Improving the Effectiveness of RT: *Interstitial Fluid Dynamics in Human Tumors*

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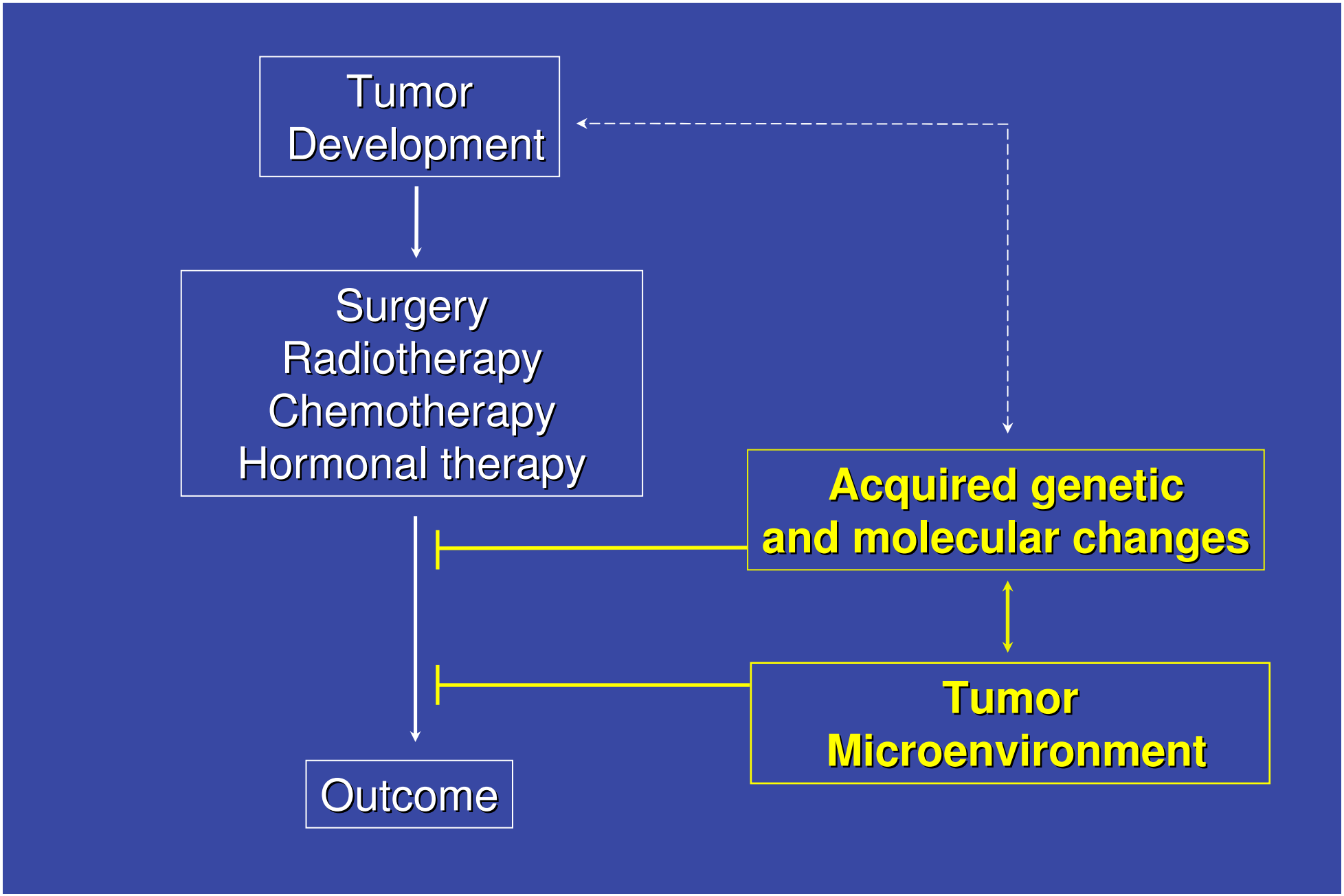
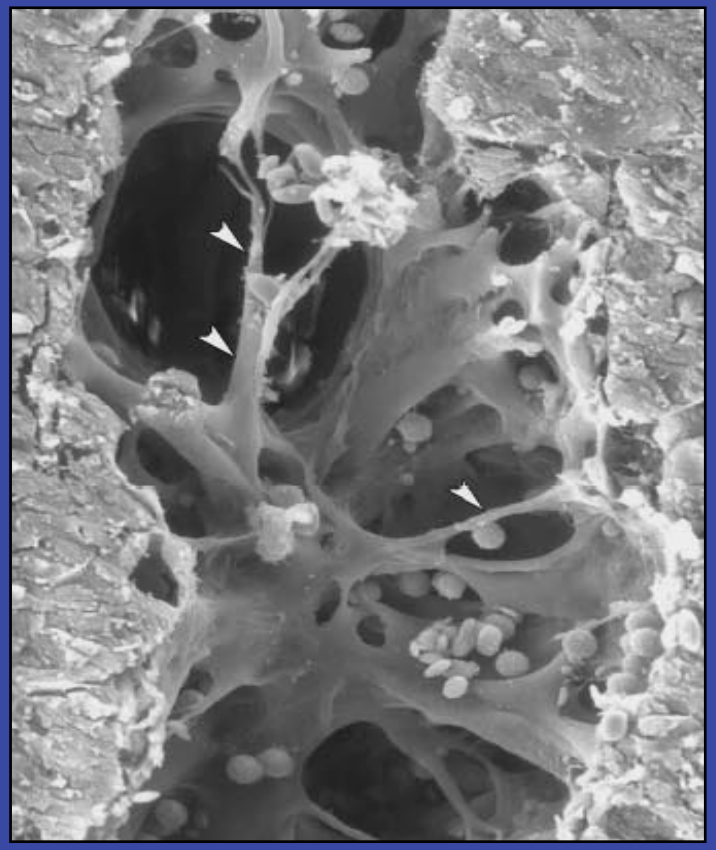
Radiotherapy Opportunities

- Precision RT (IMRT)
- Spatial variability
- Temporal variability
- Adaptive RT
- Image analysis
- Biologic imaging
- RT dose modeling
- Biologic effect modeling
- Biologic RT enhancement


Tumor Development
Surgery
Radiotherapy
Chemotherapy
Hormonal therapy
Acquired genetic and molecular changes
Tumor Microenvironment
Outcome

Tumors have…

- Chaotic vasculature
- Hyperpermeable vessels
- Abnormal lymphatics
- High interstitial protein
- High interstitial water
- Abnormal interstitium

