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| RESEARCH ARTICLE

Correlation between Response Assessment in Neuro-Oncology (RANO) Criteria and Clinical Outcome in Patients with Brain Tumor

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| ABSTRACT
Response assessment in neuro-oncology (RANO) criteria was established to improve the assessment of tumor response and provide guidance on the assessment of response and endpoints in neuro-oncology clinical trials. Neurologic assessment in neuro-oncology (NANO) scale is an instrument used for assessing neurological function objectively and practical in intracranial tumor patients. This study aimed to determine the association between RANO criteria with clinical outcome measured by NANO scale in intracranial tumors patients. There were 36 intracranial tumor patients that were studied in Haji Adam Malik General Hospital Medan. The RANO criteria were obtained by comparing the size of the enhanced lesion using Computed Tomography (CT) scan within an interval of a minimum of four weeks of treatment. NANO scale is a quantifiable evaluation of nine relevant neurologic domains based on examination. The NANO scale included gait, strength, ataxia, sensation, visual fields, facial strength, language, level of consciousness, and behavior as assessed domains from the medical record. We analyzed the correlation between the RANO criteria and NANO scale score using the Spearman correlation test. There were 19 males and 17 females. The mean age was 45.22±9.68 years. There were 20 patients (55.6%) with meningioma, 11 patients (30.6%) with glioma, 3 patients (8.3%) with brain metastase, and 2 patients (5.6%) with craniopharyngioma. The mean NANO scale scores for stable and progressive RANO criteria were 4.29±2.02 and 7.88±2.99, respectively. There was a significant correlation between RANO criteria and NANO scale score in patients with intracranial tumor ($r = 0.468$; $p = 0.004$). Patients with stable RANO had lower NANO scale scores indicating better response to treatment and clinical outcome.

| KEYWORDS
Intracranial tumor, RANO criteria, NANO scale

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1. Introduction

A brain tumor is an abnormal mass of tissue where cells grow and divide uncontrollably by the mechanisms that usually control normal cells. It is classified into primary brain tumor and metastatic brain tumor.[1] The incidence of brain tumor has continued to increase over the past decade in several countries.[2] The worldwide incidence of malignant brain tumor based on standard world population figures is 3.4 per 100.000 population. The mortality rate is 4.25 per 100.000 population per year, where mortality is higher in men. In the United States, the incidence of malignant and benign brain tumor is 21.42 per 100.000 population per year, i.e. 7.25 per 100.000 population for a malignant brain tumor, 14.17 per 100.000 population per year for a benign brain tumor.[3] A hospital-based study in North Sumatra showed no significant difference in the proportion of brain tumor according to gender, which was 50.7% and 49.3% for males and females, respectively. [4]

Brain tumor is the second leading cause of death from all cancer in men aged 20-39 years. In addition, brain tumor is the fifth leading cause of death for all cancer patients in women aged 20-39 years. One of the main causes of morbidity and mortality in brain tumor patients is the development of uncontrolled cerebral edema, which causes cerebral herniation.[5] Available treatment options, including surgery, radiation therapy and chemotherapy. Diagnosis of a brain tumor at an early stage has become an

important topic of research recently. Detection of tumor at an early stage of primary treatment increases the patient's survival rate.[6]

Over the past decade, there has been a growing interest in how to better assess the response of treatment in neuro-oncology. The predominant method is by measuring contrast-enhancing conventional T1-weighted MRI according to MacDonald criteria. The Response Assessment in Neuro-oncology (RANO) working group was established with the aim of improving the assessment of brain tumor response to therapy, particularly in the context of clinical trials. It was mainly developed to overcome the challenges of previous criteria that lack guidance regarding pseudoprogression, pseudoresponse, and nonenhancing tumor progression. This criterion has now been widely used in many areas of neurooncology, including gliomas, brain metastases, meningioma and other brain tumors. [7]

