Quality of life outcomes in patients presenting for evaluation of CNS tumors

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Abstract

Background

We describe patient-reported outcomes (PROs) in adults with CNS tumors and evaluate their correlation with physician-reported functional status.

Methods

We completed a retrospective cohort study of patients managed at a high-volume CNS tumor institute between September 2013 and September 2014. PROs were measured using 6 domains from the PROs Measurement Information System (PROMIS): anxiety, physical function, pain interference, sleep disturbance, fatigue, and satisfaction with social roles. Physician-reported outcomes were measured using the Eastern Cooperative Oncology Group Scale of Performance Status (ECOG). We compared differences in PROMIS scores across tumor types using analysis of variance and measured the correlation between PROMIS scores and ECOG scores using spearman correlations. Finally, we compared the range of PROMIS physical function scores within each ECOG level.

Results

In a cohort of 2,828 patients, 1,284 (45.4%) completed all 6 PROMIS domains. There were significant differences in PROMIS scores across tumor types for all domains except anxiety. The strength of the correlation between PROMIS and ECOG scores was weak to moderate for all PROMIS domains (all $p < 0.001$). The correlation was the strongest between the physical function domain and ECOG score ($\rho = -0.54$), although there was a broad distribution of physical function scores within ECOG level, with scores spanning nearly 5 SDs within most ECOG levels.

Conclusions

Symptom burden was associated with tumor type. There were only weak to moderate correlations between PROMIS and ECOG scores, underscoring the importance of integrating PROs into clinical practice for patients with CNS tumors.

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The founding of the Patient-Centered Outcomes Research Institute under the Affordable Care Act¹⁻³ represents a shift towards using patient-reported outcomes (PROs) to measure

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We evaluated patient-reported health across multiple domains using PROMIS in a population of adults with CNS tumors seen at a single high-volume center.

quality in patient-centered health care models.⁴ While a patient's experience of their disease is difficult to capture using traditional measures, PROs can inform our understanding of a disease process by measuring its social, emotional, and physical burden on a patient.⁵ As a result, PROs are being actively recommended as adjuvant measures that may serve to guide clinical practice regarding treatment decisions, evaluation of treatment response, discussions of prognosis, and need for auxiliary care.^{6,7}

The PROs Measurement Information System (PROMIS) was established by the NIH as a national resource to improve techniques for measuring PROs for multiple domains of health across chronic conditions.^{5,8} PROMIS has been implemented and validated in multiple sclerosis,⁹ osteoarthritis,¹⁰ heart failure,¹¹ HIV,¹² and adult and pediatric cancers^{13–15} among other conditions. However, PROMIS has not been well-studied in the adult CNS tumor population. With more than 368,117 incident CNS tumors (117,906 malignant; 250,211 non-malignant) diagnosed between 2009 and 2013, CNS tumors represent a significant disease burden on the U.S. healthcare system.^{16,17} While this disease process commonly leads to functional impairment and reduced quality of life for patients, disease progression varies widely depending on CNS tumor histology; for example, 5-year survival rates are 94.2% for pilocytic astrocytoma but are 5.5% for glioblastoma.¹⁷ Within this population, measures of quality of life are still often physician-reported, with common instruments being the Karnofsky Performance Status (KPS) and Eastern Cooperative Oncology Group Scale of Performance Status (ECOG).^{18,19} These scales may be suboptimal, as past work has suggested that these scales, which focus on functionality, do not necessarily accurately capture patient's true quality of life.²⁰

Given the prevalence of CNS tumors in the US yet the scarcity of studies comparing how the disease process affects patients' quality of life, we evaluated patient-reported health across multiple domains using PROMIS in a population of adults with CNS tumors seen at a single high-volume center. In order to better describe how PROs and physician-reported measures correlate amongst a population of adults with CNS tumors, we also evaluated the correlation between the PROMIS scores and a physician-reported measure of functional status. We hypothesized that patients with higher-

grade tumors would report more symptoms on the PROMIS scales, and that there would be substantial variability between PROMIS scores and physician-reported measures of functional status.

