

Role of MR imaging in studying tumor physiology: a clinical perspective

Contributions of Spontaneous Canine Tumors

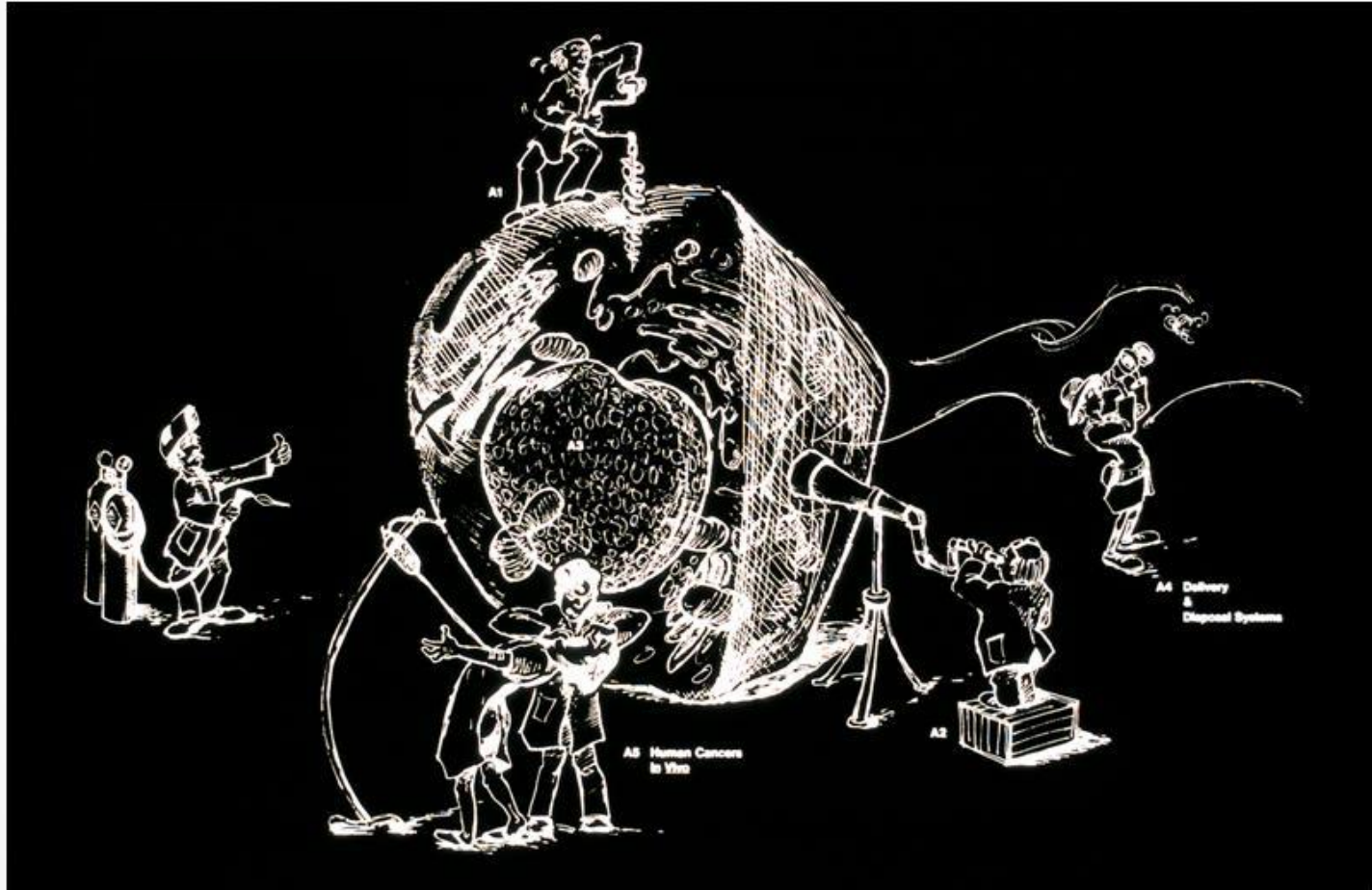
Mark W. Dewhirst, DVM, PhD



Canine clinical Trials – a legacy of discoveries in radiotherapy, hyperthermia and tumor physiology

- Papers published involving spontaneous companion canine tumors
 - 75 papers since 1980
- Funding – NIH/NCI, ACS

Early concept regarding important features of hyperthermia treatment & biology



Commissioned by M Dewhirst for G. Gerner, on occasion of
Hyperthermia Program Review, 1980

First success in calculating temperature distributions using heat transfer modeling

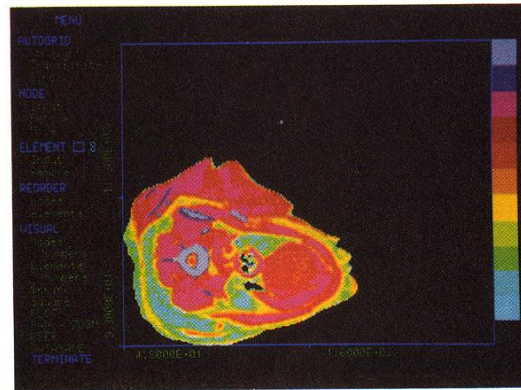
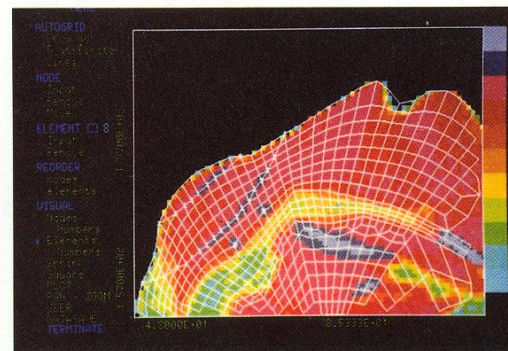
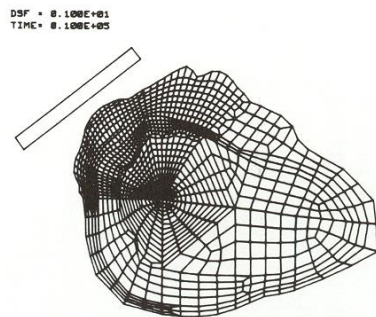
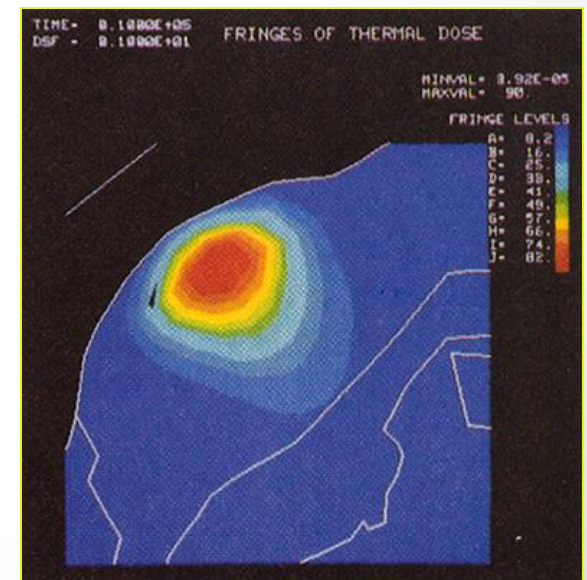
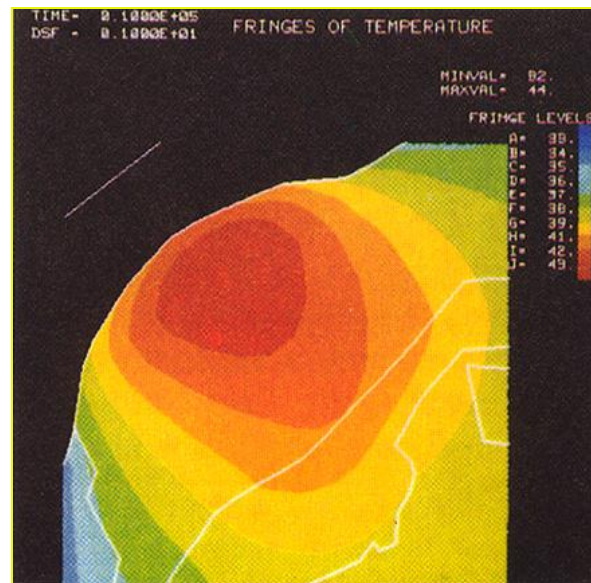
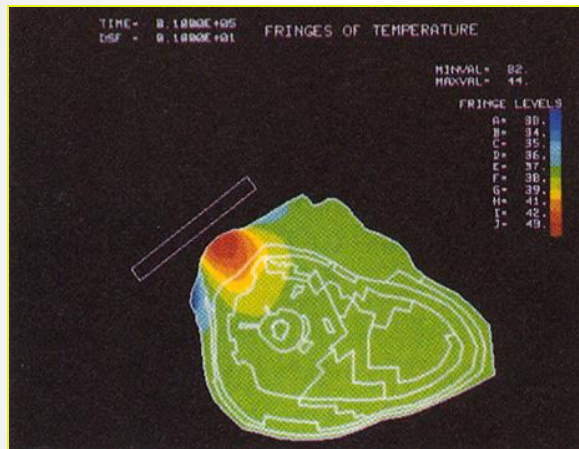


Figure 5. CT scan of the same dog shown in colour display after data transfer to VAX computer. Note the catheter tracks, which are shown in blue.



