

A randomized trial of stereotactic versus conventional radiotherapy in young patients with low-grade brain tumors: occupational therapy-based neurocognitive data

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Abstract

Background. Radiotherapy for brain tumors in young patients is not only associated with improved survival but also long-term neurocognitive sequelae. We aimed to compare group differences in the executive neurocognitive outcomes in young patients with low-grade brain tumors treated with stereotactic conformal radiotherapy (SCRT) and conventional RT (ConvRT) techniques.

Methods. This a phase 3 randomized trial that enrolled 200 young patients with benign brain tumors and low-grade gliomas. Patients were randomly allocated (1:1) to either SCRT or ConvRT arms and treated to a dose of 54 Gy in 30 fractions over 6 weeks. Lowenstein Occupational Therapy Cognitive Assessment battery was performed at preradiotherapy baseline, 6 months, and annually thereafter until 5 years. Executive functions measures included orientation, visual perception, spatial perception, motor praxis, visuomotor organization, thinking operations, and attention and concentration. The trajectory of these parameters was compared between the treatment arms over 5 years.

Results. Two hundred patients were enrolled in the study (SCRT: 104 and ConvRT: 96). The median age was 13 years (interquartile range: 9–17); mean total neurocognitive scores over 5 years were significantly superior in SCRT arm as compared to ConvRT (difference in slope: 2.27, $P = .024$). Outcomes improved in the SCRT arm vis-à-vis ConvRT for the subdomain of visuomotor organization (difference in slope: 0.66, $P < .001$). Visuomotor organization scores significantly improved in majority of the substratification groups. Spatial perception improved in craniopharyngioma patients with SCRT technique as opposed to ConvRT.

Conclusions. SCRT achieved superior outcomes compared to ConvRT in certain executive neurocognitive functional domains. We provide high level of evidence in favor of SCRT.

Trial Registration. ClinicalTrials.gov Identifier: NCT00517959.

Key Points

- We provide level 1 evidence of improved executive neurocognitive functional outcomes in brain tumor patients treated with high precision radiotherapy.
- Children and adolescents with brain tumors treated with stereotactic conformal radiotherapy achieved superior long-term executive neurocognitive functional outcomes.

Importance of the Study

Children and adolescents diagnosed with benign and low-grade brain tumors treated with radiation therapy survive long enough to develop long-term sequelae especially decline in various neurocognitive domains. This can be annulled or at least reduced by utilizing high precision radiotherapy techniques. However, the utility of such techniques in brain tumors was never examined in a randomized study. Our group examined the utility of high precision radiotherapy technique called stereotactic radiation therapy (SCRT) against conventional radiotherapy in a randomized controlled setting to investigate if

SCRT improved executive neurocognitive functions measured by Lowenstein's Occupational Therapy and Cognitive Assessment test (LOTCA). This study provides level 1 evidence favoring SCRT in maintaining long-term executive neurocognitive integrity. The results provide an ideal platform to test high precision RT techniques like proton or heavy ions to reduce doses to certain association areas involved in coordinating executive neurocognitive functions like visuomotor organization, visual perception (eg, the entorhinal cortex and the inferior parietal lobule).

Children and young adults with residual/progressive benign and low-grade brain tumors treated with radiation therapy (RT) show excellent long-term survival but may develop the risk of long-term consequences of treatment having considerable implications on their quality of life and activities of daily living.^{1,2} Post-RT damage has been shown to occur in the setting of pre-existing brain pathology in the majority (90%) of patients³⁻⁵ and is accentuated by disruption of neural pathways and cognitive networks.^{6,7} The rapid evolution of technology has allowed us to deliver RT with increasing precision to target (tumor) with incremental sparing of normal tissues as we have progressed from conventional to conformal radiotherapy techniques. Despite obvious dosimetric advantages of technological advances, the near-axiomatic assumption that technological advance equates with tangible benefit in terms of improved efficacy and long-term sequelae, has often been difficult to prove. Modern RT techniques can potentially minimize additional damage, thereby limiting neurocognitive sequelae. Stereotactic conformal radiotherapy (SCRT) is one such high precision technique, whereby highly focused doses of radiation can be delivered to the tumor tissue with excellent sparing of adjacent critical neural structures. The superiority of SCRT over conventional RT (ConvRT) has been demonstrated in a large phase 3 randomized controlled trial, which demonstrated preservation of various domains of intelligence quotients (IQs) and neuroendocrine function with equivalent tumor control.⁸ The secondary analysis focused on investigating the effect of radiotherapy on the trajectory of multidimensional neurocognitive assessment using the Lowenstein Occupational Therapy Cognitive Assessment (LOTCA-II)⁹ among these patients. This is a validated battery to test neurocognitive recovery in patients with cerebrovascular injury, and thereby closely approximates late radiation induced injury in its pathogenesis and evolution.

