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14. ABSTRACT

The goals of this application are to develop methods to non-invasively differentiate fast and slow growing prostate tumors and also develop methods to evaluate response to anti-angiogenic agents. Validation of the results will be based on tumor growth, metastases, and microvessel density measurement (anti-angiogenic studies). To date, we have focused on optimizing the pulse sequences necessary for lactate detection, synthesizing a macromolecular contrast agent and optimizing its use. These goals have been more difficult to achieve but we are now able to localize lactate within an image plane of the tumor and have finished synthesizing the macromolecular contrast agent and optimizing its use.

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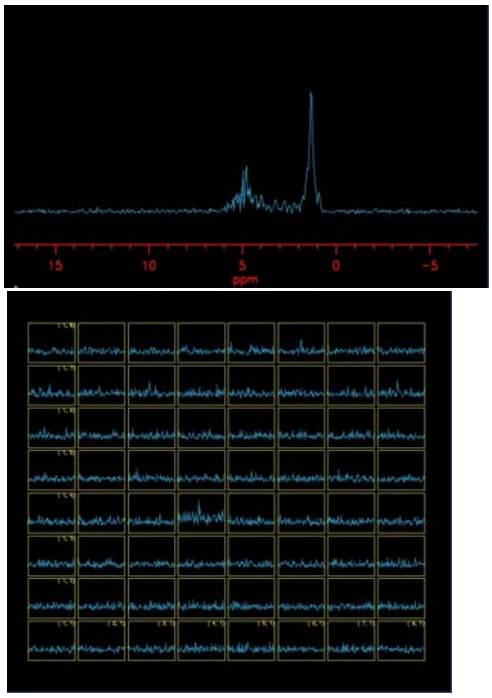
Introduction



1A. 1H spectra of lactate obtained from Dunning R3327 tumor. Acquisition parameters include 32 excitations (NEX) over 64 seconds. B. Localized lactate spectra obtained with a field of view (FOV)= 3.0 x 3.0cm; 1024x8x8 matrix; NEX = 8; Slice Thick = 4.0mm; Acq time = 27:26 min)

The goals of this proposal are to determine if non-invasive magnetic resonance (MR) techniques can distinguish between slow growing and aggressive prostate tumors and if anti-angiogenic therapy is effective as in treating low tumor burden tumors and as adjuvant treatment post radiation (XRT). Technically, we proposed using 1H spectroscopy and dynamic contrast enhanced MR imaging (DCE-MRI) as potential non-invasive markers of aggressive disease and to study the effect of anti-angiogenesis agents. One of the reasons for the emphasis on these techniques is due to the fact that these methodologies are readily translated to the clinic. A series of prostate models with different growth rates, metastatic potential and hormone sensitivity were chosen for study. This project evaluates non-invasive MR techniques to ascertain response to anti-angiogenesis therapy based on the hypothesis that changes in tumor lactate, choline, vascular permeability and volume, and interstitial space (EES) predict response and will be compared with outcome and MVD (microvascular density).

Body

The first year has had setbacks. Research has focused on 1) implementing the requisite pulse sequences 2) construction of appropriate radiofrequency coils, 3) growing the Dunning H (slow growing) tumors.

The issues of implementing the pulse sequences and construction of radiofrequency coils are tightly connected. In the application, we presented preliminary data showing in vivo detection of lactate in tumor models in rats. Extrapolating to rat tumors which are located in a different position and are larger was not simple. After multiple unsuccessful attempts (despite successes on phantoms), it was decided to change the design of the radiofrequency resonator in order to increase the homogeneity of the B1 coil. We have gone through several iterations before deciding to use a large transmit and surface coil receive coil. The decision was based on 1) the need for B1 homogeneity for spectral editing and 2) tumor geometry. We did a lot of our pulse sequence optimization with a 2 turn parallel wound copper foil solenoidal coil tuned to 200 MHz for simplicity but for a tumor on the leg of a rat which will range from 10-18 mm potentially, there were significant concerns about B1 inhomogeneities with this design.

We have been able to selectively detect lactate using SelMQC (Selective Multiple Quantum Coherence) (1,2) in non-localized mode (Figure 1, top) although some further optimization is necessary. However, when trying to localize the signal, the data were far poorer. Figure 1 shows both non-localized (top) and localized spectra of lactate (bottom) which was repeated 2

days later (not shown). Lactate is readily detected in the non-localized spectra and is possibly present in some of the voxels obtained with localized techniques, but these results are not satisfactory. The spectra were obtained using the Sel-MQC sequence (Selective multiple Quantum Coherence). Localization involves both a slice select gradient and phase encoding gradients for in plane resolution. We are currently trying to optimize each step separately. In addition, we are evaluating another pulse sequence for editing lactate. Most recently, we have succeeded in optimizing the in-plane imaging methods and are able to obtain in-plane localized data and will now try to implement the slice selection software. The preliminary studies are being done on the Dunning R3327AT tumor. This is a fast growing tumor and provides rat bearing tumors allowing us to at modest cost to optimize hardware and software.