Dewhirst et al, Int J. Hyperthermia, 1987

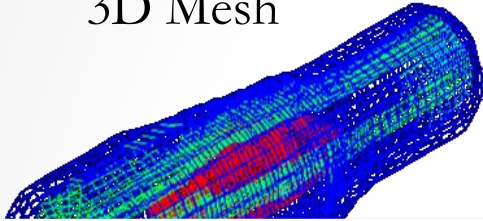
Calculated temperature distributions vs. thermal dose



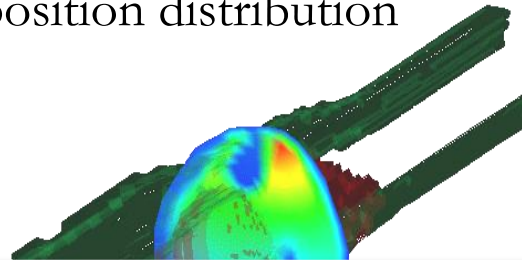
Dewhurst et al, Int J. Hyperthermia, 1987

FINITE ELEMENT MODELING of a lower limb extremity sarcoma

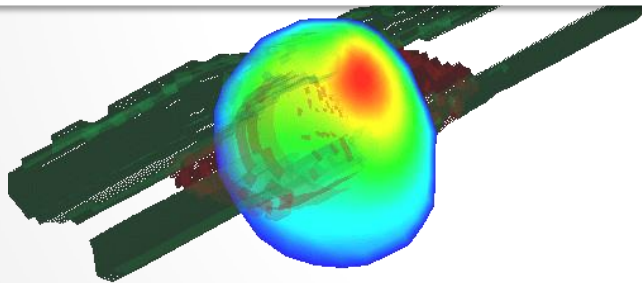
3D Mesh



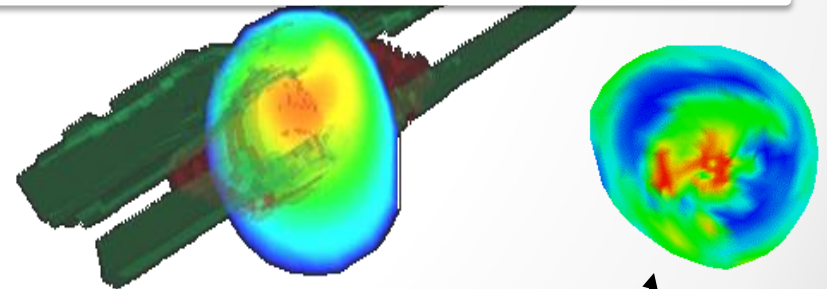
Power Deposition distribution



These studies greatly influenced RTOG QA guidelines for clinical application of hyperthermia
Dewhirst et al., IJROBP, 1990



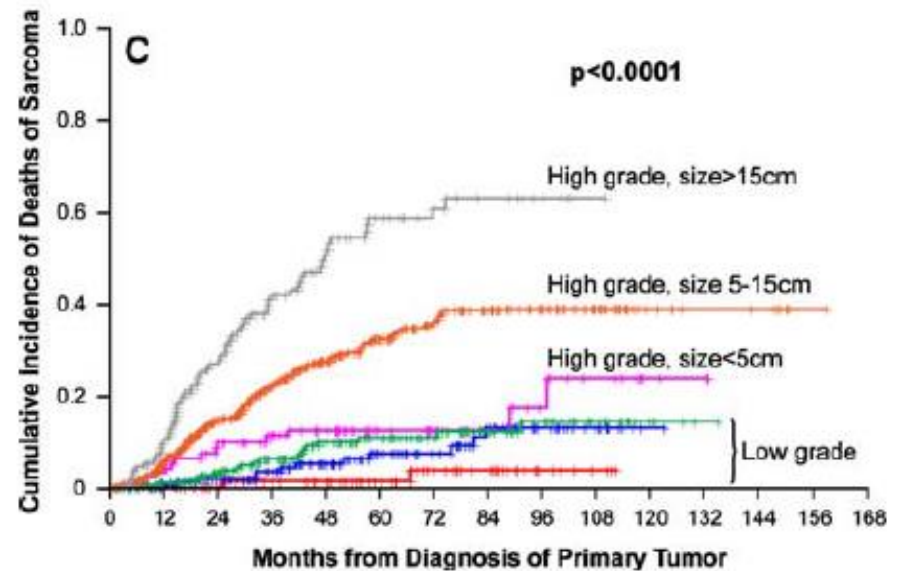
Temperature map
with constant perfusion



Temperature map
with perfusion/permeability maps (MRI)

Metastasis occurs in 40-50% of human patients with high grade soft tissue sarcoma

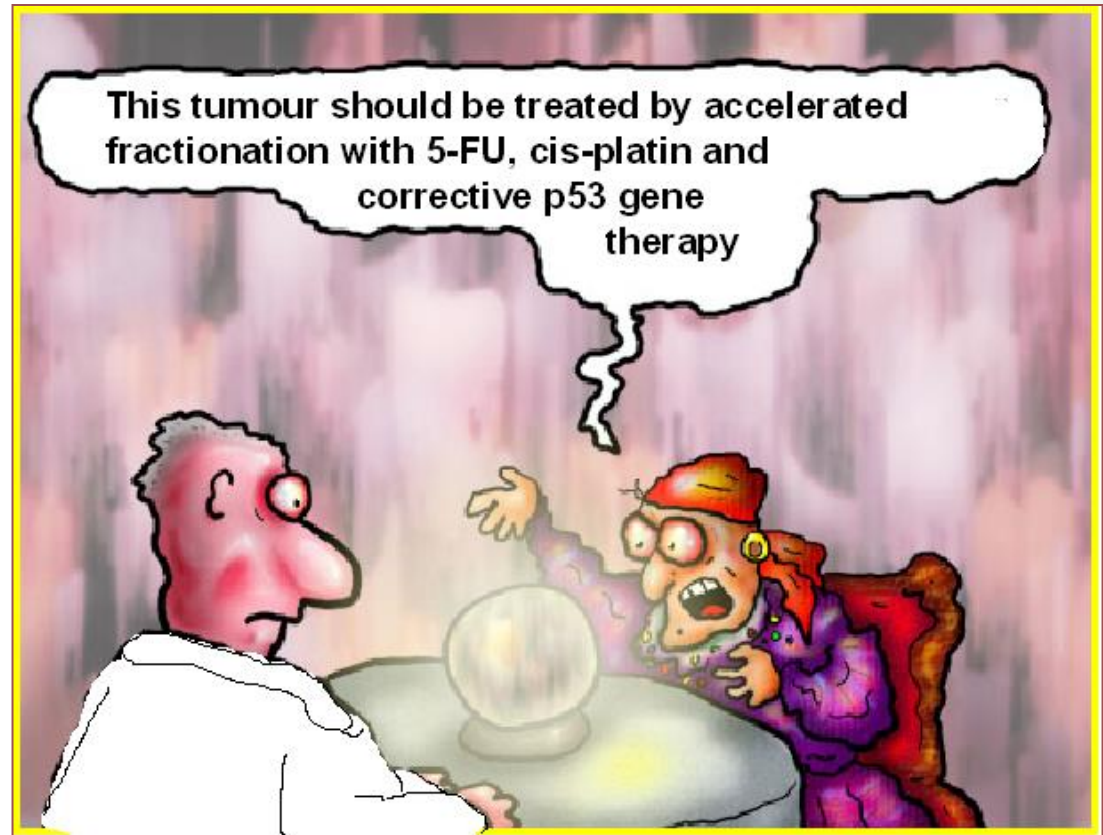
- Multivariate analysis result
 - Grade
 - Tumor Size
 - Margin Status
 - Histology
 - Primary Site



For high grade tumors, there is no accepted biomarker to assist in treatment decision making

Physiologic parameters related to overall and metastasis free survival in canine patients with soft tissue sarcomas

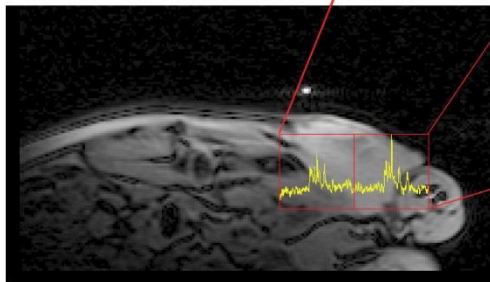
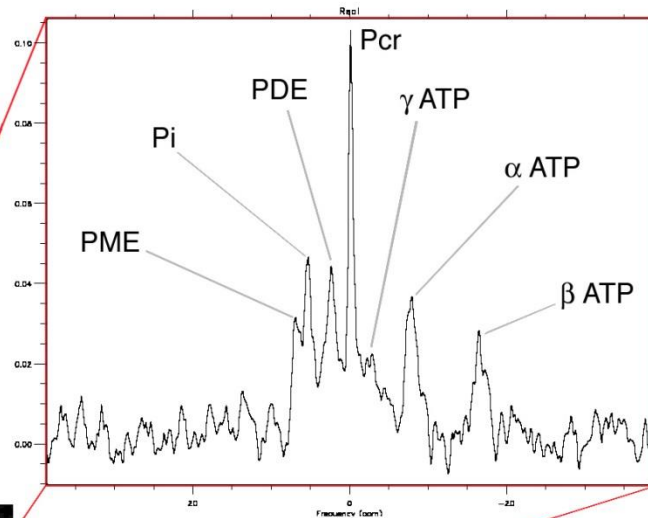
- Physiologic parameters
 - Lactate & pH
 - Perfusion
- Metabolic parameters
 - Phosphomono-ester
 - Phosphodiester



