ESTIMATION OF % TUMOR NECROSIS BY 3D COMPARTMENTAL ANALYSIS OF DYNAMIC CONTRAST-ENHANCED MRI IN SPONTANEOUS CANINE OSTEOSARCOMAS

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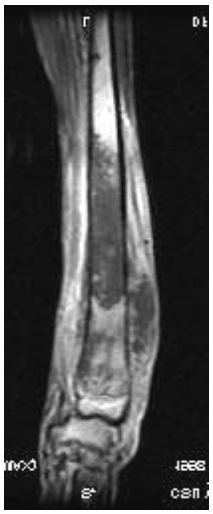
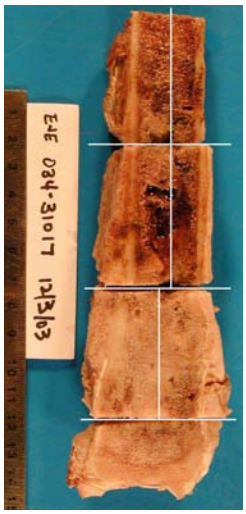
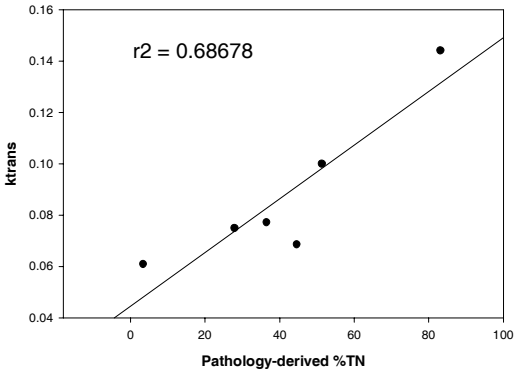
Introduction: A standardized, practical *in vivo* estimation of percent tumor necrosis (%TN) of osteosarcoma would be highly advantageous for evaluating response to neoadjuvant therapy, tailoring treatment and for prognostication. The induction of ≥90% TN is a strong predictor of local control of human osteosarcoma; similarly, 80% TN is predictive for local tumor control in dogs.[1-2] In people, induction of ≥90% TN also ultimately predicts disease-free interval and survival.[1] Various factors derived from dynamic contrast enhanced MRI (DCE-MRI) have proven useful in identifying necrotic tumor regions and degree of response to neoadjuvant therapy, but DCE-MRI analytical methods remain unstandardized and are continuing to evolve. We are using a 3D compartmental analysis method to derive pharmacokinetic factors in relationship with %TN in dogs with spontaneous osteosarcoma. Dogs with naturally-occurring tumors make an excellent translational model because imaging, medical and surgical procedures are similar to those used in people and yet, more intensive sampling and invasive procedures are feasible for pathological and physiological correlation.

Methods: DCE-MRI was done on dogs in two differing Phase I/II oncology trials that utilized novel therapy to induce tumor necrosis. The novel therapies included 1.) isolated limb perfusion with 153-Samarium-EDTMP (n=4) and 2.) combination of radiation and immunotherapy using L-MTP-PE (n=2). MRI was performed prior to, and 2-3 weeks after treatment in the Phase I/II dogs. The last MRI preceded surgical limb amputation by not more than 1-2 days. Dogs were placed under general anesthesia for imaging, with maintenance of blood pressure and other cardiovascular parameters within normal range. Routine anatomic imaging included pre-contrast T1-weighted and STIR imaging. DCE-MRI was done by gadolinium DTPA IV injection (0.1 mmol/kg by controlled injector at 3 ml/sec) and repeated scans of the tumor volume using 3D SPGR scans, 30 degree flip, 8 mm slice thickness. Temporal resolution was 10-12 sec per phase for a total of 8-10 minutes of scanning. DCE-MRI analysis was compartmental-based, done by region-of-interest analysis of the entire tumor volume using 3D geometrically constrained region growth (3D GEORG) (Perfusion Analyzer, VirtualScopics Inc., Rochester NY). Biomarkers such as transfer rate constant (k^{trans}), instantaneous area under the curve (IAUC), volume of extracellular space (Ve) and % nonenhancing voxels were derived by "intensity based" two compartment modeling. Pathology-derived %TN was derived from the surgically-amputated limb specimens. Image analysis was done of the decalcified, paraffin-embedded, haematoxylin-eosin stained 4 micron thick longitudinal tumor sections through the centers (Carl Zeiss KS 400 analysis software) to calculate total % necrosis/ total tumor area.

Results: The figures below show typical sagittal DCE-MRI slice through a canine osteosarcoma of the distal radius (left) and the corresponding gross pathology specimen (right). For the 6 dogs, pathology-derived %TN averaged 40.5% (range 3.37 – 83.15%). K^{trans} (min^{-1}) averaged 0.0852 (range 0.0541 – 0.1442) and showed moderate correlation with pathologically-derived %TN (r^2 – 0.68678). Other factors such as IAUC, Ve, and % nonenhancing voxels did not strongly correlate with %TN.







Discussion: There are few reports relating compartmental analysis from DCE-MRI to percent necrosis for this tumor type.[1,2] Detection of tumor necrosis might prove to be particularly challenging with DCE-MRI because of the existing background of an osteoid matrix in osteosarcomas. Studies evaluating different analytical approaches are still needed to develop recommendations for a standardized clinically-relevant method.[1] DCE-MRI provides insight into alterations in tumor vasculature that can then be related to the biological effects of novel therapeutics. In these dogs, k^{trans} for small molecular weight gadolinium-DTPA was moderately related to the degree of %TN. K^{trans} is the most widely accepted kinetic parameter relating to transfer of low molecular weight contrast media into the extravascular space.[4] K^{trans} is related to vascular flow and permeability. This study contained few animals, and % TN was induced by two different forms of radiation that could have had differing effects on tumor vasculature, particularly permeability. Furthermore, DCE-MRI analysis was done on a 3D basis of the entire tumor volume, whereas the pathology-derived %TN was from a single longitudinal section of the tumor. These factors may all have negatively impacted the degree of correlation of k^{trans} with %TN. This is an ongoing study with additional dogs already entered into the Phase I/II trials. Future plans are to perform other forms of analysis on the same data for comparative purposes while accumulating more patients into the study.

References:

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