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

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Introduction

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 pervious 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 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 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.

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 m^2) 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 hyper fractionated 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 analysed.

Regarding our study protocols addressing neuropsychological and oncological outcomes in chronological order, the third unique and different disease entity under ongoing investigation is radiation-naive 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 their 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

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
Hippocampal-Sparing Prophylactic Cranial Irradiation in Pathologically Nodal Positive Non-Small-Cell Lung Cancer	Adult patients with NSCLC have received definitive surgery and then then the presence of pathologically nodal positive disease makes the patient referred to undergo the subsequent adjuvant platinum-based radiotherapy.	Experimental arm: PCI via a course of hippocampal-sparing WBRT Control arm: Observation without the administration of PCI	The time to the development of brain metastasis/metastases (BM), irrespective of the absence of active neurological symptoms	NCT02448992
Neurocognitive Impact and Dose-Effect Relationship of Hippocampal Avoidance During Whole Brain Radiotherapy Plus Simultaneous Integrated Boost - A Prospective Follow-up Study	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 3 cm	A course of HS-WBRT plus simultaneous integrated boost (SIB)	The primary outcome measure is 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.	NCT03223675
Neuropsychological and Oncological Outcomes in Grade 2 or 3 Glioma Patients Undergoing Postoperative Modern Radiotherapy	Patients with infiltrative gliomas excluding the presence of GBM who have received craniotomy plus tumor resection or at least biopsy with pathologic conformation	Postoperative adjuvant RT is indicated in this prospective observational study. Prescription dose will be 5000 - 6000 cGy in 25 - 30 fractions during 5 - 7 weeks.	The primary outcome measure is delayed recall, as determined by the change in verbal memory or non-verbal memory from the baseline assessment to 4 months after the start of postoperative adjuvant RT.	NCT03534050
Prospective Neurobehavioral Functions in Newly-diagnosed Patients With Primary CNS Lymphoma Treated With Hyperfractionated Conformal Whole-brain Radiation Therapy Plus Simultaneous Integrated Boost	Newly-diagnosed patients with primary CNS lymphoma	Each freshly-diagnosed patient with primary CNS lymphoma will be treated with combined chemoradiation in a sandwiched way, in which 2 cycles of induction chemotherapy with intravenous methotrexate (MTX in a conventional dose of $1g/m^2$) and intrathecal MTX are followed by a complete course of hyper fractionated WBRT* and then high-dose cytarabine for 2 cycles.	The primary outcome measure is the change in patients' capability of information processing indicated by the Paced Auditory Serial Addition Test - Revised (PASAT-R), from the baseline before undergoing the WBRT course to the timing after going through the entire courses of combined chemoradiation.	Under protocol review by ClinicalTrials.gov

or RT-naïve infiltrative glioma, it is highly recommended to spare the contralateral hippocampus of being unnecessarily irradiate, 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.

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