Published in final edited form as:

J Neurooncol. 2018 January ; 136(1): 73–78. doi:10.1007/s11060-017-2618-2.

Development of the Pediatric Neuro-Oncology Rating of Treatment Intensity (PNORTI)

Matthew C. Hocking^{1,2}, Wendy Hobbie¹, and Michael J. Fisher^{1,2}

¹Division of Oncology, The Children's Hospital of Philadelphia, 3501 Civic Center Blvd., 10211 CTRB, Philadelphia, PA 19104, USA

²Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

Abstract

Measures of treatment intensity for childhood cancer are needed in research in order to control for variability in treatments. Existing measures of treatment intensity for childhood cancers do not reflect the complexities of treatment protocols for central nervous system (CNS) tumors. This paper describes the development of the Pediatric Neuro-Oncology Rating of Treatment Intensity (PNORTI). PNORTI development occurred in three phases. Phase 1: five experts in pediatric neuro-oncology created a 5-point scale of treatment intensity and 42 pediatric neuro-oncology providers completed a three-part online questionnaire to evaluate the classification system and apply the rating system to 16 sample patients. Validity was determined by respondents classifying therapy modalities into intensity levels. Interrater reliability was calculated from ratings of the 16 sample patients. Phase 2: three experts revised the PNORTI based on survey results and 18 pediatric neuro-oncology providers evaluated the classification system. Phase 3: ten experts in pediatric neuro-oncology refined and finalized the PNORTI and rated 10 sample patients using the PNORTI. Agreement between median ratings of the survey respondents and criterion raters for chemotherapy intensity (r 's = .82 and 1.0) and overall treatment intensity level (r 's = .91 and .94) were high in Phases 1 and 2. Inter-rater reliability also was very high when using the PNORTI to classify the 16 sample patients in Phase 1 (median agreement of r = .93 and κ = .99) and the 10 sample patients in Phase 3 (median agreement of r = .92 and κ = .98). The PNORTI is a valid and reliable method for classifying the intensity of different treatment modalities used in pediatric neuro-oncology.

Keywords

Brain tumor; Pediatric neuro-oncology; Treatment intensity

Conflict of interest The authors have no conflicts of interest to declare.

Compliance with ethical standards

Electronic supplementary material The online version of this article (doi:10.1007/s11060-017-2618-2) contains supplementary material, which is available to authorized users.

Introduction

Advances in the therapies used to treat children with central nervous system (CNS) tumors have enhanced 5-year survival rates to an estimated 73.6% [1], thus increasing the focus on health-related quality of life and psychosocial outcomes across the continuum of treatment and survivorship. Variability in treatment intensity is important to account for when investigating survivor and family outcomes across these domains. Although the field of pediatric neuro-oncology is moving towards examining psychosocial and neurodevelopmental outcomes within homogenous groups of youth with CNS tumors to enhance validity, this is often unfeasible in many studies given the extremely rare nature of childhood CNS tumors. Studies with homogenous samples often require multiple sites or cooperative trials to accrue sufficient samples of specific CNS tumor diagnoses that receive the same tumor-directed therapies. Relying solely on these approaches limits the generalizability of findings of psychosocially-focused research to other tumor groups and slows advances that can be made through clinical research. Research that examines psychosocial and neurodevelopmental outcomes across patients with varying CNS tumor diagnoses and treatment combinations is still needed. Therefore, methods for evaluating treatment intensity across CNS tumor groups are needed in order to combine samples and minimize the number of covariates.

Treatment intensity refers to the degree of intensity, or harshness, of the treatment as an individual goes through it and encompasses factors such as duration, side effects and recovery time [2]. Treatment intensity is relevant given that it might be related to other important variables of interest, including school attendance, family functioning, patient or family member distress [3] and survivor health-related quality of life [4, 5]. Additionally, it is often important to establish that treatment intensity is not related to certain variables, such as fatigue [6], physical activity [7] or adherence to medical regimens [8]. While treatment intensity may be related to the level of risk for late effects, they are not necessarily directly related. For example, focal radiation may not be a very intense treatment, yet is related to many potential late effects.

