

Quantitative dynamic MRI(DCE-MRI) of bone metastases in breast and prostate cancer

1 The aims of the study

1. To determine whether DCE-MRI can detect early changes associated with response to therapy and predict clinical outcome in patients with bone metastases from breast cancer or from prostate cancer.
2. To correlate the changes in the DCE-MRI dynamic parameters from before to after initiation of therapy with therapeutic response.

2 Background

The skeleton is the most frequently affected organ in both metastatic breast cancer and metastatic prostate cancer. The primary aim of bone-metastasis treatment is to achieve optimal control of patient pain and to reduce pathological complications. The usual treatment for bone metastases is a proper combination of chemotherapy, endocrine therapy, radiotherapy and surgery.

Current methods of bone-metastasis assessment do not accurately predict pathological response during therapy. Bone scintigraphy and traditional X-ray characterize the response to therapy indirectly, are relatively nonspecific, and detect changes after a relatively long period from the beginning of treatment. More sensitive diagnostic tools are necessary in order to identify positive or negative responses shortly after beginning therapy.

Semiquantitative analysis of images obtained from Dynamic Contrast Enhancement Magnetic Resonance Imaging (DCE-MRI) is able to identify early signal modifications in bone metastases after biphosphonate treatment. According to our experience, these modifications, related to bone tissue repair, are strongly correlated with patient prognosis (3). The DCE-MRI technique is reported by others to accurately evaluate the degree of tumor response to

the applied therapy (4-5-6-7-8-9) in soft-tissue cancers and sarcomas of bone. It is based on rapid acquisition sequences repeated several times, allowing the characterization of contrast pharmacokinetic parameters associated with tissue perfusion and vascular permeability (10-11). In recent studies, it was shown that DCE-MRI imaging findings can be used for accurate in-vivo measurements of tissue perfusion and permeability (12-13). Cancer tissue shows a peculiar angiogenesis different from normal tissue. These differences are better characterized in malignant lesions by physiological features rather than by morphological appearance.

DCE-MRI is a method to determine parameters related to the intravascular and extravascular tissue spaces and the transport parameters that characterize the transfer of solutes between these spaces. The diagnostic study is carried out by performing T1-weighted MRI before and after infusion of a T1-reducing contrast medium that is capable of being transported to the extravascular space. The after-contrast scan is dynamic, with sufficient time resolution to provide a detailed time-intensity curve, which is used to estimate the tissue contrast agent (CA) concentration in selected regions of interest (ROI) during the infusion.

There are two common approaches to analysis of the data, based on semi-quantitative and quantitative models respectively (14). In the semi-quantitative analysis, parameters are obtained that characterize the shape of the time-intensity curve, i.e. the early contrast uptake, the maximum enhancement, the wash out ratio, etc. These parameters are not directly related to physiology and are dependent on the acquisition sequence and experimental conditions. Therefore the semi-quantitative method suffers from a relative lack of standardization and reproducibility.

The quantitative approach is based on a pharmacokinetic model applied to the time-intensity curve. The most widely used model describes contrast agent exchange between two compartments (15), the blood plasma and the extra-vascular extracellular space (EES). Transport rates between the two compartments and concentration of CA in the EES are dependent on tissue perfusion and permeability. Starting from the time-intensity curve, it is possible to compute kinetic parameters that quantitatively characterize the physiology of tissue. This method is shown to be reproducible and to yield detailed insight into tumor response to treatment.

3 Patients

We will perform DCE-MRI on two groups of patients, chosen because of the high frequency of treatable skeletal metastases in patients who are relatively stable. Patients will be enrolled in the study before the commencement of therapy.

3.1 Breast cancer

The first group is patients with proven bone metastases and estrogen and/or progesterone receptor positive advanced breast cancer, where the patient will be treated with the biphosphonate zoledronate. Skeletal complications of breast cancer are frequently observed in women with cancers characterized by receptor-positive cancer. In most cases, disease with bone metastasis demonstrates a slow clinical course and is associated with prolonged survival compared to disease with liver or lung metastasis. The availability of effective anti-endocrine agents makes endocrine therapy associated with biphosphonate treatment a valuable anticancer treatment in this illness. This combination therapy is less aggressive than alternative chemotherapies, with fewer and less severe complications.(1-2).

