Published in final edited form as:

Int J Radiat Oncol Biol Phys. 2013 April 1; 85(5): 1301–1306. doi:10.1016/j.ijrobp.2012.10.031.

Longitudinal Investigation of Adaptive Functioning following Conformal Irradiation for Pediatric Craniopharyngioma and Low-Grade Glioma

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Abstract

Purpose—Children treated for brain tumors with conformal radiation therapy experience preserved cognitive outcomes. Early evidence suggests that adaptive functions or independent living skills may be spared. This longitudinal investigation prospectively examined intellectual and adaptive functioning during the first 5 years following irradiation for childhood craniopharyngioma and low-grade glioma (LGG). The effect of visual impairment on adaptive outcomes was investigated.

Methods and Materials—Children with craniopharyngioma ($n=62$) and LGG ($n=77$) were treated using conformal or intensity-modulated radiation therapy. The median age was 8.05 years (3.21 years–17.64 years) and 8.09 years (2.20 years–19.27 years), respectively. Serial cognitive evaluations including measures of intelligence quotient (IQ) and the *Vineland Adaptive Behavior Scales* (VABS) were conducted at pre-irradiation baseline, 6 months after treatment, and annually through 5 years. A total of 588 evaluations were completed during the follow-up period.

Results—Baseline assessment revealed no deficits in IQ and VABS indices for children with craniopharyngioma, with significant ($p < .05$) longitudinal decline in VABS Communication and Socialization indices. Clinical factors associated with more rapid decline included females and pre-irradiation chemotherapy (interferon). The only change in VABS Daily Living Skills correlated with IQ change ($r = .34$; $p = .01$) in children with craniopharyngioma. Children with LGG performed below population norms ($p < .05$) at baseline on VABS Communication, Daily Living Indices, and the Adaptive Behavior Composite, with significant ($p < .05$) longitudinal decline limited to VABS Communication. Older age at irradiation was a protective factor against

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CONFLICT OF INTEREST NOTIFICATION PAGE

There are no conflicts of interest with the authors or materials in this manuscript.

longitudinal decline. Severe visual impairment did not independently correlate with poorer adaptive outcomes for either tumor group.

Conclusions—There was relative sparing of post-irradiation functional outcomes over time in this sample. Baseline differences in functional abilities prior to the initiation of irradiation suggested that other factors influence functional outcomes above and beyond the effects of irradiation.

Keywords

Conformal radiation; craniopharyngioma; low-grade glioma; adaptive functioning; neurocognitive outcomes

INTRODUCTION

The risks of neurocognitive deficits resulting from central nervous system (CNS) tumors and CNS-directed therapies that include radiation therapy are well established in the pediatric oncology literature (1, 2); however, functional outcomes including intelligence, academic achievement, and adaptive functioning (e.g., independent activities of daily living) have been investigated less thoroughly. Declines in global skills such as intellect and academic achievement have prompted concerns about the quality of life in long-term childhood cancer survivors. More sophisticated radiation therapy methods such as conformal radiation therapy (CRT), including intensity-modulated radiation therapy, shape the prescribed dose to affected brain tissue, while sparing healthy brain tissue. There is early evidence of improved outcomes for intelligence quotient (IQ), verbal learning ability, and adaptive functioning in young patients with posterior fossa tumors treated with CRT (2, 3). Considering the relationship between radiation dose and cognitive outcomes, the observed improvement should not be surprising.

Less is known about the effects of irradiation on children diagnosed with supratentorial tumors including those with craniopharyngioma and low-grade glioma (LGG). Craniopharyngioma accounts for 1%–4% of all childhood brain tumors (4). Radiation therapy is commonly required because these tumors arise in proximity to critical areas and are considered unresectable (5). Approximately 62%–84% of children diagnosed with craniopharyngioma present with visual changes at the time of diagnosis (6). Pre-diagnosis visual impairment serves as a predictor for persistent post-treatment vision loss (5). Despite significant tumor-related and treatment-related complications, survivorship is excellent (7, 8).