Although patient and family perspectives on treatment intensity are important, they are likely to be highly subjective and variable, even within the same treatments. Therefore, prior attempts at classifying the treatment intensity of childhood cancer protocols, including the Intensity of Treatment Rating Scale 2.0 (ITR-2) [2] and the Intensity of Treatment Rating-3 (ITR-3) [9], relied on more objective, expert opinions of pediatric oncology providers. The ITR-2 and ITR-3, however, encompassed all potential childhood cancer diagnoses and were not specific to neuro-oncology. They differentiated the intensity of treatment for brain tumors based on the number of treatment modalities used, which may not fully represent the nuances associated with current treatment protocols in pediatric neuro-oncology. For example, in the ITR-3 [9], brain tumors were classified as either a Level 2 (one treatment modality, not including biopsy), a Level 3 (two or more treatment modalities) or a Level 4 (brain tumor with stem cell transplant). Current protocols for pediatric CNS tumors often include multiple treatment modalities with varying intensities within each modality. Classifying intensity based on the number of modalities and not the degree of intensity of each modality is suboptimal in the neuro-oncology population. Another method for

classifying treatment intensity focused on therapies directed to the CNS in general but was not specific to CNS tumors [10]. The goal of the current paper is to describe the development and validation of a measure of treatment intensity specific to pediatric neuro-oncology: the Pediatric Neuro-Oncology Rating of Treatment Intensity (PNORTI).

Methods

Development of the PNORTI occurred in three phases with each phase consisting of scale revision by pediatric neurooncology experts and scale validation with pediatric neurooncology providers. The versions of the PNORTI from phases 1 and 2 are presented in a supplemental appendix. This study was granted an exemption from the Institutional Review Board at The Children's Hospital of Philadelphia (CHOP).

Phase 1: scale construction and validation

Five experts in pediatric neuro-oncology from CHOP met to review, discuss and evaluate the items from the ITR-3 with respect to their applicability to current therapy protocols for CNS tumors. As part of this revision process, the internal work group created a 5-point scale of treatment intensity, ranging from Minimal (1) to Most Intensive (5) that integrates three levels of chemotherapy intensity including Non-Intensive, Moderate and Intensive. This new classification system was termed the PNORTI and was created for use as part of a larger study [11, 12].

To validate the PNORTI, pediatric neuro-oncology providers, including both neuro-oncologists and nurse practitioners, internal and external to CHOP were recruited by email to complete a three-part online survey. External respondents were identified through a combination of an internal database of the study team and through examination of websites for major pediatric oncology programs in North America. The internal survey respondents did not participate in the earlier development of the PNORTI. The survey defined treatment intensity as "the intensity of the treatment as a child goes through it and NOT as the likelihood of whether or not the treatment will cause late effects." First, respondents across 29 institutions (n = 48; n = 40 outside our institution; n = 1 international) classified the different chemotherapy approaches into one of three levels. Second, respondents (n = 45; n = 37 outside our institution; n = 1 international) categorized overall treatment approaches into one of five levels. Finally, respondents (n = 42; n = 34 outside our institution; n = 1 international) applied the PNORTI rating system to rate the treatment intensity of 16 hypothetical patients so that inter-rater reliability could be calculated. The cases depicted representations across the five intensity levels as determined by the authors (4 cases presented for level 2 to reflect the varying combinations of chemotherapy and radiation and 3 cases for every other level).

Phase 2: scale revision and validation

In Phase 2, three experts at CHOP (MCH, WH, MJF) revised the PNORTI based on survey results with the goals of clarifying chemotherapy intensity levels by reducing from four to three descriptors of chemotherapy regimens, specifying surgery intensity by noting the number of post-operative days in the hospital and constructing more specific combinations

of chemotherapy intensity levels and cranio-spinal radiation. Following scale revision, 18 pediatric neurooncology providers across 13 institutions who finished the survey in Phase 1 (n = 15 outside our institution; n = 1 international) completed an online questionnaire to evaluate the classification system where they classified the different chemotherapy approaches into one of three levels and categorized overall treatment approaches into one of five levels.

Phase 3: final scale revision and validation

In Phase 3, three experts at CHOP (MCH, WH, MJF) again revised the PNORTI for a final time (see Fig. 1) based on survey results. The scale was revised to adjust the intensity levels attributed to surgical resection and cranio-spinal radiation, and more carefully specify chemotherapeutic agents and doses indicative of high intensity chemotherapy. The resulting PNORTI consisted of three levels of overall treatment intensity that integrates three levels of chemotherapy intensity. Following scale revision, 10 internal pediatric neuro-oncology providers completed an online survey where they applied the revised PNORTI rating system to grade the treatment intensity of ten hypothetical patients.

Data analytic plan

In Phases 1 and 2, Spearman-rho correlations were calculated to estimate inter-rater agreement between the survey respondents and the criterion ratings of scale items for both chemotherapy and overall intensity levels. Median ratings across survey respondents were computed for each item and then correlated with criterion ratings in order to assess the level of association across all items. Additionally, individual respondent ratings for each item were correlated with the criterion ratings and summarized to assess the range of agreement between the survey respondents and the criterion raters.