ConvRT. Patients were randomized to SCRT or ConvRT based on a computer-generated stratified block randomization method. Stratification parameters like pubertal status (prepubertal vs postpubertal status), neurological performance scale score (0–1 vs 2–3), supratentorial versus infratentorial location, and whether patients had no or minimal versus moderate or severe hydrocephalus. In addition, craniopharyngiomas versus other histologies as a presumed subclassification of interest was also tested as craniopharyngiomas was the most common histology.

The study was approved by the institutional ethics committee of the Tata Memorial Centre and conducted in adherence to principles of Good Clinical Practice. All the patients provided written informed consent. The complete study protocol is available in [Supplementary Material 1](#).

Participants and Treatment

Between April 2001 and March 2012, 200 children and young adults aged between 3 and 25 years with residual and/or progressive low-grade and benign brain tumors were invited to participate in the trial (NCT00517959). One hundred and four patients were randomized to receive SCRT (delivered with conformal fields using multi-leaf collimator shaping) and 96 patients ConvRT (2–4 open-field radiation was delivered to a total dose of 54 Gy in 30 fractions) delivered 5 days a week. Details of RT techniques have been published previously.⁸

Outcome Measures

Outcome measures were the group differences (between the SCRT vis-à-vis ConvRT) in the change in the executive neurocognitive functional subdomains as measured by the LOTCA-II battery. The LOTCA battery represents a sophisticated multidimensional cognitive assessment tool covering 7 key subdomains namely orientation, visual perception, spatial perception, motor praxis, visuomotor organization, thinking operations, and attention and concentration. In our study, the test battery was administered

Methods

Study Design

This study was executed as a single-center phase 3 randomized controlled trial comparing efficacy of SCRT with

by a neuro-occupational therapist with experience in assessment and rehabilitation of brain tumor survivors. The scores were collected for all subdomains and summed up to obtain total scores. Baseline scores were obtained prior to starting RT and thereafter at 6 months, 2, 3, 4, and 5 years post-RT.

Statistical Considerations

Sensitivity analyses were performed using unadjusted models. Missing data imputation was carried out using the last observation carried forward for the missed visits of the patients till occurrence of death, lost to follow up, or conclusion of the study. The raw scores for each domain of LOTCA were determined and the total scores determined by adding the sums of each domain and were reported as mean scores and SEM. To assess for change in LOTCA total and domain specific scores between arms and over time, a linear mixed-effects (LME) regression model was developed using R and the "lme4" package. Participants were used as "by-subject" random effect and the interaction between arms received (conventional RT or SCRT) and time of assessment was included as fixed effects. For each subdomain, the raw scores (including the baseline) were used as dependent outcomes in the model to test the primary hypothesis of a difference in rate of change in the scores (difference in slopes) between the 2 arms, and the various subdomains in patients followed longitudinally up to 5 years and were obtained using the LME model. A *P* value of less than .05 was considered to be statistically significance. Data were analyzed using IBM SPSS version 25.0 (IBM Corp) and R Studio Version 1.2.5019.

Results

A total of 200 patients were enrolled in the original study, and 170 patients who had completed at least one assessment post-RT were considered for the final analysis of the executive neurocognitive functional outcomes. Median follow-up for the entire cohort was 61 (interquartile range [IQR]: 31–86) months. Mean scores of all the 7 executive neurocognitive functional subdomains assessed over a period of 5 years between SCRT and ConvRT arms are reported in [Table 1](#). The baseline (pre-RT) total LOTCA scores (mean [SEM]) for the conventional and SCRT arms were 99.15 (1.79) and 93 (2.22), respectively.

The total scores of both arms improved over time between 6 months and 5 years post-RT. The improvement in the SCRT arm showed a statistically significant superiority (difference in slope: 2.27, *P* = .024; [Figure 1A](#)) with mean (SEM) scores rising from 96.09 (2.52) at 6 months post-RT to 113.56 (3.27) at 5 years post-RT vis-à-vis ConvRT, where scores rose from 99.81 (1.95) at 6 months post-RT to 109.04 (3.35) at 5 years post-RT. The mean total scores showed a constant improving trend in both the arms; however, the trajectory of the curve was steeper in the SCRT arm after 3 years post-RT and further increased at 5 years, while

the mean total scores in the ConvRT arm although improved initially but seemed to plateau after 3 years post-RT. Analysis of various subdomains of the LOTCA battery revealed a significant improvement in visuomotor organization scores in the SCRT vis-à-vis ConvRT arm (difference in slope: 0.66, *P* < .001), with scores improving from 20.46 (0.76) at 6 months post-RT to 28.28 (2.61) at 5 years post-RT in SCRT arm vis-à-vis ConvRT arm, where scores rose from 21.79 (0.63) at 6 months post-RT to 23.42 (0.95) at 5 years treatment. The trajectory of the mean visuomotor organization curve in the SCRT arm rose up compared to the ConvRT arm, which was stable all throughout the follow-up period ([Table 2](#), [Figure 1B](#)). None of the other subdomains measured showed a statistically significant difference between the SCRT arm and the ConvRT arm ([Supplementary Material 2](#), [Figure 1A–F](#))

