Título: TOWARDS IMPROVEMENT OF PRECLINICAL GLIOBLASTOMA MANAGEMENT: DETECTION, THERAPY AND ASSESSMENT OF RESPONSE USING MAGNETIC RESONANCE TECHNIQUES

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Resumen: Glioblastoma (GB) is the most common and aggressive primary brain tumour with poor prognosis and survival, with no cure available at present. Relapse usually takes place in a short time even after aggressive standard treatment (chemotherapy with Temozolomide, TMZ and radiotherapy). This PhD thesis was focused in the improvement of GB diagnosis, therapy follow-up and management with Magnetic Resonance (MR) techniques (Magnetic Resonance Imaging, MRI and Magnetic Resonance Spectroscopic Imaging, MRSI) in the preclinical GB GL261 mice model.

Contrast agents (CA) currently used in GB diagnosis are based in Gadolinium (Gd) which is not exempt of risks in case of patients with renal pathology. In addition, most of its effects are appreciated in T1w MRI although

novel studies are pointing to the potential advantages of using dual (T1-T2) agents. In this thesis, a set of novel CA with dual potential was evaluated in collaboration with ICN2 (Institut Català de Nanociència i Nanotecnologia), with a well established path of ex vivo studies for selecting the best agent to proceed with in vivo contrast-enhanced dynamic studies. Dual enhancement MRI image algebra calculated showed the dual properties of candidate CAs. An Fe-based agent was chosen for in vivo studies. This CA proved to be safe in tolerability studies and to show both T1 and T2 effects in a short time frame, allowing to gather both type of data in the same exploration. This type of agents could have clear translational potential in the near future.

Once diagnosed, GB should be treated and one of the challenges faced by clinicians is the therapy response follow-up. We have optimized a volumetric, 3D-like MRSI analysis which was applied to GL261 GB tumour-bearing mice either untreated or under TMZ treatment. Then, nosological images were obtained through semi-supervised pattern recognition analysis and classifying tissues in responding, unresponsive or normal. We established the parameter TRI, Tumour Responding Index, which allowed objective categorization of the response level taking into account the percentage of ¿responding¿ tissue detected. Mice were then categorized within arbitrary cut-off values: low response (LR), intermediate response (IR) and high response (HR). Histopathological studies confirmed an inverse correlation between the TRI and Ki67 proliferation rate, provided Ki67 cells/mm2 was used instead of percent, due to variable cell morphology and cellular volume. The TRI presented an oscillatory pattern with peak maxima every 6-7 days, as opposed to tumour volume changes. This 6-7 day oscillation would be in agreement with host immune system recruitment for therapy response, also supported by histopathological findings of lymphocyte-like cells infiltrating responding tissue.

The potential of gold nanoparticles (NP) for hyperthermia was investigated as an alternative treatment in GL261 GB. For this, a set-up for laser NIR irradiation inside the MR scanner was implemented for hyperthermia ex vivo/in vivo with wt and GL261 tumour-bearing mice. Hollow Gold Nanospheres and Nanorods were studied for heating potential in vitro and ex vivo, achieving discrete results. In vitro studies showed that PEGylated Hollow Gold Nanospheres did not affect GL261 cell viability and were internalized by ca 30% of GL261 cells. Several words of caution resulted from this study, namely: tolerability issues should be improved through new NP synthesis with suitable levels of endotoxin; care should be taken in order to avoid excessive/abrupt brain temperature increase; NIR irradiation inside the MR scanner is not exempt of risks and a whole safety system was developed to prevent fire break incidents; the use of orthotopic brain tumours is challenging for NIR irradiation, due to either need of high accumulation of NP inside tumours and NIR dissipation through tissues until reaching the inner part of the brain.