In Phases 1 and 3, inter-rater reliability estimates were generated for when respondents to the two separate surveys applied the different versions of the PNORTI to the sample patient cases. Two sets of analyses assessed inter-rater reliability for each Phase. First, Kendall's Tau-b was calculated to estimate the association between each rater's judgment of intensity and the set of clinical cases. Second, two-way randomized, intraclass correlation coefficients (ICC) were generated across raters for each survey. A more stringent assumption of absolute agreement across all raters for each survey was used to estimate the ICC. All analyses were conducted using SPSS v22 (IBM Corp, Somers NY).

Results

Survey respondents

In Phase 1, 42 of the 49 survey respondents provided information regarding the number of years they have provided care for children with brain tumors and the number of new brain tumor diagnoses seen at their institution each year. In Phase 2, all 18 survey respondents provided this information. Table 1 presents these data. For both Phase 1 and Phase 2, ratings of chemotherapy and overall intensity did not differ in chi square analyses based on respondent experience in neuro-oncology or brain tumor patient volume of respondent's institution ($p > .05$).

Phase 1: scale validation

Validation—Spearman-rho correlations indicated high agreement between the median ratings of the survey respondents and the criterion ratings for the chemotherapy intensity items ($r = .82$, range 0.54–0.94). The median rating did not match the criterion rating on two of the four items and was off by one level for each. Forty-nine percent of respondents rated the item “Any outpatient chemotherapy regimen” as Moderate intensity while the criterion rating was Non-Intensive. Additionally, 83.7% of respondents rated “Planned in-hospital admission for no more than 1 night/cycle for chemotherapy per institutional guidelines” as Moderate intensity while the criterion rating was Non-Intensive.

For items for overall treatment intensity, there was high agreement between the median ratings of survey respondents and the criterion ratings ($r = .91$, range 0.42–0.99), although the median did not match the criterion on three of the six items. Approximately 43% of the sample agreed with a Minimal intensity rating for “Surgical resection only” with the rest of the sample viewing it as a more intensive therapy (average = 30.6%, moderate = 12.2%, intensive = 6.1%). Respondents viewed “Craniospinal radiation with or without Moderate or Non-Intensive chemotherapy” as less intensive than the criterion raters (Criterion = Intensive, Median = Moderate) with 38.8% agreeing with the criterion rating (moderate = 38.8%, average = 14.3%). Similarly, the median rating for “Craniospinal radiation AND Intensive chemotherapy” was Intensive (46.9%) rather than the criterion rating of Most Intensive (42.9%).

Inter-rater reliability—Inter-rater reliability of the survey respondent’s ratings of the 16 cases using Kendall’s Tau-b indicated a high median level of agreement between the respondent’s ratings of each case and the criterion rating ($r = .93$, range 0.49–0.98). The intraclass correlation coefficient also revealed a high level of agreement and reliability among the raters ($r_{ICC} = .99$).

Phase 2: scale validation

Validation—Spearman-rho correlations indicated perfect agreement between the median ratings of the survey respondents and the criterion ratings for the chemotherapy intensity items ($r = 1.00$, range 0.50–1.00). The median ratings matched the criterion ratings on all three items and 89.5% of the respondents agreed with the criterion ratings for each of the chemotherapy items.

For the items on overall treatment intensity, there was high agreement between the median ratings of survey respondents and the criterion ratings ($r = .94$, range 0.72–0.99). In this Phase, the median did not match the criterion on one of the seven items. Respondents rated “Craniospinal radiation with Medium intensity chemotherapy” as less intensive than the criterion rating (average = 5.6%, moderate = 55.6%, intensive = 38.9%).

Phase 3: scale validation

Inter-rater reliability—Inter-rater reliability of the survey respondent’s ratings of the 10 cases using Kendall’s Tau-b indicated a high median level of agreement between the respondent’s ratings of each case and the criterion rating ($r = .92$, range 0.65–1.00). The

intraclass correlation coefficient also revealed a high level of agreement and reliability among the raters ($r_{ICC} = .98$).

Discussion

The PNORTI offers a psychometrically sound approach to classifying the intensity of treatment approaches used within pediatric neuro-oncology. The PNORTI was created through an iterative process that included expert opinion and empirical feedback from pediatric neuro-oncologists across the country. Neuro-oncology providers classified the majority of treatment approaches in a manner consistent with the criterion ratings and applied the rating system to evaluate sample patients in a reliable fashion. The resultant PNORTI is a brief, reliable measure of treatment intensity that can be generated efficiently through a review of medical treatment information.