Similar clinical features are observed in children with LGG who require radiation therapy. LGG encompasses a number of unique histological diagnoses and accounts for 30%–50% of childhood brain tumors (4). Progression-free survival rates are approximately 80% with long-term follow-up (9). Similar to children with craniopharyngioma, patients who require irradiation are generally those with tumors arising in the diencephalon or optic pathways for which radical surgery is contraindicated. Visual impairment and hormone deficiencies are also common at diagnosis and following treatment. Unique to LGG, chemotherapy may effectively delay radiation therapy for 3–5 years (10); however, most children with centrally located LGGs will eventually require irradiation.

Adaptive functioning, or the ability to perform the tasks of daily living at an age-appropriate level, has only recently been investigated in brain tumor survivors. Adaptive behaviors represent the practical application of cognitive skills, and reduced adaptive skills when combined with intellectual deficits result in a diagnosis of intellectual disability (11). While deficits in adaptive and intellectual skills frequently occur in tandem, some types of brain

dysfunction may result in preserved intellectual function with poor adaptive skills (e.g., ADHD) (12). Small to moderate correlations between adaptive and intellectual skills are typically seen in children (13), and adaptive behaviors with a heavier cognitive load (e.g., social skills and communication) tend to correlate more strongly with cognitive assessment measures.

One study of adaptive functioning in ependymoma survivors treated with conformal radiation therapy revealed relative sparing of most adaptive skills, with improvement in some domains over time (3). Communication skills showed the greatest decline over time, suggesting ongoing need for the investigation and development of preventive measures and interventions. The cognitive sparing may be largely attributed to a relatively less vulnerable posterior fossa tumor location. Considering that children diagnosed with craniopharyngioma and LGG are much older than those diagnosed with ependymoma, we anticipated that older age at treatment would offset the relatively more vulnerable supratentorial sites of irradiation and contribute to adaptive skills.

A specific area of concern for the study of children diagnosed with diencephalon or optic pathway tumors is the influence of visual impairment on adaptive behaviors. In children with visual impairment due to etiologies other than brain tumor, adaptive behavior deficits are observed in a number of areas including daily living skills, written communication, and coping skills (14, 15). Protective factors include increased parental education and level of independent mobility (15). The effects of visual impairment in childhood have exhibited a long-term impact on the quality of life and functional abilities well into adulthood. A review of studies suggests that even mild visual acuity loss can negatively affect an individual's perception of daily living skill performance, tendency toward social interaction, and feelings of loneliness (16). The higher risk of visual impairment in patients diagnosed with craniopharyngioma and LGG suggests a need to investigate the association with adaptive functioning in this pediatric brain tumor population.

In this report we investigate adaptive functioning in children diagnosed with craniopharyngioma and LGG and the effects of a treatment regimen that included conformal radiation therapy on functional outcomes in a pediatric population, with the anticipation that focused irradiation would result in spared functional outcomes. Accordingly, it was hypothesized that intellectual and adaptive functioning scores would remain stable and in the average range for the group as a whole over time, that the variation in intellectual and adaptive functioning scores would be correlated, and children with severe visual impairment would experience more marked decline in daily living and socialization domains.

METHODS AND MATERIALS

Participants

Between July 1997 and January 2008, children diagnosed with craniopharyngioma ($n=62$) and LGG ($n=77$) were enrolled in a Phase II clinical trial of conformal radiation therapy for pediatric brain tumors ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00187226) identifier: NCT00187226). Parental consent and patient assent were obtained for the neurocognitive assessment portion of this institutional review board-approved investigation. The cohort completed a total of 588 neurocognitive evaluations across the 5-year follow-up period. English was required as the primary language. Given the higher rate of visual impairment in the current study, verbal tests alone were administered when participants were unable to complete visually-based measures. During the time interval of the study, only one patient was unable to participate due to visual impairment. This patient was blind in both eyes as a result of a stroke suffered at the time of the initial surgery. The longitudinal models presented herein include all participants who completed at least two neurocognitive assessments (craniopharyngioma, $n=54$; LGG, $n=68$).

Patients were no longer followed if they completed the protocol or experienced disease progression. Neurocognitive data were used even when obtained during the same follow-up visit when MRI demonstrated asymptomatic tumor progression.