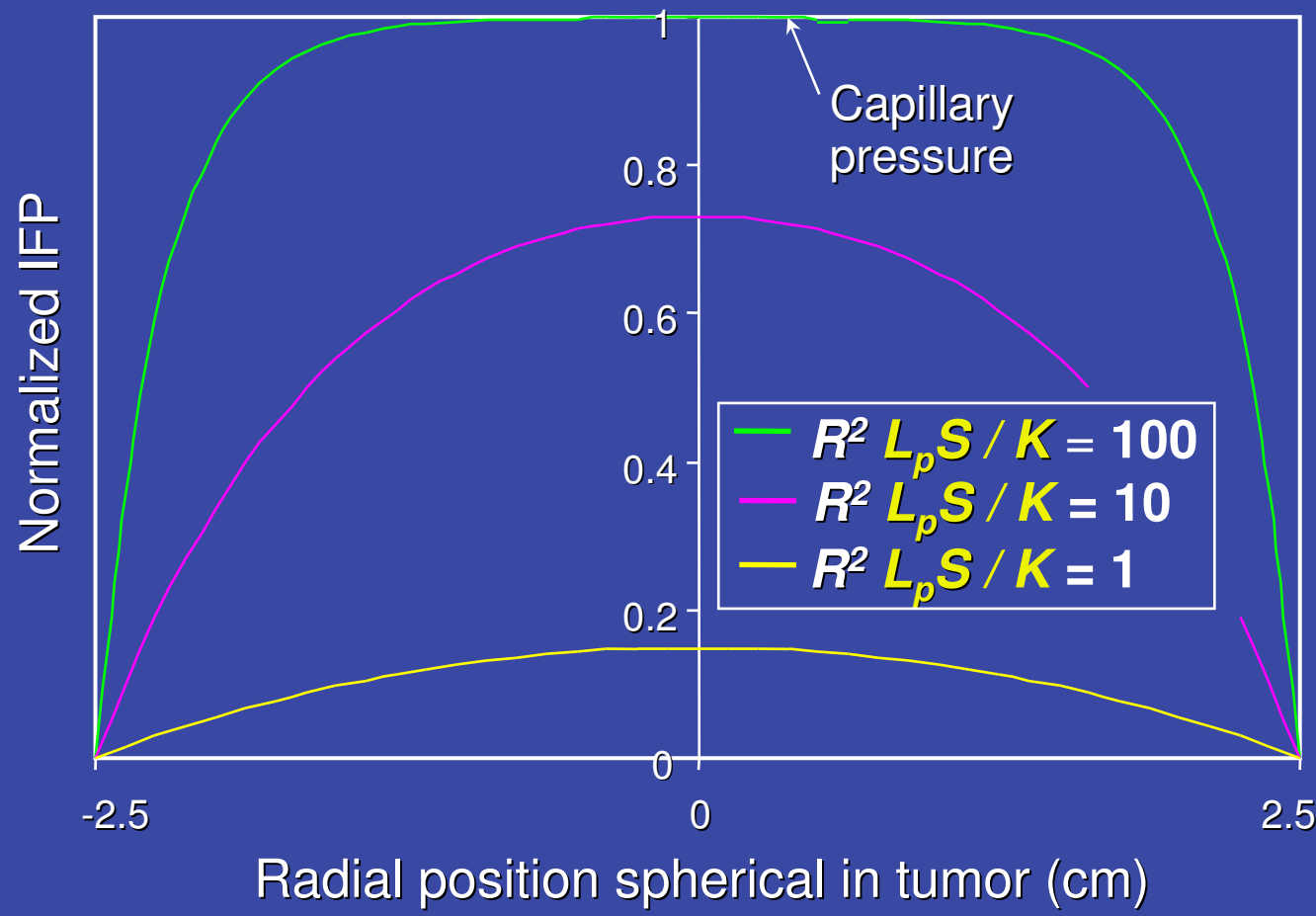


Hashizume, 2000

What Causes High IFP in Tumors?

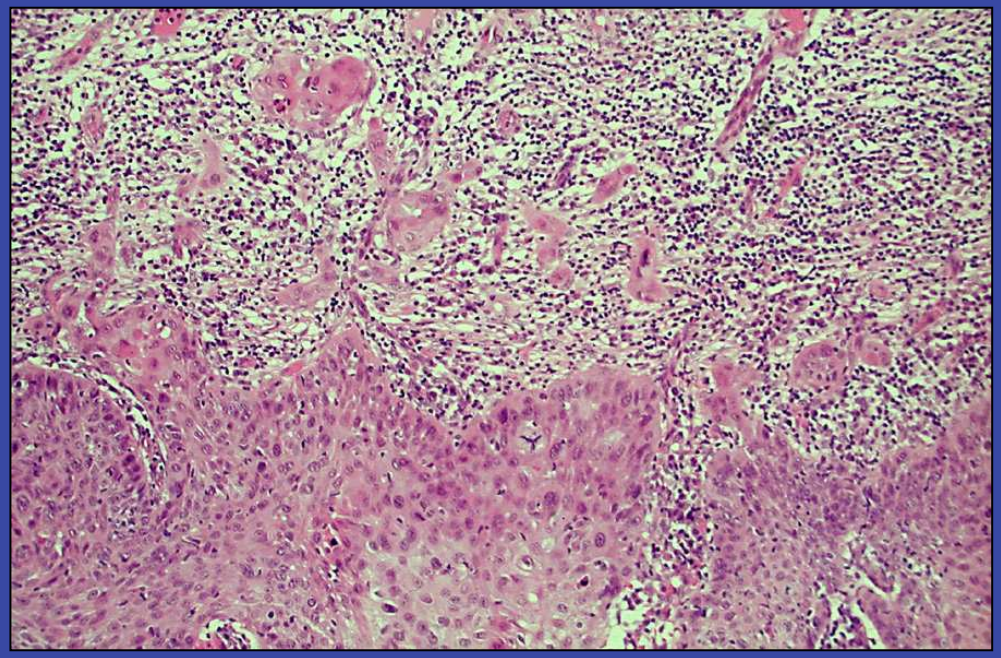
- High vascular conductivity ***(L_pS)***
- Low interstitial conductivity ***(K)***
- No lymphatics
- High geometric and viscous blood flow resistance