Cartoon Courtesy of George Wilson

3D Chemical Shift ^{31}P MR Imaging reveals metabolic information

Doubly tuned surface
Coil -
Proton decoupling-
1.5 T magnet



T2 weighted image

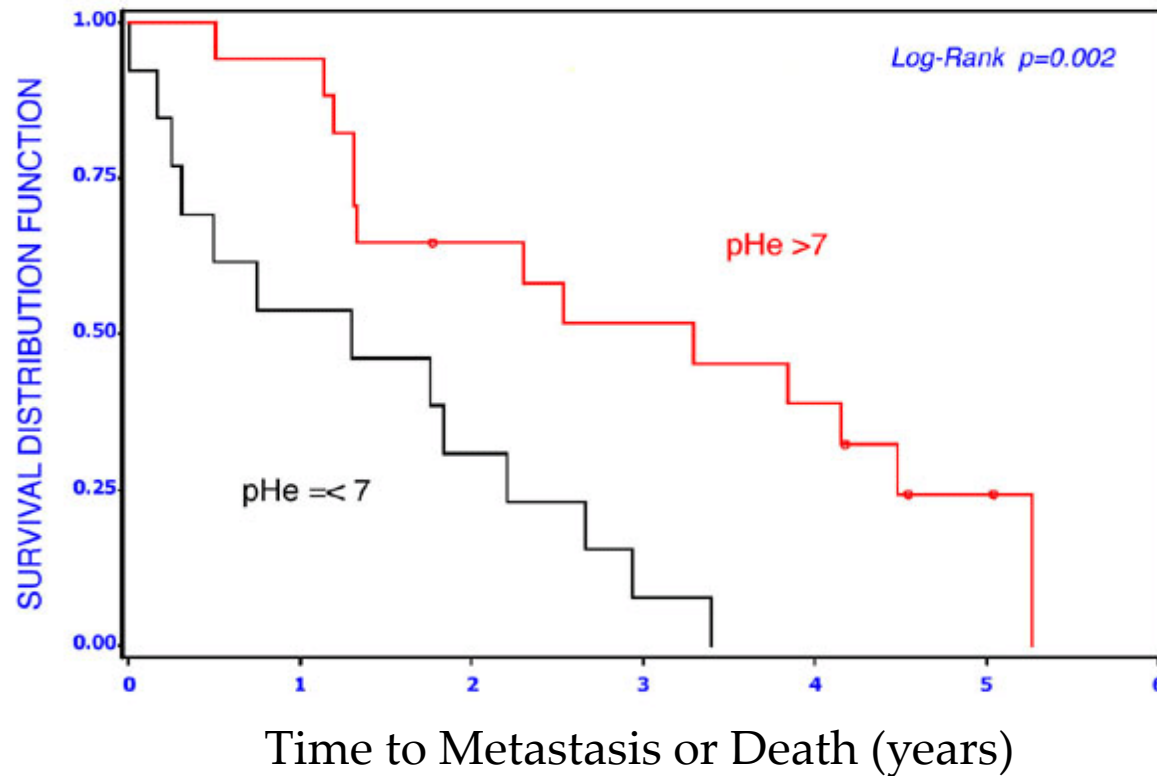
STS on flank of canine patient

Clinical Trial – canine sarcomas
Randomized phase II
High vs. low thermal dose + radiotherapy
N=122
39 had MRI and MRS studies performed

Variables associated with metastasis free & overall survival in companion dogs with soft tissue sarcomas

- Tumor Grade (low vs. intermediate + high) $p=0.0014$
- Tumor Volume $p=0.052$
- Phosphodiester / ATP ratio $p=0.027$
- Extracellular pH, $p=0.002$

Extracellular pH associated with metastasis free survival: Canine sarcomas



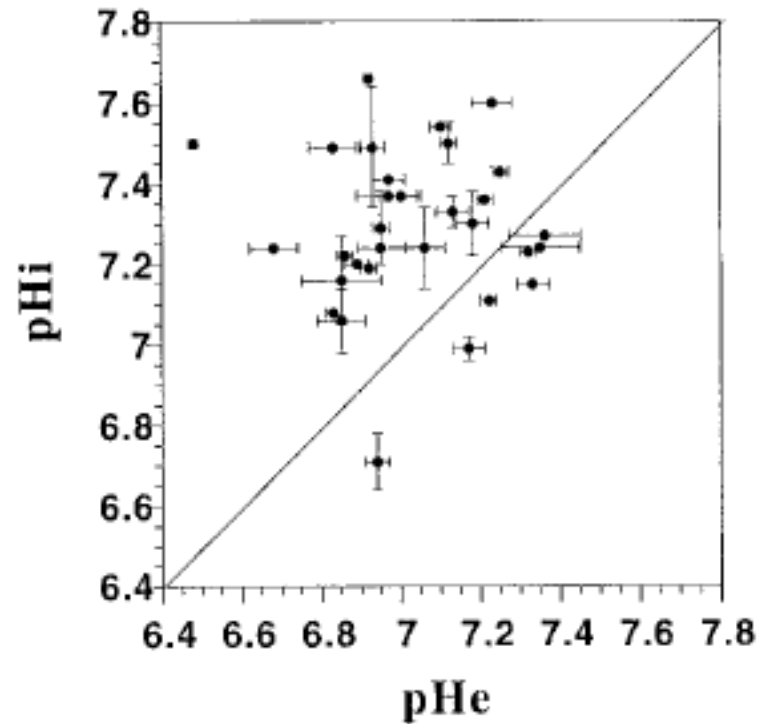
Intracellular pH was not associated with outcome

