Diffusion MRI as a Biomarker in Cancer Therapy

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INTRODUCTION

Cancer is a debilitating disease that affects all cultures. Its diversity is amplified by the fact that there are so many different kinds of cancer that can vary in their malignancy. Causes of cancer are important in understanding its nature and thus its treatment. The efficacy of any given cancer treatment, such as chemotherapy, is invaluable to a patient's survival. More importantly, whether or not the cancer is being attacked successfully by chemotherapy in enough time to save a patient's life is one of the more important concerns of many doctors who treat cancer patients.

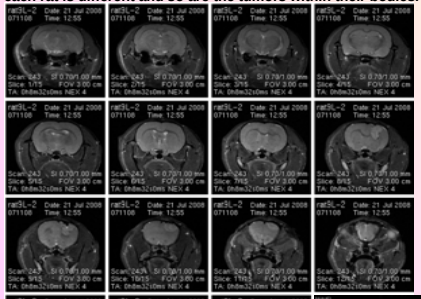
Magnetic resonance imaging has many practical applications and using its sensitivity in being able to detect and depict different particles has been employed in cancer imaging for some time. It is able to "characterize the difference between the magnetic relaxation properties of cancer and noncancer tissues".[2] This said, one begins to wonder whether or not MR imaging can indeed help doctors diagnose or predict whether or not a patient's chemotherapy is successfully killing their cancerous cells. MR imaging can clearly tell a doctor when a patient has a certain cancer but that is when a tumor is already present. By employing MR imaging techniques here at the NHMFL and using their powerful magnet, testing whether or not MR imaging is a good biomarker and predictor of the efficacy of cancer treatment will aid in cancer treatment research.

ABSTRACT

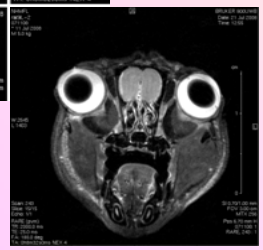
The NHMFL's 900 MHz 21.1 T has many capabilities, one of which is MR imaging; because no other research facility has this tool available in its arsenal to scientists, this large magnet is letting my group gain data which is state-of-the-art. Also, this sort of imaging is unique in the way it was acquired because each imaging protocol had to be created specifically geared toward diffusion and sodium imaging. Thus, everything in this experiment is performed for the first time and still going on until early 2009.

Male Fisher rats were imaged using both the hydrogen and sodium probes; they were divided into groups of four which were all injected with 9L rat glioma cells. A few rats did not have the cancer cell implantations in order to test for the imaging protocols. The four groups in which the rats were divided into consisted of nontreated rats and three groups of treated rats with chemotherapy; the chemotherapy used in this case is Carmutine, or BCNU. The three groups which were treated with BCNU varied in the concentration of the dosage of their chemotherapy. Also, the aggressiveness of each of the tumors in the groups of rats varied and thus so did how often they were imaged. Some tumors were more aggressive than others and so some rats did not survive long enough to reach the stage where they could be imaged.

How large a tumor is also affects the image produced from the magnet because one can manipulate how large and how clear the image obtained is. In manipulating how large the image is, one is changing the imaging protocol for the magnet. Although the exact physics theory behind MR imaging is beyond the scope of this presentation, imaging was made more accessible via these protocols. For every rat, certain tuning must be done and this is where the probe's flexibility comes in. Although these probes require some structural changes in order to be more efficient in the tuning process, they allowed us to tune each rat differently within the probe for the magnet. This is important because each rat is different and so are the tumors within their bodies.



Rat Brain with 9L Rat Glioma Tumor as seen by the 900 MHz 21.1 T Magnet



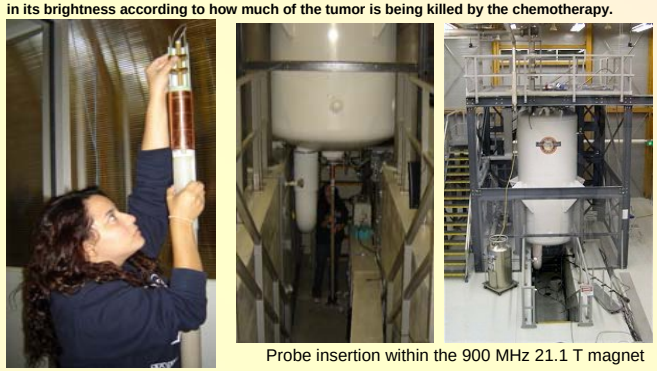
METHODS

Magnetic Resonance Imaging

Using the 900 MHz 21.1 T magnet, we were able to acquire images with remarkable detail. Using two probes which provided different kinds of images containing different data on the state of the rat's brain, one can make a correlation between the data received from the two.

The hydrogen probe is able to provide images which detected the amount of diffusion in the patient's body. In this case, the patients were male rats and how much water is diffused in their brains according to how much chemotherapy they are treated with has a direct affect to the efficacy of their cancer treatment.

