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Scientific Article

Hippocampal dose volume histogram predicts Hopkins Verbal Learning Test scores after brain irradiation

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Abstract

Purpose: Radiation-induced cognitive decline is relatively common after treatment for primary and metastatic brain tumors; however, identifying dosimetric parameters that are predictive of radiation-induced cognitive decline is difficult due to the heterogeneity of patient characteristics. The memory function is especially susceptible to radiation effects after treatment. The objective of this study is to correlate volumetric radiation doses received by critical neuroanatomic structures to post–radiation therapy (RT) memory impairment.

Methods and materials: Between 2008 and 2011, 53 patients with primary brain malignancies were treated with conventionally fractionated RT in prospectively accrued clinical trials performed at our institution. Dose-volume histogram analysis was performed for the hippocampus, parahippocampus, amygdala, and fusiform gyrus. Hopkins Verbal Learning Test-Revised scores were obtained at least 6 months after RT. Impairment was defined as an immediate recall score ≤15. For each anatomic region, serial regression was performed to correlate volume receiving a given dose ($V_{D(Gy)}$) with memory impairment.

Results: Hippocampal $V_{53.4Gy}$ to $V_{60.9Gy}$ significantly predicted post-RT memory impairment ($P < .05$). Within this range, the hippocampal V_{55Gy} was the most significant predictor ($P = .004$). Hippocampal V_{55Gy} of 0%, 25%, and 50% was associated with tumor-induced impairment rates of 14.9% (95% confidence interval [CI], 7.2%-28.7%), 45.9% (95% CI, 24.7%-68.6%), and 80.6% (95% CI, 39.2%-96.4%), respectively.

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Conclusions: The hippocampal V_{55Gy} is a significant predictor for impairment, and a limiting dose below 55 Gy may minimize radiation-induced cognitive impairment.

Introduction

Cranial radiation therapy (CRT) is commonly used to treat brain tumors, particularly for high-grade or malignant lesions. Unfortunately, radiation-induced neurocognitive toxicity after CRT is a relatively common complication of CRT, occurring in 50% to 90% of treated patients.[1-6] The treatment options for neurocognitive toxicity are quite limited once symptoms are present.[5] Survival rates for patients who experience radiation-induced cognitive decline (RICD) have been increasing due to the improved survival of patients with malignant brain tumors.[7] Furthermore, indications for therapy in patients with aggressively behaving benign tumors such as atypical meningiomas[8] and low-grade gliomas continue to increase.[9]

The time course and underlying mechanisms of CRT-related neurocognitive changes are complex.[10] Early-onset symptoms are usually associated with transient demyelination, and delayed symptoms are associated with vascular abnormalities, demyelination, and/or white matter necrosis.[2] Processes leading to chronic RICD are believed to occur at doses below those that result in radiographically detectable anatomic injuries such as radionecrosis.

RICD has been reported in patients receiving doses <60 Gy to brain regions that are involved in adult neurogenesis.[11] However, dosimetric thresholds for damage to such brain structures have not been convincingly defined. Identifying dosimetric factors that are predictive of RICD is difficult due to the heterogeneity of patients who receive CRT as well as the contribution of confounding factors such as baseline neurocognitive status, disease progression, medical comorbidities, and use of chemotherapy. Furthermore, cognitive outcomes can be affected by tumor progression and regression. Patients with greater tumor regression after whole brain radiation therapy (WBRT) tend to have better recovery of executive and fine motor functions after treatment.[12] However, even in the setting of achieving local tumor control, it appears that immediate recall and delayed recall, as assessed with the Hopkins Verbal Learning Test (HVLT), declines after WBRT.[13]

The susceptibility of memory function to radiation effects makes it a useful outcome for which to establish dosimetric thresholds for neurocognitive decline after treatment. The objective of this study is to correlate volumetric dose received by critical neural structures to cognitive decline through the use of cognitive function test scores as a measure of overall cognition.

Methods and materials

Patient population

Patients in this study were treated for a primary brain tumor between February 2008 and October 2011 in one of two National Cancer Institute–approved prospective clinical trials (WFU97100/91105)[14,15] assessing the use of donepezil (Aricept) in patients who receive CRT. Patients treated at our institution with available dosimetric data were included in the analysis. All patients were ≥18 years of age with a clinically predicted life expectancy of ≥30 weeks and Karnofsky Performance Status ≥70. Electronic medical records were reviewed to determine patient characteristics (ie, age, sex, Eastern Cooperative Oncology Group performance status, prior WBRT, prior surgery, and education level) and disease characteristics (ie, tumor histology, tumor size, and location).

Treatment

Patients were treated with partial- or whole-brain CRT. All treatments were planned with the Pinnacle Treatment Planning System (Philips, Andover, MA). Doses and treatment fields were determined by the treating physician but were generally based on the guidelines used in major Radiation Therapy Oncology Group trials. Each patient underwent pre-CRT computed tomography (CT) and magnetic resonance imaging (MRI) of the brain. Patients also had follow-up MRI brain scans to assess tumor response ≥6 months after treatment.

Cognitive testing

Per clinical trial criteria, all patients were enrolled at least 6 months after completing brain RT.[14] Postrandomization, baseline cognitive batteries were administered. We analyzed baseline HVLT-Revised (HLVT-R) scores as a measure of cognitive functioning and Functional Assessment of Cancer Therapy-Brain (FACT-Br) as a measure of health-related quality of life. Because no pre-RT baseline data could be collected, impairment was defined as an HVLT-R immediate recall score of ≤15 based on studies reporting optimal sensitivity and specificity for detecting impairment with HVLT-R cutoff scores of 14.5 to 15.5.[16-19] HVLT total score and subsection scores (total recall, delayed recall,