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

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

• Papers published involving spontaneous companion canine tumors
  o 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

Dewhirst et al, Int J. Hyperthermia, 1987
Calculated temperature distributions vs. thermal dose

Dewhirst 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
  - Phosphomonoester
  - Phosphodiester

Cartoon Courtesy of George Wilson

This tumour should be treated by accelerated fractionation with 5-FU, cis-platin and corrective p53 gene therapy.
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

Prescott et al, Clin Ca Res, 2000
PDE/ATP ratio is related to metastasis free survival – canine sarcomas

Cox proportional hazard = p=0.03

Lora Michiels et al, Clin Ca Res, 2006
PME/PDE relates to metastasis-free survival: human sarcomas

P = 0.047, Hazard Ratio = 4.32

Dewhirst et al, IJROBP, 2005
DCE-MRI and treatment outcome in canine sarcomas

Washout vs. time to metastasis

Viglianti et al., Clin Ca Res, 2009
DCE-MRI and treatment outcome in canine sarcomas

AUC$_{t\text{-}max}$ 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 H$_2$O

Pre

Post

Canine patient with STS on paw

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

Chi et al, Clin Ca Res, 2011
Variable changes in apparent diffusion coefficient of water (ADC) post RT + Heat

Chi et al, Clin Ca Res, 2011
Linkages between physiology and genomics illustrate mechanisms underlying Trt responses

Chi et al., Clin Ca Res, 2011

A. B.

C.

Δ Diffusion coefficient

Group I Group II

p=0.0275

Hrsp12 Mdm2 p21
SEPINB6 SRF
CCR1 IL1β

Change in gene expression 24h post HT
Change in ADC post Trt positively correlated with fold change in VEGF receptor expression

Chi et al., Clin Ca Res, 2011
Tumor response related to change in TERT, BRCA1 and RAD23A expression

Chi et al., Clin Ca Res, 2011
Associations between baseline and post-treatment parameters and outcome

<table>
<thead>
<tr>
<th>Pre-treatment</th>
<th>Post Treatment</th>
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</thead>
<tbody>
<tr>
<td>Grade ★</td>
<td>Reoxygenation ★</td>
</tr>
<tr>
<td>Tumor Volume ★</td>
<td>△Gene Expression</td>
</tr>
<tr>
<td>Perfusion ★</td>
<td>- Inflammation</td>
</tr>
<tr>
<td>pH★</td>
<td>- Tissue remodeling</td>
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<tr>
<td>Thermal Dose ★</td>
<td>- DNA Damage Repair</td>
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<tr>
<td></td>
<td>- Rad 53, BRCA1</td>
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<tr>
<td></td>
<td>- Proliferation</td>
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<tr>
<td></td>
<td>- Telomerase</td>
</tr>
<tr>
<td>PDE/ATP</td>
<td>Re-alkalinization ★</td>
</tr>
</tbody>
</table>
| PME/PDE              | Metastasis Free and Overall Survival

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

Commissioned by M Dewhirst for G. Gerner, on occasion of Hyperthermia Program Review, 1980
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Comparison of perfusion patterns in locally advanced breast cancer
47 patients enrolled in phase I/II study

37 patients had sufficient RNA
Gene expression analysis done

20 patients in phase II portion of study
Had DCE-MRI studies performed

13 patients with IBC

Survival analysis

15 patients had both gene expression and DCE-MRI, includes 3 IBC patients

Comparison of DCE-MRI patterns and Gene expression
Results of genomic analysis in locally advanced breast cancer

SULT1A1 = sulfotransferase – involved in estrogen metabolism
Incorporation of perfusion into thermal models

Colorized CT Scan

Perfusion PET Scan

Thermal Model

Dog with STS on chest wall

Rhine et al., IJROBP, 1992
Topics

• Thermal Dosimetry
  o Thermal modeling

• Physiology
  o pO2
  o Functional imaging (MRI)
  o DCE/MRI
  o pH