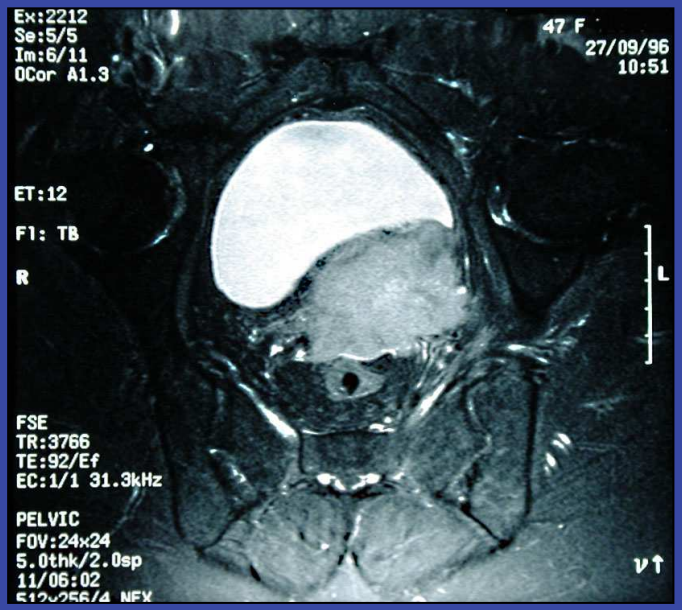
IFP = Capillary Pressure in Tumors



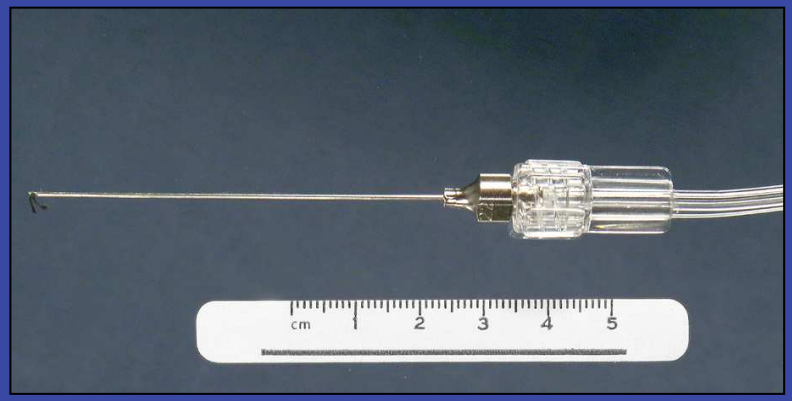
Baxter, 1989

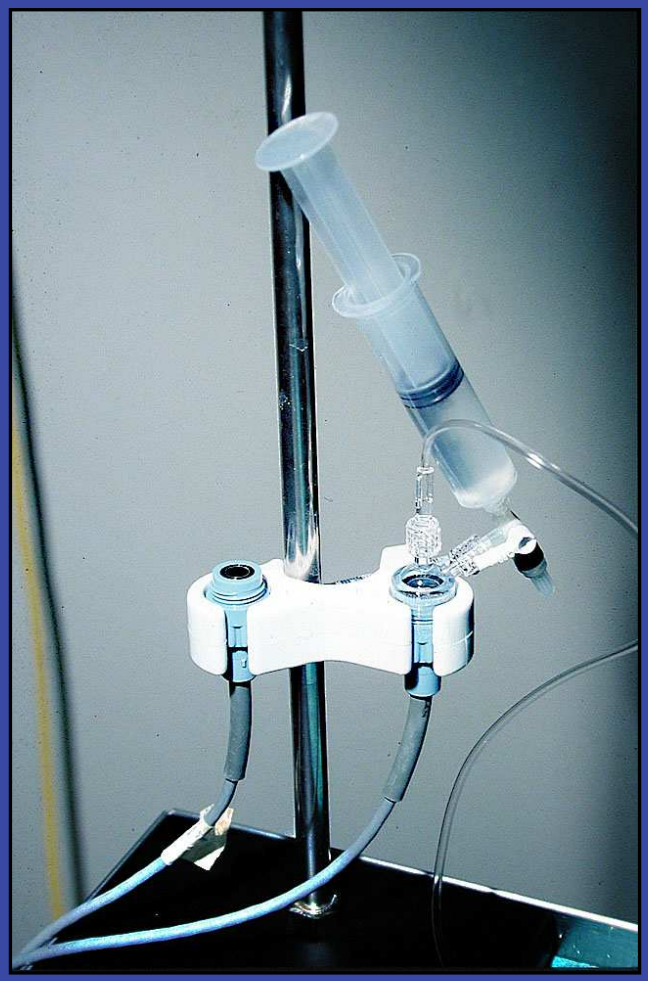
Cervix Cancer



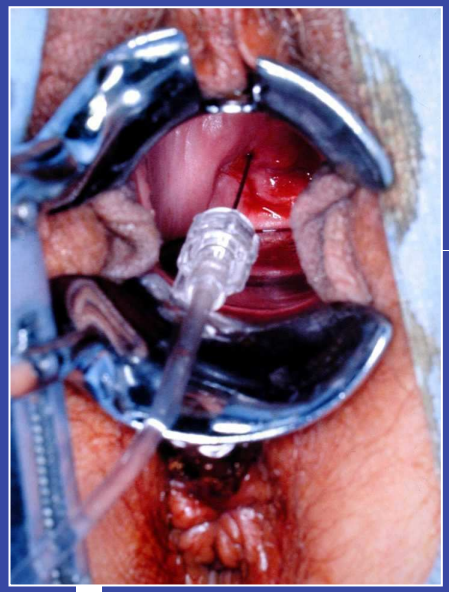


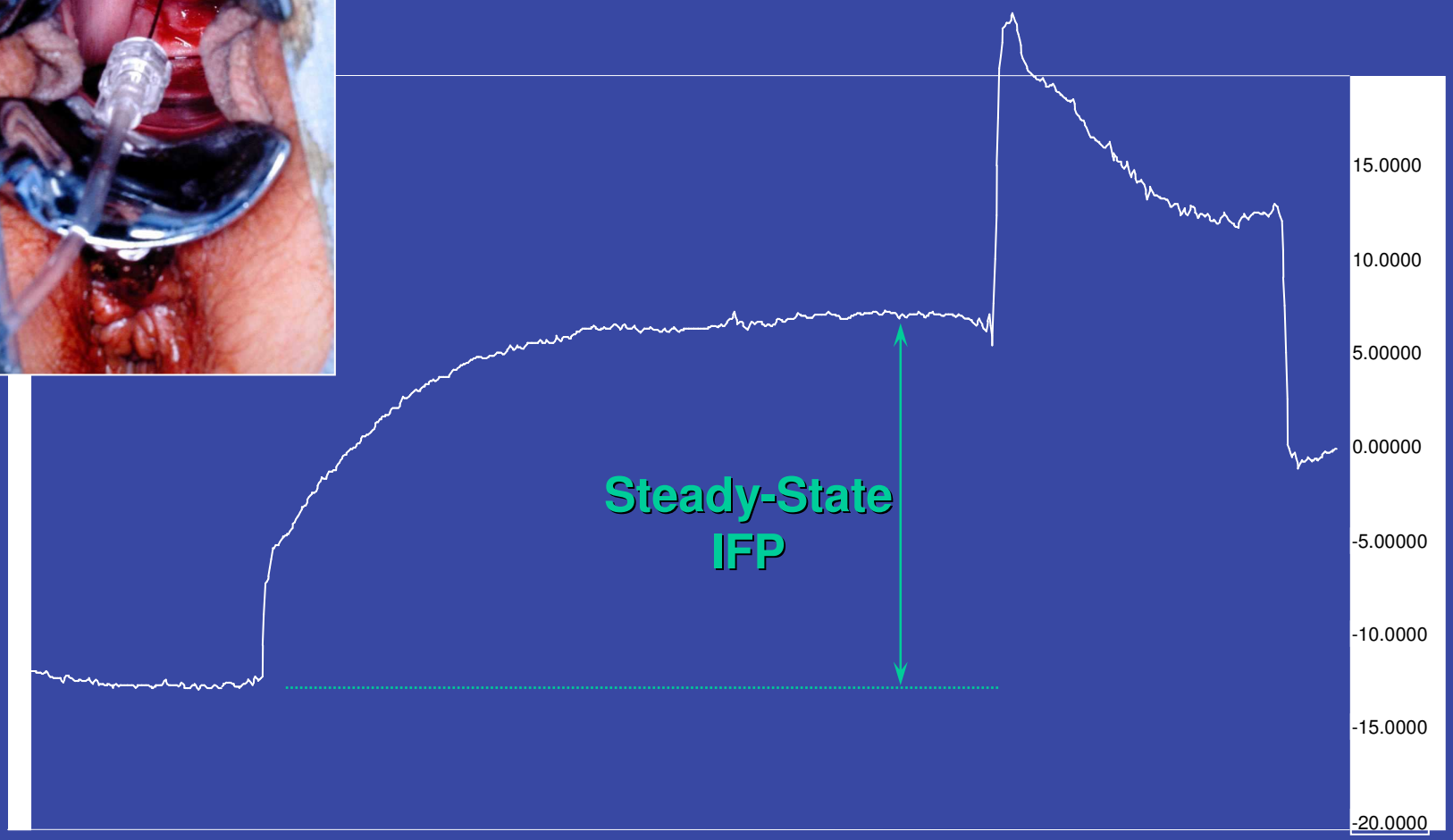
IFP Measurement



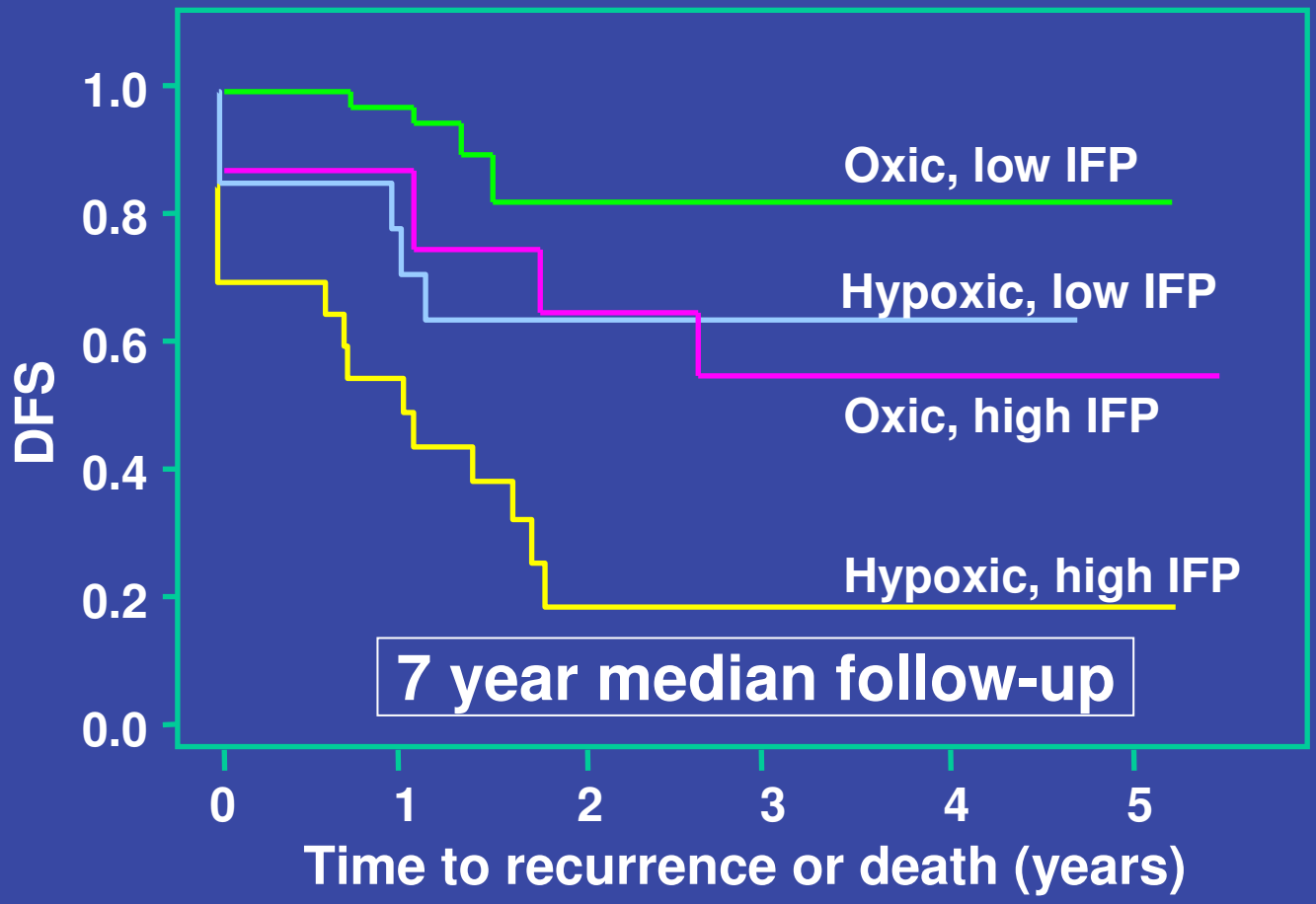


IFP Measurement

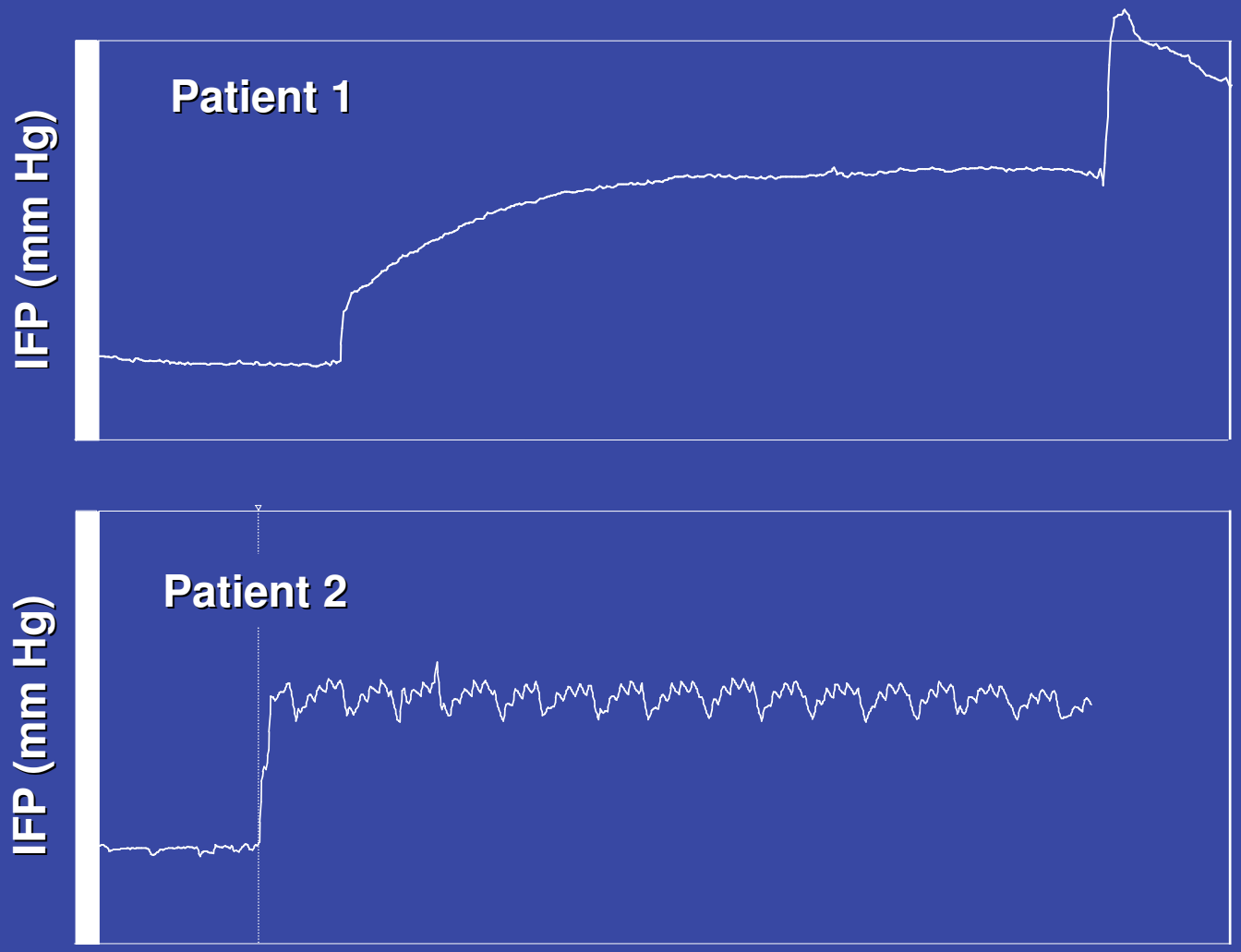




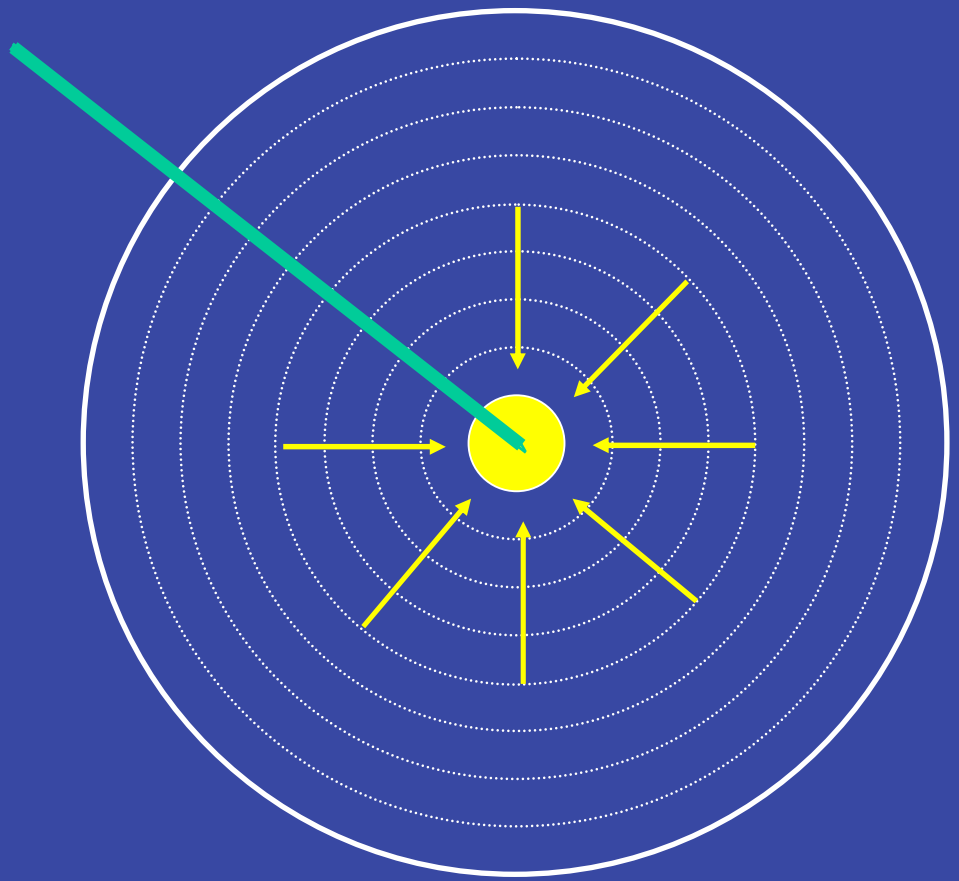
IFP: An Independent Prognostic Factor in Cervix Cancer



Time Response of IFP Measurements



Spatio-Temporal IFP Model



Spatio-Temporal IFP Model

- Homogeneous fluid model
- Transducer characteristics known
- Transient fluid flow depends on ***L_pS, K, E***
- Steady-state prior to needle insertion
- Transient disruption of steady-state
- Starling's law for transmural plasma flow
- Darcy's law for interstitial flow
- Conservation of mass