Methods

Study cohort

This was a retrospective cohort study of patients evaluated and managed at a high-volume CNS tumor institute at a tertiary care hospital. All adults aged 18 + who were evaluated at our institute by a neurologist, neuro-oncologist, neurosurgeon, and/or radiation oncologist between September 2013 and September 2014 and completed all 6 PROMIS tools were included in the study.

Measurements

Six PROMIS v 1.0 scales were completed by patients: anxiety, fatigue, physical function, pain interference, sleep disturbance, and satisfaction with social roles. PROMIS is a set of instruments developed using item response theory that has been validated in more than 20,000 individuals derived from the general US population.^{3,5,8} Results are reported using a T-score with a mean of 50 and SD of 10 and are normalized to the US population, with higher scores representing more of the attribute being assessed. The scales were administered using computer adaptive testing, in which the most informative questions are selected from an item bank based on the patient's prior responses. This administration method has been shown to improve score precision and reduce patient burden.^{21–23}

Each patient's physician-reported functional status was measured using both the KPS and ECOG. The KPS is a one item scale with 11 response options ranging from 0 to 100, with 0 corresponding to dead and 100 corresponding to normal health without evidence of disease.¹⁹ The KPS has been validated in a variety of populations, including those with brain tumors.^{24,25} The ECOG is a similarly well-validated²⁶ one item scale with responses ranging from 0 to 5, with 0 corresponding to fully active without restriction due to disease and 5 corresponding to death.¹⁸ There is overall a high-degree of correlation between the 2 scales,²⁷ and because the ECOG has been shown to have slightly less inter-rater variability amongst populations of cancer patients,²⁸ stratification by ECOG score was used for the purposes of displaying comparisons with PROMIS scores.

Data collection

Through the Knowledge Program (KP) patient-entered data collection system,²⁹ patients visiting any ambulatory clinic within the Cleveland Clinic Neurologic institute are asked to complete electronic questionnaires relevant to their condition on tablet computers. Proxies may complete the questionnaires on behalf of patients who are unable to complete questionnaires due to physical or cognitive limitations. Results are immediately

Table Patient characteristics for patients who did and did not complete all 6 PROMIS scales

	All patients	Completed all PROMIS scales	Did not complete all PROMIS scales	p Value
N	2828	1284	1544	
Age, mean (SD)	55.6 (15.4)	53.6 (15.1)	57.3 (15.4)	<0.001
Female	1620 (57.3%)	726 (56.5%)	894 (57.9%)	0.491
Race				
White	2482 (87.8%)	1168 (91.0%)	1314 (85.1%)	<0.001
Black	227 (8.0%)	77 (6.0%)	150 (9.7%)	—
Other	58 (2.1%)	14 (1.1%)	44 (2.8%)	—
Missing	61 (2.2%)	25 (1.9%)	36 (2.3%)	—
Marital status				
Married	1834 (64.9%)	862 (67.1%)	972 (63.0%)	<0.001
Single	565 (20.0%)	264 (20.6%)	301 (19.5%)	—
Divorced	236 (8.3%)	99 (7.7%)	137 (8.9%)	—
Widowed	148 (5.2%)	44 (3.4%)	104 (6.7%)	—
Missing	45 (1.6%)	15 (1.2%)	30 (1.9%)	—
Diagnosis				
Meningioma	659 (23.3%)	288 (22.4%)	371 (24.0%)	<0.001
CNS lymphoma	64 (2.3%)	29 (2.3%)	35 (2.3%)	—
CNS metastases	473 (16.7%)	170 (13.2%)	303 (19.6%)	—
Grade 1–2 glioma	301 (10.6%)	170 (13.2%)	131 (8.5%)	—
Grade 3 glioma	124 (4.4%)	81 (6.3%)	43 (2.8%)	—
Grade 4 glioma	250 (8.8%)	135 (10.5%)	115 (7.4%)	—
Pituitary tumors	162 (5.7%)	70 (5.5%)	92 (6.0%)	—
Schwannoma/Neurofibroma	71 (2.5%)	34 (2.6%)	37 (2.4%)	—
Other CNS tumor	221 (7.8%)	89 (6.9%)	132 (8.5%)	—
No CNS tumor—other diagnosis	287 (10.1%)	117 (9.1%)	170 (11.0%)	—
Non-specific CNS lesion on MRI	216 (7.6%)	101 (7.9%)	115 (7.4%)	—
ECOG				
0	1208 (42.7%)	587 (45.7%)	621 (40.2%)	0.008
1	775 (27.4%)	380 (29.6%)	395 (25.6%)	—
2	378 (13.4%)	158 (12.3%)	220 (14.2%)	—
3	129 (4.6%)	48 (3.7%)	81 (5.2%)	—
4	17 (0.6%)	5 (0.4%)	12 (0.8%)	—
Missing	321 (11.4%)	106 (8.3%)	215 (13.9%)	—
KPS				
90–100	1478 (52.3%)	707 (55.1%)	771 (49.9%)	0.114
70–80	820 (29.0%)	387 (30.1%)	433 (28.0%)	—
30–60	212 (7.5%)	85 (6.6%)	127 (8.2%)	—
0–20	1 (0.0%)	0 (0.0%)	1 (0.1%)	—
Missing	317 (11.2%)	105 (8.2%)	212 (13.7%)	—