We performed post hoc analyses on the predefined stratification factors with regard to both total LOTCA scores and subdomain scores. On subgroup analysis, patients with Neurological Performance Score (NPS) (NPS score 0–1: good neurological performance and NPS score 2–3: poor neurological performance), patients with NPS 0–1 seemed to derive more benefits as total LOTCA scores significantly improved in this cohort of patients when treated with SCRT technique vis-a vis ConvRT technique (difference in slope: 1.35, *P* = .01), with total scores showing dramatic improvement from 95.1 (2.9) at 6 months post-RT to 113.6 (4.2) at 5 years post-RT vis-à-vis ConvRT, where scores marginally improved from 100.6 (2.2) at 6 months post-RT to 111 (3.3) at 5 years post-RT. This improvement was however not seen in patients with NPS 2–3, where both the treatment techniques did not have any statistical differences ([Figure 1C](#) and [D](#)).

Further analysis of various subdomains of the LOTCA battery for different subgroups showed that spatial perception improved significantly in patients of craniopharyngiomas when treated with SCRT vis-à-vis ConvRT (difference in slope: 0.16, *P* = .04; [Figure 2A](#); [Table 3](#)). Additionally, these patients seemed to derive maximum benefit in the subdomain of visuomotor organization when treated with SCRT technique (difference in slope: 0.52, *pP* = .04; [Figure 2B](#); [Table 3](#)). Visuomotor organization functions also improved significantly with SCRT as compared to ConvRT in patients with other histologies (eg, gliomas) (difference in slope: 0.72, *P* = .003; [Figure 2C](#), [Table 3](#)). Prepubertal children (difference in slope: 0.51, *P* = .01) and postpubertal young adults (difference in slope: 0.97, *P* = .002) when treated with experimental SCRT technique had statistically improved visuomotor functional outcome when followed longitudinally for 5 years, respectively ([Figure 2D](#) and [E](#), [Table 3](#)). The major increment in the visuomotor curve was seen after fourth year in both the subgroups. Patients with no/minimal hydrocephalus, a significant increment in the visuomotor organization scores in the SCRT vis-à-vis conventional RT arm (difference in slope: 0.58, *P* = .001), with scores showing a steady increase over a period of 5 years ([Figure 2F](#)). A similar significant change was not seen in patients with moderate to severe hydrocephalus ([Supplementary Material 2](#), [Table 2](#)). SCRT techniques compared to ConvRT seemed to significantly

Table 1. The Mean Scores for LOTCA-II Domains With SEM Measures at Various Time Points Between the SCRT Arm and the Conventional RT Arm