Medical Treatment & Clinical Factors

Surgical resection was performed before irradiation, with additional surgery performed as needed to maximize the extent of resection prior to treatment. Hydrocephalus was categorized as present or not present based on neuroimaging at the time of diagnosis. Severe visual impairment was defined as legal blindness (20/200) in one eye with any impairment of visual acuity or visual field function in the contralateral eye. Radiation treatment parameters have been reviewed in detail previously (7, 17). Participants received 3-dimensional conformal or intensity-modulated radiation therapy (CRT for purposes of this report) using conventional fractionation (1.8 Gy per day) and a prescribed dose of 54 Gy. The irradiated clinical target volume included a 5–10 mm margin surrounding the tumor and/or tumor bed to control microscopic disease, and an additional 3–5 mm margin expansion in three-dimensions to form the planning target volume and account for uncertainty in patient positioning and image registration.

Neurocognitive Assessment

Participants underwent serial neurocognitive assessment at pre-irradiation baseline, 6 months after treatment, and annually for 5 years. The neurocognitive battery and age appropriate measures of estimated intelligence (EIQ) have been described previously (3). Adaptive functioning was assessed with the *Vineland Adaptive Behavior Scale (VABS)* (13), which is a psychometrically validated parent interview administered by a trained psychological examiner. The VABS provides norm-referenced scores on a range of adaptive behaviors at developmental levels from birth through adulthood. Parents are asked to rate a series of behaviors on a scale of 0–2, where 0 indicates the child is unable to perform or never performs the behavior and 2 indicates general mastery of the skill. Behaviors are assessed in several domains, yielding index scores for Communication, Daily Living Skills, Socialization, and an overall Adaptive Behavior Composite. A Motor Skills domain is available for children age birth to 5 years; however, given the age range of participants in the current sample, this scale was not included in the current investigation. All index scores have an age-referenced mean of 100 and a standard deviation of 15, where higher scores reflect better skills.

Analyses

Descriptive analyses were conducted to characterize the sample's clinical, demographic, and neurocognitive features at baseline. Longitudinal changes in EIQ and adaptive functioning were examined using linear mixed models, which included all participants who completed at least two neurocognitive assessments ($n = 122$). The intercept served as the standard score at baseline and the slope represented mean change in score per month. Pearson correlations were then used to compare the trajectory of change (i.e., slope values) of EIQ and VABS Index scores over the 5-year follow-up period. Finally, univariate linear mixed models were employed to examine the impact of demographic, clinical, and treatment-related variables on changes in adaptive functioning. Statistical analyses were done using SAS for Windows software (version 9.1.3., SAS Institute, Cary NC).

RESULTS

Demographic and clinical features of the sample are summarized in Table 1. The median age at time of radiation therapy (RT) was approximately 9 years (range, 2 years–19 years). Tumor groups were divided evenly with respect to gender. Significantly more children with

LGG received chemotherapy prior to irradiation, consistent with current treatment standards. The incidence of Neurofibromatosis Type 1 (NF-1) was higher in the LGG group. Groups were equivalent with respect to hydrocephalus, extent of pre-radiation surgical resection, and frequency of severe visual impairment.

The initial hypothesis was that adaptive functioning would be spared by the use of highly focused methods of irradiation and thus, adaptive scores would remain stable in the average range across the 5-year follow-up period. Children diagnosed with craniopharyngioma obtained average scores at baseline for intellectual scores and all adaptive indices except Socialization for which their mean score was above the normative sample ($p = .003$). These patients experienced a statistically significant decline over time in Communication ($p = .006$) and Socialization ($p = .003$; Table 2). Factors influencing more rapid decline in Socialization included female gender ($p = .041$) and history of pre-irradiation systemic therapy (interferon; $p = .008$). In contrast to the hypothesis, children with LGG performed below normative means ($p < .05$) at baseline on Communication, Daily Living Skills, and the Adaptive Behavior Composite (Table 3). Longitudinal decline was noted only for the Communication Index ($p = .002$). Age at time of irradiation influenced rate of decline in IQ ($p = .016$) and Socialization ($p = .016$) indices, but with variable influence. Younger aged patients had a more rapid decline in IQ, but less rapid decline in Socialization.

It was also hypothesized that variation over time in intellectual scores would correlate with variation in adaptive functioning indices. Neither tumor group exhibited strong correlations across indices. In fact, change only in the Daily Living Skills index correlated with change in IQ for the craniopharyngioma group ($p = .01$; Tables 2 and 3).