pH measured with needle electrodes

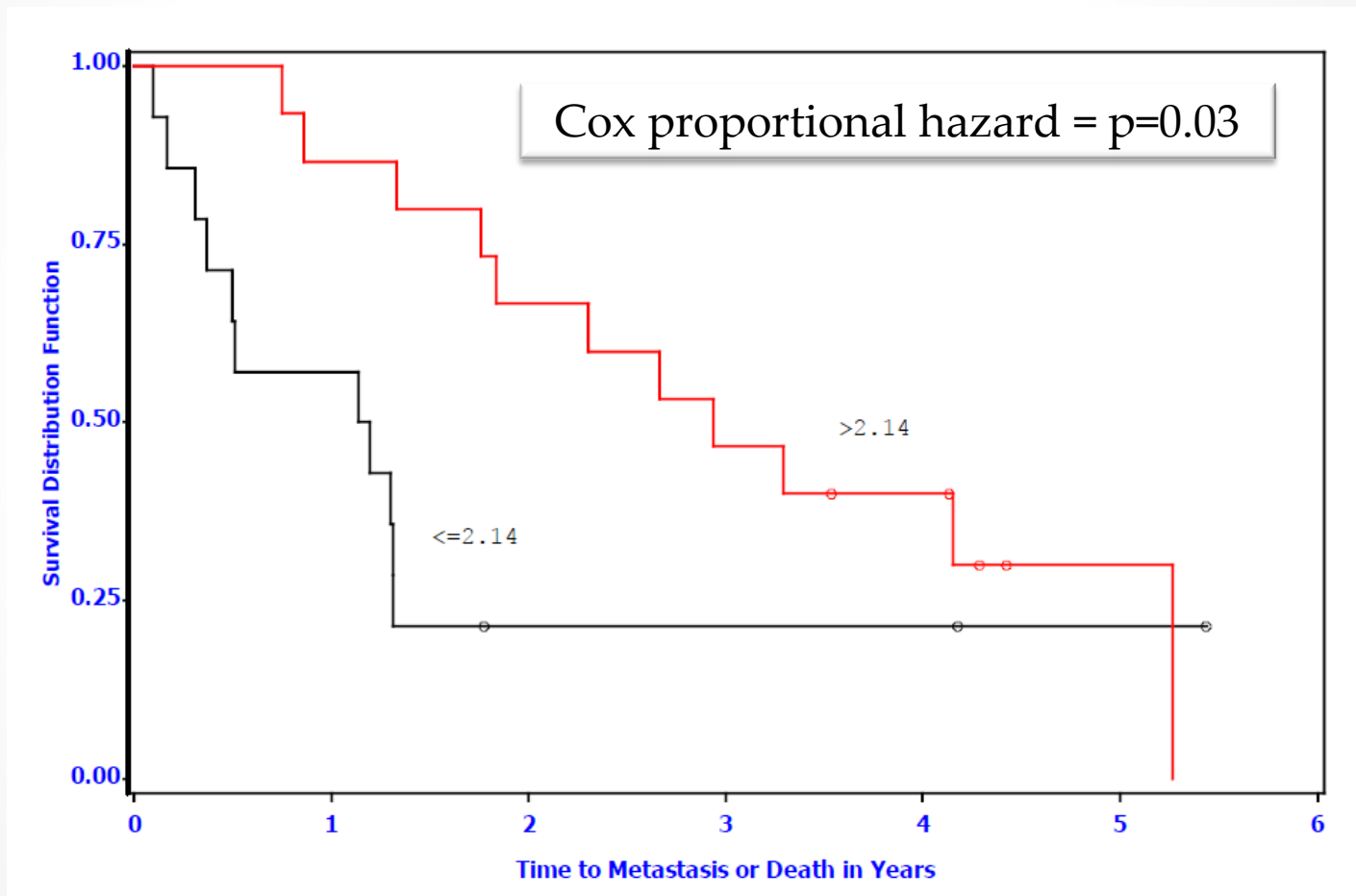
Lora Michiels et al, Clin Ca Res, 2006

Intracellular pH is more alkaline than pH_e

33 canine patients with soft tissue sarcomas

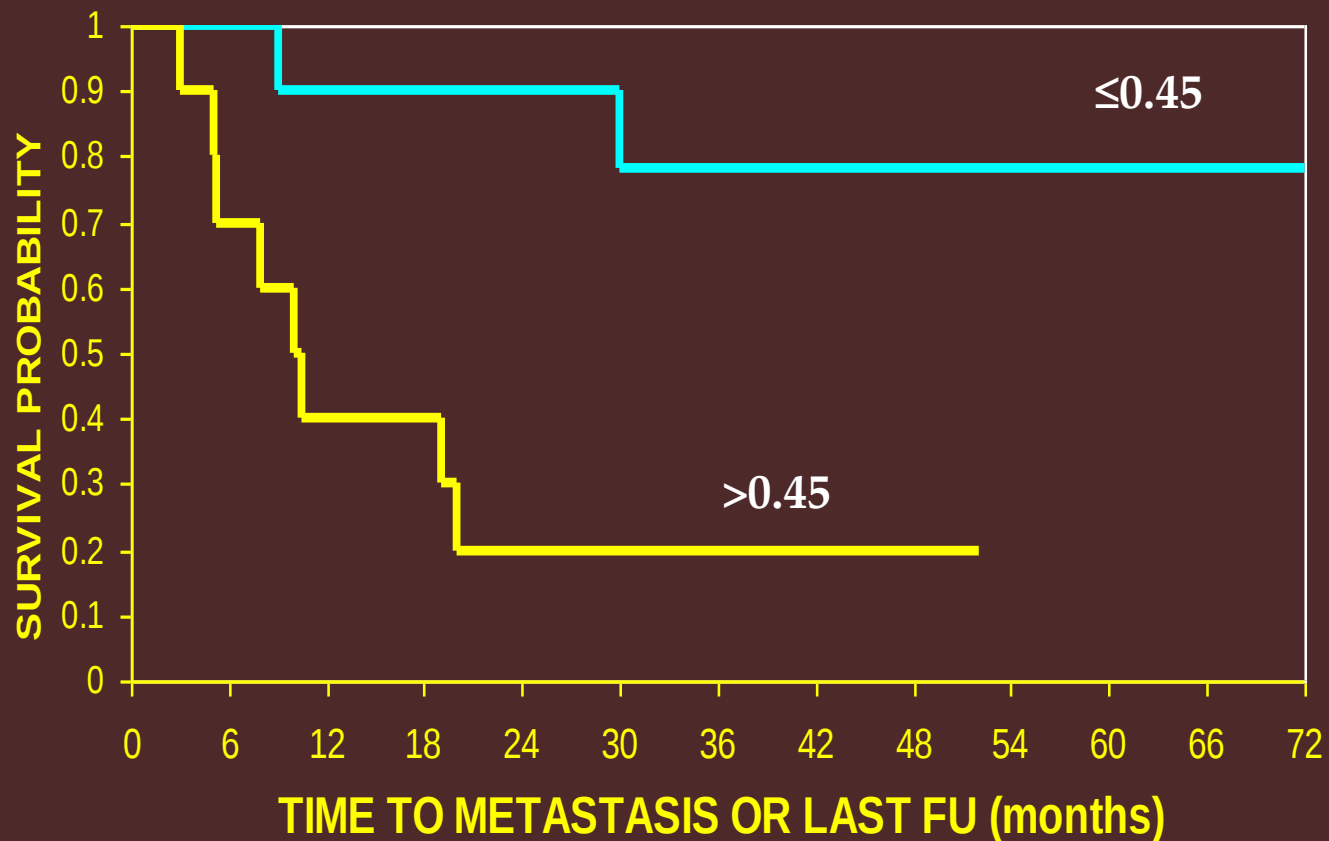


PDE/ATP ratio is related to metastasis free survival – canine sarcomas

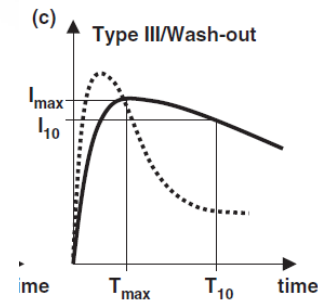
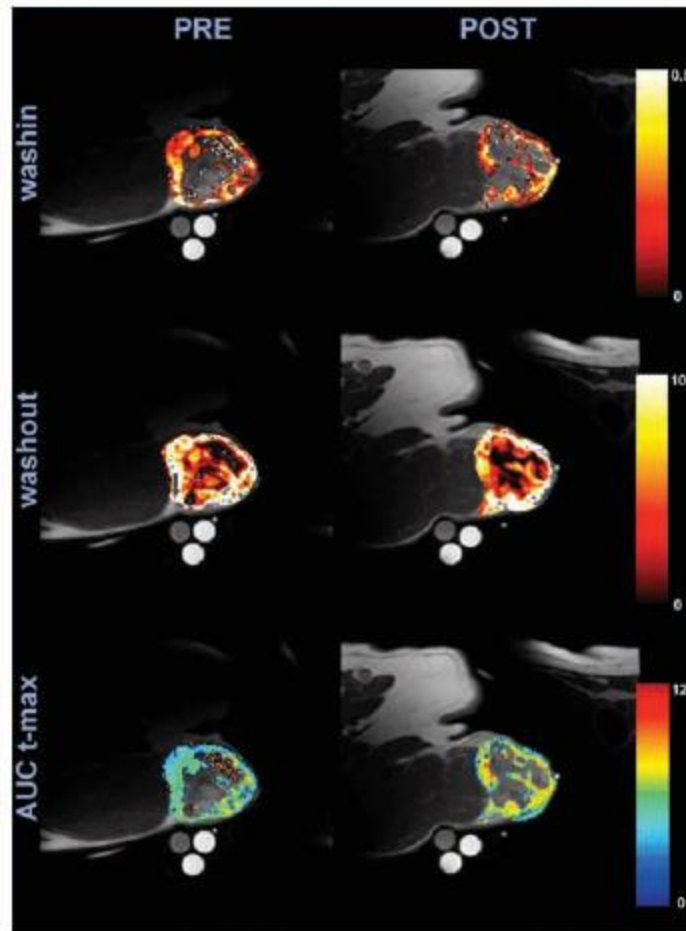


PME/PDE relates to metastasis-free survival: human sarcomas

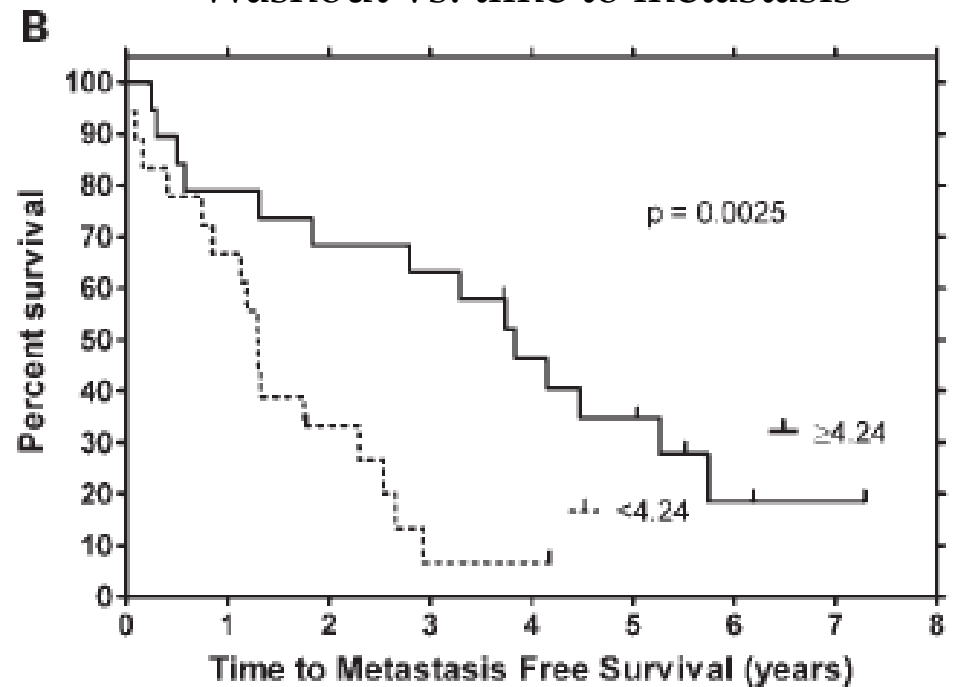
$P = 0.047$, Hazard Ratio = 4.32



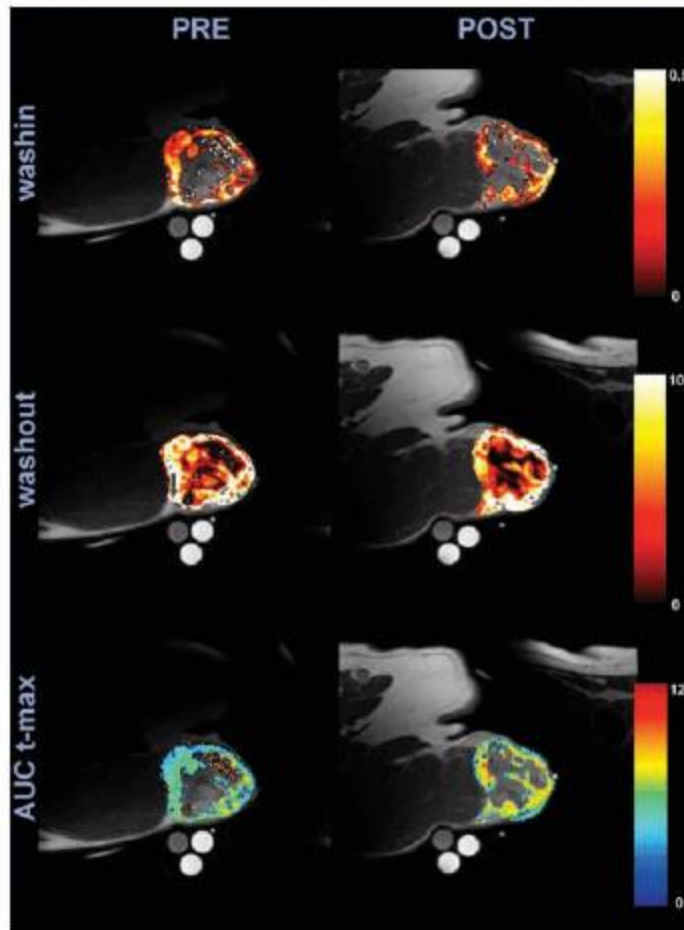
DCE-MRI and treatment outcome in canine sarcomas