Patients with rapidly progressive disease, with internal soft-tissue-organ metastases, who are negative for receptors, or who will be treated by other chemotherapies are not eligible for this study. The endocrine therapies eligible for the study are the following:

1. Tamoxifen
2. LH-RH agonists such as Zoladex(goserelin) [pre-menopausal patients]
3. aromatase inhibitors such as Arimidex(anastrozole) (post-menopausal patients)

3.2 Prostate cancer

MUST DESCRIBE PROSTATE PATIENTS IN SIMILAR WAY

4 Study design

Patients are required to provide written informed consent before study entry.

For the metastatic breast cancer cohort, DCE-MRI is planned before the beginning of therapy (baseline), between the 15th and the 21th day of the treatment (post 1st cycle), between the 30th and the 42th day of therapy (post 2nd cycle), and after the 4th month of therapy. Multislice CT is carried out together with the baseline and last DCE-MRI, and as indicated clinically. Serum and urine tests are carried out at each DCE-MRI.

DESCRIBE THE COURSE OF THERAPY AND SCAN SCHEDULE FOR THE PROSTATE PATIENTS.

5 Materials and methods

The DCE-MRI imaging procedure is designed to have the following features:

- A simple and fast data acquisition paradigm that is well-tolerated by patients;
- Automatically performed analysis of the data yielding accurate, precise, and quantitative results.

The examination is acquired with a 1.5 T scanner (GE Medical Systems) using a phased-array coil. Preliminary morphological T_1 FAST SE and STIR sequences are acquired. GIVE TIME REQUIRED.

The DCE-MRI protocol starts with the pre-contrast acquisition to determine R_1^{pre} , the longitudinal relaxivity ($1/T_1$) prior to CA injection. It consists of a series of 2D SPGR (T_R/T_E 50ms/1.4ms, NEX 1) with the following flip angles: $5^\circ, 20^\circ, 45^\circ, 60^\circ$. For a $256 \times 256 \times 10$ image, this protocol will take 12.8 sec for each flip angle for a total of 51.2 sec. [For a nominal T_1 of 500 ms, θ_E , the angle of maximum signal is 25.2° .]

The subsequent dynamic scan employs a T1-weighted 3D fast-SPGR sequence with the following parameters: T_R/T_E 5.3ms/1.2ms, NEX 1, flip angle 12° , equivalent slice thickness 4 mm, matrix size 256x192 and FOV 380 mm (t=11 s). After 3 pre-contrast acquisitions, the Gd-DTPA bolus is injected intravenously using a power injector and 40 post-contrast images are acquired. This acquisition requires 10 sec per image for a total of 430 sec. [For this parameter set $\theta_E = 8.3^\circ$.]

An alternative pre-contrast acquisition paradigm that potentially will provide an accurate value of R_1^{pre} for flowing arterial blood would conform to the dynamic sequence. If we acquire three images for each of 4 angles, 120

sec will be required. Additional advantages of this approach are that the acquisition parameters (matrix, field of view, T_R , T_E) would be the same as for the dynamic acquisition, leading to cancellation of possible systematic biases. The flip angles must be smaller, for example 5,10,15,20 degrees.

DCE-MRI images are submitted to the post-processing analysis performed with dedicated software. R_1^{pre} and R_1^{post} are measured for each pixel. Then v_p , K^{trans} and k_{ep} are computed by fitting the pharmacokinetic model. Finally statistical analysis of output values is applied in the metastatic regions.

Region of Interest (ROI) selection is performed by radiologists, viewing morphological and dynamic images. Selected ROIs are reproduced in the subsequent study stages and modified only through translation and rotation, keeping the screening volume constant. Pixel-wise maps of the kinetic parameters provide a sufficient set of values associated to the ROI to carry out statistical investigation.

At the first level of analysis, mean value and standard deviation are computed for parameters v_p , K^{trans} and k_{ep} inside the ROI. Assuming independent populations at each study stage, Kolmogorov-Smirnov test is applied to compare statistical distributions.

Investigating the existence of clusters of values inside the ROI, proper algorithms can be applied to identify subpopulation of parameters values and to associate spatial information.

