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Translation and validation of the Neurological Assessment in Neuro-Oncology scale to Brazilian Portuguese

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Introduction: The Neurological Assessment for Neuro-Oncology (NANO) scale was elaborated to assess neurologic function in integration with radiological criteria to evaluate neuro-oncological patients in clinical setting and enable the standardization of neurological assessment in clinical trials. The objective of this study is the translation to Brazilian Portuguese and transcultural adaptation of NANO scale in patients with the diagnosis of glioblastoma, brain metastasis and low-grade glioma.

Methods: Patients with diagnosis of glioblastoma, brain metastasis, and low-grade glioma were prospectively evaluated between July 2019 and July 2021. The process of translating and cross-culturally adapting the NANO scale included: translation from English to Portuguese, synthesis and initial revision by an expert committee, back-translation from Portuguese to English, a second revision by the expert committee, and the application of the NANO scale. Regarding the reliability of the NANO scale, Cronbach's alpha was employed to measure the internal consistency of all scale items and assess the impact of item deletion. Additionally, Spearman's correlation test was used to evaluate the convergent validity between the NANO scale and Karnofsky Performance Scale (KPS).

Results: One hundred and seventy-four patients were evaluated. A statistically significant inverse relation ($p < 0.001$) between KPS and NANO scale was founded. The Cronbach's alpha values founded for NANO scale were 0.803 for glioblastoma, 0.643 for brain metastasis, and 0.482 for low grade glioma.

Discussion: The NANO scale Brazilian Portuguese version proves to be reproducible and valid to evaluate neuro-oncological patients with glioblastoma and brain metastasis, presenting a strong correlation with KPS scale. Further studies are warranted to assess the validity and reliability of the scale in patients diagnosed with low-grade glioma.

KEYWORDS

glioblastoma, brain metastasis, low-grade glioma, neuro-oncology, neurological performance, NANO scale

Introduction

Central nervous system (CNS) tumors are responsible for 1.5% of all cancers and for 2.4% of all cancer deaths annually (1). In Brazil, the latest estimative predicted around 11,000 new cases of primary CNS tumors for 2020 (2). In the last years, a constant increase in studies evaluating new treatments in neuro-oncology, such as immunotherapy and target therapy, showed the necessity of a more precise response assessment in clinical trials and clinical practice. However, the best way to establish the evaluation criteria is not well defined in literature. While overall survival is considered an objective parameter and a gold standard in most studies, this outcome is limited to evaluate response assessment in diseases with prolonged course, as observed in low grade gliomas or meningiomas. Therefore, it is essential the implementation of response criteria that include both clinical and radiological findings, to promote a more complete evaluation (3, 4).

Even with the well established radiological response evaluation proposed by RANO group (4–7), the neurological outcome incorporated is simplified as “better,” “stable” or “worse.” The usual measurement of functional and clinical outcome in the oncological clinical practice and trials is by the Karnofsky Performance Status (KPS) (8) and Eastern Cooperative Oncology Group Performance Status (ECOG) (9). Despite the easy applicability in clinical trials and practice, the main limitation of these instruments in the neuro-oncologic patient is the inefficacy to translate the neurological status even with its direct influence in functional performance. Additionally, functional deterioration does not always signify disease progression. Prolonged use of corticosteroids, chemotherapy, immunotherapy, radiotherapy, infections, pre-existing comorbidities, and psychiatric conditions are examples of potential confounders in the functional evaluation of neuro-oncologic patients.

In 2017, a multidisciplinary international committee composed by neuro-oncology experts developed the Neurological Assessment in Neuro-Oncology (NANO) scale and evaluates neurological function in neuro-oncologic patients. The primary goal of NANO is to define clinical parameters objectively, to measure clinical response and disease progression related to tumoral activity. This scale was developed to be a simple, easy and fast-to-use tool that can be employed by any healthcare professional. To maintain its objectivity, the evaluation is based in direct observation rather relying on clinical history or reported symptoms (10).

Instruments that quantify and stratifies variables are essential to reproduce new data and aggregate more substantial information to evaluate outcomes and, finally, guide therapeutical decisions. Therefore, the translation and validation support the use of an instrument across different languages and cultures, standardizing the evaluation worldwide. The objective of this study is to translate and validate of the NANO scale to Brazilian Portuguese.

Methods

Patients diagnosed with brain tumors (presumably glioblastoma, low-grade glioma and brain metastasis) were prospectively evaluated between July 2019 and July 2021 at Sirio-Libanês Hospital, including both outpatient clinics and hospital admissions. Eligible patients were 18 years of or older with the previously mentioned CNS tumors, providing informed consent.

This study protocol was approved by the Institutional Review Board (ID 1294). Each patient underwent a neurological evaluation by a senior

author’s staff neurosurgeon. The translation process of NANO scale included the following steps: translation from English to Portuguese, synthesis and initial revision by an expert committee composed by the senior authors (M.V.C.M, M.C.V., D.A.G., J.A.N.J., C.F., and G.F.G.), back-translation from Portuguese to English, a second revision by the expert committee, and the application of the NANO scale.

