Neuro-Oncology Advances 3:vi1–vi31, 2021.
doi:10.1093/noajnl/vdab159

NEURO-ONCOLOGY ADVANCES

Abstracts

INVITED LECTURES

IL-1

SRS WITHOUT THE BUNKER: INTRODUCTION AND CLINICAL EXPERIENCE OF ZAP-X GYROSCOPIC RADIOSURGERY

John R. Adler; Emeritus Dorothy & TK Chan Professor of Neurosurgery at Stanford University and Founder & CEO of ZAP Surgical Systems

Each year more than two million patients worldwide are potential candidates for SRS, yet due to the significant costs and complexities of historical delivery systems, only 150,000 patients currently receive such treatment. Japan Shonin-cleared in 2020, ZAP Surgical's ZAP-X Gyroscopic Radiosurgery platform was designed to solve this challenge, and ultimately bring world-class SRS to more patients in more places.

ZAP-X is recognized for being the first and only vault-free SRS delivery system, thereby typically eliminating the need for providers to build costly shielded radiation treatment rooms. Utilizing a modern linear accelerator to produce radiation, ZAP-X is also the first and only dedicated radiosurgery system to no longer require Cobalt-60 radioactive sources, thereby eliminating the significant costs to license, secure and regularly replace live radioactive isotopes.

Built on a distinctive dual-gimbaled gantry design, the ZAP-X system uses gyroscopic mobility to direct radiosurgical beams from hundreds of unique angles to precisely concentrate radiation on the tumor target. This pioneering approach supports the clinical objective of protecting healthy brain tissue and patient neuro-cognitive function, as well as enable future potential SRS re-treatments without the unnecessary risks associated with multi-purpose radiation delivery technologies.

IL2

NEURAL STEM CELL REGULATION AND BRAIN DEVELOPMENT

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Quiescent neural stem cells (NSCs) in the adult mouse brain are the source of neurogenesis that regulates innate and adaptive behaviors. Adult NSCs in the subventricular zone (SVZ) are derived from a subpopulation of embryonic neural stem-progenitor cells (NPCs) that is characterized by a slower cell cycle relative to the more abundant rapid cycling NPCs that build the brain. We have previously shown that slow cell cycle can cause the establishment of adult NSCs at the SVZ, although the underlying mechanism remains unknown. We found that Notch and an effector Hey1 form a module that is upregulated by cell cycle arrest in slowly dividing NPCs. In contrast to the oscillatory expression of the Notch effectors Hes1 and Hes5 in fast cycling progenitors, Hey1 displays a non-oscillatory stationary expression pattern and contributes to the long-term maintenance of NSCs. These findings reveal a novel division of labor in Notch effectors where cell cycle rate biases effector selection and cell fate. I will also discuss the heterogeneity of slowly dividing embryonic NPCs and the lineage relationship between adult NSCs and ependymal cells, which together form the niche for adult neurogenesis at the SVZ.

