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Pharmacokinetic of DCEMRI

DCEMRI of spontaneous canine tumors during fractionated radiotherapy: A pharmacokinetic analysis

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ABSTRACT

Purpose: To estimate pharmacokinetic parameters from dynamic contrast-enhanced magnetic resonance (DCEMR) images of spontaneous canine tumors taken during the course of fractionated radiotherapy, and to quantify treatment-induced changes in these parameters.
Materials and methods: Six dogs with tumors in the oral or nasal cavity received fractionated conformal radiotherapy with 54 Gy given in 18 fractions. T_1-weighted DCEMR imaging was performed prior to each treatment fraction. Time–intensity curves in the tumor were extracted voxel-by-voxel, and were fitted to the Brix pharmacokinetic model. The dependence of the pharmacokinetic parameters on the accumulated radiation dose was calculated.
Results: The Brix model reproduced the time–intensity curves well. A reduction in the k_{ep} parameter with accumulated radiation dose was found for five (three significant) out of six cases, while the results for the A parameter were less consistent. Both pre-treatment k_{ep} and the change in k_{ep} with accumulated dose correlated significantly with tumor regression.
Conclusions: Pharmacokinetic parameters derived from DCEMR images taken during fractionated radiotherapy may predict response to radiotherapy. This may potentially impact on patient stratification and monitoring of treatment response for image-guided treatment strategies.
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Recent advances in tumor imaging now allow the assessment not only of tumor anatomy, but also of functional and molecular tumor characteristics [1–3]. Coupled with an increasing interest in individualization of cancer treatment, such images may provide a basis for selection of the most appropriate treatment modalities for individual patients, as well as monitoring of the therapeutic effect and subsequent adaptation of therapy [4,5]. However, to adapt treatment according to the changes in image parameters during treatment, the relationship between these changes and treatment response has to be elucidated.

Dynamic contrast-enhanced magnetic resonance imaging (DCEMRI), often employing Gd-based chelates as tracers, provides information on tumor perfusion, blood vessel density and permeability and the composition of the extracellular extravascular space [6,7]. Hence, information on physiological factors related to tumor response to radiotherapy, such as tumor hypoxia and angiogenesis, can potentially be derived from DCEMR images [6,8]. The role of DCEMRI as a predictor of response to radiation therapy has recently been reviewed [6], and correlations between DCEMR image parameters and tumor histopathological features as well as treatment outcome were demonstrated for several treatment sites.

Several methods for the analysis of DCEMR images have been proposed. The tissue signal intensity as a function of time can be analyzed semiquantitatively, yielding parameters such as initial signal enhancement rate, time to and value of the maximum signal enhancement, and rate of contrast wash-out [6,7]. While easy to obtain, these parameters do not have a direct physiological interpretation, and cannot be readily compared between centers, as they depend on the MR scanner and the imaging protocol used [6,7]. Alternatively, the images can be analyzed quantitatively, through the use of pharmacokinetic modeling. Here, the contrast enhancement kinetics is described by the parameters that relate to the underlying tumor physiology [6,7]. Several models for Gd-DTPA kinetics in tumors have been developed [9–11].

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In the present study, we aimed to estimate pharmacokinetic parameters from DCEMR images, taken during the course of fractionated radiotherapy, of spontaneous canine tumors, and to quantify treatment-induced changes in these parameters. Furthermore, the correlation between pharmacokinetic parameters and treatment response was investigated.

Materials and methods

Patients and treatment

Six dogs (A–F) with spontaneous tumors of the nasal or oral cavity were included in a prospective study investigating tumor response to radiotherapy. The treatment consisted of fractionated, conformal radiotherapy to a total dose of 54 Gy, given in 18 fractions of 3.0 Gy, with five fractions per week. The patient and tumor characteristics, follow up, and technical details concerning the radiotherapy have been described previously [12]. All treatments were given with curative intent. The study was approved by the Local Research Committee, and informed consent was obtained from the dogs' owners.