The NANO scale is an instrument that evaluates neurological function through nine domains: gait, strength, ataxia, sensibility, visual field, facial paralysis, language, level of consciousness and behavior. The scale domains were selected according to the most common neurological findings in patients with brain tumors. Each domain has three or four score levels, varying between 0 and 2 or 0 and 3. The zero score indicates normal function, and the highest level (2 or 3) refers to the worst deficit in that domain. Also, the options “not evaluated” and “not assessed” were added in each domain. “Not evaluated” is scored when any neurologic deficit is not attributed to tumoral activity, such as change in medications (corticosteroid therapy, sedatives, antiepileptic drugs), comorbid events (metabolic encephalopathy, post-ictal state, stroke), when the evaluation of one domain is affected by another domain (ataxia is not scored because of leg weakness, for example). “Not assessed” is scored when the examiner omits the evaluation of a domain (10). In Table 1, the NANO scale is described.

The descriptive analysis of the collected data included: age, gender, interview time (diagnosis or follow-up reviews), lesion location, treatment timing at the evaluation, KPS score, presence of seizures and corticosteroid use. The statistical analysis was conducted with SPSS® for Windows (SPSS Inc., Chicago, IL, USA). Categorical variables were presented as proportions and analyzed with Pearson’s Chi-square Test and Fisher’s Exact Test. The continuous variables were submitted to the Kolmogorov–Smirnov Test to verify the normal distribution. The comparison was conducted with Student T test (normally distributed data), Mann–Whitney U test and Kruskal–Wallis test (non-normally distributed data). The post-hoc Dunn test was performed when the null hypothesis was rejected in Kruskal–Wallis test. Concerning NANO scale confiability, Cronbach’s alpha was utilized to measure the internal consistency of all scale items and if item deleted. The correlation Spearman’s Test was used to evaluate the convergent validity between NANO scale and KPS.

Results

In regarding to the NANO scale translation to Brazilian Portuguese process, no inconsistency was identified in all stages, including translation, initial revision, back-translation and its final version (the Brazilian Portuguese version is described in Figure 1).

After the translation process, 174 patients were evaluated. The epidemiological and clinical characteristics are presented in Table 2. There are no difficulties in the understanding of scale items among examiners. The option “not assessed” was not scored in any patient evaluated.

Convergent validity

Figure 2 specifies the total Spearman correlation coefficients between NANO and KPS scale. The value encountered (-0.875) was statistically significant ($p < 0.001$). Figure 3 shows the amplitude of the

TABLE 1 Neurological Assessment of Neuro-oncology (NANO) scale.

Domain	Score	Function
Gait	0	Normal
	1	Abnormal but walks without assistance
	2	Abnormal and requires assistance (companion, cane, walker, etc.)
	3	Unable to walk
		Not assessed
		Not evaluable
Strength	0	Normal
	1	Movement present but decreased against resistance
	2	Movement present but none against resistance
	3	No movement
		Not assessed
		Not evaluable
Ataxia (upper Extremity)	0	Able to finger to nose touch without difficulty
	1	Able to finger to nose touch but difficult
	2	Unable to finger to nose touch
		Not assessed
		Not evaluable
Sensation	0	Normal
	1	Decreased but aware of sensory modality
	2	Unaware of sensory modality
		Not assessed
		Not evaluable
Visual Fields	0	Normal
	1	Inconsistent or equivocal partial hemianopsia (\geq quadrantopsia)
	2	Consistent or unequivocal partial hemianopsia (\geq quadrantopsia)
	3	Complete hemianopsia
		Not assessed
		Not evaluable
Facial Strength	0	Normal
	1	Mild/moderate weakness
	2	Severe facial weakness
		Not assessed
		Not evaluable
Language	0	Normal
	1	Abnormal but easily conveys meaning to examiner
	2	Abnormal and difficulty conveying meaning to examiner
	3	Abnormal. If verbal, unable to convey meaning to the examiner. OR non-verbal (mute/global aphasia)
		Not assessed
		Not evaluable
Level of Consciousness	0	Normal
	1	Drowsy (easily arousable)
	2	Somnolent (difficult to arouse)
	3	Unarousable/coma
		Not assessed

(Continued)

TABLE 1 (Continued)

Domain	Score	Function
		Not evaluable
Behavior	0	Normal
	1	Mild/moderate alteration
	2	Severe alteration
		Not assessed
		Not evaluable

Adapted with permission from 'The Neurologic Assessment in Neuro-Oncology (NANO) scale: a tool to assess neurologic function for integration into the Response Assessment in Neuro-Oncology (RANO) criteria' by Nayak et al. (10), licensed under Oxford University Press-Journals.

Spearman correlation coefficients founded between NANO and KPS scale in each disease. A significant inverse correlation ($p < 0.001$) was observed in all diseases. The coefficients were: $r = -0.886$ in glioblastoma, $r = -0.827$ in brain metastasis and $r = -0.872$ in low grade glioma.

Confiability

The Cronbach's alpha values for NANO scale founded for each disease is specified as follows: 0.803 for glioblastoma, 0.643 for brain metastasis and 0.482 for low grade glioma. The total Cronbach's alpha is 0.777. In Table 3, detailed information about Cronbach's alpha when items are deleted is provided. Differences between patient groups were identified. When the items "gait," "strength," "ataxia," "facial paralysis," and "behavior" were excluded, the Cronbach's alpha dropped below the total value, indicating that these items are essential for the scale's reliability. In regarding to the exclusion of "consciousness" item, higher scores were observed in all groups, which infers the reduction of scale reliability with the presence of this domain. The "visual field" and "language" items showed lower scores when deleted in the glioblastoma and brain metastasis groups. Finally, the "sensibility" domain was important only in the glioblastoma group.