The development of the PNORTI followed the same rigorous process as the ITR-2 and the ITR-3 and focused on establishing the psychometric properties of the measure. It is the only known measure of treatment intensity for pediatric neuro-oncology that has been evaluated in terms of its psychometrics. It is generalizable across institutions and classifies the intensity of treatment of each child in a systematic way that minimizes subjectivity through the review and application of concrete medical treatment information.

There are many potential uses for the PNORTI in clinical research, particularly for research focused on psychosocial outcomes, including studies evaluating survivor or family distress, health-related quality of life, family functioning and school attendance or engagement. For example, studies seeking to examine psychological distress in brain tumor survivors may want to determine whether distress varies as a function of the intensity of tumor-directed therapies. Such knowledge could address whether modifiable psychosocial factors, such as family functioning factors or friendship quality, predict survivor distress over and above the contributions of treatment intensity. Furthermore, the PNORTI can be used to categorize heterogeneous brain tumor survivors into smaller groups when recruiting samples comprised of only the same diagnosis and treatment history is not feasible.

Although treatment intensity may be associated with survivor late effect, the PNORTI is intended to be a measure of the intensity of the tumor-directed treatments as a child is going through them and not a rating system of the probability of a child developing late effects. For example, although craniospinal radiation is a strong contributor to the development of late effects, neuro-oncology raters in this study did not view it as having the same level of treatment intensity as high-dose chemotherapy plus stem cell rescue.

When rating youth who are well off therapy, clinicians should rate the highest level of treatment that a child has experienced in the case of multiple rounds of therapy and try to avoid consideration of the child's late effects. If seeking to quickly predict neurocognitive late effects, an existing measure, the Neurological Predictor Scale NPS; [13], attempts to quantify a child's exposure to treatment and medical factors that increases the risk for neurocognitive deficits. Increased exposure to risk factors as measured by the NPS have been associated with poorer global intellectual functioning [13], verbal reasoning, working

memory, attention, executive function and processing speed in childhood brain tumor survivors [14]. Future research is needed to establish whether treatment intensity as rated by the PNORTI is associated with medical and neurodevelopmental late effects in CNS tumor survivors.

The PNORTI should be considered within the context of the limitations of the current study. The validation of the measure with neuro-oncology providers primarily occurred in Phases 1 and 2 prior to the revisions of the final version of the scale presented here. Additionally, the Medium Intensity chemotherapy level does not account for the variable number of cycles of inpatient chemotherapy that may occur across different protocols. The current version of the PNORTI sacrificed simplicity of the tool for fine-grained specificity, particularly within the chemotherapy protocols.

The PNORTI represents the intensities of current therapy modalities used to treat pediatric CNS tumors in the United States. With scientific advances being integrated into clinical trials at an increasing rate, including use of molecular typing of tumors and targeted therapies based on tumor genetics, current treatment approaches will be outdated and will require regular updates to the PNORTI.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

The authors wish to acknowledge the support of Janet Deatrick, PhD to the initial development of the PNORTI, as well as the colleagues that provided feedback on the initial version of the measure, including Jean Belasco, MD; Jill Ginsberg, MD; Jane Minturn, MD; and Rosanna Pollack, CRNP. Additionally, the authors want to thank the members of the neuro-oncology program at The Children's Hospital of Philadelphia and the pediatric neuro-oncology providers across the country who served as raters for this study.

Funding

The preparation of this article was supported in part by Grants 1K07CA178100 and 1R03CA162970 to Matthew C. Hocking.

References

1. Ostrom QT, Gittleman H, Fulop J et al. (2015) CBTRUS statistical report: primary brain and central nervous system tumors diagnosed in the United States in 2008–2012. *Neuro-Oncology* 17(Suppl 4):iv1–iv62 [PubMed: 26511214]
2. Werba BE, Hobbie WL, Kazak AE, Ittenbach RI, Reilly AF, Meadows AT (2007) Classifying the intensity of pediatric cancer treatment protocols: the intensity of treatment rating scale 2.0 (ITR-2). *Pediatr Blood Cancer* 48(7):673–677 [PubMed: 17427232]
3. Bitsko MJ, Cohen D, Dillon R, Harvey J, Krull KR, Klosky JL (2016) Psychosocial late effects in pediatric cancer survivors: a report from the Children's Oncology Group. *Pediatr Blood Cancer* 63:337–343 [PubMed: 26488337]
4. Kuhlthau KA, Pulsifer MB, Yeap BY et al. (2012) Prospective study of health-related quality of life for children with brain tumors treated with proton radiotherapy. *J Clin Oncol* 30(17):2079–2086 [PubMed: 22565004]