Tumor imaging

DCMR imaging was performed before the start of radiotherapy and prior to most treatment fractions. Image acquisition has been described previously [12]. Briefly, T_1-weighted images were obtained using a spoiled gradient recalled sequence on a 1.5-T scanner (Genesis Signa, GE Medical Systems), with Gd-DTPA as the contrast agent (Magnevist 469 mg/ml, Schering AG). The in-plane image resolution was $(0.7 \times 0.7)\,mm^2$ for all patients, while slice thickness varied from 3 to 6 mm. The infusion time of Gd-DTPA was 4 s, and the image acquisition interval was 35 s. Both MR imaging and radiotherapy were performed under general anesthesia (for details, see Ref. [12]).

In total, 88 dynamic scans, each consisting of more than 20 time frames, were analyzed for the present study.

Image analysis

The tumor volume was delineated manually in the post-contrast images for each treatment fraction, and the entire set of tumor voxels was included in the pharmacokinetic analysis. The DCEMR images were analyzed with the Brix model [10], a two-compartment pharmacokinetic model. Contrast agent is assumed to distribute between two individually well-mixed compartments, namely the blood plasma and the extracellular extravascular space (EES) in the tumor. The contrast agent injected into the plasma compartment is transported to the tumor by perfusion. In the tumor, the contrast agent diffuses between the plasma and the EES, and elimination of the contrast agent is assumed to occur at a constant rate. If the contrast agent is injected in the form of a bolus, the resulting relative signal intensity increase as a function of time, RSI(t), can be expressed as follows [13]:

$$RSI(t) = \frac{S(t) - S(0)}{S(0)} = \frac{Ak_{ep}}{k_{el} - k_{ep}}\left(e^{-k_{ep}t} - e^{-k_{el}t}\right) \quad (1)$$

where $S(0)$ is the pre-contrast signal value for a given voxel and $S(t)$ is the signal value in the voxel at time t. The parameter A is an amplitude parameter related to the size of the EES. k_{ep} is the rate

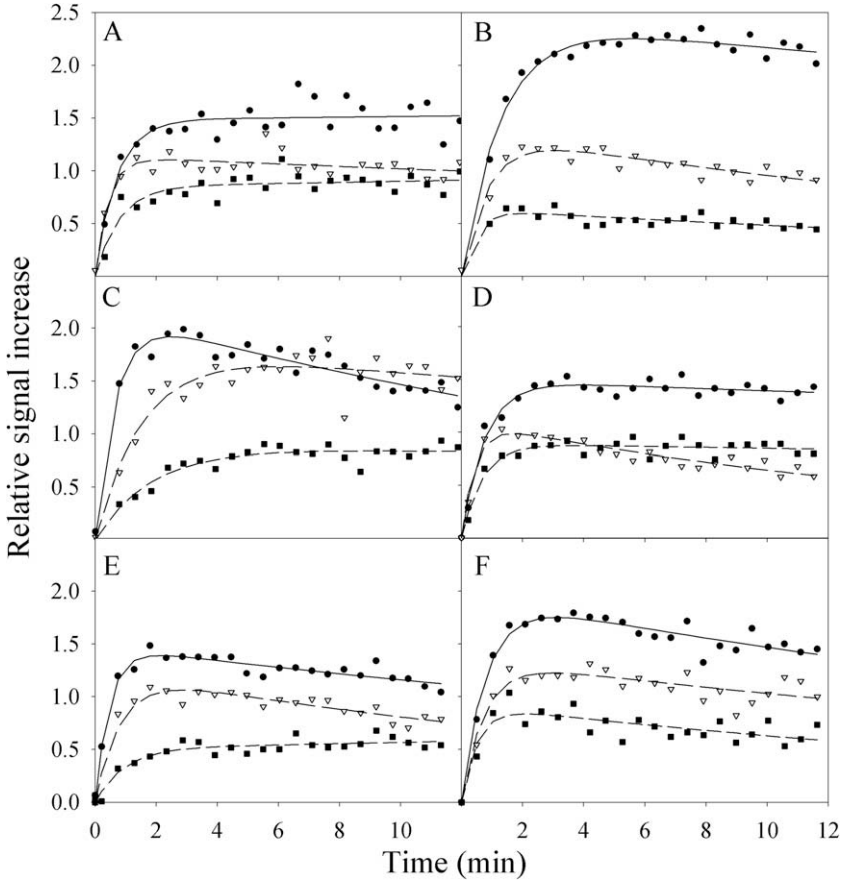

Fig. 1. Examples of single voxel uptake curves in the respective canine tumors (A–F). Fitted uptake curves are given as solid lines.