Discussion

This was the first study of translation and cross-cultural validation of NANO scale into Brazilian Portuguese. The primary objective was to translate and validate the NANO scale into Brazilian Portuguese with glioblastoma, brain metastasis and low-grade glioma patients. We chose these diseases due to the potential variability of identified symptoms and to assess whether there are specific particularities in each disease that could impact the NANO scale approach.

The radiological response criteria have already been validated, and the RANO criteria and its offspring (RANO-LGG, RANO-HGG, RANO-BM) (4–7, 11) are widely used in clinical trials. However, the clinical criteria also included in those instruments are too simplified and are commonly associated with the KPS and ECOG/WHO scores, which reflect only the general functional condition, without providing further details on the neurological status. Besides, radiological parameters not always mirror the neurological status. The greatest examples are the pseudoprogression and pseudo response phenomena (4, 6, 12). It is essential to perform a combined evaluation of radiological and

more specific clinical criteria to determine treatment response. The NANO scale effectively addresses the limitations of other scores by characterizing the clinical status through nine domains that can be quantified and assessed longitudinally. The scale is suitable for use by all professionals involved in patient care.

Although it is a novel instrument, the NANO scale has been utilized in various studies to date. These studies were heterogeneous, including patients with different diagnoses such as glioblastoma, low-grade glioma, meningioma, and neurological patients in general. The NANO scale has been employed in both prospective studies (13–17) and retrospective ones (18–23). Despite the need for NANO validation with retrospective data, there appears to be no significant loss of clinical information.

In Rahman et al. and Nayak et al., the NANO scale was used to measure neurological deficits in clinical trials in conjunction with the RANO criteria, following the approach proposed by the instrument's authors (15, 16). Additionally, the NANO scale serves as an early predictor of disease progression in gliomas and a predictor of survival in glioblastoma when compared to other commonly used scales for assessing functional status. Good initial NANO and KPS scores predict 4–5 times better functional recovery 2 months after resection. Compared to KPS, the NANO scale exhibits a stronger correlation with better outcomes and is superior in predicting functional improvement (13). In a Korean study, 76 glioblastoma patients were retrospectively reviewed. In this study, the NANO scale demonstrated greater prognostic value at diagnosis and disease progression compared to the KPS and ECOG/WHO scales (21). In a retrospective study, a worse NANO score was the only metric associated with lower survival when compared to the RANO and MacDonald criteria at 6 and 12 months after treatment (23). As per Heiland et al.'s study, they assessed the functional response following surgical treatment in 342 elderly patients with glioblastoma. Patients with higher NANO scores were more likely to be submitted to biopsy than gross total resection (GTR: 2.57 vs. biopsy: 2.74; $p < 0.05$). In addition, lower NANO scores were significantly associated to longer survival ($p = 0.001$) (18). In Table 4, all the published studies that utilized the NANO scale are described.

As presented in the NANO validation publication (10), the option 'not assessed' was included in all domains. This option applies to situations in which the interviewer deliberately does not assign any scores to a particular domain, and subsequently, that domain should be excluded from further evaluations. However, during data collection, we observed that such circumstances did not arise. This observation suggests that the option 'not assessed' may be omitted in all domains in future studies. Few patients received 'not evaluated' scores, and as a result, it cannot be determined if this

Domínio		Considerações
Marcha		<ul style="list-style-type: none"> • Marcha é idealmente avaliada por pelo menos 10 passos
0	Normal	
1	Anormal, porém deambula sem ajuda	
2	Anormal e necessita de ajuda (andador, bengala, outra pessoa...)	
3	Não deambula	
	Não avaliado	
	Não avaliável	
Força		<ul style="list-style-type: none"> • Teste cada membro separadamente • Avalie grandes grupos musculares proximais (acima do joelho ou cotovelo) e distais (abaixo do joelho ou cotovelo) • Escore deve refletir a pior resposta motora • Paciente com baseline grau 3 em um grande grupo muscular ou membro pode ser avaliado baseado na avaliação de outro grupo muscular ou membro
0	Normal	
1	Movimento presente porém reduzido contra resistência	
2	Movimento presente porém ausente contra resistência	
3	Sem movimento	
0	Não avaliado	
0	Não avaliável	
Ataxia (extremidade superior)		<ul style="list-style-type: none"> • Não avaliável se força comprometida • Tronco/extremidade inferior são avaliados pelo domínio "marcha" • Particularmente importante em pacientes com tumores cerebelares ou em tronco cerebral • Escore baseado na melhor resposta em pelo menos 3 tentativas
0	Índex-nariz normal	
1	Índex-nariz realizado com dificuldade	
2	Incapaz de realizar índex-nariz	
	Não avaliado	
	Não avaliável	
Sensibilidade		<ul style="list-style-type: none"> • Recomendado avaliar áreas corporais maiores separadamente (face, membros e tronco) • Escore deve refletir área com pior sintoma • Modalidade sensorial inclui mas não está limitada a sensibilidades tátil, dolorosa, térmica e propriocepção • Paciente com basal nível 2 em uma grande área pode ser classificado baseado na avaliação de outras grandes áreas
0	Normal	
1	Sensibilidade reduzida, porém consciente da modalidade sensorial	
2	Ausência da sensibilidade	
	Não avaliado	
	Não avaliável	
Campo visual		<ul style="list-style-type: none"> • Pacientes que requerem lentes de correção devem ser avaliados usando estas; • Cada olho deve ser avaliado e o escore deve refletir o olho com pior performance
0	Normal	
1	Hemianopsia parcial inconsistente ou equívoca (\geq quadrantanopsia)	
2	Hemianopsia parcial consistente ou inequívoca (\geq quadrantanopsia)	
3	Hemianopsia completa	
0	Não avaliado	
0	Não avaliável	