Finite Difference Equations

$$RTM(r) = \frac{1}{4/3\ \pi\ r^3\ L_p S}$$

Transmural flow resistance

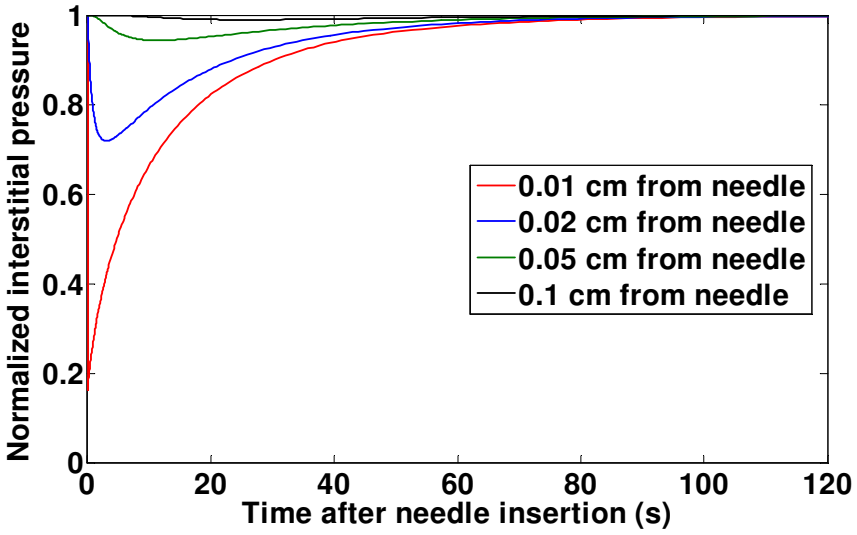
$$RI(r) = \frac{1}{4\ \pi\ K\ r}$$

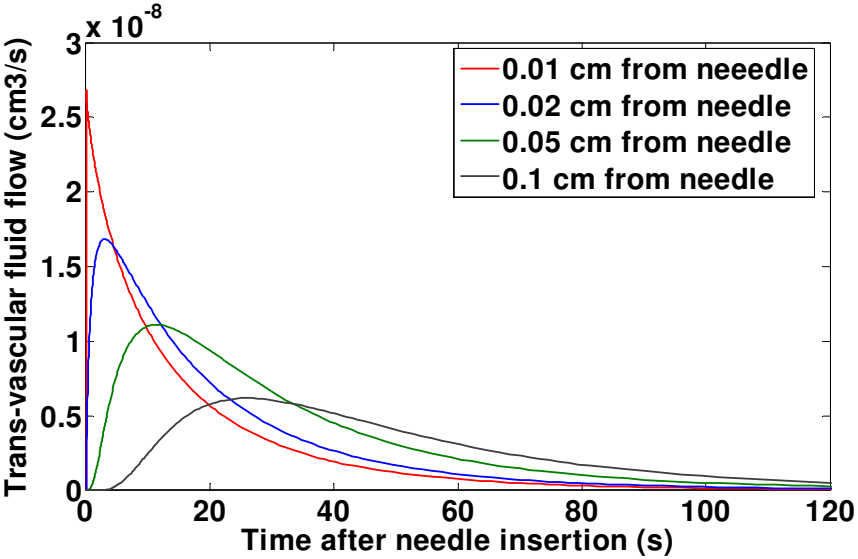
Interstitial flow resistance

$$CI(r) = \frac{4/3\ \pi\ r^3}{E}$$

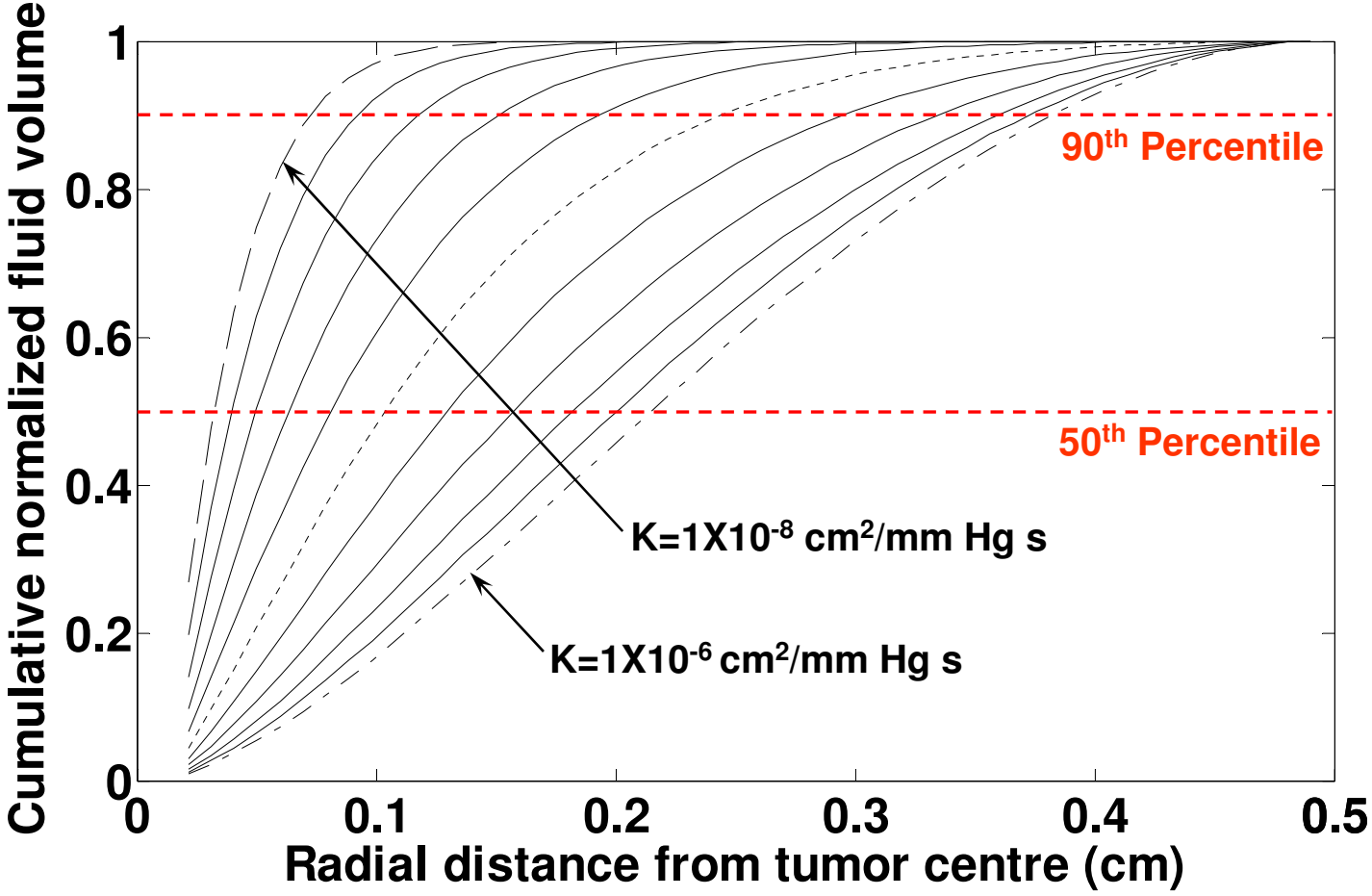
Interstitial Compliance

Transient Disruption of Interstitial Fluid Equilibrium

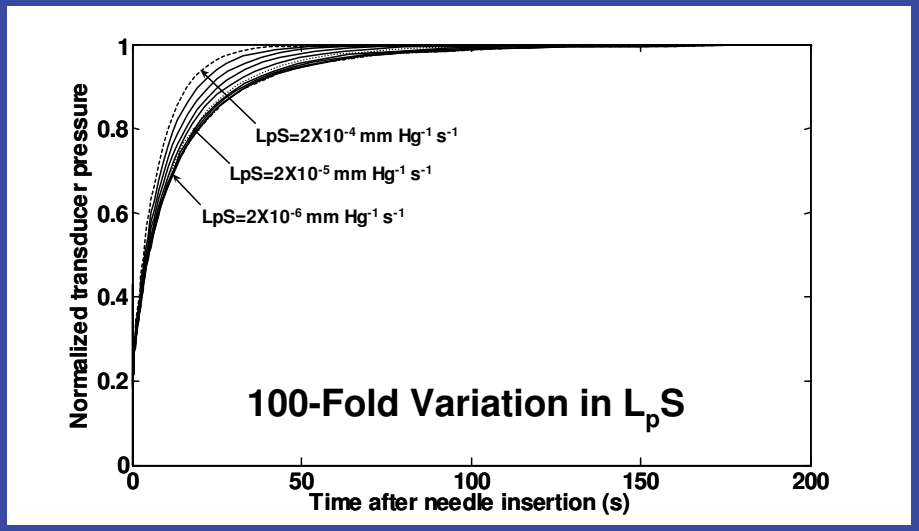


