

Integrating Neuropsychological Outcomes into Clinical Studies for Treating Secondary or Primary Intracranial Malignancies in the Era of Modern Radiation Therapy

Shinn-Yn Lin^{1,2*},
Din-Li Tsan^{3,4},
Chi-Cheng Chuang^{4,5},
Ping-Ching Pai^{1,2},
Yin-Yin Chiang¹,
Chi-Cheng Yang⁶,
Yu-Jen Lu^{4,5},
Yin-Cheng Huang^{4,5} and
Wen-Chi Chou^{4,7*}

Received: June 27, 2019; Accepted: July 17, 2019; Published: July 26, 2019

Short Communication

In managing patients with brain metastasis in the disciplines of neuro-oncology, neurosurgery, and radiation oncology, intracranial control and care [1-3]. Of note, the controversies and problems associated with delayed radiation-related cognitive dysfunction cannot be ignored, particularly in patients who have undergone whole-brain radiation therapy (WBRT) [4,5]. Concerning neurocognitive consequences related to cranial irradiation, previous studies have shown that impaired hippocampal neurogenesis [6,7] may be responsible for such cognitive impacts resulting from the delivery of WBRT. Therefore, it has been hypothesized that conformal hippocampal sparing during the course of WBRT (HS-WBRT) [8,9] would contribute to meaningful preservation with regard to neurocognitive functions (NCFs).

Herein we would like to explicitly mention our previous publications and ongoing research work. First, a preliminary report published in a local academic journal affiliated with our institute documented that incorporating objective neurobehavioral evaluations greatly enhances our understanding of neurocognitive functional outcomes when treating patients with oligometastatic brain disease. In addition, it was disclosed that relevant NCFs would be preserved through the delivery of HS-WBRT. Second, according to our preliminary and robust findings regarding the correlations between various hippocampal dosimetric parameters and relevant NCFs of interest, particularly hippocampus-dominated memory functions [10], a dose-effect relationship was observed; specifically, the dosimetric variables concerning left-side hippocampus were significantly associated with the status of verbal memory function. Definitely a deeper and more clarified understanding of the correlations between hippocampal dosimetry and neuropsychological outcomes would guide us when formulating and proposing future study protocols [11,12].

In addition to our first prospective observational study (HS-WBRT clinical study) essentially integrating neuropsychological outcomes with common oncological study endpoints in real

- 1 Department of Radiation Oncology, Chang Gung Memorial Hospital and Chang Gung University, Taoyuan, Taiwan
- 2 Department of Medical Imaging and Radiological Sciences, College of Medicine, Chang Gung University, Taoyuan, Taiwan
- 3 Department of Radiation Oncology, Chang Gung Memorial Hospital, Keelung, Taiwan
- 4 College of Medicine, Chang Gung University, Taoyuan, Taiwan
- 5 Department of Neurosurgery, Chang Gung Memorial Hospital, Taoyuan, Taiwan
- 6 Department of Psychology, National ChengChi University, Taipei, Taiwan
- 7 Department of Hematology-Oncology, Chang Gung Memorial Hospital and Chang Gung University, Taoyuan, Taiwan

*Corresponding authors: Shinn-Yn Lin;
Wen-Chi Chou

✉ rt3126@gmail.com;
f12986@cgmh.org.tw

Department of Radiation Oncology, Proton and Radiation Therapy Center, Chang Gung Memorial Hospital and Chang Gung University, Taoyuan, Taiwan.
Department of Hematology-Oncology, Chang Gung Memorial Hospital and Chang Gung University, Taoyuan, Taiwan.

Tel: +886-3-3281200 ext: 7000;
+886-3-3281200 ext: 8825, 2517

world practice, our research team has also attempted to elaborate further the subsequent study protocols in several directions. First of all, for patients with oligometastatic brain disease who still have intracranial gross metastatic lesion(s), the planning technique of simultaneously integrated boost (SIB) had better be incorporated into the course of HS-WBRT [13] in order to accomplish both improved intracranial local control and preserved neurocognitive functional outcomes. Second, in contrast to the clinical setting tailored to the above HS-WBRT plus SIB study, our research team has also started to aims at exploring the role of prophylactic cranial irradiation (PCI) via the technique of HS-WBRT in managing patients with pathologically nodal positive non-small-cell lung cancer (NSCLC) who have just undergone curative thoracic surgery for treating newly-diagnosed primary lung cancer [14]. As shown in **Table 1**, the scope of our neurocognitive research has been extended to investigate other disease entities such as primary CNS lymphoma and infiltrative gliomas requiring postoperative adjuvant RT. Besides, almost all study protocols listed in **Table 1** were prospective observational studies except for the PCI study via HS-WBRT for postoperative patients with nodal positive NSCLC.

