Characterizing an orthotopic Luciferase transduced C6 glioblastoma rat model with Multiparametric magnetic resonance imaging and Bioluminescence imaging.

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Introduction. Glioblastoma multiforme (GBM) is the most aggressive and invasive type of glioma and accounts for approximately 50% of all brain tumours. Despite various aggressive therapeutics, patients rarely survive past 18 months after diagnosis. Due to the unpredictable and complex nature of this disease, a more thorough understanding of GBM tumorigenesis is required to improve treatment of this disease. The C6 orthotopic rat model is a GBM model that shares many characteristics of human GBM tumour progression and reflects the highly invasive nature of the disease. The purpose of this study was to investigate the biological behaviour of the C6 GBM model during tumor progression and to identify key characteristics of the disease using bioluminescence imaging (BLI) and multiparametric magnetic resonance imaging (mpMRI).

Methods. Rat C6 glioma cells were transduced to express Firefly luciferase (Luc). $1 \times 10^6$ C6-Luc cells were stereotactically implanted into the right hemisphere of Wistar rat brains. All rats were imaged with BLI, and mpMRI on days 4, 8, 11, 15 and 18, post-implantation. BLI was performed on an IVIS Lumina XRMS in the lateral position following an i.p. injection of 300mg Luciferin/kg body weight. A 500-mT/m insertable gradient system was used for high-resolution mpMRI on a 3 Tesla scanner (GE Healthcare Discovery MR750). Anatomical images were obtained using a 3D T2-weighted and 3D T1-weighted post contrast (Magnevist) imaging sequence. Functional imaging included diffusion tensor imaging and dynamic susceptibility contrast imaging to assess perfusion. At end point, frozen sections of the rat brain were prepared for histology and compared with imaging data.

Results. Average BLI signal increases up to and peaks on Day 11, then decreases on Day 18. Measured tumour volume on both T1 and T2*-weighted images increase over time. Relative cerebral blood flow and volume inside the tumour decreases over time during tumour progression. Additional functional parameters such as apparent diffusion coefficient (ADC), mean transit time (MTT) and fractional anisotropy (FA) were also obtained. ADC was increased compared to the contralateral hemisphere and decreased over time while FA and MTT increased over time.

Conclusion. This study has demonstrated the importance of characterizing the C6-Luc rat model during tumorigenesis using multi-modality imaging. Contrary to our initial hypothesis that BLI signal should increase with tumour size, this model showed an unexpected development in terms of BLI signal, tumour burden and functional information, as seen in Fig. 1. An expanded analysis is being performed to obtain evidence to explain the decrease in BLI signal despite increasing tumour volume. One potential hypothesis is limited perfusion of larger tumours leading to reduced D-luciferin delivery and/or increased necrotic regions in larger tumours that do not contribute to BLI signal but do to tumour volume. Functional information such as ADC, FA and MTT may provide further information to better understand this disease model. A deeper understanding of this model will help with future studies that examine treatment response or novel imaging modalities.