Abbreviations: ECOG = Eastern cooperative oncology group scale of performance status; KPS = Karnofsky performance status; PROMIS = patient reported outcome measurement information system.

available within the electronic health record (EHR; Epic, Epic Corporation, Verona, WI). During the neuro-oncology clinic visit, physicians complete the KPS and ECOG scales within structured fields of the KP. PROMIS scores and physician-reported measures of functioning from the first visit during the study period in which they were available were used in the analysis.

Patients' socio-demographic information, including age, sex, race/ethnicity, and marital status, was electronically extracted from the EHR. CNS tumor histopathologic diagnosis was manually abstracted and categorized into the following diagnosis groups: grade 1 to 2 glioma, grade 3 glioma, grade 4 glioma, meningioma, pituitary tumor, schwannoma and neurofibroma, CNS lymphoma, and CNS metastases. For diagnoses that did not fit into the above designated categories, histopathologic diagnosis was described as other CNS tumor, non-specific lesion on MRI, or non-tumor diagnosis. These categories reflect the World Health Organization brain tumor classification system, which is based on histopathology and corresponds generally with different disease outcomes and treatment paradigms.³⁰

Statistical analysis

We computed baseline descriptive statistics for the entire cohort and for the patients who did and did not complete PROMIS scales in all 6 domains. For both the entire cohort

and for patients with a glioma, we described average PROMIS scores, where higher scores in physical function and social satisfaction scales represent better function and satisfaction, respectively, and higher scores in the other domains indicate higher symptom burden. For each PROMIS domain, we compared average scores amongst the 3 most common diagnosis groups—meningioma, glioma stratified by grade, and CNS metastases—using One Way analysis of variance. We also compared the correlation of PROMIS scores with ECOG scores using spearman correlation coefficients. Finally, we generated histograms to compare the variability of PROMIS physical functioning scores within each ECOG score level for both the entire cohort and for patients with glioma. Computations were done in R, version 3.4.1 (R Core Team, Vienna, Austria). *p*-values less than 0.05 were considered statistically significant.

Data availability

Anonymized data relevant to this study will be shared by request with any qualified investigator pending appropriate institutional review board approvals.

Results

From September 2013 to September 2014, there were 5,812 visits (counting multiple encounters within the same day only once) for 2,828 unique patients. Of these patients, 1,284

Figure 1 Mean PROMIS domain scores for all brain tumor patients

Horizontal line represents the mean score of the U.S. general population. The thick horizontal bar within each box represents the median score for each PROMIS scale. The ends of the boxes represent the first and third quartiles. The vertical lines extending from each box ("whiskers") represent values that are within 1.5 times the interquartile range from each quartile or the min/max if inside 1.5 interquartile range. The small circles represent outliers (more than 1.5 times the interquartile range from a quartile.)