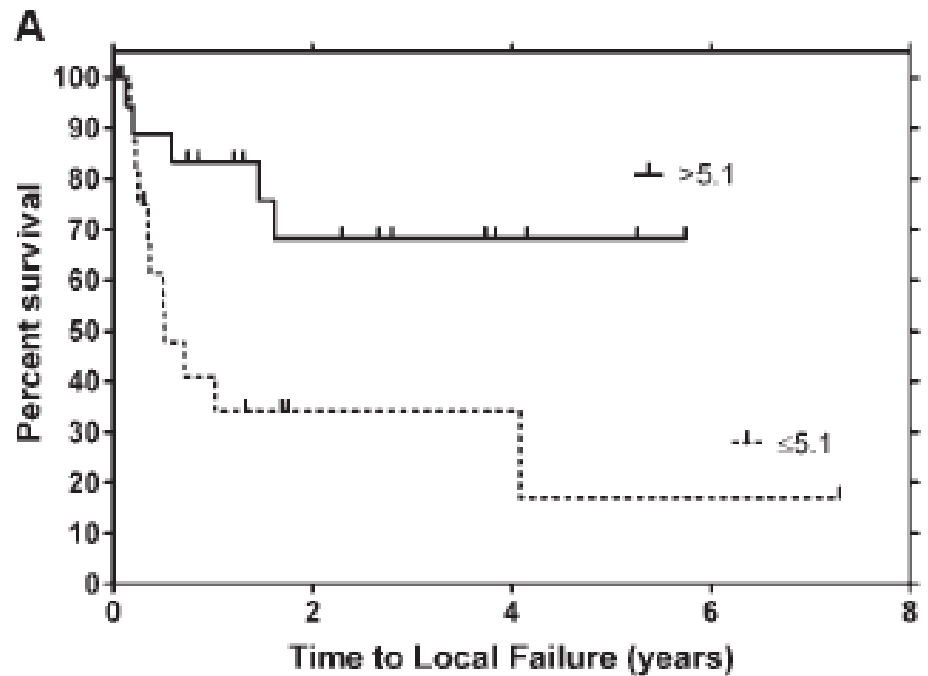
Washout vs. time to metastasis



DCE-MRI and treatment outcome in canine sarcomas



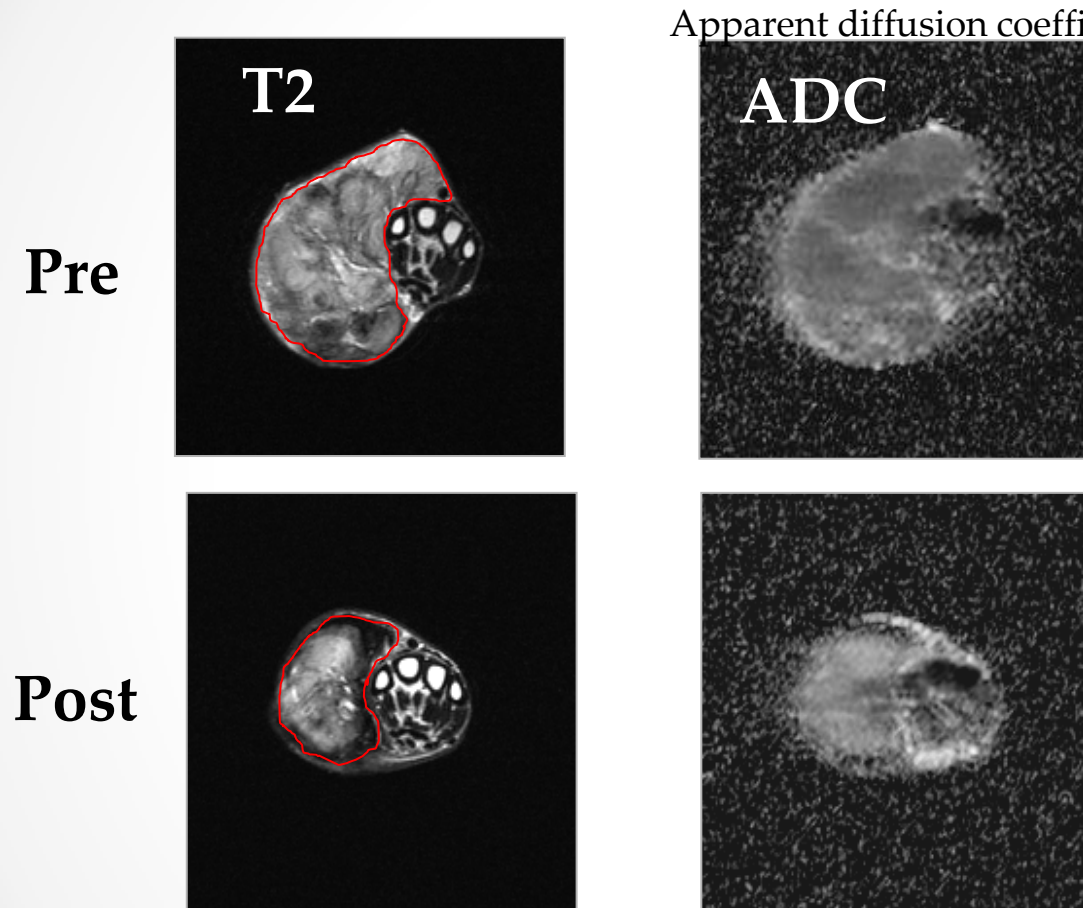
AUC_{t-max} vs. time to local failure



Similar results were seen in human sarcomas (unpublished)

Viglianti et al., Clin Ca Res, 2009

Using diffusion weighted imaging to evaluate pathophysiologic response to thermoradiotherapy

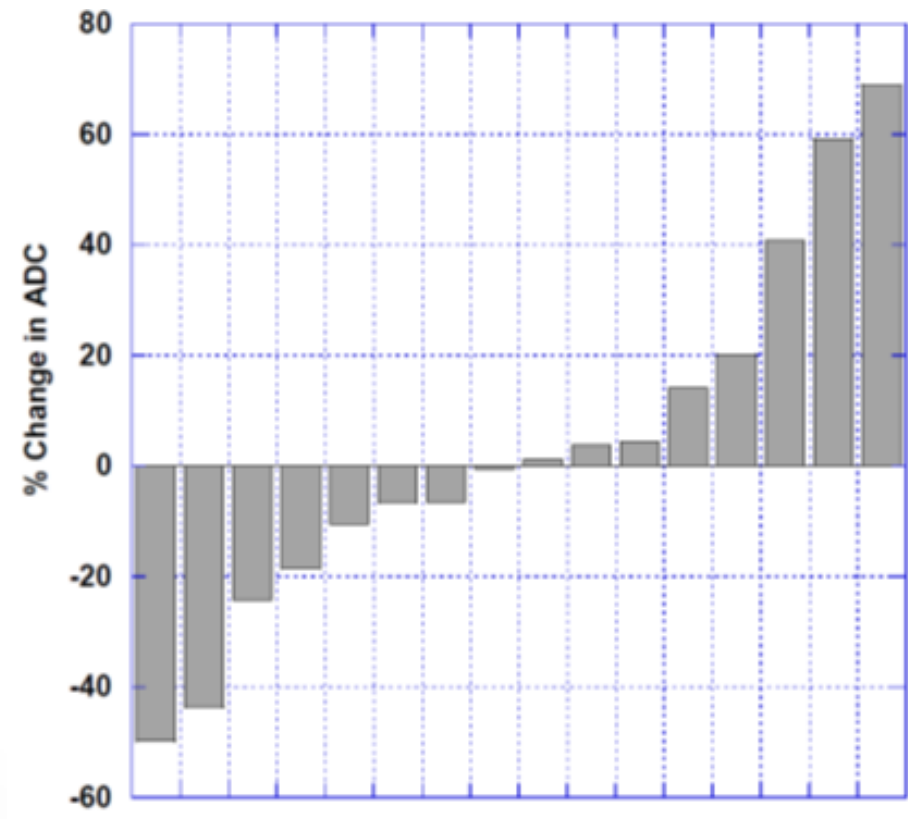


Apparent diffusion coefficient of H₂O

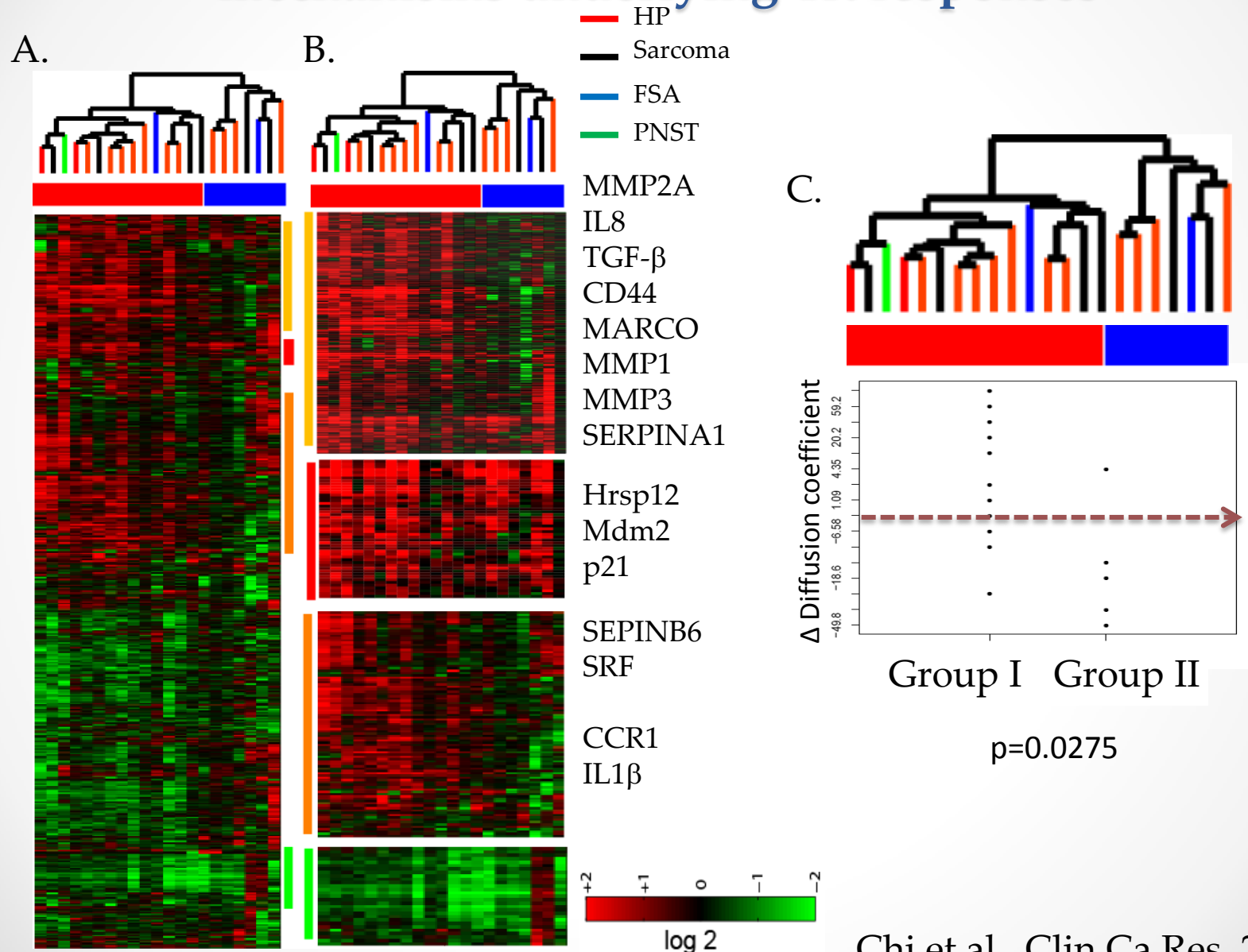
22 canine patients with STS were evaluated as part of a larger randomized Thermoradiotherapy trial.
Thrall et al, Int J Hyperthermia, 2012