The final hypothesis concluded that individuals experiencing severe visual impairment would exhibit significant deficits in Daily Living Skills and Socialization indices relative to their non-visually impaired peers. Participants with severe visual impairment ($n=27$) obtained lower scores on many IQ and adaptive indices across the 5-year follow-up period; however, the only differences that reached statistical significance were for Daily Living Skills and the Adaptive Behavior Composite at 12 months and 48 months after treatment (Table 4). There was no deficit in the Socialization index related to visual impairment at any time point.

DISCUSSION

Adaptive Outcomes Differ by Tumor Diagnosis

Although these tumor groups were similar with respect to age and clinical morbidity including hydrocephalus and visual impairment, adaptive outcomes differed across the 5-year follow-up period of the study. Children diagnosed with craniopharyngioma had average or better scores on IQ and all adaptive behavior measures at baseline, generally suggesting typical development of skills prior to diagnosis. In contrast, children diagnosed with LGG performed below population-based norms in some areas at baseline (e.g., Communication, Daily Living Skills, and Adaptive Behavior Composite). Given that these results were obtained before irradiation, they suggest that at least some of the intellectual and adaptive late effects experienced by children with brain tumors are the result of non-radiation-related clinical factors including tumor burden, visual impairment, endocrinopathies, and pre-irradiation chemotherapy. Despite these statistically significant differences, all mean scores fell within the average range at baseline.

During the course of the 5-year follow-up period, significant decline was noted in the VABS Communication Index for both tumor groups. Skills comprising this index score include spontaneously speaking, using developmentally appropriate grammar and language

conventions, and reading and writing at an age-appropriate level. The decline seen in craniopharyngioma and LGG survivors was clinically significant, as mean scores approached the lower limits of the “average” range at the 5-year time point. In a prior study of ependymoma survivors, a less pronounced decline in communication skills was observed over time and some adaptive functions improved over a 5-year follow-up period (3). Given the younger age at diagnosis for ependymoma survivors (i.e., approximately 4 years), this difference may reflect increased plasticity in younger children, intervention prior to school age, or response to improvement in clinical factors (e.g., motor impairment). Clinical decline in this older age group will require targeted interventions. Given the heavy load of academic skills on this index, school-based interventions addressing reading, writing, and language organization may be most appropriate.

Clinical, Demographic, and Treatment Variables Influence Outcome

The differential impact of clinical, demographic, and treatment variables on adaptive outcome further highlights the need to examine tumor groups separately. In the craniopharyngioma group, girls had a different pattern of performance than boys, with more rapid decline over time in the VABS Socialization Index, which includes the use of manners, appropriate social conventions, and the understanding of subtle social cues. Also noted in the craniopharyngioma group was the impact of pre-RT chemotherapy (interferon) on the VABS Communication and Socialization Indices, where children who received chemotherapy exhibited more rapid decline in these skills. It is noteworthy that only two children in the craniopharyngioma group received pre-RT chemotherapy; thus, conclusions are drawn with caution and warrant further investigation. Chemotherapy is often used to delay RT in children who are very young at the time of diagnosis. As such, it is heavily linked to age at time of treatment, which had a variable association with intellectual and adaptive skills, both across tumor diagnoses and across skills assessed. Younger age at time of treatment was associated with faster decline in IQ in the LGG cohort. In contrast, younger age at RT appeared to be a protective factor against decline in the Socialization Index for the same group.

These findings are interesting in light of a previous investigation using alternate measures of social competence in craniopharyngioma survivors, which found that only extent of surgical resection was associated with baseline differences in social scores (18). There was no indication of longitudinal decline in that investigation. The variability among findings highlights a need for further investigation of the most accurate method to assess these critical functional skills in childhood cancer survivors. Additionally, the differential impact of these various clinical and demographic factors may lend itself to the development of risk adaptation models. The use of such models may provide more tailored predictive information about the risk to specific functional skills. Pre-emptive interventions may help mitigate the functional impact of the brain tumor experience and associated treatments by identifying high-risk populations and the specific skills at risk (e.g., social skills training for girls diagnosed with craniopharyngioma).

Group Means Remain in the Average Range

Deficits in adaptive behavior have been found in different diagnoses (19) and treatment regimens not including radiation therapy (20). Although significant decline was noted in some specific skill areas for those included in the study, group means for all index scores remained in the average range of functioning, suggesting relatively intact adaptive skills for the group as a whole. This finding of relative sparing of skills does not; however, minimize the significant declines that individual participants may experience. The use of individually tailored risk models may help with the implementation of appropriate behavioral and environmental interventions.