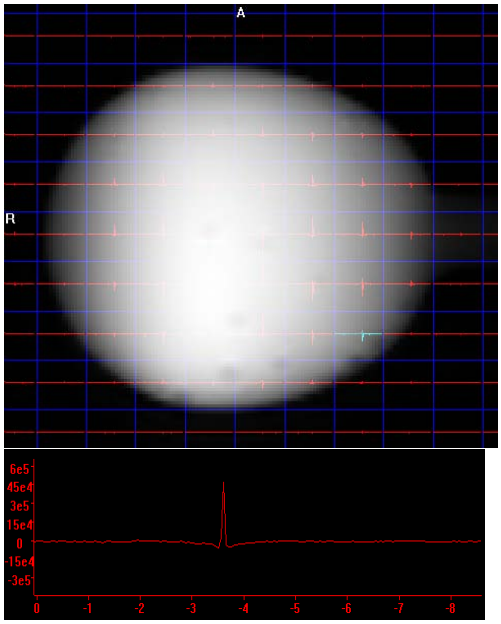


Fig. 1C and 1D. Recently obtained chemical shift image of a phantom. Fig 1C shows the full image with multiple voxels showing lactate and Fig. 1D shows a spectrum from a single voxel

Our second important goal that we are having trouble with is growing the Dunning H which we secured from Johns Hopkins University School of Medicine (Drs. Isaacs and Dalrymple). We have successfully but not reproducibly grown the tumor in Fischer- Copenhagen rats. We are in regular contact with Dr. Dalrymple and are optimistic that the next transplant will be more successful (>75% take). Part of the problem is that these tumors grow so slowly that it is 5-6 months before we can declare the transplant attempt as a success or failure.

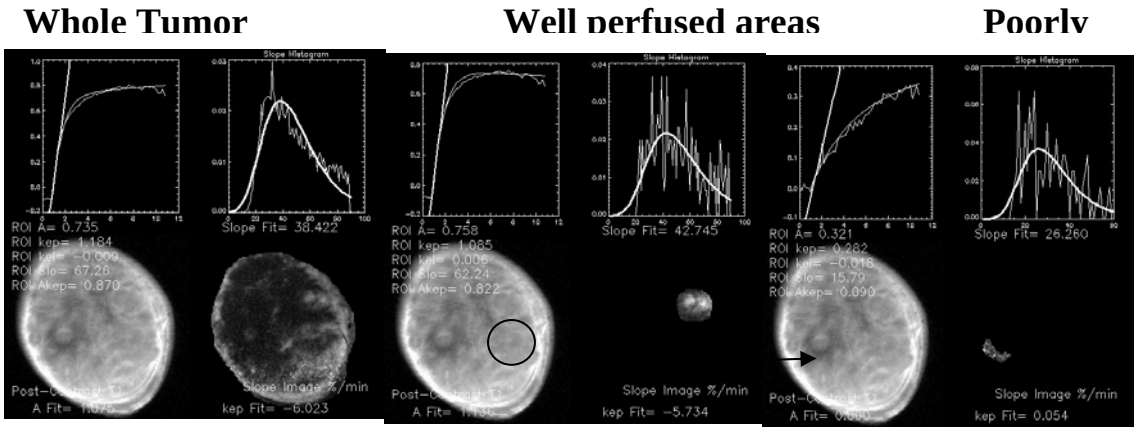


Figure 2 Dynamic contrast enhanced MRI obtained after injection of Gd-DTPA. Acquisition parameters include FOV = 3.0x3.0cm; 128x128 matrix; St=2.0mm (single slice, Coronal); TR/TE/θ = 50/2.5/30^0; 12 sec/image; 55 time pts; total ~11 min acquisition time. Left figure shows data from the whole tumor and shows the signal intensity vs time graph, a histogram of the slope of all the pixels, a post contrast image and a parametric image of the parameter Ak_{ep}. The middle and left figures are similar but correspond to well perfused and poorly perfused regions.

Some of our recent preliminary studies on the fast growing R3327AT tumor are shown below. Technically, the studies require the

detection of lactate, dynamic contrast enhanced MRI of tumors using either Gd-DTPA (the standard contrast agent) and Gd-DTPA-albumin which was synthesized at MSKCC using the method of Ogan et al (3). As discussed above, detection of lactate was problematic and has remained the focus of our work on this project.

Figure 2 show time intensity uptake curves obtained from the tumor after injection of Gd-DTPA. The acquisition parameters include a field of view (FOV) = 3.0x3.0cm; 128x128 matrix; Slice thickness=2.0mm (single slice, Coronal); TR/TE/θ = 50/2.5/300; (TR= repetition interval; TE= echo time; θ= flip angle) 12 sec/image; 55 time points; total ~11 min acquisition time. There was higher uptake noted when the studies were repeated 48 hours later as the tumor grows. Areas of low and high perfusion are readily discriminated on the post GD-DTPA images. Similar data were obtained after injection of Gd-DTPA-albumin, which we successfully synthesized at MSKCC. A dose titration study was performed and after multiple attempts at various doses, successfully found an appropriate dose, not too different from that used previously in the literature.

It is acknowledged by the PI that progress has been slow. Correspondingly, the PI has spent minimal amounts of the funding provided (specifically focused on the synthesis of the Gd-DTPA-albumin), so that if necessary, funding can be stretched (with permission of the Army, if necessary) to a fourth year to complete the original goals of the grant. This has been a particularly difficult start but it appears that most of the technical goals have been achieved or are fairly close. There is a new postdoctoral fellow who arrived recently and has been working on this full time and we are optimistic that this will help achieve progress in a timely style. In addition, to address the unresolved issues of lactate, I have added Dr. Kristen Zakian to the effort (10%) – she has significant experience in this area.

KEY RESEARCH ACCOMPLISHMENTS: Bulleted list of key research accomplishments emanating from this research.

1. We can now obtain lactate localized (in-plane) data
2. we have synthesized the Gd-DTPA-albumin necessary for use as a contrast agent and shown that it works and determine appropriate timing parameters

REPORTABLE OUTCOMES: Provide a list of reportable outcomes that have resulted from this research to include:

None

CONCLUSION:

We are behind schedule but clearly making slow but steady progress. We are hopeful that within one more month, all technical obstacles will have been surmounted.

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