Radiotherapy and Oncology xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original article

A prospective evaluation of hippocampal radiation dose volume effects and memory deficits following cranial irradiation

Ting Martin Ma [a], Jimm Grimm [a], Riley McIntyre [a], Heather Anderson-Keightly [a], Lawrence R. Kleinberg [a], Russell K. Hales [a], Joseph Moore [a], Tracy Vannorsdall [b,c], Kristin J. Redmond [a,*]

[a] Department of Radiation Oncology and Molecular Radiation Sciences; [b] Department of Psychiatry and Behavioral Sciences; and [c] Department of Neurology, The Johns Hopkins University, Baltimore, MD, United States

ARTICLE INFO

Article history:
Received 24 July 2017
Received in revised form 26 September 2017
Accepted 29 September 2017
Available online xxxx

Keywords:
Dose response
Memory
Neurocognitive function
Hippocampus
Radiation therapy
Hopkins Verbal Learning Test-Revised

ABSTRACT

Background and purpose: To prospectively evaluate hippocampal radiation dose volume effects and memory decline following cranial irradiation.
Material and methods: Effects of hippocampal radiation over a wide range of doses were investigated by combining data from three prospective studies. In one, adults with small cell lung cancer received hippocampal-avoidance prophylactic cranial irradiation. In the other two, adults with glioblastoma multiforme received neural progenitor cell sparing radiation or no sparing with extra dose delivered to subventricular zone. Memory was measured by the Hopkins Verbal Learning Test-Revised Delayed Recall (HVLT-R DR) at 6 months after radiation. Dose–volume histograms were generated and dose–response data were fitted to a nonlinear model.
Results: Of 60 patients enrolled, 30 were analyzable based on HVLT-R DR testing completion status, baseline HVLT-R DR and intracranial metastasis/recurrence or prior hippocampal resection status. We observed a dose–response of radiation to the hippocampus with regard to decline in HVLT-R DR. D50% of the bilateral hippocampi of 22.1 Gy is associated with 20% risk of decline.
Conclusions: This prospective study demonstrates an association between hippocampal dose volume effects and memory decline measured by HVLT-R DR over a wide dose range. These data support a potential benefit of hippocampal sparing and encourage continued trial enrollment.
 Radiotherapy and Oncology xxx (2017) xxx–xxx

It is well known that decline in neurocognitive function (NCF) is an iatrogenic side effect of brain irradiation [1]. Preclinical and human studies suggest that bilateral or unilateral hippocampal radiation injury may be a key mediator of subsequent NCF decline, most notably in learning and memory [2,3]. The precise pathophysiology of radiation induced neurotoxicity remains to be elucidated; nevertheless, radiation induced damage to neural progenitor cells (NPCs) within the hippocampus may be one of the most compelling [4]. NPCs are exquisitely sensitive to radiation, since doses as low as 2 Gy delivered to human NPCs lead to decreased numbers of cells undergoing neuronal differentiation [5]. Similarly, human studies have demonstrated cognitive deficits after cranial irradiation [6,7]. In light of this, hippocampal-sparing studies have been attempted, most notably in the setting of prophylactic brain irradiation (PCI) in patients with small cell lung cancer [8] and whole-brain radiotherapy (WBRT) for brain metastases [9]. However, these studies largely determined the hippocampal dose constraint by what is technically feasible while maintaining coverage of the normal brain, whereas data regarding the dose–response relationship are still lacking. Gondi et al suggested that a biological equivalent dose in 2-Gy fractions (EQD2) greater than 7.3 Gy applied to 40% of hippocampus was associated with worse NCF [10].

The purpose of this study is to evaluate radiation dose volume effects on memory deficits over a wide range of radiation doses, using data from three prospective trials. These data will provide a framework for future investigations and recommendations for dose reduction to the hippocampus in treating brain metastases and primary brain tumors.

Materials and methods

Patient selection

Patients in the current study were pooled from 3 prospective trials: 21 patients from a phase II trial of hippocampal-sparing PCI for limited-stage small cell lung cancer (SCLC) (HA-PCI group

* Corresponding author at: Department of Radiation Oncology and Molecular Radiation Sciences, The Johns Hopkins University, 401 North Broadway, Suite 1440, Baltimore, MD 21231, United States.
E-mail address: kjanson3@jhmi.edu (K.J. Redmond).

https://doi.org/10.1016/j.radonc.2017.09.035
0167-8140/

[8]), 30 from a prospective trial of NPC sparing radiation therapy plus temozolomide for newly diagnosed glioblastoma multiforme (GBM) (NPC-GBM group, NCT01478854, accrual complete and manuscript in preparation [11]), and 9 from an ongoing randomized phase II study of subventricular zone (SVZ) irradiation plus concurrent and adjuvant temozolomide in newly diagnosed GBM (SVZ-GBM group, NCT02177578). The study was approved by the Johns Hopkins University Institutional Review Board. The study was performed in accordance with the Declaration of Helsinki. Informed consent was obtained from patients involved in the study.

In the SVZ-GBM group, patients were randomized at a 3:1 ratio to the SVZ irradiation group and NPC sparing group. Eligibility criteria for the HA-PCI group can be found in [8]. The primary inclusion criteria for patients for the latter two GBM trials had newly diagnosed, histologically confirmed GBM, age ≥18 years with KPS >60% and no prior brain radiation, with start of radiation therapy within 12 weeks of biopsy or surgery. In all 3 groups, exclusion criteria for the analyses presented here include failure to complete baseline or follow-up NCF testing (6-month and 12-month), baseline HVLT-R DR (Hopkins Verbal Learning Test-Revised Delayed Recall) score <3, intracranial metastasis/recurrence before NCF testing and prior resection of hippocampus at the time of diagnosis. Among the 41 patients who completed baseline and follow-up NCF testing, 1 (5.2%) in the HA-PCI cohort, 3 (17.6%) in the GBM-NPC cohort and 0 in the GBM-SVZ cohort had intracranial progression before the time of follow-up NCF testing and were therefore excluded from the analysis. None of the patients included in the analysis had progressive disease, received re-irradiation or Avastin chemotherapy at the time of or prior to follow-up that included HVLT-R DR testing. Patients with gross tumor involving the hippocampus were excluded.