As shown in the above table listing the study protocols conducted by our research team, the second different and distinct disease entity our research has been focusing on is newly-diagnosed primary central nervous system lymphoma (PCNSL) [15]. Thanks to the multidisciplinary management combining neuro-oncology, neurosurgery, radiation oncology, hematology, and even neurobehavioral sciences, undoubtedly intracranial control and survival outcomes have been improving under multidisciplinary cancer care. Nevertheless, previous evidence

Citation: Lin SY, Tsan DL, Chuang CC, Pai PC, Chiang YY, et al. Integrating Neuropsychological Outcomes into Clinical Studies for Treating Secondary or Primary Intracranial Malignancies in the Era of Modern Radiation Therapy. *Neurooncol Open Access* 2019, 4:1.

has shown that delayed treatment-related cognitive sequelae emerged as a significant debilitating complication of combined modality treatment encompassing whole-brain irradiation in treating PCNSL patients, especially when effective treatment can eventually achieve better disease control and even prolong survival profiles. Thus, we have originally proposed and carried out a prospective cohort study with a longitudinal assessment of neuropsychological/neurocognitive functions, neuroimaging, and quality of life for newly-diagnosed PCNSL patients who would be treated with cranial radiotherapy combined with/without methotrexate (MTX)-based chemotherapy on the basis of multidisciplinary treatment guidelines actually and consistently implemented at our institute.

Although RT-associated techniques employed in delivering WBRT might not be the key research question addressed in the above study, actually whole brain irradiation delivered in this PCNSL study mainly relied on a conformal treatment planning rather than conventional WBRT via simply laterally opposed fields. As a consequence, a highly conformal 3-dimensional treatment planning with an additional planning technique of simultaneously integrated boost (SIB) must have attained optimized dose distributions and contributed to a significantly more favourable intracranial disease control and even better survival outcomes in this era of contemporary and modern radiotherapy.

Table 1 Protocol Registration of Our Neuropsychological Studies on ClinicalTrials.gov.

Title	Patients	Intervention	Outcomes	Website
A Prospective Study of the Impact of Hippocampal Avoidance During Whole Brain Radiotherapy on Neurocognitive Function Decline	Patients with oligometastatic brain disease (i.e., the number and extent of brain metastatic lesions should be no more than three metastatic foci with a greatest diameter no more than 4 cm) Patients with lung cancer referred for arranging prophylactic cranial irradiation	A course of whole-brain radiation (WBRT) using the technique of hippocampal sparing during the course of WBRT (HS-WBRT)	Primary endpoint: delayed recall, as determined by the change in verbal and non-verbal memory functions from the baseline assessment to 4 months after the start of HS-WBRT.	NCT02504788
Prospective Neurobehavioral Outcomes Follow-up in Primary CNS Lymphoma Patients Treated With Cranial Radiotherapy Combined With or Without MTX-based Chemotherapy According to the Multidisciplinary Treatment Guidelines Implemented at a Single Institute	Newly-diagnosed patients with primary CNS lymphoma	A conventional treatment protocol with courses of combined chemoradiation in a sandwiched manner at our institute	Neuropsychological outcome measures involve four domains sensitive to disease and treatment effects including executive function and verbal memory; the change in these domains are acquired from baseline to 4 months after completing all courses of chemoradiation is our primary endpoint.	NCT02655744
Neurobehavioral Outcomes and Quality of Life in Pediatric Patients With Brain or Head/Neck Tumors Receiving Proton or Photon Radiotherapy	Newly-diagnosed pediatric/adolescent patients with brain tumors or head/neck cancers	A course of standard adjuvant cranial RT according to the treatment guidelines at our institute		NCT02608762

In the real-world clinical practice at our institute, it has been acknowledged that the administration of induction therapy with “high-dose” MTX was almost not feasible even given to younger patients because there were unsatisfactory morbidity rates resulting from high-dose MTX at our institute. As a consequence, the majority of newly-diagnosed PCNSL patients we encountered have been managed with combined chemoradiation in a sandwiched fashion in which a conventional dosage (1 g per m²) of intravenous MTX was prescribed for the past two decades.