(45.4%) completed all 6 PROMIS domains. Amongst both those who did and did not complete all 6 PROMIS scales, the most common tumor types were meningioma (22.4% vs 24.0%, respectively) and the rarest tumor type was CNS lymphoma (2.3% amongst both groups; table). Of those with primary brain tumors who completed all PROMIS scales, a preponderance had a low grade glioma (13.2%), of which the majority were grade 2 ($n = 137$). Compared with those who did not complete all PROMIS scales, patients who did were younger (53.6 vs 57.3), and more likely to be white (91.0% vs 85.1%), and married (67.1% vs 63.0%). Those who did not complete all scales were more likely to have CNS metastasis (19.6% vs 13.2%) and had higher ECOG scores, but there were no statistical differences in their KPS scores.

The distribution of scores in both the entire cohort and patients with glioma was not substantially different from the general population (figure 1 and figure e-1, links.lww.com/CPJ/A73). However, PROMIS scores between individual diagnosis groups did differ amongst tumor types in our cohort for physical function ($p < 0.01$), pain interference ($p < 0.01$), sleep disturbance ($p < 0.05$), fatigue ($p < 0.05$) and social satisfaction ($p < 0.01$) (figure 2). No difference in average scores between tumor type was observed for anxiety ($p = 0.10$). The most prominent differences in scores among tumor types were seen in patients with CNS metastases and grade 4 gliomas who had worse physical function and social satisfaction scores than either meningioma or grade 1–3

gliomas. The other PROMIS scale scores were closer to the general population average in patients with all tumor types despite differences seen in statistical testing.

In our sample, KPS and ECOG scores were very strongly correlated ($\rho = -0.81$, $p < 0.01$). The correlations between physician-reported measures of functional status (KPS and ECOG scores) and all 6 PROMIS score domains were statistically significant ($p < 0.01$). With respect to anxiety, fatigue, and pain interference, higher PROMIS scores (i.e., more symptoms) correlated with higher ECOG score (i.e., worse functioning). Similarly, with respect to physical function and social satisfaction, lower PROMIS scores (i.e., more burden) correlated with higher ECOG scores (i.e., worse functioning). The strengths of these correlations for the whole cohort and for glioma patients specifically ranged from weak to moderate (figure 3 and figure e-2, links.lww.com/CPJ/A73 respectively). For both the whole cohort and glioma patients, the weakest correlation was between ECOG and the sleep disturbance PROMIS domain ($\rho = 0.18$ and $\rho = 0.23$, respectively, both $p < 0.01$), while the strongest was between ECOG and physical functioning ($\rho = -0.54$ and $\rho = -0.65$, respectively, both $p < 0.01$). However, there was a high degree of variability of physical function scores within each ECOG score level, with ranges in the whole cohort of 49.2, 49.8, 41.9, 27.5, and 8.4 in physical function scores within ECOG levels 0–4, respectively (figure 4), a finding mirrored in the glioma subgroup (figure e-3, links.lww.com/CPJ/A73).

Figure 2 PROMIS scores stratified by histologic diagnosis

PROMIS = patient reported outcomes measurement information system. Horizontal line represents the mean score of the U.S. general population. Vertical lines represent 95% confidence intervals.

When PROMIS scores were stratified by tumor type, differences appeared in the physical function, pain interference, sleep disturbance, and social satisfaction domains.

Discussion

This large study of PRO measures in the adult CNS tumor population encompasses 1284 patients and multiple tumor types. We found that, in aggregate, patients' PROMIS scores were similar to the general population mean. However, when PROMIS scores were stratified by tumor type, differences appeared in the physical function, pain interference, sleep disturbance, and social satisfaction domains. We also found that while there were statistically significant correlations between physician-reported measures of functional status and PROMIS scores in all domains, there was also a high degree of variability in the PROMIS scores within ECOG score levels.