FIGURE 1 (Continued)

Paresia facial		<ul style="list-style-type: none"> • Particularmente importante em tumores cerebrais • Paresia inclui apagamento do sulco nasolabial, sorriso assimétrico e dificuldade ao levantar as sobrancelhas
0	Normal	
1	Fraqueza leve/moderada	
2	Paresia facial grave	
	Não avaliado	
	Não avaliável	
Linguagem		<ul style="list-style-type: none"> • Avaliação baseada no discurso falado. Escrita ou outras formas de linguagem não devem ser incluídas. • Nível 1: inclui dificuldade de incluir palavras; poucos erros como parafasia, neologismos, substituição de palavras, porém capaz de formar sentenças (completas ou incompletas). • Nível 2: inclui incapacidade de formar sentenças (<4 palavras por frase/sentença), vocabulário limitado, discurso fluente porém “vazio”.
0	Normal	
1	Anormal porém facilmente transmite significado para examinador	
2	Anormal e dificilmente transmite significado para examinador	
3	Anormal. Se fluente, incapaz de transmitir significado a examinador, ou afasia global	
0	Não avaliado	
0	Não avaliável	
Nível de consciência		
0	Normal	
1	Sonolento (facilmente despertável)	
2	Torpor (despertar difícil)	
3	Coma	
0	Não avaliado	
0	Não avaliável	
Comportamento		<ul style="list-style-type: none"> • Particularmente importante em tumores dos lobos frontais • Alterações incluem porém não estão limitadas a apatia, desinibição e confusão; • Considerar crises convulsivas quando alterações significativas.
0	Normal	
1	Alteração leve/moderada	
2	Alteração grave	
0	Não avaliado	
0	Não avaliável	

FIGURE 1
Final version of Brazilian translation of NANO scale.

has a considerable influence on the final score. Additionally, this option was excluded in the evaluation between the groups.

Since this is the first instrument specifically designed to evaluate neurological status in neuro-oncological patients, there is no established “gold-standard.” Therefore, we used the convergent correlation with KPS score in the validation process, given its widespread application in neuro-oncology. A significant inverse correlation ($p < 0.001$) was found between the scales in all groups (glioblastoma: $r = -0.886$; metastasis: $r = -0.827$; low grade glioma: $r = -0.872$). Consequently, the higher the KPS score, the lower NANO score will be. To date, there are no published studies correlating the NANO with other instruments (13, 18, 21, 23).

Among the diverse ways to measure the reliability, we used the internal consistency, applying Cronbach’s Alpha as the statistical test. The internal consistency varied between groups: in the glioblastoma and metastasis patients, the Cronbach’s Alpha were acceptable (0.803 and 0.643, respectively). However, the Cronbach’s Alpha found in the low-grade glioma group was 0.482, which is an insufficient coefficient result. This lower value may be explained by the longer disease duration and milder signals and symptoms severity and variability compared to glioblastoma and brain metastasis, which can impair the scale’s evaluation in this specific group. It is possible that with a larger sample size, we may achieve better results in terms of internal consistency in this specific population.

TABLE 2 Demographic and clinical characteristics.

	Disease (n)			p	Total 174
	Glioblastoma (76)	Metastasis (51)	Low grade glioma (47)		
Age–median (P25–P75)	57 (42.7–64.2)	58 (43–66.5)	40 (34.5–46)	<0.001*†	
Gender				0.002**	
Female	33 (43.4%)	35 (68.6%)	16 (34%)		84 (48.3%)
Male	43 (56.6%)	16 (31.4%)	31 (66%)		90 (51.7%)
Moment of NANO application				0.644**	
At diagnosis	18 (23.7%)	10 (19.6%)	13 (27.7%)		41 (23.6%)
At follow-up	58 (76.3%)	41 (80.4%)	34 (72.3%)		133 (76.4%)
Localization					
Infratentorial	5 (7.6%)	10 (19.6%)	1 (2.1%)	0.015***	16 (9.8%)
Supratentorial	61 (92.4%)	41 (80.4%)	46 (97.9%)		148 (90.2%)
Moment of treatment				0.01**	
Chemotherapy	23 (32.9%)	10 (21.7%)	2 (4.3%)		35 (21.5%)
Radiotherapy	1 (1.4%)	2 (4.3%)	2 (4.3%)		5 (3.1%)
Chemotherapy and radiotherapy	5 (7.1%)	3 (6.5%)	3 (6.4%)		11 (6.7%)
No treatment	20 (28.6%)	5 (10.9%)	16 (34%)		41 (25.2%)
Other treatment	-	2 (2.3%)	1 (2.1%)		3 (1.8%)
Before surgery	13 (18.6%)	10 (21.7%)	10 (21.3%)		33 (20.2%)
After surgery	8 (11.4%)	14 (30.4%)	13 (27.7%)		35 (21.5%)
Seizures	35 (50%)	12 (26.7%)	30 (63.8%)	0.001**	77 (47.5%)
Corticosteroid use	34 (49.3%)	27 (58.7%)	6 (13.6%)	<0.001**	67 (42.1%)

* Kruskal-Wallis test.