Domain	Follow-up	Total Cohort		ConvRT		SCRT	
		Mean Scores (SEM)	No	Mean Scores (SEM)	No	Mean Scores (SEM)	No
Orientation	Pre-RT (baseline)	13.72 (0.30)	170	14.29 (0.37)	79	13.22 (0.46)	91
	6 months	13.92 (0.32)	148	14.43 (0.38)	72	13.43 (0.51)	76
	2 years	14.63 (0.31)	123	15.10 (0.37)	62	14.15 (0.49)	61
	3 years	14.52 (0.36)	103	14.88 (0.45)	52	14.16 (0.56)	51
	4 years	14.93 (0.29)	82	15.22 (0.37)	41	14.63 (0.45)	41
	5 years	15.19 (0.33)	42	14.92 (0.55)	24	15.56 (0.26)	18
Visual Perception	Pre-RT (baseline)	14.62 (0.16)	170	14.65 (0.28)	79	14.60 (0.19)	91
	6 months	14.58 (0.16)	148	14.64 (0.23)	72	14.53 (0.23)	76
	2 years	15.26 (0.40)	123	15.89 (0.75)	62	14.62 (0.27)	61
	3 years	15.12 (0.18)	103	15.19 (0.27)	52	15.04 (0.23)	51
	4 years	16.04 (0.49)	82	15.76 (0.13)	41	16.32 (0.97)	41
	5 years	15.83 (0.08)	42	15.75 (0.14)	24	15.94 (0.06)	18
Spatial perception	Pre-RT (baseline)	11.05 (0.15)	170	11.32 (0.17)	79	10.81 (0.23)	91
	6 months	11.03 (0.16)	148	11.19 (0.21)	72	10.88 (0.24)	76
	2 years	11.37 (0.16)	123	11.50 (0.17)	62	11.25 (0.27)	61
	3 years	11.50 (0.15)	103	11.63 (0.18)	52	11.35 (0.24)	51
	4 years	11.67 (0.11)	82	11.68 (0.17)	41	11.66 (0.14)	41
	5 years	11.83 (0.11)	42	11.71 (0.19)	24	12.00 (0.00)	18
Motor Praxis	Pre-RT (baseline)	10.73 (0.14)	170	10.89 (0.19)	79	10.59 (0.21)	91
	6 months	10.64 (0.16)	148	10.94 (0.19)	72	10.36 (0.25)	76
	2 years	11.26 (0.37)	123	11.23 (0.18)	62	11.30 (0.73)	61
	3 years	11.21 (0.14)	103	11.31 (0.21)	52	11.12 (0.19)	51
	4 years	11.45 (0.14)	82	11.51 (0.19)	41	11.39 (0.21)	41
	5 years	11.74 (0.10)	42	11.63 (0.17)	24	11.89 (0.08)	18
Visuomotor organization	Pre-RT (baseline)	20.42 (0.49)	170	21.61 (0.64)	79	19.38 (0.71)	91
	6 months	21.09 (0.50)	148	21.79 (0.63)	72	20.42 (0.76)	76
	2 years	21.95 (0.49)	123	22.37 (0.63)	62	21.52 (0.76)	61
	3 years	23.20 (0.51)	103	23.17 (0.73)	52	23.24 (0.73)	51
	4 years	24.05 (0.51)	82	23.51 (0.72)	41	24.59 (0.71)	41
	5 years	25.50 (1.28)	42	23.42 (0.95)	24	28.28 (2.61)	18
Thinking Operations	Pre-RT (baseline)	21.77 (0.52)	170	22.82 (0.65)	79	20.86 (0.77)	91
	6 months	23.14 (0.56)	148	23.42 (0.73)	72	22.87 (0.85)	76
	2 years	24.37 (0.53)	123	24.79 (0.65)	62	23.95 (0.83)	61
	3 years	25.70 (0.53)	103	25.46 (0.72)	52	25.94 (0.78)	51
	4 years	25.79 (0.59)	82	25.27 (0.84)	41	26.32 (0.82)	41
	5 years	27.24 (1.52)	42	27.92 (2.54)	24	26.33 (1.15)	18
Attention and concentration	Pre-RT (baseline)	3.55 (0.06)	170	3.58 (0.08)	79	3.53 (0.09)	91
	6 months	3.50 (0.07)	148	3.39 (0.10)	72	3.61 (0.10)	76
	2 years	3.49 (0.08)	123	3.37 (0.12)	62	3.61 (0.09)	61
	3 years	3.40 (0.09)	103	3.29 (0.13)	52	3.51 (0.13)	51
	4 years	3.29 (0.11)	82	3.05 (0.17)	41	3.54 (0.14)	41
	5 years	3.64 (0.12)	42	3.71 (0.14)	24	3.56 (0.20)	18

ConvRT, conventional radiotherapy; LOTCA, Lowenstein Occupational Therapy and Cognitive Assessment test; SCRT, stereotactic conformal radiotherapy; SEM, Standard Error of Mean.

