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Report

Malignant brain tumors are still associated with a poor prognosis despite advances in neurosurgery, radiotherapy and chemotherapy. State-of-the-art treatment for patients with a glioblastome multiforme (GBM) median survival is only about 12 to 15 months. New approaches to improve the high grade glioma treatment need to be developed and optimized. One way consists to combine the injection of a high-Z element (iodine, gadolinium) or a chemotherapeutic agent (usually platinated drugs) in combination with X-irradiation. These injections are critical for the treatment process because it has to target all the tumor tissue and preserve the healthy one. However, the presence of the blood brain barrier, that is a natural regulator in normal conditions, hampers the distribution of drugs for treating brain tumors. Intracerebral injections into the tumors bypass the BBB, provide higher drug concentration in the tumoral bed than systemic injections, and lead to lower systemic toxicity. Convection-Enhanced Delivery (CED) have been proposed by Bobo *et al.* 1994[1] as a refinement of this method of injection. It consists of a direct injection into the brain tumor with low and controlled flow rate of infusion. This method allows to distribute high concentration levels over significant volumes of tissue. The final bio-distribution of the drug into the brain parenchyma is dependent on various parameters such as specific tissue properties (healthy or tumor), on infusion parameters and tissues specificities. Reflux that can occur during infusion around the catheter path can lead to agent transport into adjacent non-targeted brain structures, while reducing effective delivery to the target site. It can be modulated through infusion parameters (Morrison *et al.* 1994[2]). In addition, high interstitial intratumoral pressure has been reported to be a reason of short and heterogeneous intratumoral distribution of drugs (Jain *et al.* 2001[3]). In a previous ESRF proposal (n° 21162), we have proposed to evaluate various CED protocols using agarose-based phantoms as a surrogate of brain tissue. This study allowed us to follow iodine CED infusions in 3 min time resolution and with high spatial resolution (45.7 μm). However, agarose gels don't reproduce all tissue properties, like heterogeneity, anisotropy and physiology of tumor tissues. The study in

the present proposal was to study *in vivo* the biodistribution of iodine into rat brains (healthy / tumor) after different types of injections. The use of monochromatic X-rays is critical to perform quantitative measurements of iodine concentration in tissues. Rousseau *et al.* 2007[4] have previously studied the *in vivo* distribution of an iodinated contrast agent at low spatial and high resolution (Rousseau PhD thesis 2007, Grenoble university). In the present experiment, we varied the nature of cerebral tissue (healthy or tumoral), and we studied infusions at low and moderate flow rate. The iodine was administered alone or with epinephrine, a vasconstricator which was shown to facilitate the transport of various molecules[5]. We have used a high resolution synchrotron radiation computed tomography (SRCT) to quantify above iodine K-edge the *in vivo* tracer distribution just after the end of the intracerebral infusion. The detector used was a FReLoN camera and allowed a $(45.7\ \mu m)^3$ voxel size post-reconstruction (Coan *et al.* 2006[6]). Tumor bearing rats received a tail vein infusion of iodine several hours before CED protocols and were imaged using the same setup. These CT images were used to evaluate the tumor volume and to compare it to the iodine distribution volume after CED by virtual 3D registration. For both data, a 3D analysis was performed by extracting caracteristic volumes, concentration histograms and volumic recovery factor for tumor bearing rats. These results are under the scope of scientific publication. Among other things, we confirmed here the strong influence of tumor tissue on the local agent transport, as seen as heterogeneities on tomographic images (data not shown). According to the litterature and these results, understanding and optimization of drug distribution *in vivo* for brain tumor therapy still need developments and are under the scope of further studies.

References

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