5. Momani TG, Hathaway DK, Mandrell BN (2016) Factors affecting health-related quality of life in children undergoing curative treatment for cancer: a review of the literature. *J Pediatr Oncol Nurs* 33(3):228–240 [PubMed: 26611756]
6. Daniel LC, Brumley LD, Schwartz LA (2013) Fatigue in adolescents with cancer compared to healthy adolescents. *Pediatr Blood Cancer* 60:1902–1907 [PubMed: 23897651]
7. Hocking MC, Schwartz LA, Hobbie WL et al. (2013) Prospectively examining physical activity in young adult survivors of childhood cancer and healthy controls. *Pediatr Blood Cancer* 60(2):309–315 [PubMed: 22434746]
8. Hullmann SE, Brumley LD, Schwartz LA (2015) Medical and psychosocial associates of nonadherence in adolescents with cancer. *J Pediatr Oncol Nurs* 32(2):103–113 [PubMed: 25366574]
9. Kazak AE, Hocking MC, Ittenbach RF et al. (2012) A revision of the intensity of treatment rating scale: classifying the intensity of pediatric cancer treatment. *Pediatr Blood Cancer* 59(1):96–99 [PubMed: 21858914]
10. Vannatta K, Gerhardt CA, Wells RJ, Noll RB (2007) Intensity of CNS treatment for pediatric cancer: prediction of social outcomes in survivors. *Pediatr Blood Cancer* 49:716–722 [PubMed: 17096410]
11. Deatrick JA, Hobbie WL, Ogle S et al. (2014) Competence in caregivers of adolescent and young adult childhood brain tumor survivors. *Health Psychol* 33(10):1103–1112 [PubMed: 23957900]
12. McCurdy MD, Turner EM, Barakat LP et al. (2016) Discrepancies among measures of executive functioning in a subsample of young adult survivors of childhood brain tumor: associations with treatment intensity. *J Int Neuropsychol Soc* 22(9):900–910 [PubMed: 27667398]
13. Micklewright JL, King TZ, Morris RD, Krawiecki N (2008) Quantifying pediatric neuro-oncology risk factors: development of the neurological predictor scale. *J Child Neurol* 23:455–458 [PubMed: 18182641]
14. McCurdy MD, Rane S, Daly BP, Jacobson LA (2016) Associations among treatment-related neurological risk factors and neuropsychological functioning in survivors of childhood brain tumor. *J Neurooncol* 127:137–144 [PubMed: 26725098]

Overall Treatment Intensity Levels*	
Level 1	
Surgical resection only (biopsy does not qualify) AND/OR focal radiation AND/OR Low Intensity chemotherapy**	
Level 2	
Cranio or cranio-spinal radiation with <u>or</u> without Medium or less Intensity Chemotherapy**	
OR	
Medium Intensity Chemotherapy**	
Level 3	
High Intensity chemotherapy** with <u>or</u> without craniospinal radiation	

***In cases of relapse, please evaluate the entire treatment history when making the rating. Clinicians should rate the highest level of treatment that a child has experienced in the case of multiple rounds of therapy.**

****See description of chemotherapy intensity levels below.**

Chemotherapy Intensity Levels	
Low	
-Any outpatient chemotherapy	
Medium	
-Any inpatient chemotherapy regimen	
**DOES NOT INCLUDE chemotherapy regimens listed in High intensity chemotherapy	
High	
-High-dose chemotherapy + stem cell rescue	
OR	
-Cumulative doxorubicin dose $\geq 300\text{mg/m}^2$	
OR	
-Doses of methotrexate (1g/m^2 or above) that require leucovorin rescue	

©2017 Children's Hospital of Philadelphia. All Rights Reserved.

Fig. 1.

The Pediatric neuro-oncology rating of treatment intensity—final version (Phase 3)

Table 1

Sample characteristics of survey respondents in phase1 and 2

	Phase 1 n (%) (n = 42)	Phase 2 n (%) (n = 18)
Professional background of respondent		
Neuro-oncologist attending	29	18
Advanced nurse practitioner	13	0
Number of years treating children with brain tumors		
0-5	5 (11.9)	2 (11.1)
6-10	15 (35.7)	5 (27.8)
11-15	3 (7.1)	1 (5.6)
16-20	3 (7.1)	2 (11.1)
20+	16 (38.1)	8 (44.4)
Number of new pediatric brain tumor diagnoses seen in medical center		
0-25	4 (9.8)	2 (11.1)
26-50	3 (7.3)	1 (5.6)
51-75	12 (29.3)	5 (27.8)
75-100	8 (19.5)	5 (27.8)
100+	14 (34.1)	5 (27.8)