Canine patient with STS on paw

Variable changes in apparent diffusion coefficient of water (ADC) post RT + Heat



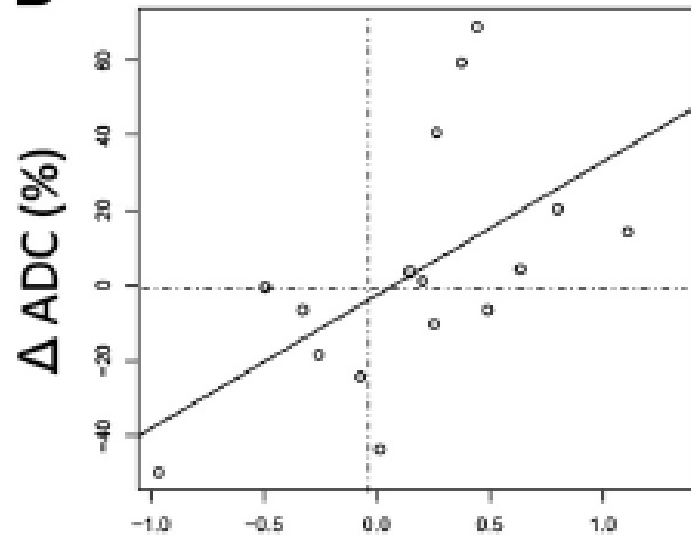
Linkages between physiology and genomics illustrate mechanisms underlying Trt responses



Chi et al., Clin Ca Res, 2011

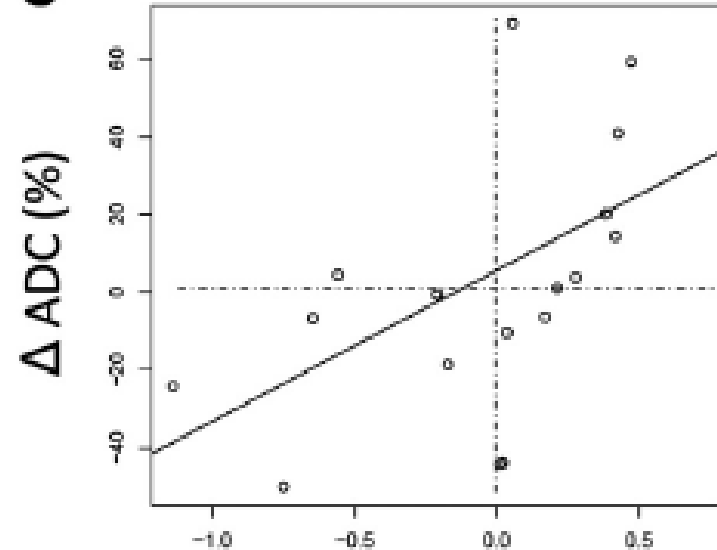
Change in ADC post Trt positively correlated with fold change in VEGF receptor expression

B



FLT1, $P = 0.0032$,
 $R = 0.7$

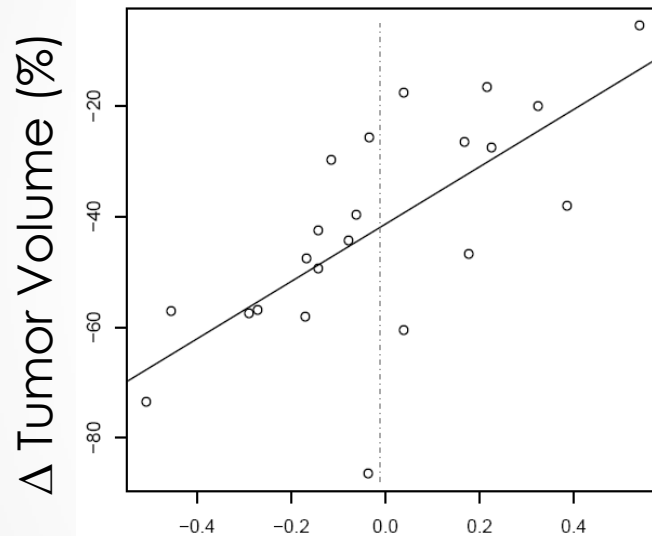
C



KDR, $P = 0.00176$,
 $R = 0.732$

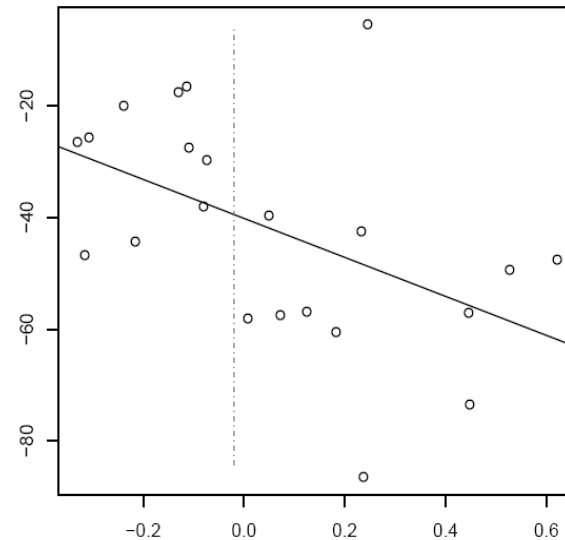
Tumor response related to change in TERT, BRCA1 and RAD23A expression

