TITLE: Quantitative Blood Oxygenation Level Dependent (qBOLD) MR Imaging of Glioblastoma Multiforme for Assessment of Tumour Hypoxia

SUMMARY OF PROGRESS AND CURRENT STATUS

This final report covers the period of October 2014 through January 2018, with a focus on April 2016 through January 2018 as our interim report has previously covered the period prior. Since the interim report, we have successfully established a working pipeline at St Michael's Hospital (SMH); approached an additional 12 patients, with 6 successfully completing all trial procedures; and have completed data analyses and manuscript submission to *Radiology*. Although our initial goal was to enrol 27 patients, our data analyses on 10 patients revealed a strong correlation between our imaging findings and our chosen validation techniques; therefore, the principal investigator (PI) has decided to close the study to lessen the burden on patients during their treatment process. Currently, the study team is waiting to hear the final results of our manuscript submission.

Below are the details of some of our major milestones from April 2016 – January 2018:

1) October 2014 – March 2016 (detailed in our interim report).

Since the initiation of this project, there were several delays – due to lower-than-anticipated GBM cases at Sunnybrook, which required the recruitment and activation of a secondary site (SMH) and its associated approvals from Health Canada, and the Toronto Academic Health Science Network Research Ethics Board of Record (TAHSN BoR). Even after activation of SMH, there were several logistical details that needed to be sorted, ranging from patient flow to obtaining a suitable nursing support pool. Although 5 patients were recruited after all approvals were in place, only 4 completed study procedures during this time. To accommodate all the unexpected delays, an extension for the project and funding until June 2018 were requested and granted.

2) Active study recruitment at SMH.

As detailed in our interim report, several issues with enrolling and activating SMH as an additional site led to long delays in patient recruitment for the study. However, shortly following our report there was active work on the patient flow and study pipeline at SMH, including the creation of a nursing pool large enough to accommodate potential cases at any time. After finalizing study-related logistics, 7 SMH patients were approached to participate in the study. Although all were very welcoming to the idea, only 3 went on to fully complete study procedures; two were disqualified part-way through due to unforeseen, logistically-related issues; and we were unable to accommodate the last two patients due to a backlog on study-related equipment.

3) Data Analyses.

After the successful completion of 10 patients, interim data analyses was performed to determine the current status of the project and whether any improvements were required. During this time, our pathology collaborators found and validated the appropriate antibodies, and scored the biopsy samples obtained from the study.

Although a direct comparison between qBOLD and intraoperative findings is not possible, we circumvented the issue by comparing the ratio of oxygen saturation (found through qBOLD imaging, SO_2) and oxygen tension (found through intraoperative

measurements, O_2T) to be positively correlated ($R^2 = 0.87$). These findings were also supported by pathological examination, with significant differences in carbonic anhydrase IX (p=0.031) between high and low oxygen sites. CD105 also displayed a similar trend, although significance was lost upon adjusting for multiple comparisons (p=0.086).

4) Achieving project objective, and publication in *Radiology.*

With these encouraging results from our interim analyses, we believe we have achieved the objective of our hypothesis in demonstrating and validating that qBOLD is a feasible technique in determining the oxygen saturation status of GBM patients. As such, it was decided that it was not necessary to recruit all 27 patients and recruitment has been halted at both sites. Currently, a manuscript on this work has been provisionally accepted by *Radiology.* A notification will be sent to BTFC once acceptance has been confirmed.

LAY SUMMARY OF RESEARCH PROJECT

Hypoxia is defined as a state of low oxygen in a tissue. In tumours, a hypoxic state is associated with increased aggressiveness and resistance to chemotherapy treatment. This is particularly evident in glioblastoma (GBM), the most common brain cancer in adults and one of the most lethal, with an average survival of less than 15 months after diagnosis. Treatment centres around a combination of aggressive surgical resection, chemotherapy, and radiation.

Currently, the most common technique of detecting hypoxia is with positron emission tomography (PET), but this method suffers from low signal-to-noise ratio, limited availability, and high cost. Our project is aimed at providing a quantitative, non-invasive way of determining oxygenation status in the tumour that bypasses these limitations with magnetic resonance imaging (MRI). With our proposed technique, surgeons can use aggressive surgical methods or radiation oncologists can deliver more focal intensified radiation to specific hypoxic regions in the effect to prolong and improve the lives of GBM patients.

This proposed MRI method utilizes a technique known as “quantitative blood oxygenation level dependent (qBOLD)” imaging to detect tumour oxygenation status. Previous iterations of qBOLD imaging has shown to be effective in rats; one study was even performed in humans with positive results. However, this study utilizes newer and more accurate approaches with two additional means of validating the technique in GBM patients.

We have successfully performed this technique on 10 patients. Our results show that there is a high correlation between qBOLD imaging, and intraoperative as well as pathological findings of hypoxia. Although further studies are required, this suggests that the qBOLD technique can act as a surrogate in the detection of tumour hypoxia.

BIBLIOGRAPHY

A summary of this work was presented as a presentation at Brain Tumour Foundation of Canada’s Research Symposium in 2017.