The RANO criteria include clinical status in the determination of progression, but there is no quantifiable measure to determine this. The Neurologic Assessment in Neuro-Oncology (NANO) scale was originally created to address this challenge and provide an instrument that can objectively and practically assesses neurological function in patients with a brain tumor. The NANO Scale assesses the nine domains of neurologic function based on the most common clinical findings in patients with brain tumors. In addition to assessing disease progression, this scale can also be used to predict the patient's survival rate. The NANO Scale assesses nine major brain domains that are closely related to the location of brain tumors in the supratentorial, infratentorial, and brainstem. These domains are gait, motor strength, upper extremity, ataxia, sensory, visual field, facial muscle strength, language, level of consciousness, and behavior. This examination can be performed at the time of initial diagnosis and subsequent routine examinations.[8] Studies about the role of the NANO scale as a predictor for prognosis of brain tumor are still limited, especially in our clinical setting. This study aimed to determine the association between the RANO criteria and the clinical outcome of brain tumor according to the NANO Scale.

2. Method

2.1 Subjects and Samples

This study was a descriptive analytic with a cross-sectional data method on secondary data obtained from medical records in Adam Malik General Hospital restropectively. Subjects were taken from the population of patients with intracranial tumors who were treated in the Neurology ward in Adam Malik General Hospital. The determination of subjects was carried out according to the consecutive non-random sampling method. Samples were taken from 36 patients who were included in the inclusion criteria. Inclusion criteria were patients who had been diagnosed with an intracranial tumor with head ct scan iv contrast, intracranial tumor patients who had been in therapy for at least four weeks, and complete medical records for all the study. Exclusion criteria were age less than 18 years old, patients, with sepsis, kidney failure, heart failure, and death patients.

2.2 Study Design

This study is analytic descriptive with a cross-sectional data collection method without treatment in secondary data sources obtained from all intracranial tumor patients treated at H. Adam Mallik General Hospital Medan for the period of time 1st January 2020-31st December 2020. The NANO scale is a simple neurological assessment conducted and reported by physicians who evaluate the patient in nine domains: gait, strength, upper extremity ataxia, sensation, visual fields, facial strength, language, level of consciousness, and behavior. Each domain contains a score from 0 to 3 or 0 to 2, depending on the domain, with higher scores indicating worse neurologic function (Table 1).[9]

Table 1. Neurologic Assessment in Neuro-Oncology (NANO) Scale

Domain	Nilai	Fungsi
Gait	0	Normal
	1	Abnormal but walks without assistance
	2	Abnormal and requires assistance (companion, cane, walker, etc.)
	3	Unable to walk
Strength	0	Normal
	1	Movement present but decreased against resistance
	2	Movement present but none against resistance
	3	No Movement
Ataxia	0	Able to finger to nose touch without difficulty
(upper extremity)	1	Able to finger to nose touch but difficult
	2	Unable to finger to nose touch
Sensation	0	Normal
	1	Decreased but aware of sensory modality
	2	Unaware of sensory modality
Visual fields	0	Normal
	1	Inconsistent or equivocal partial hemianopsia (≥quadrantopsia)
	2	Consistent or unequivocal partial hemianopsia ((≥quadrantopsia)
	3	Complete hemianopsia
Facial strength	0	Normal
	1	Mild/moderate weakness
	2	Severe facial weakness
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)
Level of consciousness	0	Normal
	1	Drowsy (easily arousable)
	2	Somnolent (difficult to arouse)
	3	Unarouseable/coma
Behavior	0	Normal
	1	Mild/moderate alteration
	2	Severe alteration

Response Assessment in Neuro-oncology (RANO) criteria is similar to McDonald's criteria, which uses two-dimensional measurements of intracranial tumor lesion, but RANO includes a definition of patient progression, i.e. 25% in the result of the perpendicular diameter measurement compared to the baseline measurement or the best response. Definition of a lesion that can be defined as measurable, i.e. two perpendicular diameters measurement at least 10 mm, visible on two or more slices, at least 5 mm apart, and allowed for up to five target lesions, and these lesions were assessed for at least four weeks after therapy.[10,12]

Table 2. Tumor Response to Therapy

	Stable	Progression
Size of target lesion	<25-50%	≥ 25%
New lesion	None	Exist
Clinical data	Stable/Improvement	Worsening

2.3 Statistical Analysis

The data were analyzed statistically using Windows SPSS (Statistical Product and Science Service) computer program version 22.0 to analyze the relationship between the RANO criteria and the clinical outcome of the intracranial tumor using the Spearman correlation test.