Radiation simulation, treatment planning, and procedure

Radiation CT simulation and MRI scan were performed as previously described in [8]. The hippocampus and hippocampus avoidance structure (defined as the hippocampus plus 5-mm radial expansion) were contoured according to the Radiation Therapy Oncology Group atlas. An example is shown in Fig. 1. For all included studies, final delineation of the hippocampus was verified by a single physician (KJR) before the commencement of treatment to ensure consistency. In the HA-PCI group, patients were treated to a total dose of 25 Gy in 10 fractions, administered 5 days per week. An intensity modulated RT plan was generated in which the mean dose to the hippocampus was <8 Gy and at least 90% of the whole brain received 90% of the prescription. In the two GBM groups, patients were initially treated to 46 Gy in 23 fractions, with subsequent cone-down boost in 7 fractions, yielding a total dose of 60 Gy with a once-daily fractionation schedule of 2 Gy per fraction.

In NPC-GBM and the NPC sparing arm of SVZ-GBM group, a treatment plan was generated which aimed to limit radiation dose to the NPC-containing niches as much as possible without compromising coverage of the planning target volume. The NPC-containing niche was defined as a 5 mm region adjacent to the lateral wall of the lateral ventricle and the entire hippocampus. In the SVZ irradiation arm of the SVZ-GBM group, relatively high doses of radiation were delivered to SVZ and resulting in higher doses to the adjacent hippocampus. In all groups, daily cone-beam CT guidance was used. All patients who initiated protocol treatment were followed per protocol.

Dose-volume histogram (DVH) analysis of hippocampus

DVHs were generated for the left and right hippocampus individually and for the composite bilateral hippocampi. Doses were converted to biologically equivalent doses in 2-Gy fractions (EQD2) assuming an α/β ratio of 2 Gy. EQD2 to deciles (D10% to D100%), and the maximum EQD2 (D_{max}) of individual and combined hippocampal volumes were determined and tabulated. The dose-volume data were loaded into the DVH Evaluator software tool [12] and an exponential form of a logistic model was used to generate the dose–response curve:

$$\mathrm{NTCP} = \frac{e^{4\gamma_{50}(V)\left(\frac{D_V}{TD_{50}(V)}-1\right)}}{1+e^{4\gamma_{50}(V)\left(\frac{D_V}{TD_{50}(V)}-1\right)}}$$

NTCP is normal tissue complication probability, D_v is the x-axis dose parameter corresponding to volume V, $TD_{50}(V)$ is the 50% tolerance dose for V, and $\gamma_{50}(V)$ is the slope parameter at 50% tolerance dose for V.

Neurocognitive instruments

Participants completed standardized batteries of cognitive tests at baseline and at 6- and 12-month follow up. Test batteries differed slightly across studies. At baseline, estimated pre-morbid intellect was determined via the Hopkins Adult Reading Test [13] in HA-PCI and SVZ-GBM participants. Global cognitive functioning was assessed at baseline via the Mini Mental Status Exam (MMSE) [14] in HA-PCI and NPC-GBM participants. All study participants completed the HVLT-R, a well-validated test of verbal learning and memory [15], as well as Trail Making Test (Part A &B) and Controlled Oral Word Association (COWA) test. However, analysis was restricted to HVLT-R DR as it is the primary end point of multiple hippocampal-sparing radiation trials ([8,9], NCT02635009 and NCT02360215). Delayed recall scores range from 0 to 12, with higher scores reflecting better memory performance.

Statistical methods

The primary endpoint was memory decline, measured by HVLT-R DR at baseline and 6 months after completion of radiation therapy. The Reliable Change Index (RCI) was used to measure meaningful change between baseline and 6 months for HVLT-R DR. The RCI is derived from the standard error of measurement (SEM). SEM, The standard error of the difference (SEdiff) and RCI were calculated as previously described in [8]. For HVLT-R DR, RCI criteria is met if the raw score change is greater than or equal to 3. Therefore a reduction in HVLT-R DR score of 3 or more at 6-month follow-up is considered clinically meaningful memory decline. Multivariate analysis using a linear regression model was performed on the change in HVLT-R DR to evaluate its relationship with age, baseline HVLT-R DR scores and dosimetric variables (D100%, D50% and D_{max}). The number of variables was limited by the sample size and number of events. Statistical significance of a predictor was based on a two-sided test of the coefficient with $p < 0.05$.

Results

Between December 2011 and January 2016, 21, 30 and 9 patients (total = 60) were accrued in the HA-PCI, NPC-GBM and SVZ-GBM studies, respectively. Of 60 patients enrolled, 37 completed both baseline and 6-month HVLT-R DR testing. Four additional patients that did not complete 6-month testing completed 12-month testing. After excluding 7 patients who had baseline HVLT-R DR score <3, 4 who had intracranial metastasis/recurrence before the time of testing, 1 who had gross tumor involvement with resection of the right hippocampus, 30 patients were analyzable. Participant characteristics are summarized in Table 1. There is

Please cite this article in press as: Ma TM et al. A prospective evaluation of hippocampal radiation dose volume effects and memory deficits following cranial irradiation. Radiother Oncol (2017), https://doi.org/10.1016/j.radonc.2017.09.035