** Pearson’s Chi-square test.

*** Fisher’s exact test extension.

† Post-hoc analysis (Dunn’s test). Differences between groups: glioblastoma and low-grade glioma ($p < 0.001$); low-grade glioma and brain metastasis ($p < 0.001$); glioblastoma and brain metastasis ($p = 0.826$).

In relation to Cronbach’s Alpha if an item is deleted, differences were observed between groups. This analysis allows us to assess the influence of each domain on the instrument’s internal consistency. If Cronbach’s Alpha decreases when an item is deleted, it indicates that this domain is important for the instrument’s reliability (25). As specified in Table 2, excluding “gait,” “strength,” “facial paralysis” and “behavior” domains decrease the Cronbach’s Alpha coefficient, indicating their key role in the instrument’s reliability. This finding may be explained by the higher objectivity and consistency in clinical evaluation, as well as their frequency, which allows for better internal consistency evaluation. Cronbach’s Alpha increases when this item is excluded, suggesting a reduction in reliability with the presence of this domain. However, this data may suggest the possibility of excluding this item to improve the scale’s performance. Nevertheless, since this is a novel instrument with recent applications, further studies are needed to confirm the significance of this item and the variability observed between groups, as shown in Table 3.

The NANO scale was developed to be applied alongside radiological criteria, providing a comprehensive evaluation and

being useful for the follow-up of neuro-oncological patients, regardless of tumor histology. However, understanding the particularities found in each subpopulation is essential for refining the instrument and maximizing its utility in neuro-oncology. For instance, excluding the NANO validation publication (10), the instrument has not yet been applied to patients with cerebral metastasis. This measurement could be important since the assessment of clinical status significantly influences therapeutic decisions. For example, asymptomatic patients may undergo systemic treatments with good central nervous system penetrance, while those with focal symptoms could be treated with more localized therapies like surgery or stereotactic radiosurgery. Furthermore, with better quantification and monitoring of neurological symptoms, patients with brain metastasis have a greater chance of being included in clinical trials, a condition that is typically an exclusion criterion in studies (26).

The NANO scale is an instrument applied by healthcare professionals, with domains characterized by technical terms widely used in clinical practice, without expressions or terms that can lead to misunderstanding or the necessity to transcultural

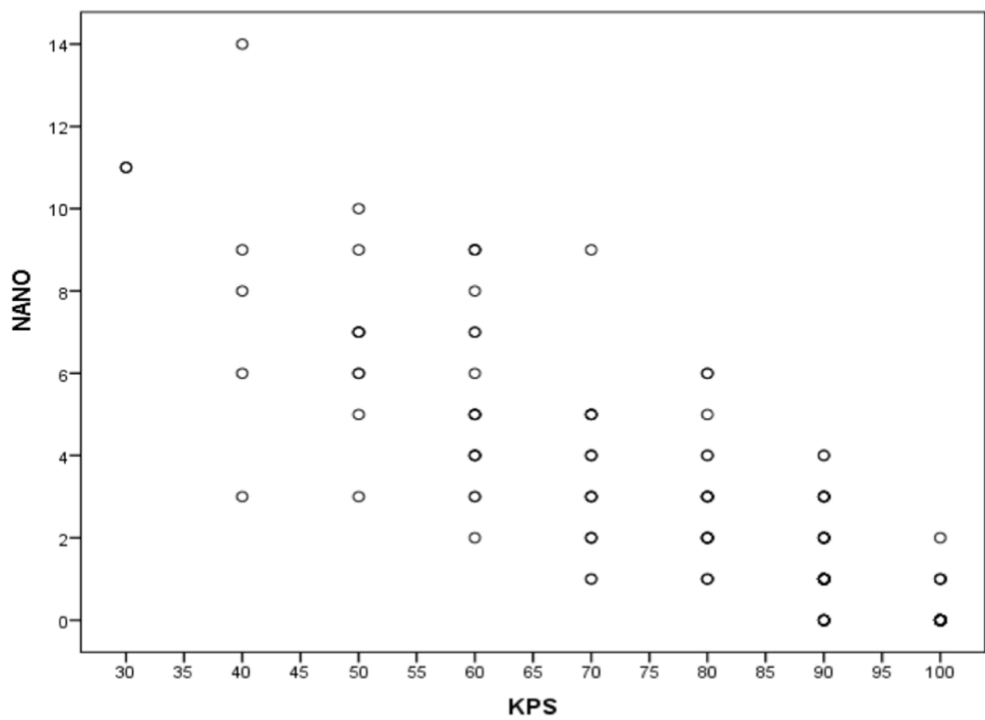


FIGURE 2 Spearman correlation coefficients between NANO and KPS scales.