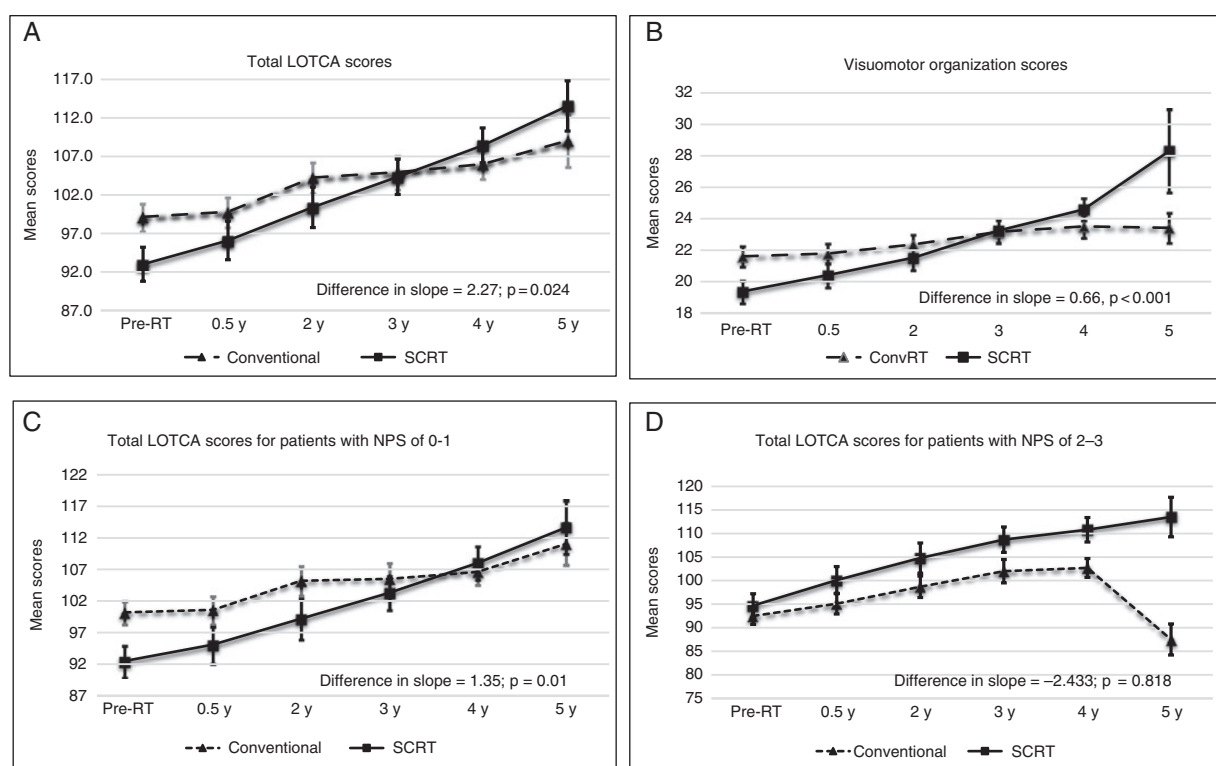


Figure 1. (A) The trends and the difference in slopes of the total Lowenstein's Occupational Therapy and Cognitive Assessment (LOTCA) scores in patients longitudinally followed up for 5 years; the difference in slopes between the stereotactic conformal radiotherapy (SCRT) and conventional radiotherapy (ConvRT) arms were compared by linear mixed effect model. (B) The trends and the difference in slopes of the Visuomotor domain scores in patients longitudinally followed up for 5 years; the difference in slopes between the SCRT and ConvRT arms were compared by linear mixed effect model. (C, D) The trends and the difference in slopes of the total LOTCA scores in patients with Neurological Performance Score (NPS) 0–1 (Figure 1C) and NPS 2–3 (Figure 1D) longitudinally followed up for 5 years; the difference in slopes between the stereotactic conformal radiotherapy (SCRT) and conventional radiotherapy (ConvRT) arms were compared by linear mixed effect model.

Table 2. Comparison of Difference in the Mean Scores of Various Subdomains of LOTCA-II Battery Between SCRT Technique and Conventional RT Technique at 6 Months and 5 Years Post-RT

Domain	Difference in Slope	P Value	Post-RT 6 Months Score		Post-RT 5-Year Score	
			ConvRT Mean (SEM)	SCRT Mean (SEM)	ConvRT Mean (SEM)	SCRT Mean (SEM)
Orientation	0.707	.48	14.43 (0.38)	13.22 (0.46)	14.92 (0.55)	15.56 (0.26)
Visual perception	0.06	.68	14.64 (0.23)	14.53 (0.23)	15.75 (0.14)	15.94 (0.06)
Spatial perception	0.06	.36	11.19 (0.21)	10.88 (0.24)	11.71 (0.19)	12.00 (0.00)
Motor praxis	0.11	.32	10.94 (0.19)	10.36 (0.25)	11.63 (0.17)	11.89 (0.08)
Visuomotor organization	0.66	<.001	21.79 (0.63)	20.42 (0.76)	23.42 (0.95)	28.28 (2.61)
Thinking operations	0.17	.39	23.42 (0.73)	22.87 (0.85)	27.92 (2.54)	26.33 (1.15)
Attention and concentration	0.03	.38	3.39 (0.10)	3.61 (0.10)	3.71 (0.14)	3.56 (0.20)

ConvRT, conventional radiotherapy; LOTCA, Lowenstein Occupational Therapy and Cognitive Assessment test; SCRT, stereotactic conformal radiotherapy; SEM, Standard Error of Mean.

improve visuomotor functions both in supratentorial and infratentorial brain tumors (Table 3, Figure 2G and H). Other subdomains measured by LOTCA-II battery did not

show any statistically significant differences in the slope of their mean scores and SEM between the 2 treatment techniques. (Supplementary Material 2, Table 2).

