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# Brain metastases' growth laws

Beatriz Ocaña-Tienda\*<sup>1</sup>, Julián Pérez-Beteta<sup>1</sup>, David Molina-García<sup>1</sup>, Estanislao Arana<sup>2</sup>, Ana Ortiz De Mendivil<sup>3</sup>, Beatriz Asenjo<sup>4</sup>, David Albillo<sup>5</sup>, Luís Pérez-Romasanta<sup>6</sup>, and Victor M. Perez-Garcia<sup>1</sup>

<sup>1</sup>University of Castilla-La Mancha – Spain

<sup>2</sup>Fundación Instituto Valenciano de Onlogía – Spain

<sup>3</sup>Sanchinarro University Hospital – Spain

<sup>4</sup>Hospital Regional Universitario Carlos Haya – Spain

<sup>5</sup>MD Anderson Cancer Center – Spain

<sup>6</sup>Salamanca University Hospital – Spain

## Abstract

Brain metastases (BM) are the most common intracranial tumor in adults with around 20% of cancer patients developing BMs. Stereotactic radiosurgery (SRS) is becoming increasingly used in the treatment of BM. However, SRS leads sometimes to radiation necrosis (RN), a transient adverse event appearing after irradiation, difficult to distinguish from tumor progression and observed in 5% to 25% of treated patients. RN may resolve spontaneously, not requiring further work-up, while progression need additional treatment. Thus, distinguishing between RN and progression is clinically relevant in the management of BM. Scaling laws (SLs) are simple mathematical models allowing to describe tumor growth. We used SLs in this study to characterize the growth dynamics of BMs subject to different treatments. To characterize the dynamics, a growth factor, the scaling law exponent beta, was used. MR images of 382 patients (1131 BMs) were collected and 104 BMs satisfied the inclusion criteria of the study: availability of three sequential volumetric contrast-enhanced T1-weighted MR imaging, increasing volumes and no SRS for four months before the first measurement. MR images were semi-automatically segmented to compute volumes and the exponent beta for each BM.

Untreated BMs showed a sustained accelerated growth rate most likely related to an underlying evolutionary dynamic even at the short time scale of weeks-months. Relapsing previously treated BMs grew exponentially, most likely due to the expected strong reduction of tumor clonal heterogeneity after SRS, what may limit the tumor evolutionary capabilities. Finally, the growth of radiation necrosis lesions was observed to be substantially faster even than untreated tumor growth. We developed mathematical models of increasing complexity to understand the dynamics of the inflammatory process and found the results to be in line with the observations.

In summary we have shown that RN and tumor relapse have different growth patterns what may help in their differentiation in clinical settings, and we have substantiated our findings using mechanistic mathematical models incorporating aspects of the tumor biology and inflammatory response.

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\*Speaker