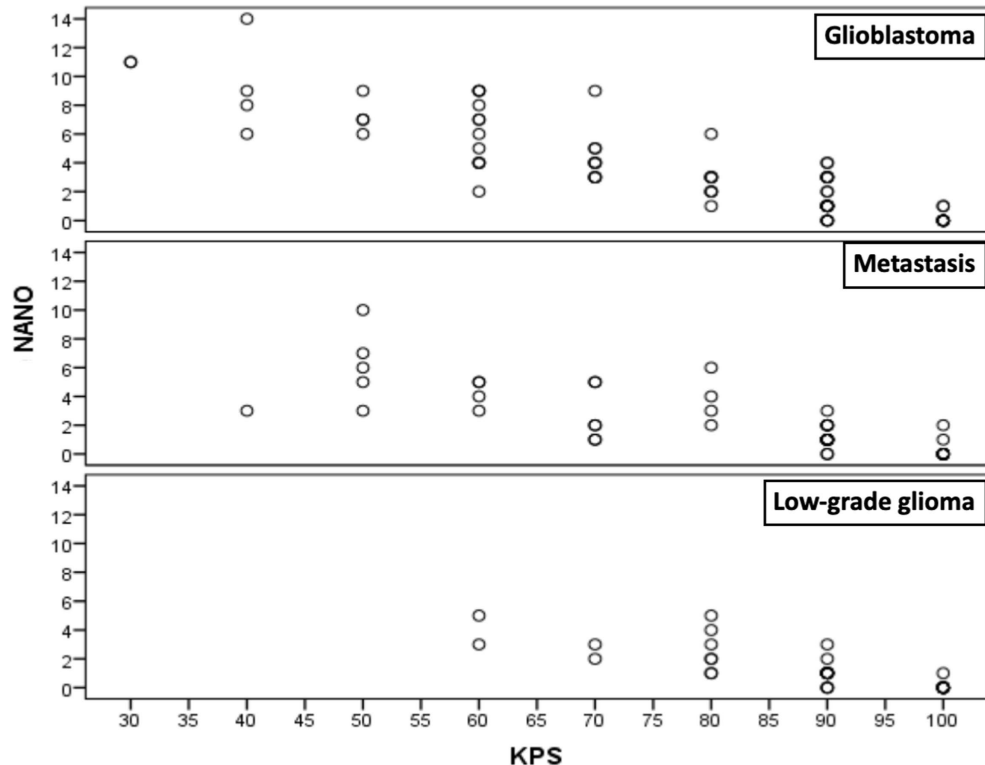


FIGURE 3 Spearman correlation coefficients between NANO and KPS scales in glioblastoma, brain metastasis and low-grade glioma groups.

TABLE 3 Total Cronbach’s alpha, by disease and if item excluded founded in NANO scale.

		Glioblastoma	Brain metastasis	Low-grade glioma
Total		0.803	0.643	0.482
If item excluded				
Item excluded	Gait	0.771	0.592	0.301
	Strength	0.784	0.594	0.342
	Ataxia	0.750	0.521	0.377
	Sensation	0.763	0.646	0.511
	Visual field	0.778	0.635	0.529
	Facial strength	0.798	0.616	0.398
	Language	0.794	0.618	0.533
	Level of consciousness	0.808	0.651	0.490
	Behavior	0.797	0.636	0.477

TABLE 4 Summary of all studies published so far using NANO scale.

Study	Population	Utilization of another criteria	Observations
Heiland et al. (18)	Glioblastoma in elderly population	KPS	Retrospective study. Treatment should be decided considering the functional/neurological status, not only age.
Lee et al. (21)	Glioblastoma	KPS, ECOG	Retrospective study. NANO provides better objective measure of neurological status than other scales, especially in disease progression.
Ung et al. (23)	Glioblastoma	KPS, ECOG, RANO-HGG	Retrospective study. Only NANO scale was associated with 1-year overall survival. NANO score progression was the only metric related to decreased survival compared to RANO and MacDonald criteria in 6 and 12 months after diagnosis.
Gunawan et al. (13)	Glioblastoma, low-grade glioma	KPS	Prospective cohort. Patients with lower scores at diagnosis have 4–5 times more probability of better outcome.
Steindl et al. (22)	Neurologic patients	No	Retrospective cohort comparing healthy individuals vs. Patients with a neurological condition. The relation between temporal muscle thickness and strength is investigated, as a tool to evaluate sarcopenia. NANO scale was used to measure neurologic deficit.
Kong et al. (20)	Low-grade glioma and glioblastoma	No	Retrospective case series evaluating neuronal plasticity in glioma patients after surgery. NANO scale used to measure neurologic deficit before and after surgical treatment.
Rahman et al. (16)	Glioblastoma	No	Prospective IB trial evaluating the effect of bortezomib e temozolamide. NANO scale measured neurologic deficit in combination with RANO criteria.
Kalasauskas et al. (14)	Meningioma	No	Prospective study comparing the psychological burden in patients with the diagnosis of meningioma, submitted to surgery vs. conservative treatment.
Nayak et al. (15)	Glioblastoma	No	Prospective randomized phase II study comparing the use of pembrolizumab and bevacizumab vs. pembrolizumab. NANO was used to measure neurological deficits, assessed in conjunction with RANO criteria.
Kalasauskas et al. (24)	Meningioma	No	Prospective study comparing distress and quality of life in patients diagnosed with meningioma undergoing surgery vs. Conservative treatment. NANO score was not related to symptoms of anxiety, depression, or distress.
Kasper et al. (19)	Glioblastoma	No	Retrospective study evaluating IDH non-mutated glioblastoma at diagnosis, post-operative period and at 3 months follow-up.
Therkelsen et al. (17)	Primary central nervous system lymphoma	KPS	Prospective case series evaluating patients submitted to chemotherapy with autologous hematopoietic stem cell transplant for Primary central nervous system lymphoma.

