

## **Stereotactic Synchrotron Radiation Therapy, from first concepts to preclinical results and towards clinical trials**

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Despite considerable efforts in cancer therapy research and relative progress<sup>1</sup>, gliomas are still of poor prognosis. Incidence of gliomas is about 5/100,000 and virtually no patient with high-grade glioma survives for more than five years after diagnosis<sup>2</sup>. The research programs developed by the INSERM U836/6 at ESRF explored and confirmed the potential of high-flux monochromatic beams for radiation therapy purposes. At ESRF appropriate infrastructure allowed the development and optimization of innovative chemo-radiotherapy treatments against brain tumors using the properties of synchrotron radiation. A review of the SSRT preclinical trials carried out at the ESRF will be presented, in the overall scope of high-Z compounds radiation therapy dose enhancement pioneered by Mello R. et al.<sup>3</sup>. We first established the enhancement of dose delivered to tumor cells, when incubated with high-Z compounds such as the iodine contained in X-ray imaging contrast agents, and then irradiating with monochromatic beams tuned to the optimal energy<sup>4</sup>. Phantom tests, Monte Carlo simulations<sup>5,6</sup> as well as preclinical trials on the F98 rat brain tumor model demonstrated the dose enhancement effect. After the first results obtained with this method<sup>7</sup>, extensive studies were then carried out; either to optimize iodine concentration or the survival rate obtained with arterial or venous iodine infusions at different X-ray doses<sup>8</sup>. Furthermore, we found that irradiated iodinated compounds lead to a radiosensitization of the tumor endothelial cells<sup>9</sup>. The same set-up and method were then utilized to drive preclinical trials based on the photon-activation of platinum compounds. Intra-cerebral CDDP injection combined with synchrotron X-rays was developed. Among all of the conditions tested, the combination of 3 mg CDDP with 15 Gy resulted in the largest survival rate at one year<sup>10</sup> (34%). Afterwards, we have varied the carboplatin or cisplatin concentrations, the X-ray beam energy, and the infusion methods (CED, bolus or osmotic pumps). Briefly, the results were the improvement of the rats' survival with the use of osmotic pumps and CED<sup>11</sup>; the irradiation was beneficial whatever the energy used; cisplatin and carboplatin provided comparable results after drug concentration optimization<sup>12</sup>. ENU induced rat brain tumor were also used to check SSRT efficiency. These experiments stress the high potential of heavy elements (iodine, platinum, others...) to increase the therapeutic index of radiation therapy with synchrotron X-rays. It should be stressed that based on these results, it sounds realistic to develop a clinical trial on brain tumor synchrotron radiation therapy.

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