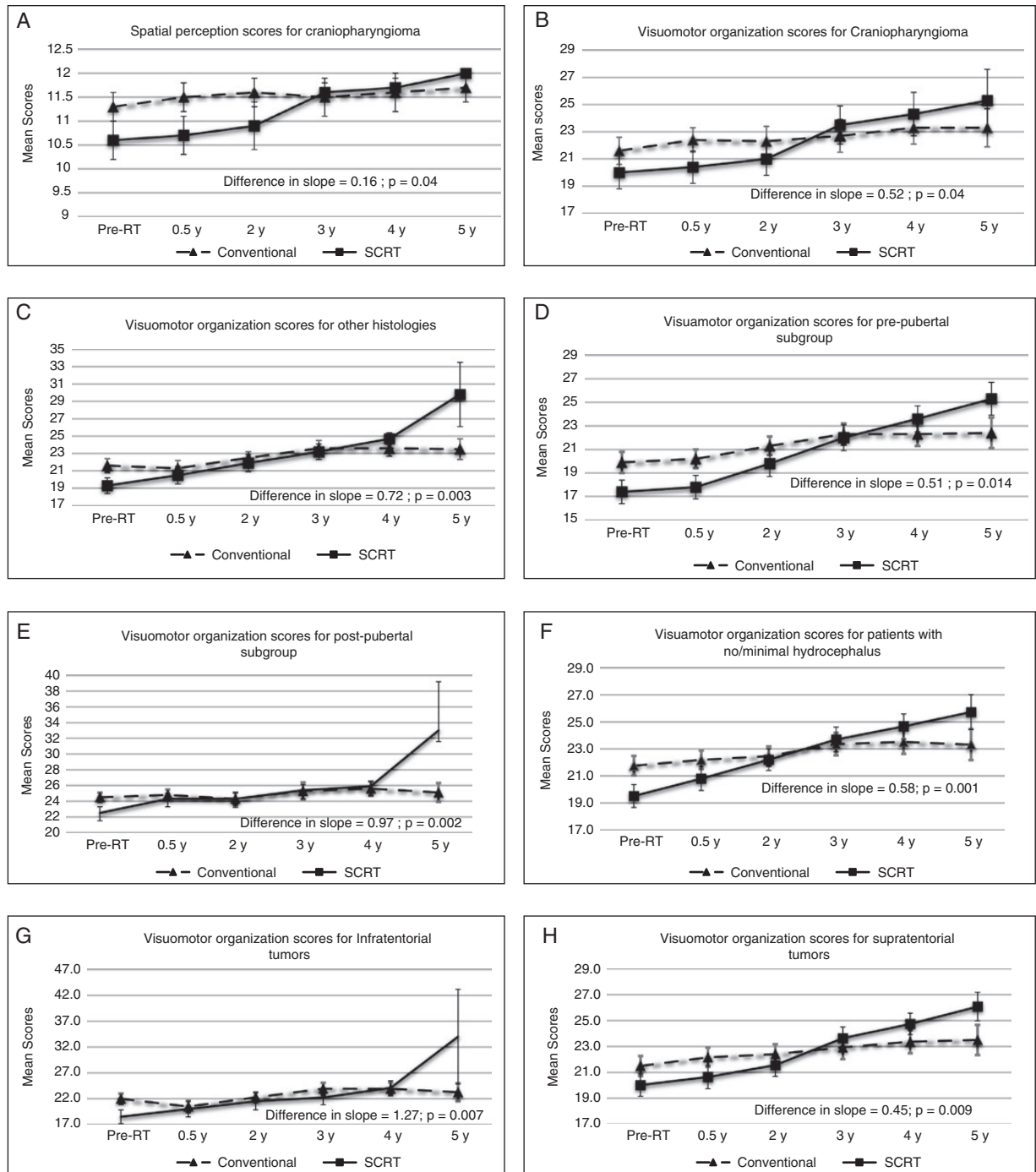


Figure 2. (A–H) The trends and the difference in slopes of various subdomains scores that were statistically significant in different subgroups of patients longitudinally followed up for 5 years; the difference in slopes between the stereotactic conformal radiotherapy (SCRT) and conventional radiotherapy (ConvRT) arms were compared by linear mixed effect model.

Discussion

The current dataset is derived from a randomized controlled trial, which conclusively showed that usage of conformal high precision RT is associated with stabilization and

improvement in several neurocognitive subdomains (particularly full-scale intelligence quotient and performance IQ).⁸ However, cognition represents a complex interplay of multiple neurological processes and RT is likely to affect its components differentially, given the differential sensitivity of the structures in the brain (neuronal, glial, and vascular).

Table 3. Comparison of Various Subdomains of LOTCA-II Battery Between SCRT Technique and Conventional RT Technique That Were Statistically Significant