adaptation. Due to these factors, there were no disagreements in none of translation steps. The instrument’s application did not require prior training, and the provided instructions were

sufficient for its execution. These characteristics encourage its use in clinical practice, promoting better communication among healthcare professionals.

Study limitations

The interobserver agreement could not be assessed due to an insufficient sample size required for this analysis. We plan to address this reliability analysis in future studies. The score ‘not evaluated’ was identified in a few cases; therefore, it was not possible to assess its influence on the validity and reliability of the NANO scale. The Cronbach’s alpha found in the low-grade glioma group was lower than recommended, and it was not possible to ensure the reliability of the NANO scale in this population. However, we intend to expand our sample size in future studies to provide better data for this specific population.

Conclusion

The NANO scale is a relatively new instrument for neuro-oncology evaluation. Consequently, the validation process is crucial to assess its ability to reliably reflect the patient’s neurological status. This instrument is not limited to one-time evaluations; rather, it can detect neurological changes throughout the clinical course of the disease. The Brazilian Portuguese version of the NANO scale proves to be a reproducible and valid tool for evaluating neuro-oncological patients, demonstrating a strong correlation with the KPS scale and adequate overall internal consistency. However, further studies are required to assess its reliability in patients with low-grade glioma, despite its good correlation with the KPS score.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Institutional Review Board of Sirio-Libanes Hospital. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

References

- Rodrigues DB, Lima LO, Rodrigues Pereira EL, Souza UO, Fernandes de Oliveira M, Lima AM, et al. Epidemiologia das neoplasias intracranianas no Hospital do Servidor Público Estadual de São Paulo: 2010-2012. *Arq Bras Neurocir.* (2014) 33:06–12. doi: 10.1055/s-0038-1626192
- BRASIL. [National Cancer Institute Jose Alencar Gomes da Silva (INCA)]. (2020). [Estimate/2020 – Incidence of Cancer in Brazil]. Rio de Janeiro: [National Cancer Institute Jose Alencar Gomes da Silva (INCA)]. Available at: <https://www.inca.gov.br/sites/ufu.sti.inca.local/files//media/document//estimativa-2020-incidencia-de-cancer-no-brasil.pdf>. (Accessed November 30, 2021).
- Ballman K, Buckner JC, Brown PD, Giannini C, Flynn PJ, LaPlant BR, et al. The relationship between six-month progression-free survival and 12-month overall survival end points for phase II trials in patients with glioblastoma multiforme. *Neuro Oncol.* (2007) 9:29–38. doi: 10.1215/15228517-2006-025
- Eisele SC, Wen PY, Lee EQ. Assessment of brain tumor response: RANO and its offspring. *Curr Treat Options Oncol.* (2016) 17:35. doi: 10.1007/s11864-016-0413-5
- Lin NU, Lee EQ, Aoyama H, Barani IJ, Barboriak DP, Baumert BG, et al. Response assessment criteria for brain metastases: proposal from the RANO group. *Lancet Oncol.* (2015) 16:e270–8. doi: 10.1016/S1470-2045(15)70057-4
- Okada H, Weller M, Huang R, Finocchiaro G, Gilbert MR, Wick W, et al. Immunotherapy response assessment in neuro-oncology: a report of the RANO working group. *Lancet Oncol.* (2015) 16:e534–42. doi: 10.1016/S1470-2045(15)00088-1
- Van Den Bent M, Wefel J, Schiff D, Taphoorn M, Jaecle K, Junck L, et al. Response assessment in neuro-oncology (a report of the RANO group): assessment of outcome in trials of diffuse low-grade gliomas. *Lancet Oncol.* (2011) 12:583–93. doi: 10.1016/S1470-2045(11)70057-2
- Karnofsky DA, Burchenal JH, Armistead GC, Southam CM, Bernstein JL, Craver LF, et al. Triethylene melamine in the treatment of neoplastic disease: a compound with nitrogen-mustard-like activity suitable for Oral and intravenous use. *AMA Arch Intern Med.* (1951) 87:477–516. doi: 10.1001/archinte.1951.03810040002001

