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Impact of radiotherapy dosimetric parameters on neurocognitive function in brain tumor patients

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See the article by Goda et al. in this issue, pp. 1677–1686.

Neurocognitive decline is a known adverse effect of radiotherapy to the brain as determined from several prospective studies of patients undergoing prophylactic cranial irradiation,[1] whole-brain radiation therapy for brain metastasis,[2] and partial brain irradiation for primary brain tumors.[3] Neurocognitive decline after radiotherapy can manifest across multiple cognitive domains, including executive functioning, psychomotor functioning, verbal and working memory, information processing speed, and attention. Previous studies have demonstrated that more than half of low-grade glioma patients treated with radiotherapy subsequently exhibit measurable neurocognitive deficits in at least 5 of 18 tested neurocognitive domains.[4] Yet, radiotherapy alone may not be the only factor leading to cognitive impairment. Several other factors such as patient age, tumor type and grade, initial versus recurrent disease, duration of disease, tumor location, tumor size, hydrocephalus, medications such as corticosteroids and anticonvulsants, metabolic/endocrine dysfunction, impact of surgery, number of surgeries, ventriculoperitoneal shunt, postoperative complications, concurrent infections, chemotherapy, underlying end-arteriolar disease processes, etc, are also associated with impairment in neurocognitive function. Therefore, the ability to discern and detect the impact of a single variable in this complicated equation of neurocognitive change—an outcome we are still trying to understand and measure adequately, is of the utmost importance to the field of neuro-oncology.

In this issue, Goda and colleagues report on the variables associated with neurocognitive decline in a prospective cohort of 48 children and adolescent patients with benign or low-grade central nervous system malignancies treated with stereotactic conformal radiotherapy to a dose of 54 Gy in 30 fractions.[5] The median age was 13 years, and all patients completed a comprehensive battery of neurocognitive evaluations before treatment, at 6 months following treatment, and annually for up to 5 years. A comprehensive analysis was performed of numerous dose-volume parameters of the left, right, and bilateral hippocampi, yielding several important outcomes: (i) left hippocampus mean dose >31 Gy was associated with a >10% decline in mean full-scale intelligence quotient scores at 3 and 5 years posttreatment; and (ii) left hippocampus mean dose >32 Gy was associated with a >10% decline in mean performance quotient scores at 5 years posttreatment. Multivariable logistic regression demonstrated that age (<13 y) and mean dose to the left hippocampus (>30 Gy) were associated with declines in various intelligence quotient domains 5 years following treatment. Interestingly, bilateral hippocampi or individual right hippocampus dosimetric parameters were not associated with neurocognitive outcomes.

Understanding the impact of individual dosimetric parameters on patient outcomes and treatment-related toxicities is one of the central tenets of radiation oncology; nonetheless, we have barely begun to understand the complex interplay between dose delivered to key substructures of the brain and the resulting impairments on neurocognitive function across multiple neurocognitive domains. For example, reduction in brain volume after whole brain radiotherapy was associated with decline in verbal memory (delayed recall and percent retained)[6]; bilateral hippocampal dosimetry was associated with verbal memory impairment in benign or low-grade brain tumor patients;[7] and mean and high doses to the temporal lobes were associated with declines in short-term memory, language ability, and list-generating fluency.[8] To date, several retrospective and prospective studies of children and adult brain tumor patients treated with various radiotherapy dose and fractionation schedules have demonstrated important dosimetric parameters associated with neurocognitive function. This work, spanning a decade, is summarized in Table 1. However, an inherent interplay exists between dose to certain substructures of the brain and individual neurocognitive parameters that can affect the assessment of multiple cognitive domains. This is underscored by a recent retrospective study of 78 adult patients who underwent a comprehensive battery of standardized cognitive tests after radiotherapy and demonstrated the importance of dose to individual and collective substructures on each neurocognitive

Table 1 Selected studies evaluating dose volume constraints associated with neurocognitive protection in brain tumor patients receiving radiotherapy