IQ and Adaptive Functioning Are Unique Constructs

Correlations between IQ and adaptive behavior change were largely non-significant. This suggests that both intellectual function and adaptive behavior should be examined as unique outcomes in brain tumor survivors. IQ tends to measure maximal ability, while adaptive function reflects application of those abilities in daily life. Examination of adaptive behavior change may yield additional targets for intervention (e.g., functional communication skills) that could impact the quality of life for brain tumor survivors and their families.

Visual Impairment

Participants in this study experienced a high rate of visual impairment. Visual impairment is a known risk factor for reduced socialization and performance of daily living skills in non-cancer patients (15, 16). It was hypothesized that these skill deficits would be observed in this group of brain tumor survivors. While deficits in daily living skills were observed for severely impaired participants at some time-points, these were not consistent across the entire follow-up period. Additionally, social skills deficits were not observed for children with severe visual impairment at any time point. Given the risk of visual impairment impacting quality of life well into adulthood, intervening to provide more structured skills training, and working to improve independent mobility will likely afford the most benefit to these brain tumor survivors. In contrast to children with visual impairment from other causes, this does not appear to be an area of particular risk for these children, and resources may be best utilized addressing other skill sets.

Conclusions

In conclusion, conformal radiation therapy appears to provide relative sparing of functional outcomes. Baseline differences in functional abilities prior to the initiation of radiation treatment suggest that other disease and demographic-related factors influence functional outcomes above and beyond the effects of RT. Additional research will be needed to delineate those clinical factors that impact the ability to perform adaptive skills (e.g., motor impairment, vision, hearing, and speech/language abilities). Item analysis within VABS subscales may also yield useful information about the component processes for performing these adaptive behaviors. Developing individually-tailored treatment plans based on specific clinical and demographic risk factors may help target the skill sets that are most at risk.

Acknowledgments

This work was supported in part by the National Cancer Institute, Cancer Center Support Grant 5 P30 CA21765-28, The Noyes Brain Tumor Foundation, Musicians Against Childhood Cancer (MACC), and the American Lebanese Syrian Associated Charities (ALSAC).

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Table 1

Comparison of baseline demographic and clinical characteristics between groups

	Craniopharyngioma (n=62)	Low-grade Glioma (n=77)	<i>p</i> -value
Gender (% Male)	48	51	.79
Age at CRT (years)	9.20 ± 4.01	9.45 ± 4.16	.72
Extent of Pre-CRT Surgery (%)			.08
Biopsy / Subtotal Resection	90	97	
Near / Gross Total Resection	9	2	
Pre-CRT Chemotherapy (% Yes)	3	31	<.01
Hydrocephalus (% Diagnosed)	48	61	.14
Shunt (% Shunted)	40	37	.75
Severe Visual Impairment (% Diagnosed)	10	17	.22
NF-1 (% Diagnosed)	0	20	<.01
<u>Baseline Evaluation</u>			
IQ	103.92 ± 20.62	95.12 ± 19.75	.11
Communication Index	99.65 ± 16.48	92.12 ± 16.41	.09
Daily Living Index	98.98 ± 16.90	92.76 ± 17.02	.12
Socialization Index	108.27 ± 15.40	96.09 ± 18.46	.01
Adaptive Behavior Composite	100.04 ± 19.11	91.30 ± 19.59	.09

Abbreviations: CRT = Conformal Radiation Therapy; NF-1 = Neurofibromatosis Type 1

Table 2**Baseline Neurocognitive Scores and Change over Time in Craniopharyngioma**

Variable	Baseline Mean (SE)	<i>p</i> -value	Correlation with Baseline IQ Pearson <i>r</i> (p-value) ^a	Annual Change	<i>p</i> -value	Correlation with IQ Change Pearson <i>r</i> (p-value) ^b
EIQ	100.55 (2.71)	.840	--	−0.725	.080	--
VABS Com	100.11 (1.92)	.956	0.21 (.13)	−1.948	.006	0.06 (.66)
VABS DL	98.43 (2.24)	.487	0.26 (.06)	−0.172	.832	0.34 (.01)
VABS Soc	105.86 (1.88)	.003	−0.04 (.79)	−2.212	.003	0.18 (.20)
VABS ABC	99.65 (2.42)	.880	0.29 (.04)	−1.139	.103	0.26 (.06)