3. Results

Subjects were patients with intracranial tumors who were treated at H. Adam Malik Hospital Medan for the period 1st January 2020 – 31st December 2020 and who met the inclusion criteria of the study. The complete characteristics of the study are presented in table 1.

The demographic characteristics of 36 subjects had a mean age of 45,22±9,68. The gender of subjects consisted of males with 19 subjects (52,8%) and females with 17 subjects (47,2). The education level of subjects was the senior high school with 19 subjects (52,8%), a bachelor's with 13 subjects (36,1%) and junior high school with 4 subjects (11,1%). The occupation of the subjects was mostly housewives with 12 subjects (33,3%) and at least college student with 1 subject (2,8%). The characteristics of intracranial tumor types were meningioma with 20 subjects (55,6%), glioma with 11 subjects (30,6%), brain metastases with 3 subjects (8,3%) and craniopharyngioma with 2 subjects (5,6%)/ Characteristics of the subject's stable NANO Scale with a mean value of 4,29±2,02 and a progressive subject's NANO Scale of 7,88±2,99.

Table 3. Demographic Characteristics of Subjects

Characteristics	Mean	n(36)	Percentage (%)
Age (years)	45,22±9,68		
Sex			
• Men		19	52,8
• Women		17	47,2
Education			
• Junior High School		4	11,1
• Senior High School		19	52,8
• Bachelor		13	36,1
Occupation			
• Housewives		12	33,3
• Government Employees		11	30,6
• Entrepreneur		9	25,0
• Farmer		3	8,3
• College Student		1	2,8
Intracranial Tumor Type			
• Meningioma		20	55,6
• Glioma		11	30,6
• Brain metastases		3	8,3
• Craniopharyngioma		2	5,6

Table 4. Correlation RANO Criteria with NANO Scale

	NANO Scale	
	r	**p**
RANO Criteria	0,468	0,004

Spearman Correlation Test

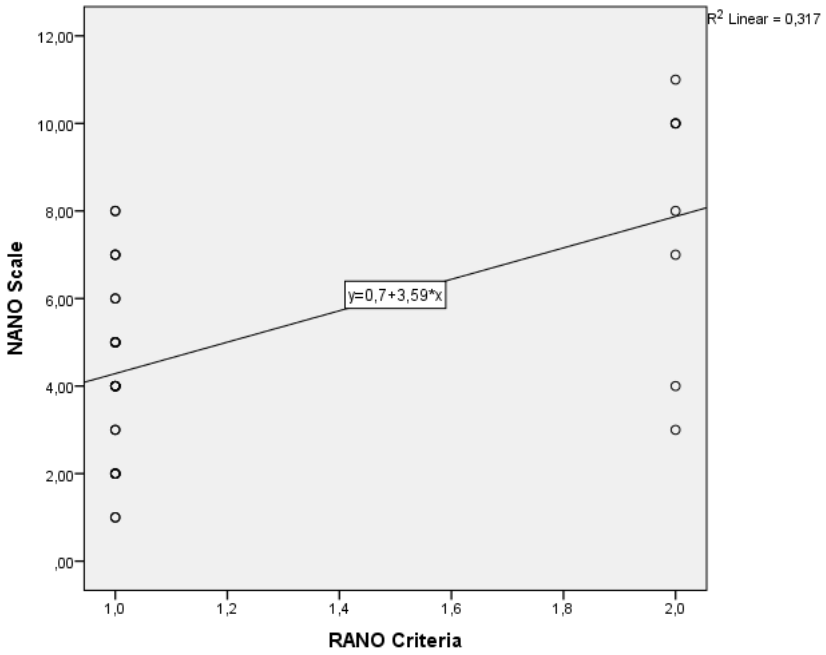

Figure 1. Correlation between RANO Criteria and NANO Scale

Table 5. Comparison of RANO Criteria with NANO Scale

Variable		RANO Criteria		*p*
		n	Mean	
NANO	Stable	28	4,2857	0,0001
	Progressive	8	7,8750	

Independent Sample T-Test

There is a significant correlation between RANO criteria and the NANO Scale with a p-value of 0,004 (p<0,05) with a positive correlation and a moderate strength of correlation with a value of r=0,468. This can be seen in table 4.