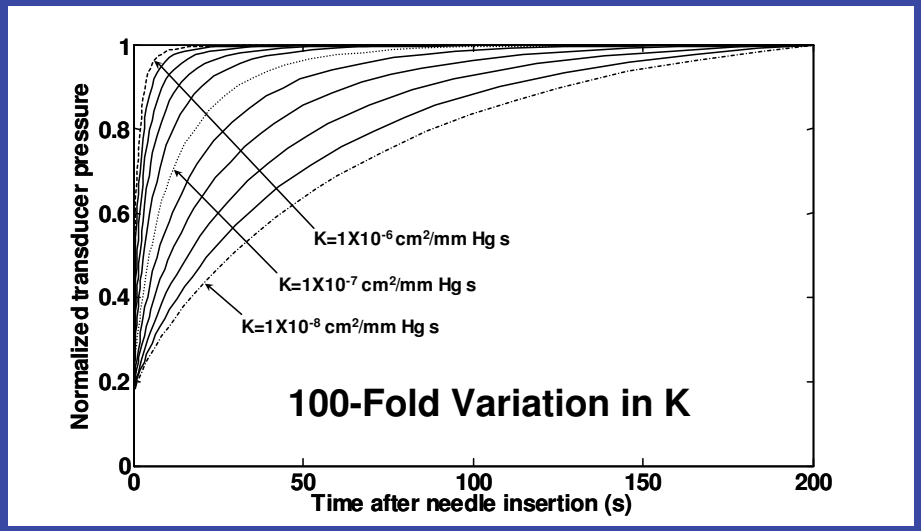


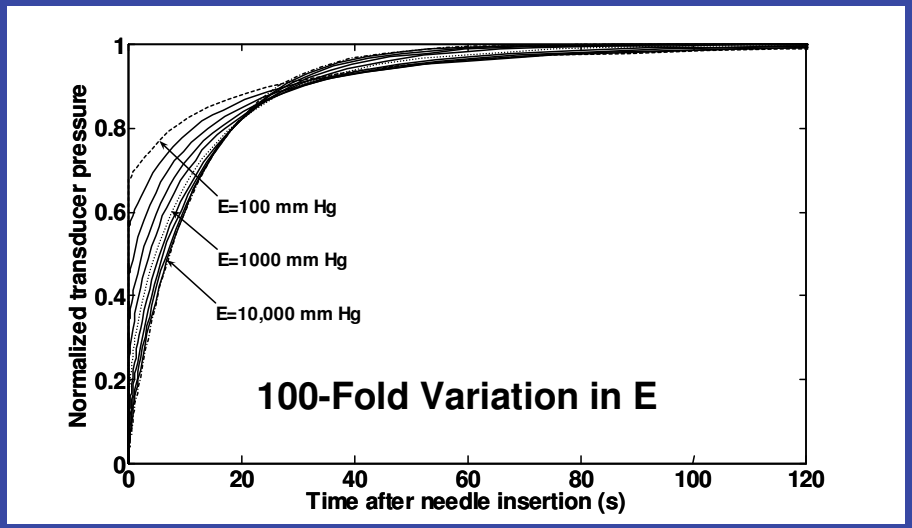
K Determines "Volume of Influence"

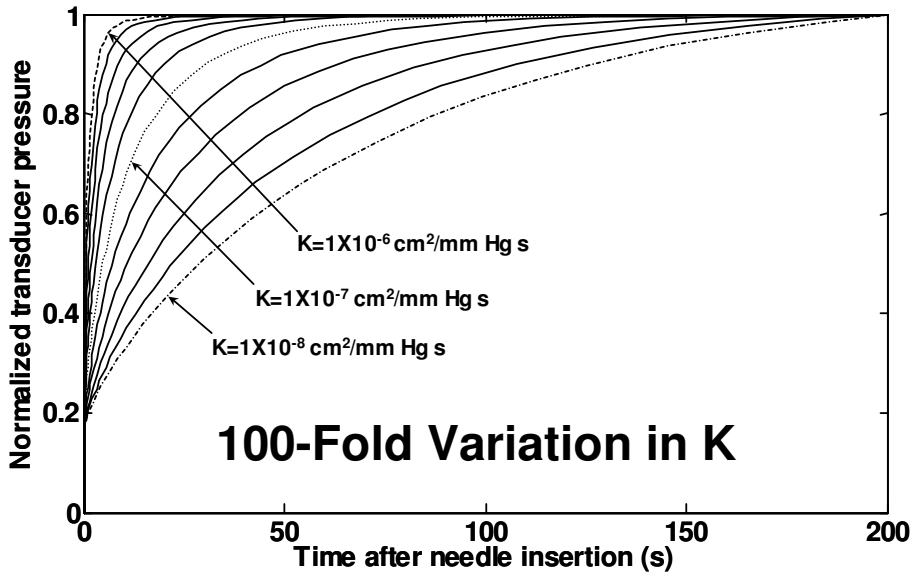


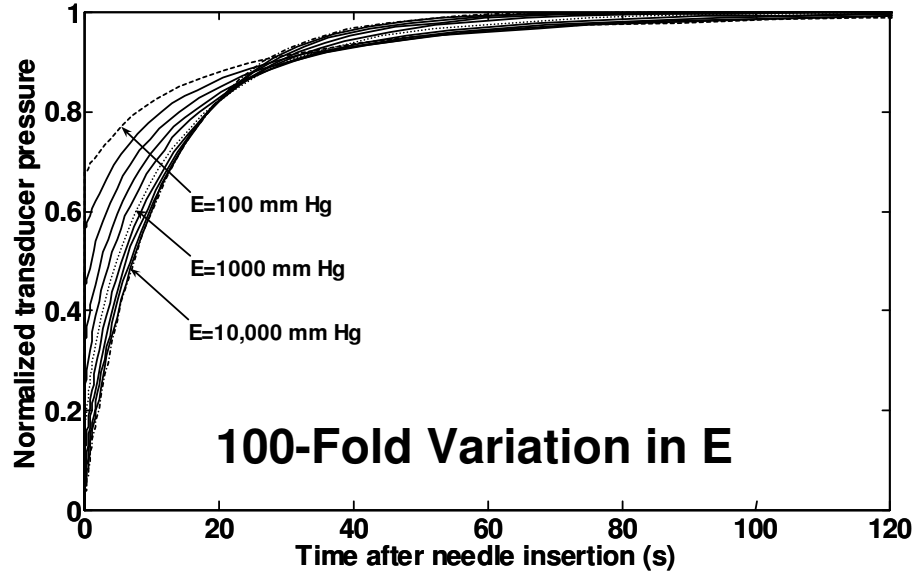
Time Response Depends on *E* and *K*



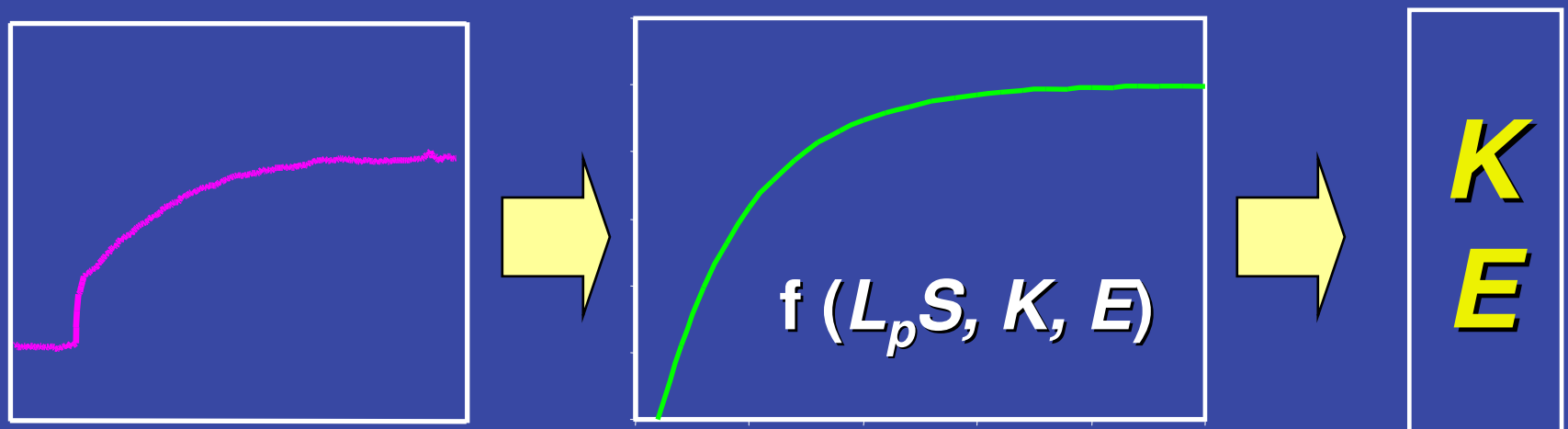





Normalized transducer pressure
Time after needle insertion (s)
K=1X10-6 cm2/mm Hg s
K=1X10-7 cm2/mm Hg s
K=1X10-8 cm2/mm Hg s
100-Fold Variation in K