6 Pharmacokinetic model

DCE-MRI provides a powerful tool to assess angiogenesis and microvessel density in tumor tissues. These factors are now considered to be important physiological measures in cancer staging and evaluation, and by monitoring them one can assess the efficacy of treatment. Cancer vasculature has a chaotic organization and a tendency to be leaky compared to the vasculature of normal tissue. A contrast agent of appropriate molecular weight will leak out of the vessels into surrounding tissue, causing reduction of T1 and enhancement of the MRI signal. DCE-MRI data reflect local variations of CA concentration, providing information about the anatomy and physiology of the cancer through modeling. Time-intensity values $S(t)$ at each voxel, corresponding to the signal intensity at each acquisition time step

(the time-intensity curve), are recorded. These data are used to infer the T1 of the tissue, which in turn is related to the CA concentration. The pharmacokinetic model is applied to the time-dependent CA concentration to extract information about physiological parameters, including permeability, perfusion, tumor plasma volume and tumor extravascular extracellular space (EES) volume. We will apply a two-compartment model to describe CA transport between blood plasma and the EES. As CA passes through the tissue vasculature, it leaks from the vessels into the EES of the surrounding tissue. The signal enhancement is determined by the sum of the CA concentrations in the two compartments, which in turn are determined by the microvessel density giving a tissue plasma volume, microvessel permeability and EES volume. We have the following equation for the EES CA concentration C_e : $\frac{dC_e}{dt} = k_{pe}C_p - k_{ep}C_e$ where C_p is the CA concentration in arterial blood plasma (the *arterial input function* or AIF) and k_{pe} and k_{ep} are the transport constants from plasma to EES and EES to plasma respectively. The tissue CA concentration is then $C_t(t) = v_p C_p(t) + v_e C_e(t)$ where v_p and v_e are the fractional tissue plasma volume and fractional EES volume respectively. Solving the equation we have

$$C_t(t) = v_p C_p(t) + v_e k_{pe} \int_0^t C_p(u) e^{k_{ep}(t-u)} du$$

where the product $v_e k_{pe}$ is referred to as K^{trans} (volume transfer constant). The tissue time-concentration curve $C_t(t)$ is determined from the time-intensity curve $S(t)$ in the region of interest. We fit $C_t(t)$ and $C_p(t)$ to compute physiological parameters v_p , K^{trans} and k_{ep} . Details of this procedure are explained below.

The tissue CA concentration $C_t(t)$ is proportional to the difference of longitudinal relaxation, R_1 , before and after CA administration:

$$C_t(t) = \rho_1^{-1} \Delta R_1 = \rho_1^{-1} (R_1^{post} - R_1^{pre})$$

where ρ_1 is the CA molar relaxivity. Assuming ρ_1 is constant and is the same in plasma and EES, $C_t(t)$ can be replaced by the measurable quantity ΔR_1 .

The usual techniques to measure R_1 (*Inversion Recovery and Saturation Recovery*) are too slow to be used in DCE-MRI, therefore ΔR_1 must be indirectly estimated. In the simplest method, T1-weighted sequences are performed and ΔR_1 is approximated by the signal intensity difference. More precise measures can be obtained from the following procedure.

Pre-contrast tissue R_1^{pre} is measured on a pixel-wise basis from a series of *static gradient echo* sequences with different *flip angles*, θ , and by fitting the signal equation:

$$S(\theta) = K\rho_0 \frac{\sin\theta [1 - \exp(-T_R R_1)]}{1 - \cos\theta \exp(-T_R R_1)}$$

where K , ρ_0 and T_R are a proportionality constant, proton density and repetition time respectively. With appropriate choice of parameters, the acquisition can be completed in several minutes. We will calibrate the acquisition with a phantom consisting of a set of samples with well known relaxivity.

It is difficult to measure the relaxivity of arterial blood, because of its rapid motion. If T_R is too long the blood that produces the signal comes from outside the field of RF irradiation and its magnetization is not in a steady state prior to its being excited.

We determine the post-contrast tissue $R_1(t)$, also on a pixel-wise basis, using a dynamic acquisition at fixed θ from the following expression:

$$R_1^{post} = 1/T_R \ln \left(\frac{1 - \cos\theta A}{1 - A} \right), \quad A = \frac{S^{postcon} [1 - \exp(-T_R R_1^{pre})]}{S^{precon} [1 - \cos\theta \exp(-T_R R_1^{pre})]}$$

Here S^{precon} is the signal just before contrast injection and $S^{postcon}$ is the signal at time t after injection.

This analysis approach represent a powerful and precise method for the assessment of bone metastases using MRI, as demonstrated previously using animal models of cancer. REFERENCE?? The procedure provides greater precision and accuracy in the than the semiquantitative method based on signal intensity. Moreover, pixel-wise analysis allows characterization of the inhomogenous regions inside metatstastic lesions.