From the viewpoint of radiation oncologists based on radiological rationales, there have been several previous prospective studies conducted by Radiation Therapy Oncology Group (RTOG) proposing the scheme of hyperfractionated WBRT (hWBRT) instead of a course of conventionally fractionated WBRT in order to alleviate the probability and severity of potential WBRT-induced neuropsychological consequences [16,17]. Theoretically and reasonably, delivering a hyperfractionated scheme of WBRT *via* 3-D conformal treatment planning with an additional SIB technique (if needed) will achieve both optimized intracranial (lymphoma) control and diminished WBRT-related neurocognitive impacts. Therefore, a prospective cohort study has just been proposed and under review for being funded by our institutional research foundation. Furthermore, by administering objective multi-domain neurocognitive and neuropsychological assessments, the status and change in NCFs before and after the course of hyperfractionated conformal WBRT will be examined and analyzed.

Regarding our study protocols addressing neuropsychological and oncological outcomes in chronological order, the third unique and different disease entity under ongoing investigation is radiation-naïve malignant glioma excluding pathological grade IV disease; namely, a prospective follow-up study has been carried out in grade 2 or 3 glioma patients indicated for receiving postoperative modern radiotherapy. This prospective observational study is anticipated to examine thoroughly neurocognitive impacts of

postoperative adjuvant RT with using modern radiotherapeutic techniques on patients’ neurocognitive performances and verify that functional preservation might be achieved by sparing the contralateral hippocampus. Meanwhile, adjuvant partial brain irradiation delivered in these glioma patients will contribute to satisfactory progress-free survival interval, attaining the international level.

In our opinions, integrating functional outcomes including NCF assessments with commonly applied neuro-oncological outcomes would help neuro-oncologists and radiation oncologists manage patients with secondary or primary intracranial malignancies in the era of modern radiation therapy. For instance, when treating cancer patients harboring brain metastases, particularly those with oligometastatic brain disease and a satisfactory/fair performance status, the delivery of HS-WBRT course indeed has achieved both functional preservation and satisfactory intracranial control by restricting the dose irradiating the hippocampus during the WBRT course. Besides, regarding postoperative adjuvant partial cranial irradiation employed in treating patients with newly-diagnosed or RT-naïve infiltrative glioma, it is highly recommended to spare the contralateral hippocampus of being unnecessarily irradiated, if technically feasible, in an attempt to diminish the extent of neurocognitive impacts related to the contralateral hippocampus, which is significantly associated with verbal or non-verbal memory functions. Last but not least, even for treating newly-diagnosed primary CNS lymphoma patients at our institute, multi-domain NCFs indeed become stabilized and generally improved after the course of conformal WBRT combined with methotrexate-based chemotherapy is completed.

Funding

This article-related studies were principally funded by Chang Gung Memorial Hospital at Keelung, Taiwan, R.O.C. (grant number CMRPG2G0472) and Chang Gung Memorial Hospital at Taoyuan, Taiwan, R. O. C. (grant number CMRPG3J0101).