Normalized transducer pressure
Time after needle insertion (s)
E=100 mm Hg
E=1000 mm Hg
E=10,000 mm Hg
100-Fold Variation in E

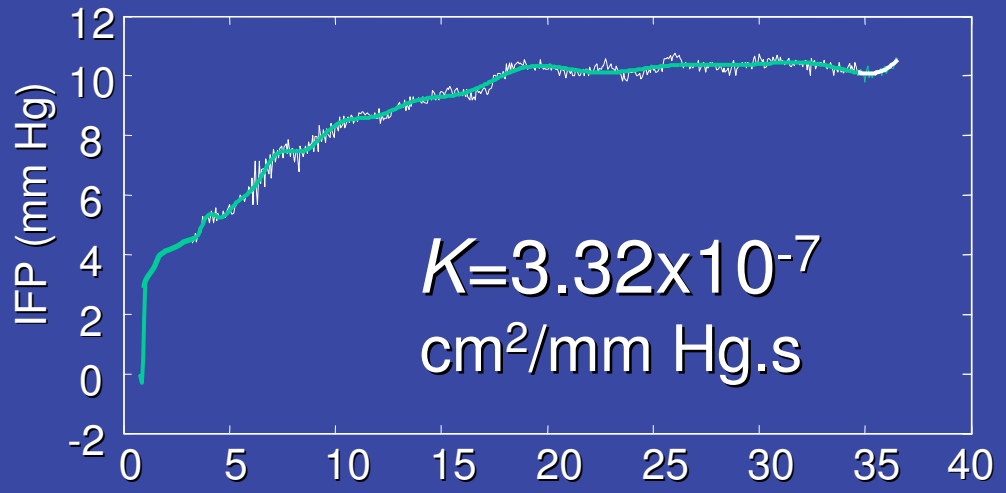
Physiologic Parameters from IFP Measurements