Although PROMIS scores have rarely been generated in large populations of adults with CNS tumors, PROMIS has

previously been evaluated in the context of various other patient populations.^{9–11,15,31} Specifically, PROMIS tools have been utilized to measure PROs amongst adult cancer patients. For example, Wagner et al.¹³ collected several PROMIS measures in 631 patients receiving outpatient care for gynecologic cancer and similarly found that mean PROMIS scores were comparable to the general US populations. Although our cohort's PROMIS scores for the overall cohort were similar to those in the general population, we did identify specific differences across diagnosis groups. Meningiomas and low-grade gliomas are characteristically described as a benign disease process with a protracted disease course and longer survival,^{16,17} so it is perhaps unsurprisingly these patients' PROMIS scores were generally comparable to the general population across all PROMIS domains. Conversely, glioblastoma portends a rapidly progressive clinical course,³² and CNS metastatic disease signifies an end-stage systemic malignant process.³³ However, our hypothesis that patients with these latter disease processes would experience higher symptom burdens across all domains was not borne out. The patients with glioblastoma and metastatic tumors had worse physical function and social satisfaction, but either no or only a small increase in symptoms related to sleep disturbance, pain, fatigue and anxiety compared with their counterparts with more benign tumor types. This may be because the diagnosis of a CNS tumor, regardless of type, is emotionally charged.³⁴ Thus PROs related to issues like fatigue, anxiety, and sleep disturbance may

Figure 3 Mean PROMIS domain scores with 95% confidence intervals for brain tumor patients within ECOG score categories

PROMIS = patient reported outcomes measurement information system; ECOG = Eastern cooperative oncology group scale of performance status, higher values indicate worse functional status. Horizontal line represents the mean score of the U.S. general population. Vertical lines represent 95% confidence intervals.

Figure 4 Distribution of PROMIS physical function scores for brain tumor patients across ECOG score categories

PROMIS = patient reported outcomes measurement information system; ECOG = Eastern cooperative oncology group scale of performance status, higher values indicate worse functional status. Red vertical line represents the mean score of the U.S. general population. Black vertical lines represent 95% confidence intervals.

be less dependent on the specific disease processes while physical functioning and abilities to carry-out desired social actions could be more affected by the more severe disease courses. Alternatively, the Cleveland Clinic has a robust palliative medicine department housed within its cancer center that utilizes multiple approaches to identify targets for symptom control in CNS tumor patients³⁵; and so our finding that PROMIS scores were not necessarily correlated with traditionally higher-grade tumor types may be due to the availability of support services amongst the studied patient population. Future work might more specifically explore the effect of palliative care on PROMIS scores in patients with CNS tumors.

Our data supported our second hypothesis that there would be a high degree of variability between PROMIS scores and physician-reported outcomes. The weak to moderate correlation between physician-reported outcomes and PROMIS score domains and our finding that PROMIS scores spanned nearly 5 SDs within multiple ECOG score levels underscores the importance of utilizing PROs in regular clinical practice. In randomized trials, oncology patients who receive palliative-focused interventions have been shown to have higher quality of life scores than their counterparts who did not receive such care.^{36,37} However, a recent systematic review and consensus review concluded that very little current literature exists describing how to identify or treat symptom burden in patients with brain tumors.^{38,39} Other work has shown physicians do not accurately predict the mood symptoms their brain tumor patients are experiencing.⁴⁰ Identifying patients experiencing undue symptom burden is the first step towards addressing this burden, and our results suggest that physician assessment of functional status is likely not enough to guide patients to appropriate care resources that have been shown to improve quality of life for other cancer patients. Including validated PROs, such as PROMIS scores, could help address this gap in patient care.