Cell proliferation



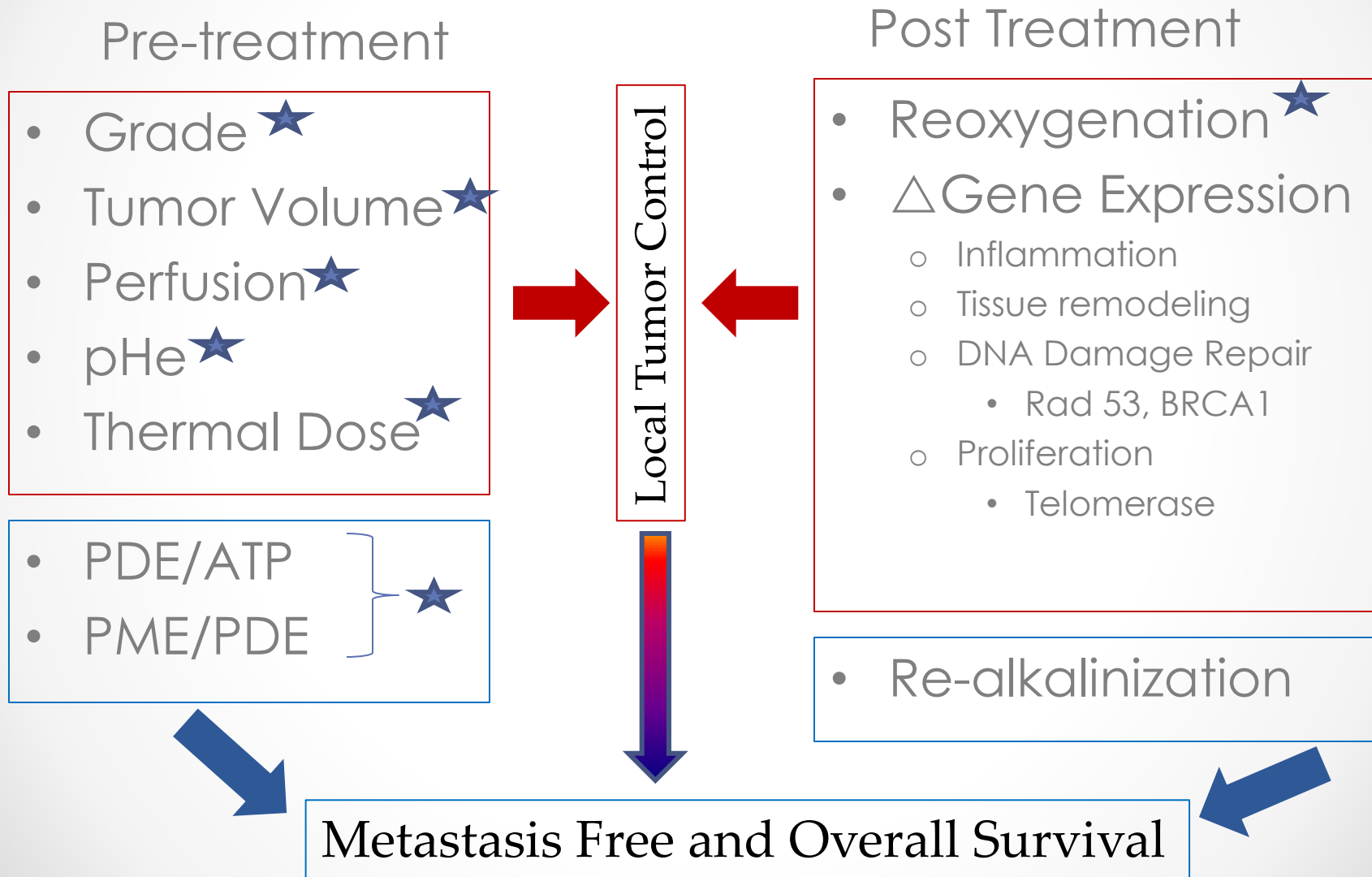
TERT, $p = 0.00013$
 $R = 0.739$

DNA Damage Response



RAD23A, $p = 0.00444$
 $R = -0.591$

Associations between baseline and post-treatment parameters and outcome

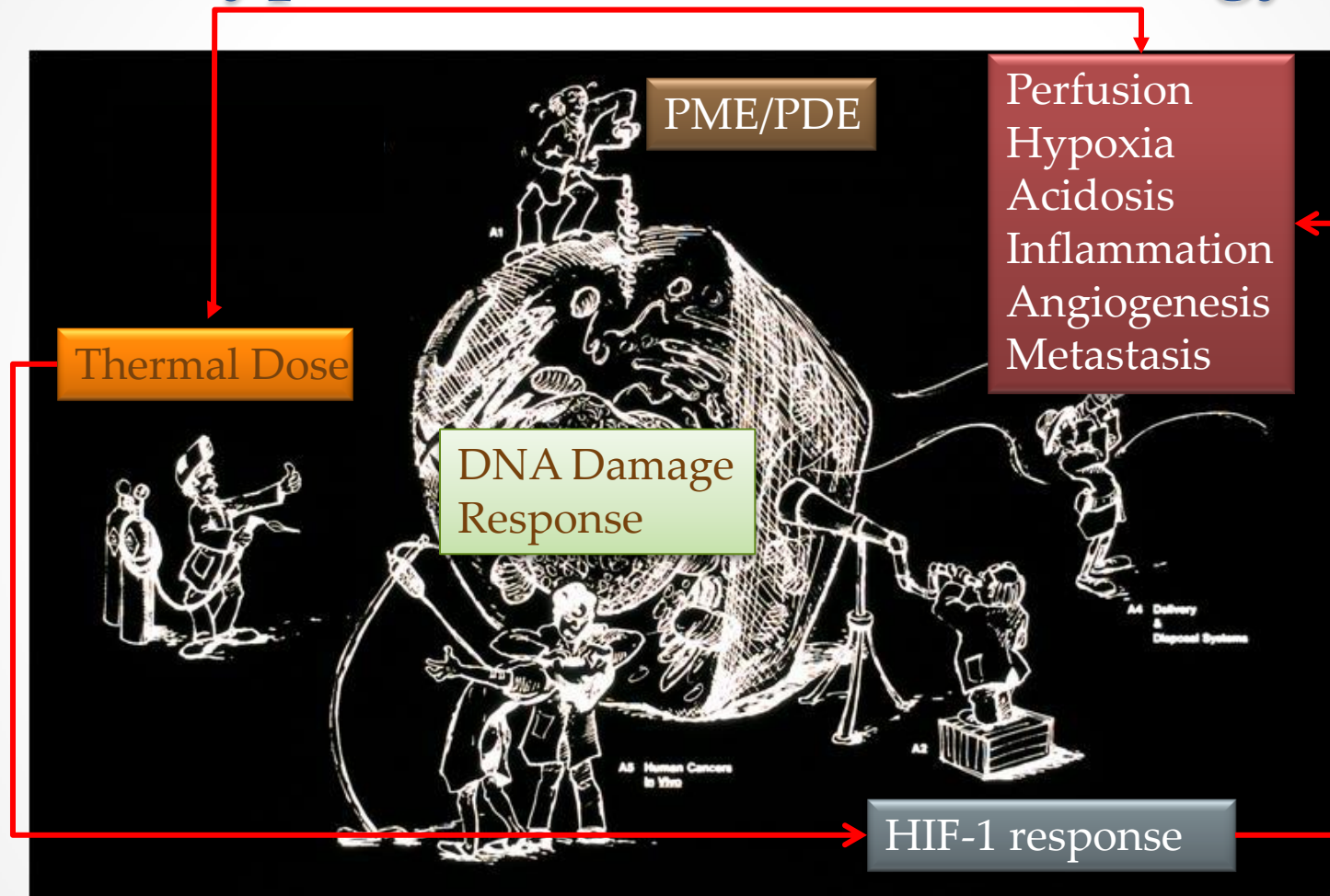


★ Similar results seen in canine and human patients

Conclusions: Utility of MR imaging using companion dogs with sarcomas

- Image data was key for thermal modeling & establishing principles for clinical trial quality assurance
- Obtaining functional imaging data in the context of therapeutic trials was used to guide and augment results from parallel human trials
- Combination of functional imaging and genomics revealed prognostically important information and therapeutic targets that cannot be gleaned from simple unsupervised genomic analyses