Subgroups	Significant Subdomain	Difference in Slope	PValue	Post-RT 6 Months Score		Post-RT 5Years Score	
				ConvRT	SCRT	ConvRT	SCRT
				Mean Scores (SEM)	Mean Scores (SEM)	Mean Scores (SEM)	Mean Scores (SEM)
Histology							
Craniopharyngiomas	Spatial perception	0.16	0.04	11.5 (0.3)	10.7 (0.4)	11.7 (0.3)	12.0 (0.0)
	Visuomotor organization	0.52	0.04	22.4 (0.9)	20.4 (1.2)	23.3 (1.4)	25.3 (2.3)
Other histologies							
	Visuomotor organization	0.72	0.003	21.3 (0.9)	20.5 (1.0)	23.5 (1.2)	29.8 (3.7)
Pubertal status							
Prepubertal	Visuomotor organization	0.51	0.014	20.2 (0.8)	17.8 (1.0)	22.4 (1.3)	25.3 (1.4)
Postpubertal	Visuomotor organization	0.97	0.002	24.8 (0.7)	24.3 (0.7)	25.1 (1.2)	33.0 (6.2)
Hydrocephalus							
No/Minimal	Visuomotor organization	0.58	0.001	22.2 (0.69)	20.8 (0.88)	23.3 (1.15)	25.7 (1.29)
Location of tumor							
Post-RT	Visuomotor organization	1.27	0.007	20.5 (1.08)	20.0 (1.51)	23.3 (1.75)	34.0 (9.14)
Supratentorial							
	Visuomotor organization	0.45	0.009	21.5 (0.78)	20.0 (0.86)	23.5 (1.17)	26.1 (1.11)

Therefore, it is pertinent to dissect the various aspects of neurocognition. LOTCA battery is a well-recognized cognitive assessment tool^{9,10} used for its versatility in targeting multiple aspects of neurocognition especially in stroke patients (who develop neurovascular injury). This battery has the additional advantages of high inter-rater reliability coefficients (0.82–0.97), thereby addressing concerns of test–retest reliability to a significant extent, high internal consistency, a high discriminatory capacity to identify cerebrovascular injury (the most common form late radiotherapy sequelae being cerebrovascular injury), localize injury, and detect time trends.⁹ Our previous experience suggested that pretreatment mean LOTCA scores in patients of low-grade brain tumors were lower than maximal achievable values, and that these gradually improved during follow-up with a steeper upward trajectory from year 3 onwards.⁵ This study summarizes our experience of long-term follow-up of executive neurocognitive functions as measured by LOTCA-II and the insights gained thereof in the context of a prospective randomized fashion.

We observed that the pre-RT median scores and IQR were lower than the maximum achievable scores (ConvRT: 103 [IQR: 93–110] and SCRT: 100 [IQR: 75–111]), a finding consistent with previous published institutional and external data.^{5,11} It is an established fact that the most deleterious effect on cognition is exerted by the tumor.¹² The total scores increased in both the arms from 6 months post-RT to 5 years post-RT, which could be

attributed to the efficacy of RT in mitigating the disease process in both arms. The degree of recovery was significantly better in the SCRT arm (with a continuous upward slope readily visible on visual perusal of the graphs), which is most likely due to the reduction in doses received by structures integral to cognition (hippocampi, para-hippocampal gyri and temporal lobes).^{5,13} The results are encouraging and with increasing availability of contemporary dose volume constraints for structures (eg, hippocampi)¹⁴ is expected to further facilitate cognitive recovery with the availability of refined technologies such as intensity modulated radiotherapy (IMRT) and charged particle beam therapy that optimizes dose conformity in the target with simultaneous sparing of adjacent brain tissue. Analysis of prestratified subgroups revealed a statistically significant increment in total scores favoring patients with NPS 0–1. This is likely because the degree of global cognitive disruption is lesser in these patients and the capacity for recovery is relatively intact, a process aided by sparing of the normal brain with SCRT. A similar consistent trend of constantly improving total LOTCA scores was observed for the SCRT arm in NPS 2–3 patients, which failed to approach statistical significance, a likely consequence of the low numbers in the group. Additionally, several associations were noticed to approach borderline statistical significance and deserve mention. Histology other than craniopharyngiomas showed a borderline significant improvement in total

LOTCA scores with SCRT vis-à-vis ConvRT (difference in slope: 1.29, $P = .067$), a trend possibly explained by the overall morbidity of the disease (propensity for relapse, morbidity entailed during multiple surgeries, optic pathway compression, endocrinopathies, and shunt placement)¹⁵ as compared to the other histologies in the trial. Additionally, the benefit for SCRT in improving LOTCA scores was seen to approach borderline significance in both pre- and postpubertal individuals (prepubertal—difference in slope: 1.34, $P = .055$; postpubertal—difference in slope: 1.09, $P = .066$). The increased scores were more remarkable for postpubertal individuals, likely due to the increased sensitivity of the brain in younger children as opposed to adolescents. This hypothesis finds support in literature for brain injury in children.^{16,17} Similar findings have been noted, wherein age less than 13 years was found to predict clinically relevant decline in neurocognition.¹⁴ Patients with supratentorial tumors showed an improvement in LOTCA scores with SCRT that approached statistical significance (difference in slope: -1.06 , $P = .059$), a likely function of the greater cognitive sparing achieved with SCRT in such tumors. The association did not approach borderline significance for infratentorial tumors, even though perusal of the curves shows a clear increase in scores.