References

- 1 Maclean J, Fersht N, Singhera M, Mulholland P, McKee O, et al. (2013) Multi-disciplinary management for patients with oligometastases to the brain: results of a 5 year cohort study. *Radiat Oncol* 8.
- 2 Owonikoko TK, Arbiser J, Zelnak A, Shu HKG, Shim H, et al. (2014) Current approaches to the treatment of metastatic brain tumours. *Nat Rev Clin Oncol* 11: 203-222.
- 3 Scoccianti S, Ricardi U (2012) Treatment of brain metastases: Review of phase III randomized controlled trials. *Radiother Oncol* 102: 168-179.
- 4 Soffietti R, Kocher M, Abacioglu UM, Villa S, Fauchon F, et al. (2013) A European Organisation for Research and Treatment of Cancer Phase III Trial of Adjuvant Whole-Brain Radiotherapy Versus Observation in Patients With One to Three Brain Metastases From Solid Tumors After Surgical Resection or Radiosurgery: Quality-of-Life Results. *J Clin Oncol* 31: 65-72.
- 5 Aoyama H, Tago M, Kato N, Toyoda T, Kenjyo M, et al. (2007) Neurocognitive function of patients with brain metastasis who received either whole brain radiotherapy plus stereotactic radiosurgery or radiosurgery alone. *Int J Radiat Oncol Biol Phys* 68: 1388-1395.
- 6 Rola R, Raber J, Rizk A, Otsuka S, VandenBerg SR, et al. (2004) Radiation-induced impairment of hippocampal neurogenesis is associated with cognitive deficits in young mice. *Exp Neurol* 188: 316-330.
- 7 Byrne TN (2005) Cognitive sequelae of brain tumor treatment. *Curr Opin Neurol* 18: 662-666.
- 8 Gondi V, Pugh SL, Tome WA, Caine C, Corn B, et al. (2014) Preservation of memory with conformal avoidance of the hippocampal neural stem-cell compartment during whole-brain radiotherapy for brain metastases (RTOG 0933): a phase II multi-institutional trial. *J Clin Oncol* 32: 3810-3816.
- 9 Lin SY, Yang CC, Wu YM, Tseng CK, Wei KC, et al. (2015) Evaluating the impact of hippocampal sparing during whole brain radiotherapy on neurocognitive functions: A preliminary report of a prospective phase II study. *Biomed J* 38: 439-449.

- 10 Zhao R, Kong W, Shang J, Zhe H, Wang YY (2017) Hippocampal-Sparing Whole-Brain Radiotherapy for Lung Cancer. *Clin Lung Cancer* 18: 127-131.
- 11 Tsai PF, Yang CC, Chuang CC, Huang TY, Wu YM, et al. (2015) Hippocampal dosimetry correlates with the change in neurocognitive function after hippocampal sparing during whole brain radiotherapy: a prospective study. *Radiat Oncol* 10: 1-15.
- 12 Ma TM, Grimm J, McIntyre R, Anderson Keightly H, Kleinberg LR, et al. (2017) A prospective evaluation of hippocampal radiation dose volume effects and memory deficits following cranial irradiation. *Radiother Oncol* 125: 234-240.
- 13 Shinn-Yn Lin, Chi-Cheng Chuang (2016) Neurocognitive Impact and Dose-Effect Relationship of Hippocampal Avoidance During Whole Brain Radiotherapy Plus Simultaneous Integrated Boost - A Prospective Follow-up Study.
- 14 Shinn-Yn Lin, Chi-Cheng Chuang (2015) Hippocampal-Sparing Prophylactic Cranial Irradiation in Pathologically Nodal Positive Non-Small-Cell Lung Cancer.
- 15 Shinn-Yn Lin, Chi-Cheng Chuang (2015) Prospective Neurobehavioral Outcomes Follow-up in Primary CNS Lymphoma Patients Treated With Cranial Radiotherapy Combined With or Without MTX-based Chemotherapy According to the Multidisciplinary Treatment Guidelines Implemented at a Single Institute.
- 16 Fisher B, Seiferheld W, Schultz C, DeAngelis L, Nelson D, et al. (2005) Secondary analysis of Radiation Therapy Oncology Group study (RTOG) 9310: an intergroup phase II combined modality treatment of primary central nervous system lymphoma. *J Neurooncol* 74: 201-205.
- 17 Glass J, Won M, Schultz CJ, Brat D, Bartlett NL, et al. (2016) [NRG Oncology RTOG 0227] Phase I and II Study of Induction Chemotherapy With Methotrexate, Rituximab, and Temozolomide, Followed By Whole-Brain Radiotherapy and Post irradiation Temozolomide for Primary CNS Lymphoma: NRG Oncology RTOG 0227. *J Clin Oncol* 34: 1620-1625.