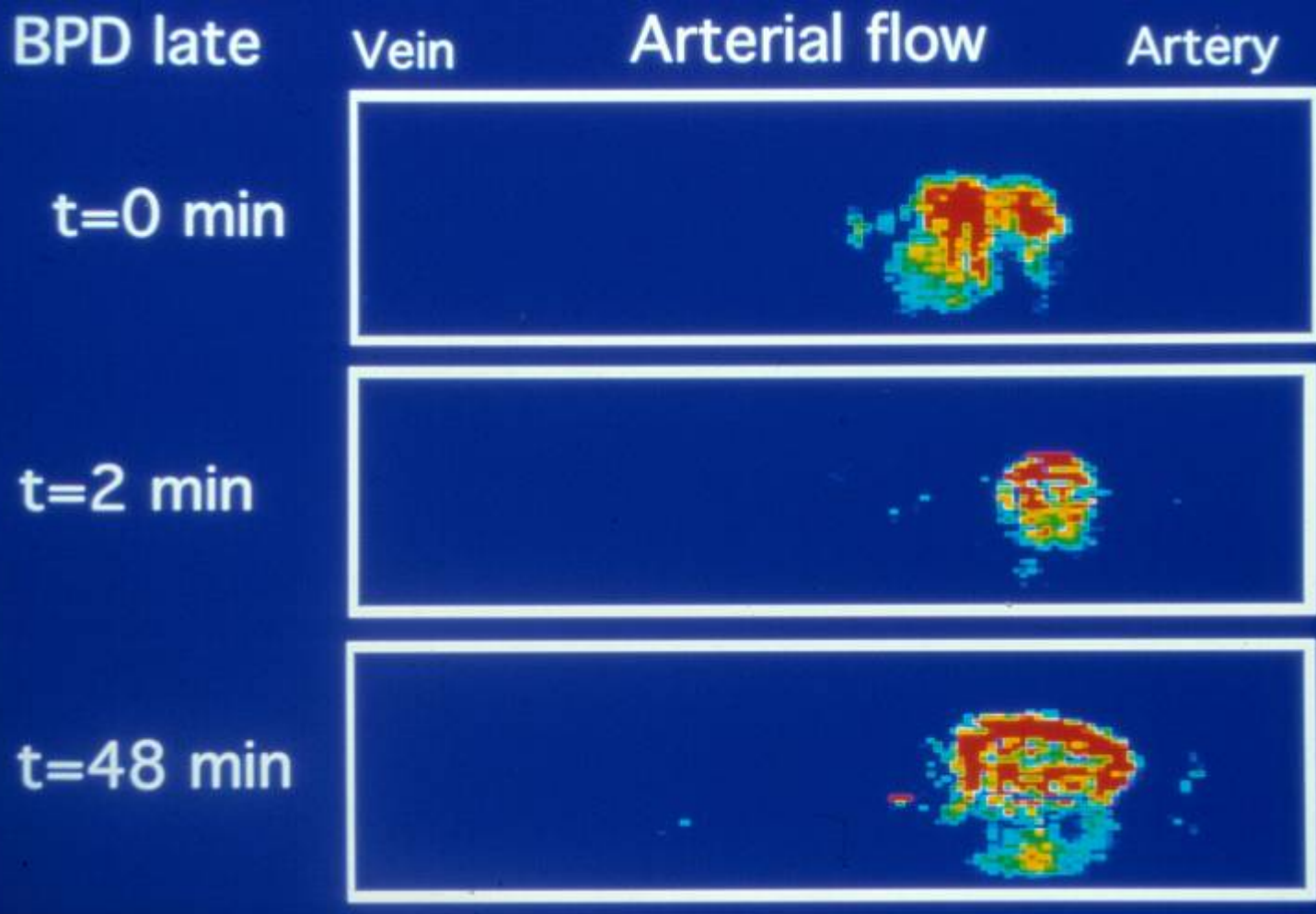




Sprague Dawley Mesenterium







CONTROL

Artery

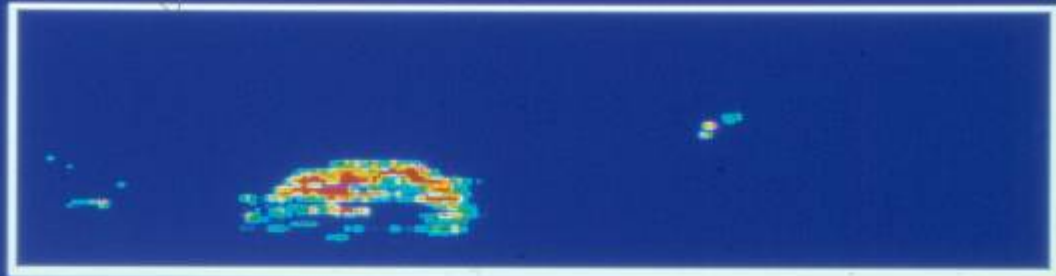
Arterial flow

Vein

t=0 min



t=15 min



t=45 min



BPD early

Artery

Arterial flow

Vein

t=0 min



t=16 min



t=71 min



Light micrographs (A) and fluorescence (B) of a peritoneal nodule (size < 0.5 mm) 6 hr after ip ALA administration.

Magnification (C) of the peritoneal serosa (boxed area in B) showing a thin layer of tumor matching with the fluorescence