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Conflict of interest

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9. Orr ST, Aisner J. Performance status assessment among oncology patients: a review. *Cancer Treat Rep.* (1986) 70:1423–9.
10. Nayak L, DeAngelis LM, Brandes AA, Peereboom DM, Galanis E, Lin NU, et al. The neurologic assessment in neuro-oncology (NANO) scale: a tool to assess neurologic function for integration into the response assessment in neuro-oncology (RANO) criteria. *Neuro Oncol.* (2017) 19:625–35. doi: 10.1093/neuonc/nox029
11. Wen PY, Norden AD, Drappatz J, Quant E. Response assessment challenges in clinical trials of gliomas. *Curr Oncol Rep.* (2010) 12:68–75. doi: 10.1007/s11912-009-0078-3
12. Pérez-Larraya JG, Lahutte M, Petirena G, Reyes-Botero G, González-Aguilar A, Houillier C, et al. Response assessment in recurrent glioblastoma treated with irinotecan-bevacizumab: comparative analysis of the Macdonald, RECIST, RANO, and RECIST F criteria. *Neuro Oncol.* (2012) 14:667–73. doi: 10.1093/neuonc/nos070
13. Gunawan PY, Islam AA, July J, Patellongi I, Nasrum M, Aninditha T. Karnofsky performance scale and neurological assessment of neuro-oncology scale as early predictor in glioma. *Asian Pac J Cancer Prev.* (2020) 21:3387–92. doi: 10.31557/APJCP.2020.21.11.3387
14. Kalasauskas D, Keric N, Ajaj SA, Von Cube L, Ringel F, Renovanz M. Psychological burden in meningioma patients under a wait-and-watch strategy and after complete resection is high—results of a prospective single center study. *Cancers.* (2020) 12:3503. doi: 10.3390/cancers12123503
15. Nayak L, Molinaro AM, Peters K, Clarke JL, Jordan JT, de Groot J, et al. Randomized phase II and biomarker study of pembrolizumab plus bevacizumab versus pembrolizumab alone for patients with recurrent glioblastoma. *Clin Cancer Res.* (2021) 27:1048–57. doi: 10.1158/1078-0432.CCR-20-2500
16. Rahman MA, Brekke J, Arnesen V, Hannisdal MH, Navarro AG, Waha A, et al. Sequential bortezomib and temozolomide treatment promotes immunological responses in glioblastoma patients with positive clinical outcomes: a phase 1B study. *Immun Inflamm Dis.* (2020) 8:342–59. doi: 10.1002/iid3.315
17. Therkelsen KE, Schaff LR, Nandakumar S, Omuro AMP, DeAngelis L, Grommes C. Long-term outcomes in primary CNS lymphoma after R-MVP and high-dose chemotherapy with autologous hematopoietic stem cell transplant. *Neurology.* (2023) 101:e710–6. doi: 10.1212/WNL.0000000000207490
18. Heiland DH, Haaker G, Watzlawick R, Delev D, Masalha W, Franco P, et al. One decade of glioblastoma multiforme surgery in 342 elderly patients: what have we learned? *J Neuro Oncol.* (2018) 140:385–91. doi: 10.1007/s11060-018-2964-8
19. Kasper J, Wende T, Fehrenbach MK, Wilhelmy F, Jähne K, Frydrychowicz C, et al. The prognostic value of NANO scale assessment in IDH-wild-type glioblastoma patients. *Front Oncol.* (2021) 11:790458. doi: 10.3389/fonc.2021.790458
20. Kong NW, Gibb WR, Badhe S, Liu BP, Tate MC. Plasticity of the primary motor cortex in patients with primary brain tumors. *Neural Plast.* (2020) 2020:1–9. doi: 10.1155/2020/3648517
21. Lee J, Park SH, Kim YZ. Prognostic evaluation of neurological assessment of the neuro-oncology scale in glioblastoma patients. *Brain Tumor Res Treat.* (2018) 6:22–30. doi: 10.14791/btrt.2018.6.e1
22. Steindl A, Leitner J, Schwarz M, Nenning KH, Asenbaum U, Mayer S, et al. Sarcopenia in neurological patients: standard values for temporal muscle thickness and muscle strength evaluation. *J Clin Med.* (2020) 9:1272. doi: 10.3390/jcm9051272
23. Ung TH, Ney DE, Damek D, Rusthoven CG, Youssef AS, Lillehei KO, et al. The neurologic assessment in neuro-oncology (NANO) scale as an assessment tool for survival in patients with primary glioblastoma. *Neurosurgery.* (2019) 84:687–95. doi: 10.1093/neuros/nyy098
24. Kalasauskas D, Keric N, Abu Ajaj S, von Cube L, Ringel F, Renovanz M. Distress and quality of life do not change over time in patients with operated and conservatively managed intracranial meningioma. *Acta Neurochir.* (2021) 163:3417–24. doi: 10.1007/s00701-021-05004-w
25. Souza AC, de Alexandre NMC, Guirardello E, de B, Souza AC, de Alexandre NMC, et al. Psychometric properties in instruments evaluation of reliability and validity. *Epidemiologia e Serviços de Saúde.* (2017) 26:649–659. doi: 10.5123/S1679-49742017000300022
26. Steindl A, Yadavalli S, Gruber KA, Seiwald M, Gatterbauer B, Dieckmann K, et al. Neurological symptom burden impacts survival prognosis in patients with newly diagnosed non-small cell lung cancer brain metastases. *Cancer.* (2020) 126. doi: 10.1002/cncr.33085