In addition to appropriately guiding patients to care resources based on each patient's experience with his or her disease, understanding PROMIS scores may be informative for clinical decision making and providing prognostic information. We are not the first to suggest PROs generally, and PROMIS scores specifically, may be informative in predicting the future course of a disease and enabling physicians and families to anticipate changes in management. For example, a single patient-reported general health status question has been shown to be predictive of mortality.⁴¹ Moreover, a review of cancer trial data suggested that PROs were actually often better predictors of survival than performance status.⁴² Concerning the use of PROMIS scores more specifically, in an analysis of 200 pediatric patient with cancer, Buckner et al.¹⁴ used PROMIS outcomes in latent profile analysis to group patients into different clinical profiles and hypothesized that such information could be used in the future to prospectively evaluate their risk for developing different degrees of symptom severity and impairment. While speculative at this point, future research could work to discern whether PROMIS scores may be useful in determining disease progression in CNS tumor patients.

The present study also illustrates the feasibility of collecting multiple PROMIS scales within the clinical workflow of a large CNS tumor clinic. In the first year that PROMIS was introduced, over 1,200 patients completed all 6 domains at a single visit, which represented 45% of the total 2,828 patients who were seen at our institute. As we continue to administer PROMIS at our institute, the goal of future studies is to incorporate multiple time points for each given patient and correlate patients' PROMIS scores with disease status and treatment regimens. In the current oncology landscape, there is

a growing emphasis on genetic and molecular markers as a tool for the assessment and management of cancer.⁴³ Additionally, it is well-known that chemotherapies are associated with a host of adverse effects,^{44,45} as are non-medication treatments, such as surgery and radiation.^{46,47} Evaluating PROMIS outcomes as a function of these biomarker and treatment characteristics may be informative in anticipating future health care needs for CNS tumor patients.

Our study included several limitations. First, this study was conducted at a single center. It is possible that the magnitude of PROMIS scores could vary based on institutional resources available to patients or patient complexity, both of which may be greater at a tertiary care center. As such, future studies should attempt to reproduce the results presented here. Moreover, we used scores from the first available visit for each patient, and we were unable to correlate variables such as progression of illness, neuroanatomical location, and comorbid related conditions such as seizures, aphasia, apraxia, ataxia, and hemiparesis with PROMIS score. Because of this, we cannot comment on how PROMIS scores may change across the course of the disease or if it is driven by particular symptomatology in this patient population, which is an area for future research. However, this likely does not limit our ability to compare the correlation of physician-reported outcomes with PROMIS scores. Additionally, while the 46% of patients who did complete all 6 PROMIS score domains were descriptively similar to those that did not, there is still potential for nonresponse bias. While this may have influenced PROMIS scores, it is less likely to have affected the correlation between PROMIS scores and physician-reported outcomes.

Conclusion

In a large population of CNS tumor patients, we found that symptom burden was associated with tumor type. There were only weak to moderate correlations between PROMIS scores and physician-reported assessment of patient physical function. These findings underscore the potential importance of integrating PROs into clinical practice for patients with CNS tumors. Future work might seek to explore how PROMIS scores correlate with CNS tumor progression and if they can be added to prognostic models based on more traditional clinical characteristics. Additionally, future explorations could describe how PROMIS scores fluctuate before, during, and after various treatment regimens. Ultimately, work describing how standardized PROs influence clinician decisions, such as treatments or referrals, is needed to better describe the role PROs might play when introduced into the course of clinical care.

Author contributions

A. Chaitoff: drafting/revising the manuscript, analysis or interpretation of data. N. Sarmey: drafting/revising the manuscript, data acquisition, analysis or interpretation of data. N.R. Thompson: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, statistical analysis.

TAKE-HOME POINTS

- Patient-reported outcomes can inform our understanding of the effect of a disease process.
- We report that in patient with CNS tumors, patient reported outcomes vary by tumor type.
- In patients with CNS tumors, patient and physician-reported measures quality of life are only weakly-to-moderately correlated.
- The gathering of patient reported outcomes can be implemented into normal clinic workflow using validated tools and might be used to guide patient care.

Y. Fan: data acquisition, analysis or interpretation of data, statistical analysis. M. Ahluwalia: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, contribution of vital reagents/tools/patients, study supervision. I.L. Katzan: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, study supervision.

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