7 Bibliography

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8 MRI Sequences

The role of the contrast agent in this study is to decrease T_1 . By measuring T_1 we obtain the time-dependent CA concentration in tissue and blood, providing the data required for the kinetic model. We choose MRI sequences that are T1 sensitive, in order to accurately measure the T_1 of tissue and aortic blood. The post-contrast sequence must be fast enough to measure T_1 with a 10 second time resolution. A fast T_1 -weighted sequence requires a small flip angle; the consequence is that the tissue or blood must experience a significant number of excitations (separated by T_R) to reach an asymptotic longitudinal magnetization. However aortic blood is in the excitation field for a relatively short time. The average aortic blood velocity for a subject at rest can be estimated as follows: The stroke volume (SV) is usually in the range 60-100 ml and the heart rate 60-80/min, for a cardiac output of 4-8

l/min. The mean diameter of the descending aorta is 2.5 cm. Taking SV to be 80 ml and a heart rate of 70/min we have $v_{av} \sim \frac{80 \times 60}{70 \pi 1.25^2} = 14$ cm/s. In fact, the instantaneous aortic blood velocity just after systole is much larger; the motion of blood is pulsatile.

We consider a gradient-echo sequence such as those described above. Beginning with longitudinal magnetization M_0 , the longitudinal magnetization after the n th T_R interval is

$$M_n = M_{n-1} \cos\theta + (1 - e^{-T_R/T_1})(M_0 - M_{n-1} \cos\theta) = (1 - e^{-T_R/T_1})M_0 + K M_{n-1} \quad (1)$$

where $K = \cos\theta e^{-T_R/T_1}$. Writing as a sequence we have

$$M_n = (1 - e^{-T_R/T_1})M_0[1 + K + K^2 + \dots K^n] + K^n e^{-T_R/T_1} M_0 \quad (2)$$

$$= (1 - e^{-T_R/T_1})M_0 \frac{1 - K^{n+1}}{1 - K} + K^n e^{-T_R/T_1} M_0 \quad (3)$$

Since $K < 1$, $M_n \rightarrow (1 - e^{-T_R/T_1})M_0/(1 - K)$

In order to achieve a fraction $> (1 - f)$ of the steady-state signal, we have $(1 - K^{n+1}) > (1 - f)$ and $n + 1 > \ln f / \ln K$. For small θ and small T_R/T_1 we have $n > n_f = \frac{-\ln f}{\theta^2/2 + T_R/T_1} - 1$. In the steady state, the signal size for each echo for small θ and small T_R/T_1 is $S \sim \frac{\theta T_R/T_1}{\theta^2/2 + T_R/T_1}$.

For given T_R , The angle at which S is a maximum is the Ernst angle, give by $\cos\theta_E = e^{-T_R/T_1}$. Under this condition we have, again for small T_R/T_1 , $n_{fE} = \frac{-\ln f}{2T_R/T_1}$ where $T_{fE} = n_{fE} T_R = -\ln f T_1/2$ is the corresponding time, and $S_E \sim \theta_E/2 \sim \sqrt{\frac{T_R}{2T_1}}$. For $(1 - f) = 0.8, 0.9, 0.95$, $T_f = 0.8T_1, 1.15T_1, 1.50T_1$ respectively, i.e. independent of T_R . Arterial blood has $T_1 \sim 450$ ms (venous blood ~ 650 ms), so if we have a ~ 20 cm excitation field above the lesion(s) being studied, we should satisfy the steady state requirement at $\theta = \theta_E$. The excitation field depends upon the rf coil used. A surface coil will yield a larger field and a smaller signal/noise ratio than a body coil. A great advantage accrues if the heart and ascending aorta are present in the excitation field, since the contents of the left side of the heart (> 200 ml) are much greater than one second of aortic flow (~ 80 ml).

We can approach the steady state in a shorter time by working at $\theta > \theta_E$. For small T_R/T_1 and arbitrary θ we have $T_f = \frac{2T_1 \ln f}{\theta^2 + \theta_E^2}$. We can, for example, halve the time required for a near steady state by setting $\theta^2 = 3\theta_E^2$. The relation between T_f and S is $\frac{S/S_E}{T_f/T_{fE}} = 1$, so we also halve the signal.