Abbreviations: EIQ=Estimated IQ; VABS=Vineland Adaptive Behavior Scale; Com=Communication Index; DL=Daily Living Skills Index; Soc=Socialization Index; ABC=Adaptive Behavior Composite; SE=Standard Error

^a Pearson correlation between baseline IQ score (first row) and VABS Indices

^b Pearson correlation between change in IQ (slope) and change in VABS Indices

Table 3

Baseline Neurocognitive Scores and Change over Time in Low-Grade Glioma

Variable	Baseline Mean (SE)	<i>p</i> -value	Correlation with Baseline IQ Pearson <i>r</i> (p-value) ^a	Annual Change	<i>p</i> -value	Correlation with IQ Change Pearson <i>r</i> (p-value) ^b
EIQ	96.78 (2.42)	.188	--	−0.647	.124	--
VABS Com	93.68 (1.99)	.003	0.27 (.03)	−1.512	.002	0.09 (.48)
VABS DL	92.76 (4.47)	.005	0.22 (.07)	−0.074	.909	0.20 (.12)
VABS Soc	98.25 (2.06)	.400	0.10 (.43)	−0.490	.373	−0.08 (.51)
VABS ABC	93.50 (2.30)	.006	0.24 (.05)	−0.817	.119	0.11 (.39)

Abbreviations: EIQ=Estimated IQ; VABS=Vineland Adaptive Behavior Scale; Com=Communication Index; DL=Daily Living Skills Index; Soc=Socialization Index; ABC=Adaptive Behavior Composite; SE=Standard Error

^a Pearson correlation between baseline IQ score (first row) and VABS Indices

^b Pearson correlation between change in IQ (slope) and change in VABS Indices

Table 4

Mean (SD) Intellectual and Adaptive Scores in Severe vs. Non-Severe Visual Impairment in Low-grade Glioma and Craniopharyngioma Survivors Across Time

		IQ	Communication	Daily Living Skills	Socialization	Adaptive Composite
Baseline	Severe	100.11 (23.90)	93.50 (16.76)	86.00 (15.66)	97.80 (28.72)	89.00 (18.10)
	Non-Severe	98.58 (19.97)	95.84 (17.27)	95.39 (21.29)	102.20 (15.41)	96.41 (19.96)
Month 6	Severe	93.88 (22.35)	91.22 (19.30)	89.56 (20.15)	98.44 (16.06)	89.67 (21.04)
	Non-Severe	101.28 (18.03)	96.77 (13.56)	96.67 (17.02)	99.98 (14.66)	96.58 (17.02)
Month 12	Severe	85.33 (26.749)	85.14 (21.50)	81.57 (17.20) *	93.71 (19.08)	80.86 (18.48) *
	Non-Severe	98.49 (17.68)	94.80 (15.19)	96.89 (15.71)	97.71 (15.53)	94.80 (16.95)
Month 24	Severe	93.57 (16.85)	89.25 (20.46)	90.38 (21.92)	109.88 (13.87)	94.38 (22.37)
	Non-Severe	93.89 (17.80)	93.99 (17.43)	93.99 (20.10)	99.75 (16.64)	94.71 (19.46)
Month 36	Severe	93.38 (19.14)	88.69 (18.60)	91.69 (20.39)	100.23 (15.07)	91.38 (18.85)
	Non-Severe	99.00 (19.072)	92.95 (17.90)	97.08 (17.59)	100.22 (14.88)	95.89 (18.24)
Month 48	Severe	89.36 (24.21)	80.73 (20.70)	84.27 (22.52) *	97.40 (11.91)	83.55 (20.99) *
	Non-Severe	101.78 (19.27)	92.03 (18.83)	98.53 (16.67)	98.51 (15.71)	95.42 (17.86)
Month 60	Severe	82.00 (24.83)	82.00 (22.67)	89.50 (26.47)	90.67 (25.71)	86.90 (26.15)
	Non-Severe	94.18 (19.35)	89.35 (16.33)	91.82 (18.92)	93.75 (17.86)	90.06 (16.69)

* Severe group performed significantly worse than non-severe group at $p = .05$