Analysis of subdomains in the trial dataset revealed a statistically significant benefit favoring SCRT toward improving LOTCA scores in the visuomotor organization subdomain. Visual memory has been shown to be more robust than verbal and auditory memory.¹⁸ In addition, it has been demonstrated that RT-related cognitive dysfunction affects verbal and semantic long-term retrieval to a greater extent than visual-perceptual memory.^{19,20} Therefore, it is possible that the robustness of this aspect of cognition is further enhanced in its recovery by limiting the subcortical brain irradiation with SCRT.

Analysis of LOTCA subdomain scores among the stratified subgroups revealed several significant associations. Craniopharyngioma histology significantly benefited from the usage of SCRT in both the spatial perception and visuomotor organization subdomains, whereas other histologies benefited in the visuomotor organization alone. The incremental benefit for craniopharyngiomas is probably explained by the lesser degree of posterior parietal cortex irradiation in the irradiated volumes (which are typically anteriorly placed in sellar-suprasellar locations). Stratification analysis on the basis of puberty revealed that using SCRT in both in pre- and postpubertal individuals resulted in significant improvement in visuomotor organization scores. In congruence with the findings from total scores, the degree of improvement was more in postpubertal individuals. Patients with no or minimal hydrocephalus showed a statistically significant improvement in visuomotor organization scores when treated with SCRT, whereas patients with moderate to severe hydrocephalus showed only borderline statistical significance (difference in slope: 0.73, $P = .095$), probably due to greater cortical atrophy seen with long-standing hydrocephalus, a common and unfortunate consequence of the long-standing disease processes represented in the trial population. Stratification on the basis of location (supratentorial vs infratentorial) also

showed benefit using SCRT in both subgroups in terms of improved visuomotor organization, though the benefit was more pronounced for infratentorial tumors (likely due to lower volumes of associative areas irradiated). Lastly, an association between superior motor praxis scores was seen for both pre- and postpubertal individuals, though this did not approach statistical significance (prepubertal—difference in slope: 0.18, $P = .08$; postpubertal—difference in slope: 0.18, $P = .08$).

Strengths, Limitations, and Opportunities

The strengths of the study lie in its systematic and blinded acquisition of data as part of a prospective randomized trial. Conclusive evidence favoring high precision RT in terms of improved cognitive functioning is scarce, and this trial possibly represents the first evidence of its kind in a randomized setting, where the entire patient cohort has been longitudinally followed up for 5 years. At the same time, one must also consider the logistic difficulties in doing such trials with relevant endpoints that have far reaching consequences in deciding the type of therapy to be given in pediatric brain tumor patients. One of the limitations of the trial was the relatively long duration it took to accrue and collect long-term data. The limitations of the LOTCA battery in failing to compensate for sociocultural differences have been previously acknowledged²¹ and may possibly be important in the context of this trial recruiting patients from diverse sociocultural milieu within our country which could possibly reflect in the differential baseline scores between the 2 arms. Notwithstanding these limitations, the present work does provide high-level evidence in favor of using high precision radiotherapy techniques to maintain long-term neurocognitive integrity. Moreover, the results of the study provide an opportunity to use these RT techniques to reduce doses to certain association areas involved in coordinating visuomotor organization, visual perception (eg, the entorhinal cortex and the inferior parietal lobule). Clinical studies have shown excessive cortical thinning in these association areas (even greater than the primary visual/somatosensory/motor cortices). This thinning has been seen at RT doses as low as 20 Gy and becomes significant at doses above 40 Gy.²² It is possible that the association areas responsible for visuomotor orientation and integration (dorsal stream²³ and middle temporal or visual area—MTV/V5²⁴) represents a similarly sensitive area and likely benefits from minimizing radiation doses by conformal techniques. High precision radiotherapy techniques like IMRT and proton or heavy ion therapy (which can reduce these doses to near zero) may indeed go a long way toward preserving cognitive integrity in patients. Resting state functional MRI has already been demonstrated to have the potential to reduce doses to the Default mode network,²⁵ a set of cortical regions which show enhanced activity at rest and reduced activity during tasks.²⁶ One can possibly extrapolate this scenario to identify multiple functional areas on task based activity with particular attention paid to the temporal and limbic cortices which is particularly sensitive to RT²⁷ that can be spared without compromising tumor control in the future.

Conclusions

High precision conformal RT (SCRT) is associated with clinically meaningful benefits in cognition as measured by the LOTCA battery. The benefit appears differentially toward associative tasks, whose controlling areas in the brain may be particularly sensitive to ionizing radiation. High precision radiotherapy protocols in future should attempt at further mitigating these late sequelae by fusing state of art anatomical and functional imaging with contemporary RT techniques.

Supplementary Material

Supplementary material is available at *Neuro-Oncology Advances* online.

Keywords

executive neurocognitive functions | randomized trial | stereotactic conformal radiotherapy

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