Study	Study Type	*n*	Ages, y	Diagnoses	Radiotherapy Dose	Critical Substructures	Neurocognitive Measures	DVH Constraint
Jalali, 2010	Prospective	28	5–25	Low grade/benign tumors	54 Gy (1.8 Gy/fx)	Temporal lobe (L)	Intelligence quotient	V43.2Gy <13% (L)
Hsiao, 2010	Prospective	30	≥18	Nasopharyngeal cancer	70 Gy (2 Gy/fx)	Temporal lobes (B)	CASI	Mean <36 Gy V60Gy <10%
Gondi, 2013	Prospective	18	≥18	Low grade/benign tumors	50.4–54 Gy (1.8 Gy/fx) 20 Gy (4 Gy/fx)	Hippocampus (B)	Multiple neurocognitive tests	D40% <7.3 Gy
Gondi, 2014	Phase II	42	≥18	Brain metastasis	30 Gy (3 Gy/fx)	Hippocampus (B)	Hopkins Verbal Learning Test–Revised	D100% <9 Gy Dmax <16 Gy
Greenberger, 2014	Retrospective	12	2–22	Low grade/benign tumors	48.6–54 Gy (1.8 Gy/fx)	Hippocampus (L) Temporal lobe (L)	Intelligence quotient VCI	V20 <15 Gy
Mahajan, 2014	Retrospective	25	1–15	Low or high grade tumors	45–60 Gy (1.8–2 Gy/fx)	Hippocampus (R)	Intelligence quotient	Dmax <50 Gy D10% >30 Gy
Tsai, 2015	Prospective	24	≥18	Brain metastasis	30 Gy (3 Gy/fx)	Hippocampus (B)	Multiple neurocognitive tests	Dmax <12.60 Gy D10% <8.81 Gy D50% <7.45 Gy D80% <6.80 Gy Dmin <5.83 Gy Dmax <12.41 Gy (L)
Ma, 2017	Prospective	30	≥18	PCI High grade gliomas	25 Gy (2.5 Gy/fx) 60 Gy (2 Gy/fx)	Hippocampus (B)	Hopkins Verbal Learning Test–Revised	D50% <22.1 Gy
Okoukoni, 2017	Prospective	53	≥18	Low or high grade tumors	54 Gy (1.8 Gy/fx)	Hippocampus (B)	Hopkins Verbal Learning Test–Revised	V55 Gy
Zureick, 2018	Retrospective	70	5–23	Low or high grade tumors	30–59.4 Gy (1.5–1.8 Gy/fx)	Hippocampus (L)	Multiple neurocognitive tests	V20 Gy (L)
Kim, 2018	Retrospective	26	≥18	Low or high grade tumors	56–60 Gy (2 Gy/fx)	Hippocampus (B)	Seoul Verbal Learning Test	Mean <11 Gy Mean <12 Gy (L)
Acharya, 2019	Phase II	80	6–21	Low grade glioma	54 Gy (1.8 Gy/fx)	Hippocampus (B)	Verbal recall (memory)	V40 Gy
Goda, 2020	Prospective	48	3–25	Low grade/benign tumors	54 Gy (1.8 Gy/fx)	Hippocampus (L)	Intelligence quotient	Mean <30 Gy (L)

Abbreviations: DVH = dose-volume histogram; fx = fraction; CASI = Cognitive Abilities Screening Instrument; L = left; R = right; B = left and right; VCI = Verbal Comprehension Index; PCI = prophylactic cranial irradiation.

parameter: (i) left hippocampus, left temporal lobe, left frontal lobe, thalamus, and total brain dose were associated with verbal learning and memory, verbal fluency, executive function, and processing speed; (ii) left hippocampus, left temporal lobe, left frontal lobe, and total frontal lobe dose were associated with verbal fluency; (iii) left frontal lobe and thalamus dose were associated with executive function; and (iv) total brain and thalamus dose were associated with processing speed.[9] The current study by Goda and colleagues refines our understanding further by suggesting the importance of mean dose to a unilateral structure in the brain and corroborates the findings of several other studies suggesting the unique sensitivity of left-sided substructures, including the hippocampus and temporal lobes. Yet, in each of these aforementioned studies, as in the study by Goda and colleagues, specific effort was not made to reduce extraneous radiotherapy dose to these critical areas of neurocognitive importance. Moreover, it was not assessed whether dose to multiple brain substructures may additively contribute to specific delayed neurocognitive impairments.

As we translate these findings to the clinic, readers should strongly consider the following important principles: (i) careful evaluation and delineation of all substructures responsible for neurocognition should be implemented, potentially with the aid of automated software; (ii) patients should undergo neurocognitive assessments at baseline and in follow-up as part of routine neuro-oncologic care and management; and (iii) decisions regarding radiotherapy technique (ie, use of non-coplanar arcs or pencil beam scanning proton therapy vs photon therapy) and treatment plan quality should include the review of dose delivered to critical substructures, including the temporal lobes and hippocampus, in addition to the "routine" CNS avoidance organs at risk (ie, brainstem, optic nerves, etc). With modern imaging and sophisticated treatment planning and delivery techniques, incorporation of the principles listed above into clinical practice is not only possible, but also necessary to minimize the potential decline in neurocognition and quality of life in our brain tumor patients, particularly those with long-term expected survival.

Keywords

dosimetry | hippocampus | memory | neurocognition | radiation | temporal lobe

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