New concepts regarding important features of hyperthermia & tumor biology

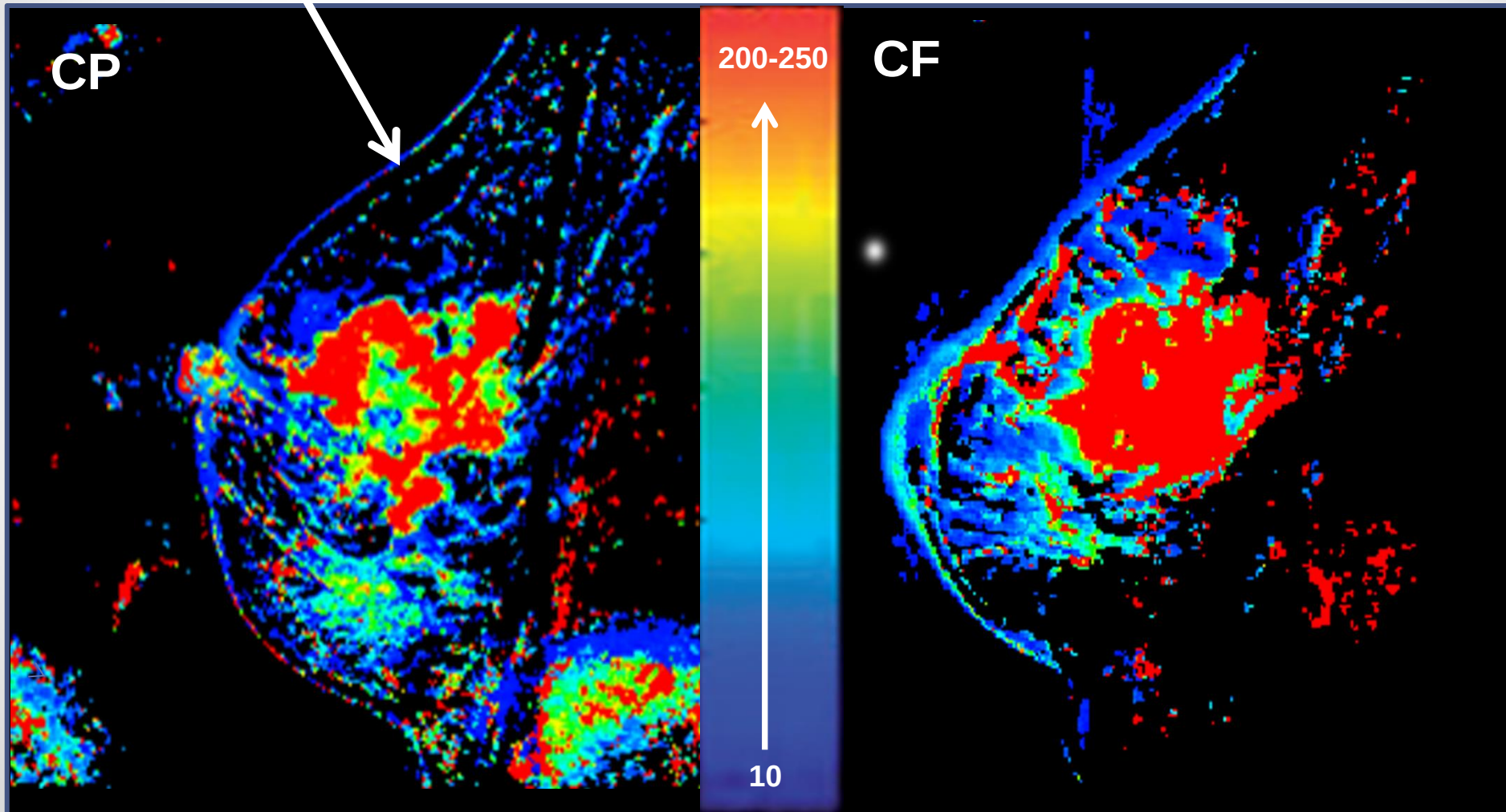


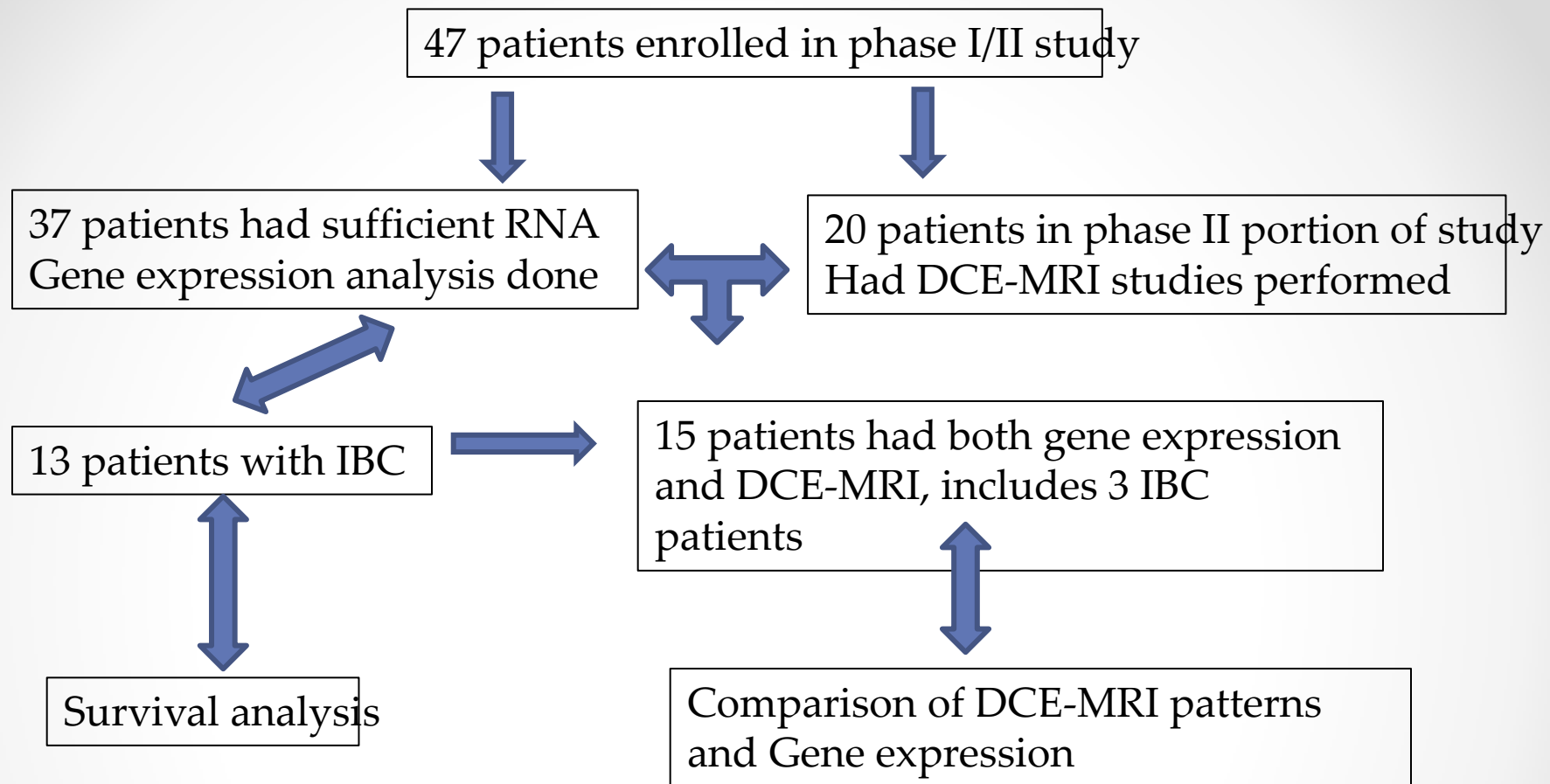
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Hyperthermia Program Review, 1980

Acknowledgements

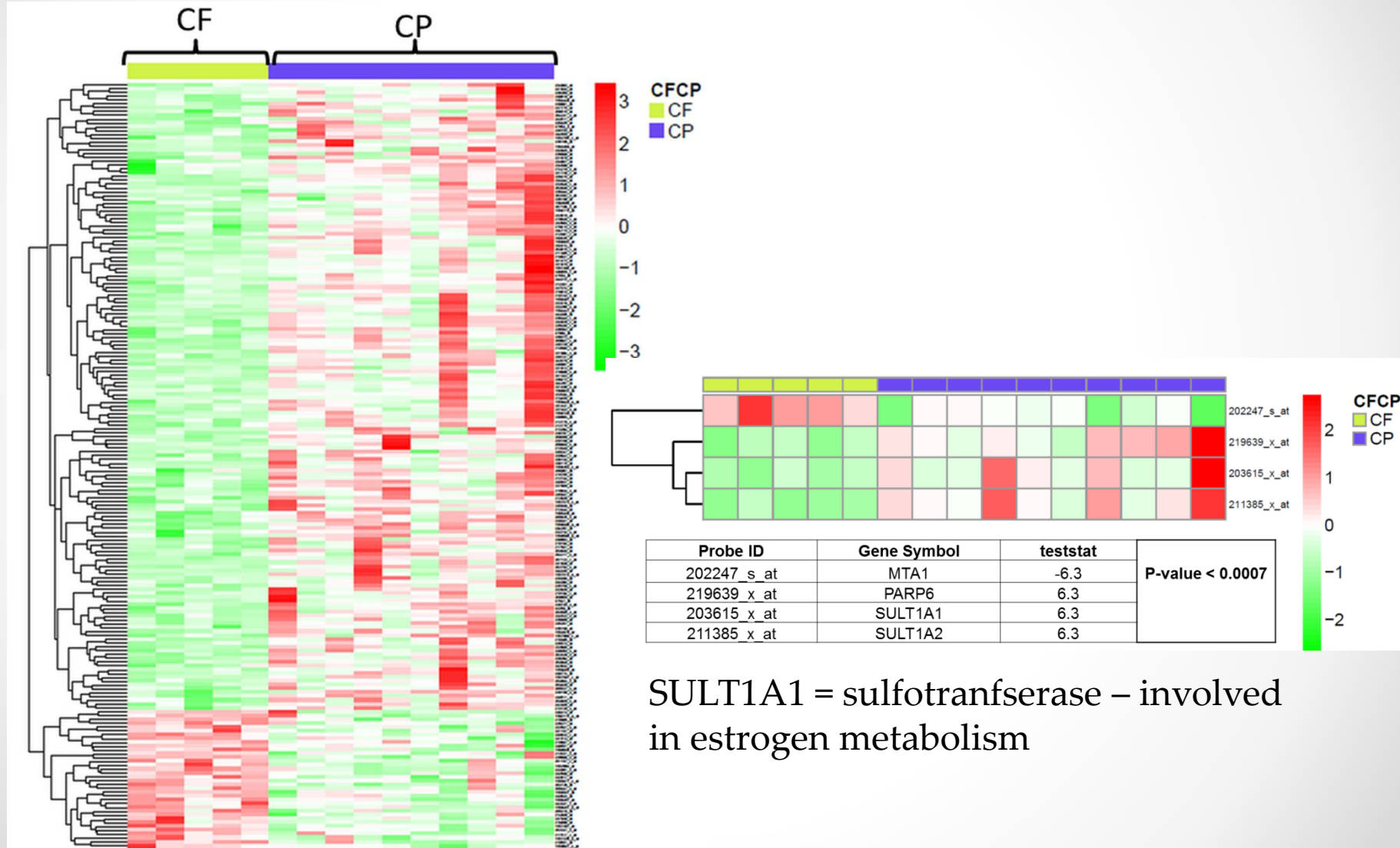
- Donald Thrall
- Edward Gillette
- Sue Larue
- Mary Kay Klein
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- Rod Page
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- Deborah Prescott
- Kevin Concannon
- Jeanne Poulson
- Susan Ettinger
- Katherine Hansen
- Marlene Hauck
- Roberto Legoretta
- David Denman
- H. Cecil Charles
- Dirk Sostman
- James MacFall
- Oana Craciunescu
- Thaddeus Samulski
- Shiva Das
- Paul Stauffer
- Grant Rhine
- James Winget
- David Brizel
- James Oleson
- Leonard Prosnitz
- Ellen Jones
- Zeljko Vujaskovic
- Benjamin Viglianti
- Ejung Moon
- Shara Reihani
- Jen-Tsan Chi
- Daohai Yu
- Gary Rosner
- Lan Lan
- Kouros Owzar

Comparison of perfusion patterns in locally advanced breast cancer



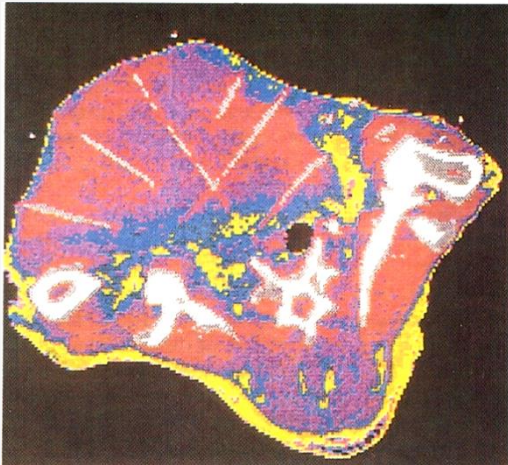


Results of genomic analysis in locally advanced breast cancer



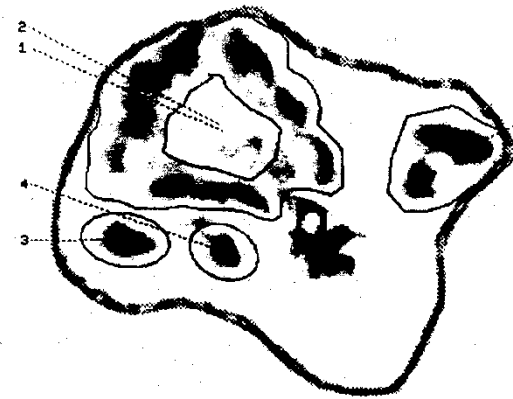
Incorporation of perfusion into thermal models

Colorized CT Scan

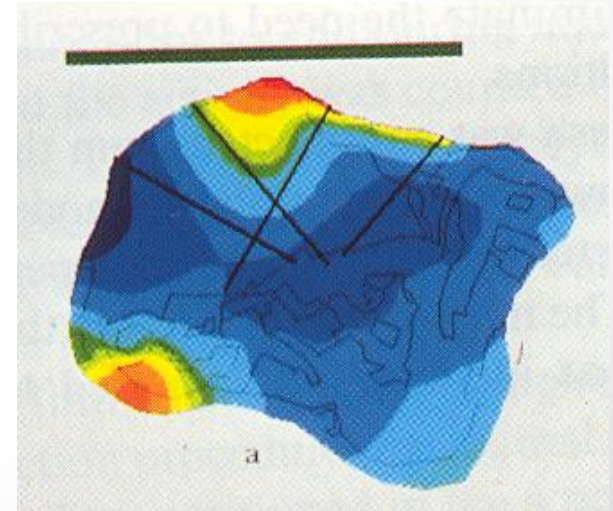


Dog with STS on chest wall

Perfusion PET Scan



Thermal Model



Rhine et al., IJROBP, 1992

Topics

- Thermal Dosimetry
 - Thermal modeling
- Physiology
 - pO₂
 - Functional imaging (MRI)
 - DCE/MRI
 - pH