Likewise, the sodium probe is able to provide images which detected the amount of sodium present in the patient's body; how much sodium is present in the patient's body is indicative of how much cell death is also present. Thus, the image obtained from the sodium probe will vary in its brightness according to how much of the tumor is being killed by the chemotherapy.



Probe insertion within the 900 MHz 21.1 T magnet

Both probes are share the same design. They are comprised of a heating pad (to compensate for the rat's heat loss while anesthetized inside the magnet), tuning stations, a copper coil, a sensor to monitor breathing, tubing to facilitate breathing and sleeping while inside of the magnet, and holding stations for the rat to remain attached while the probe is suspended.

Male Rats

Four groups of male Fisher rats have been used so far. These groups were all injected with 9L rat glioma cells; the first of these groups was not treated with BCNU while the second group was treated with the highest concentration of BCNU out of all of the groups. The remaining two groups were treated with decreasing BCNU concentrations. This allowed for variation in the imaging data obtained from the magnet and allowed for contrast to be seen within the rat tumors. In more experiments, the dosages will be further varied in order to allow differences in the experimental data.

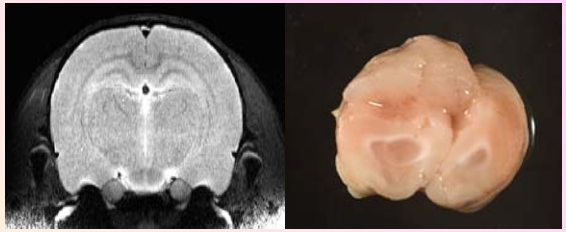
Male Rat with Implanted 9L Rat Glioma

Isoflurane

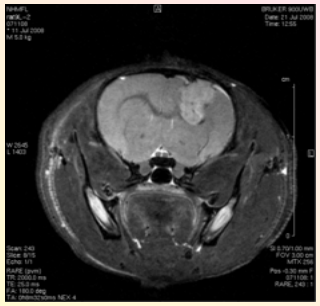
Throughout the imaging process, using the 900 MHz 21.1 T magnet required that the probes we used were inserted into the magnet horizontally which would mean that the rat in the probe had to be suspended inside of the magnet. Thus, we anesthetized each of the male rats so that they would maintain their tranquility. Using isoflurane as our anesthetic of choice, we were able to put the rats to sleep noninvasively through a mist which the rats were able to breathe without compromising them or the experiment.

Chemotherapy: BCNU (Carmutine)

The remaining thirty-eight rats with the 9L rat glioma were not all treated with chemotherapy. This was done for various reasons. To begin, we encountered some complications with the growth of the 9L rat glioma cells within the rats. Some of the cells multiplied to such an extent where the growth of the tumors was too much for the rat to handle. Thus, some of the rats had to be euthanized far in advance in comparison to their group counterparts. As such, a total of thirteen rats were treated with chemotherapy as of 18.07.2008. The remaining groups will be treated differently and accordingly so as to fit their cancer treatment.



Healthy Rat Brain[1] 9L Rat Glioma Brain Tumor Slice



Rat Brain with 9L Rat Glioma Tumor as seen by the 900 MHz 21.1 T Magnet

ANALYSIS

By using the 900 MHz 21.1 T magnet my group was able to collect detailed images of cancerous rat brains which held unique data. The images acquired varied in their brightness and contrast according to how each rat was responding to their cancer treatment. We wanted to see which rats would show a response to the BCNU so far in advance for us to make a prediction in how their bodies would respond to the cancer treatment. In using hydrogen and sodium probes, this contrast was obtained. The images from the hydrogen probe are indicative of the brain tumor's response to the BCNU and thus if more diffusion is seen in the hydrogen probe's images from hydrogen molecules, then this means that the cancer treatment is working.

Likewise, a similar comparison may be made with the sodium probe. The sodium probe's capabilities lies in that it is able to show how much sodium is present in any given object. This sensitivity to sodium is quite important in our case because if there is more sodium present in the patient's body then this can be attributed to more tumor cell death within the patient.

CONCLUSIONS

Further investigation is required in order to determine whether or not MR imaging is truly a good biomarker for cancer treatment. Pictures of great detail were collected from the 900 MHz 21.1 T magnet, but many more must be gathered in order to conclude if MR imaging will indeed predict successfully if chemotherapy is going to work for a patient's brain cancer. Here, 9L rat glioma was used as the model for brain cancer in humans, and as such, more images will be needed before MR imaging can be depended on in aiding a doctor's diagnosis and potential treatment of a patient's brain cancer; bearing in mind that this is not the end of this experiment and that more trials are going to be made in the near future.

ACKNOWLEDGEMENTS

This is a collaborative effort between various groups not including myself. I would like to thank Dr. Victor Schepkin at the National High Magnet Field Laboratory, Silvia Figueiroa with Florida State University and Dr. Cathy Levenson with Florida State University at the department of Food, Nutrition and Exercise Science, and Neuroscience.

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