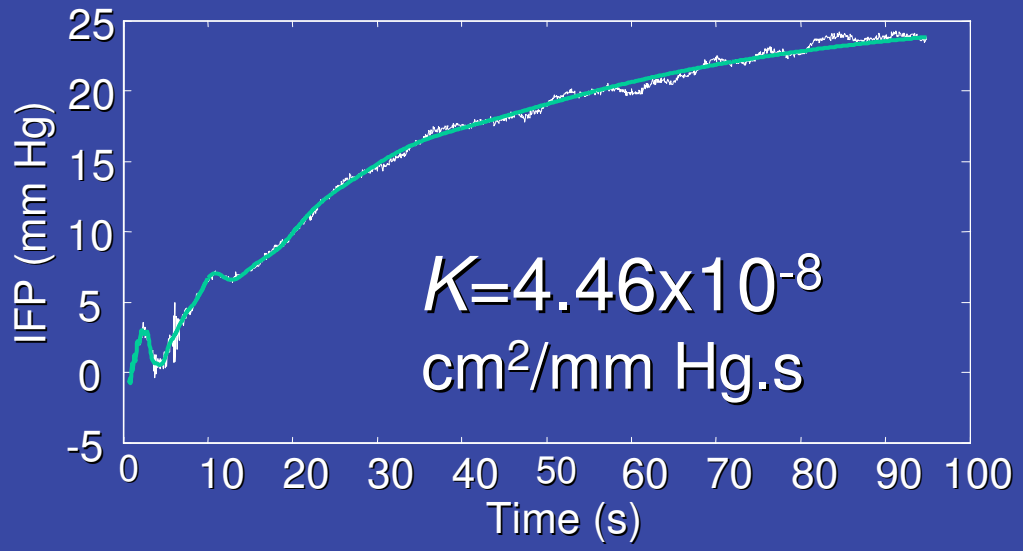
Measured IFP Time Response

Model Optimization

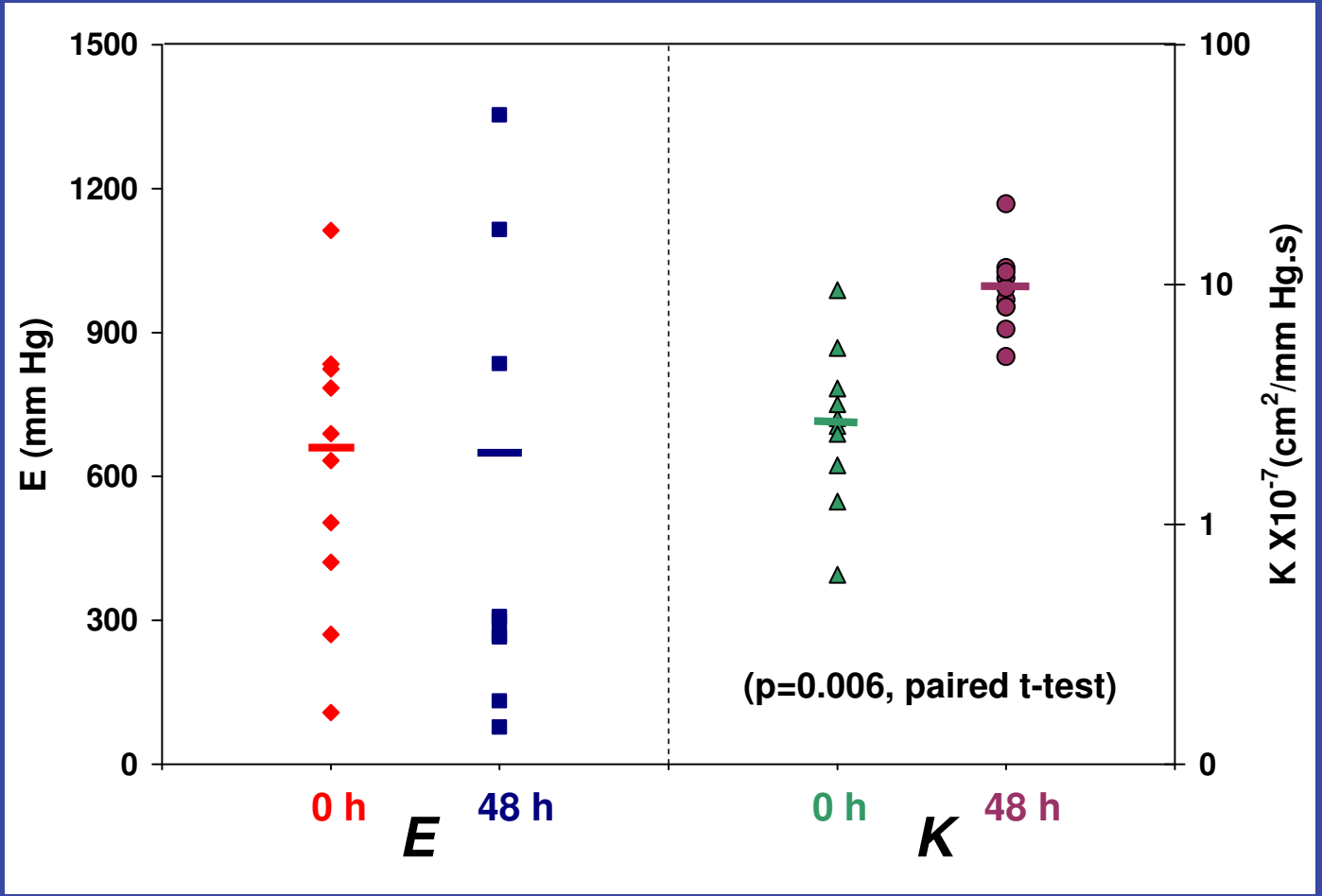
Patient 1



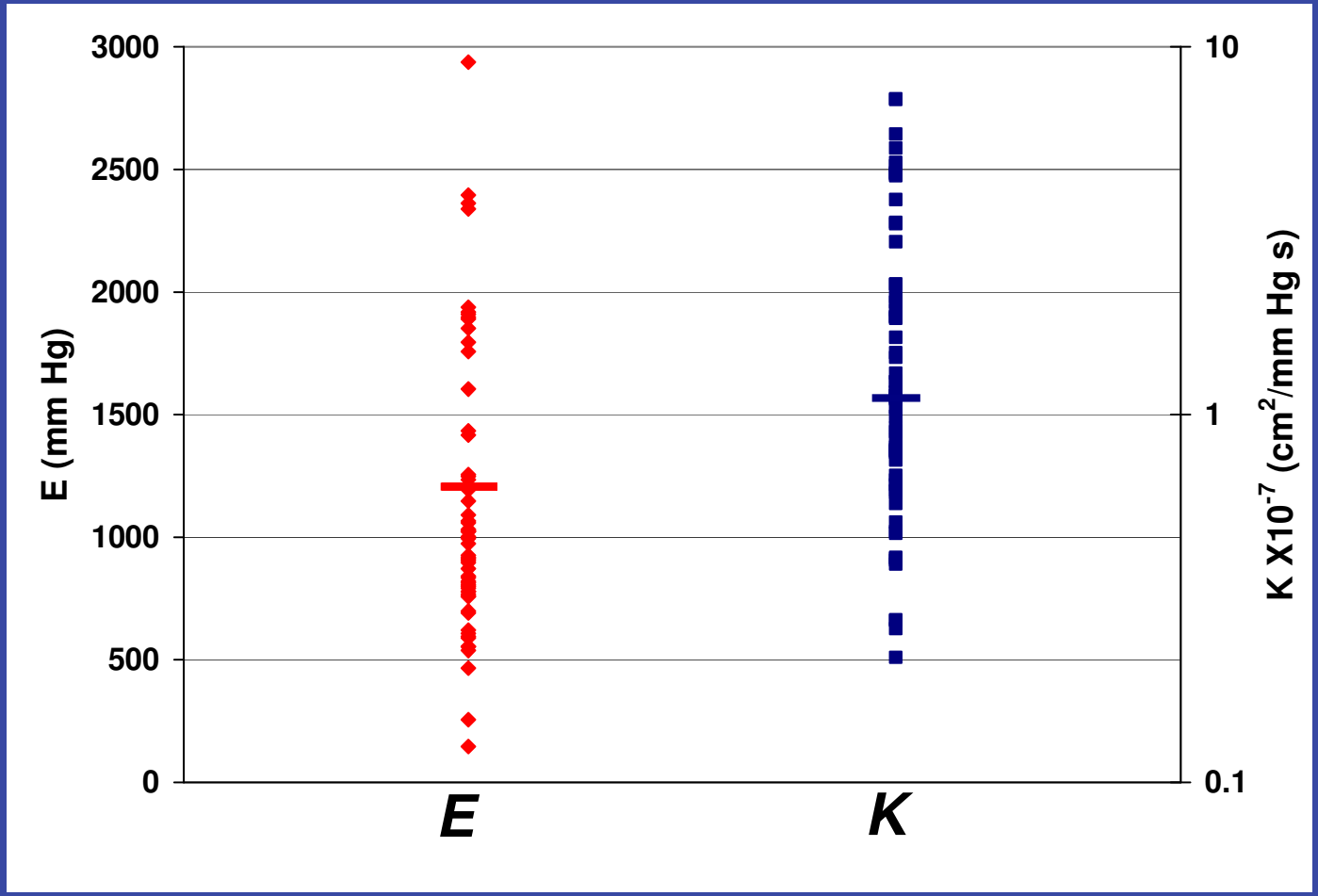
Patient 2



E and *K* in KHT-C



E and *K* in Cervix Cancer



E and *K* for Cervix Cancer

209 measurements in 63 patients:

E 1218 $\pm$ 198.1 mm Hg

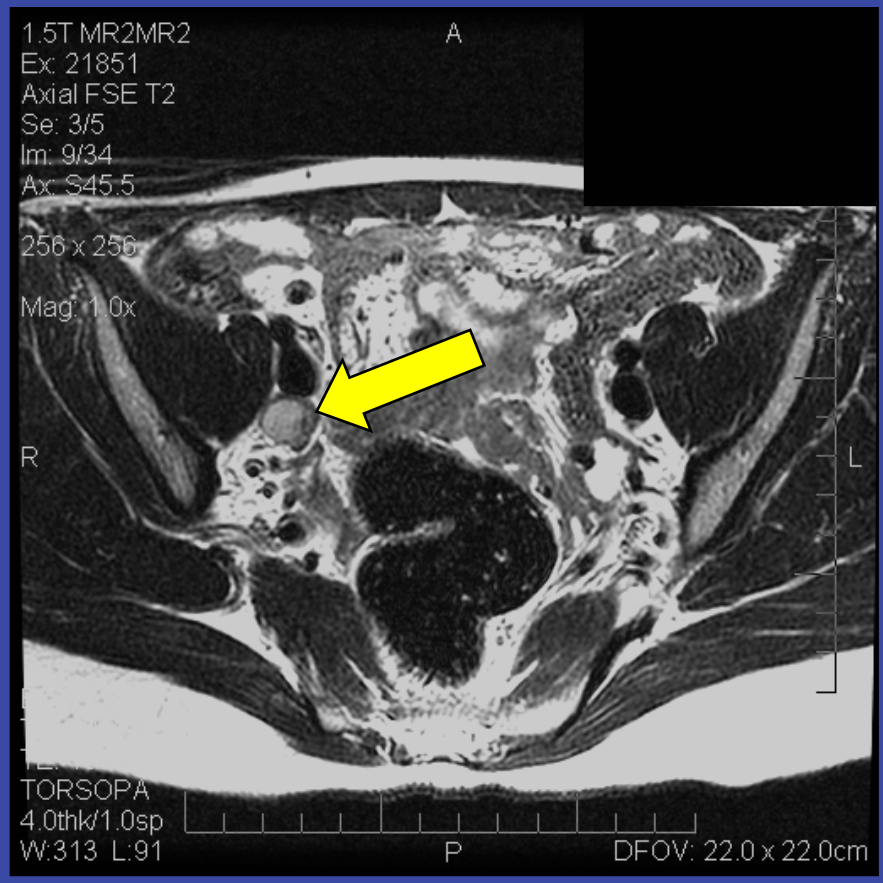
K $1.84 \times 10^{-7} \pm 4.32 \times 10^{-8}$ cm^2/mm Hg s

E Correlates with Lymph Node Metastases?

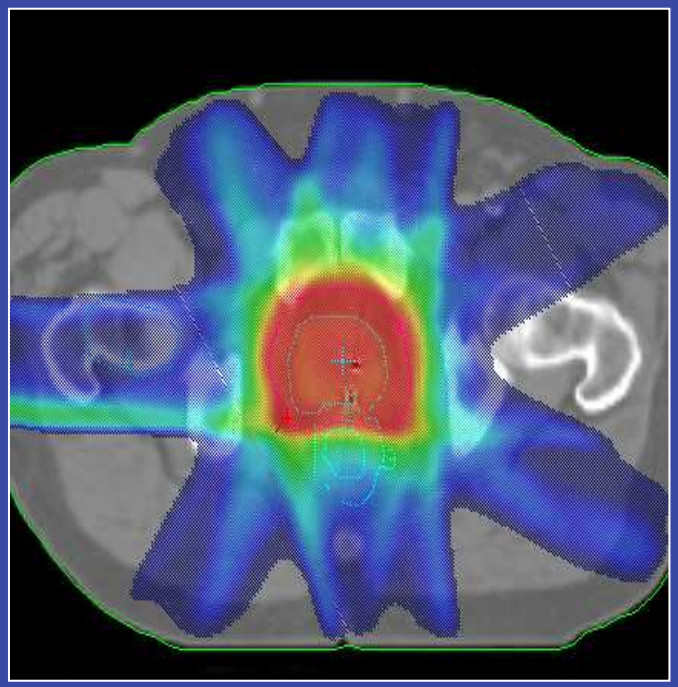
N0 **1086 ± 167 mm Hg**

N1 **1693 ± 700 mm Hg**

(p=0.01)



The way forward …



Adaptive, Precision RT

Biologic Response Enhancement (BRE)

Improved Patient Outcome

Thanks to…

Clinical

Anthony Fyles
Wilfred Levin
Lee Manchul
Amit Oza
Philip Chan
Rob Dinniwell

Modeling

Eric Leung

Imaging

Masoom Haider
David Jaffray
Igor Sitartchouk
Ivan Yeung

Biostatistics

Melania Pintilie
Gina Lockwood

Clinical Support

Ami Syed
Sue Billingsley
Geri Ottewell

Laboratory

Rob Bristow
David Hedley
Dick Hill
Julia Skliarenko
Sarah Jane Lunt