IL-3

CHANGING CANCER GENOMICS AND CANCER GENOMIC MEDICINE BY ARTIFICIAL INTELLIGENCE AND LARGE-SCALE DATA ANALYSIS

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In MEXT Program for Scientific Research on Innovative Areas "Systems Cancer" and "Systems Cancer in Neo-Dimension" (2010-2019), we developed a large-scale genome data analysis pipeline called Genomon in collaboration with Professor Seiji Ogawa (Kyoto University). Our efforts successfully produced innovative results on cancer genomics. This system is implemented on the supercomputers SHIROKANE and FUGAKU. One of the contributions unraveled the overall picture of genetic abnormalities in malignant brain tumors (Mutational landscape and clonal architecture in grade II and III gliomas. Nat Genet 2015) that exploited Genomon on SHIROKANE. However, with the spread of new measurement technology and new computing environments, no one thinks that the future can be figured on this simple extension. On the other hand, for cancer genomic medicine, Institute of Medical Science University of Tokyo made a research team analyzing whole genome sequences. The challenge we faced was to transform thousands to millions of genomic aberrations per case into precision medicine. It is what we now call "digital transformation." IBM's Watson for Genomics was introduced for our research purpose. In the process, we identified the effectiveness of AI, the indispensability of specialist intervention, and bottlenecks. We recognized that natural language processing technology such as BERT and Google Knowledge Graph AI technology will open up the future. Automatic document creation is also a realistic issue. Cancer research is getting more difficult and larger in scale. For example, analysis of genomic data from 60, 954 cases revealed a new underlying mechanism in which multiple mutations within the same oncogene synergistically work (Nature 2021). AI with an accuracy of X% does not seem to be the goal. What is needed is not a black box, but explainable AI that explains "why" in a human-understandable way. We are currently conducting research with Fujitsu Laboratories for this direction.

Key words: cancer genomics | artificial intelligence | large-scale data analysis

ANGIOGENESIS/INVASION (ANGI)

ANGI-1

IMPACT OF NEOADJUVANT BEVACIZUMAB ON TRANSCRIPTIONAL FACTOR FOR STEMNESS, MACROPHAGE POLARIZATION, AND OXYGENATION OF TUMOR MICROENVIRONMENT IN GLIOBLASTOMA

Toshihide Tanaka[1], Jun Takei[2], Akihiko Teshigawara[1], Kyoichi Tohmoto[1], Yohei Yamamoto[3], Yuzuru Hasegawa[1], Ryouta Tamura[4], Hikaru Sasaki[4], Yasuharu Akasaki[2], Yuichi Murayama[2]; [1]Department of Neurosurgery, Jikei University School of Medicine Kashiwa Hospital [2]Department of Neurosurgery, Jikei University School of Medicine [3]Department of Neurosurgery, Jikei University School of Medicine Dai-San Hospital [4]Department of Neurosurgery, Keio University School of Medicine

Background: Previously we reported that bevacizumab (Bev) produces tumor oxygenation with immunosupportive tumor microenvironment (TME) and inhibition of stemness. To confirm whether those effects might contribute prolongation of clinical outcome, in the present study paired samples from same patients with newly diagnosed GBM who received Bev during its effectiveness and refractoriness were investigated by immunohistochemistry. *Methods:* Eighteen samples from 9 patients with newly diagnosed GBM who received preoperative neoadjuvant Bev (neoBev) followed by surgical operation and chemoradiotherapy in addition to salvage surgery after recurrence were investigated. Expressions of FOXM1, HIF-1, and CD163 were evaluated by immunohistochemistry. Overall survial (OS) were analyzed with the present cohort divided into two groups between good and poor responder (GR and PR, respectively) of Bev defined as tumor regression rate judged by T1 gadolinium enhancement (T1Gd) and fluid attenuated inversion recovery (FLAIR) images. *Results:* In the group of good responder of T1Gd (T1Gd-GR; defined as >38% of regression rate after neoBev), OS was prolonged compared with T1Gd-PR along with inhibition of FOXM1 expression and HIF-1a. In contrast, in the group of good responder of FLAIR (FLAIR-GR; defined as >54% of regression rate after neoBev), there were no significant differences of OS and FOXM1 expression between GR and PR. HIF-1a expression tended to be elevated in T1Gd-PR of initial tumors, T1Gd-GR of recurrent tumors, and FLAIR-PR of both initial and recurrent tumors.*Conclusion:* T1Gd-GR after neoBev might attribute to inhibition of FOXM1 and oxygenation. Bev might provide tumor oxygenation, leading to inhibition of stemness and M2 TAM infiltration during its effectiveness. These results suggested that Bev combined with immunotherapy for newly diagnosed GBM might provide clinical benefits including inhibition of stemness and induction of immunosupportive TME, when tumor volume assessed by T1 Gd. was significantly decreased following neoBev.

Key words: neoadjuvant bevacizumab | glioblastoma | tumor microenvironment