There is a significant comparison in RANO criteria between the stable NANO scale with progressive NANO scale with a p-value of 0,0001 (p<0,005). This can be seen in table 5.

4. Discussion and conclusion

The RANO criteria developed by the Response Assessment in Neuro-oncology working group aim to improve assessment and standardize various criteria for assessing treatment response. This criterion is an improvement of the McDonald's criteria that have previously been used. At first, the RANO criteria were developed for high grade glioma (HGG). Along with its development, RANO has also been developed for the assessment of other intracranial tumors, such as brain metastases, leptomeningeal metastases, leptomeningeal metastases, spinal tumor, pediatric intracranial tumor, and meningioma.

Similar to McDonald's, the RANO criteria continue to use two dimensional measurements, but this criterion includes the definition of patients progression, i.e. 25% in results of perpendicular diameter measurement compared to the baseline measurement of the best response, definition of a lesion that can be measurable is two perpendicular diameters with the measurement at least 10 mm, seen in two or more slice, at least 5 mm apart, and allowed for up to five target lesions.[11] The RANO component is a specific lesion that is evaluated serially with a cross-sectional enhancement that is used to determine the size of lesion that enhances contrast on CT or MRI; minimum size lesion with 10 mm diameter for which volumetric anatomic assessment was assessed for at least four weeks.[12] The RANO criteria uses a bidirectional measurement of contrast enhancement tumors; bidimensional volume measurement is carried out by determining the response and progression that shows a correlation with benefits life sustainability or time to respond to therapy.[13] Therapy given to patients with intracranial tumor consists of the use of corticosteroid, chemotherapy, radiotherapy, chemoradiotherapy, and surgical therapy. The corticosteroids used were dexamethasone and chemotherapy using temozolomide or bevacizumab.[7] The Response Assessment Committee in Neuro-Oncology (RANO) was established for endpoint assessment criteria in neuro-oncology in order to streamline the assessment of the new therapy and uniform the assessment. RANO was first published in 2010; the RANO criteria were widely adapted and used generally. The

application of the RANO criteria is used to assess the results of clinical data stronger, which can be used as an assessment of therapeutic sufficiency.[14]

The Neurologic Assessment in Neuro-Oncology (NANO) Scale can assess neurological function objectively and practically so that it can be used by neurologists and other health workers. The NANO Scale assesses the nine domains of neurologic function based on the most common clinical findings in patients with a brain tumor. In addition to being used to assess the progress of patients with glioblastoma multiforme (GBM), the NANO Scale is also able to predict patients' survival rates. The NANO Scale can be an alternative for assessing the clinical outcome of GBM patients compared to the Karnofsky Performance Status Scale (KPS) and the Eastern Cooperative Oncology Group (ECOG). NANO Scale is able to eliminate subjective bias in clinical evaluation able to evaluate clinical changes and neurological function objectively in glioma patients.[15]

The NANO Scale provides a more detailed and objective assessment of neurologic function than other assessments that are used to predict the prognosis of glioblastoma patients, especially regarding the time of disease progression.[13] Although RANO was initially focused on the assessment of gliomas. The RANO criteria were expanded to be used in other neuro-oncological cases, including brain metastases, meningioma, pediatric tumor, spinal metastases, and other leptomeningeal diseases.[14]

The RANO criteria and the McDonald criteria define the radiological parameters for classifying the therapeutic outcome in patients with malignant glioma and, in particular, the clinical status that should be combined and prioritized for the overall assessment. The standardized measures needed to measure neurological function can provide more effective results for all response assessments in the field of neuro-oncology. For example, some patients may deteriorate neurologically while the radiographic findings are stable; or the image may be found to be deteriorating while the patient is clinically improving. Response Assessment in Neuro-oncology (RANO) was developed to more reliably standardize radiographic parameters used to assess outcome in patients with high-grade glioma, low-grade glioma, or brain metastases.[15]

From the literature, it was found that the NANO Scale can be used in conjunction with the RANO criteria during clinical therapy to assess the patient's response to therapy. This study found there is a correlation between RANO criteria and clinical outcome in intracranial tumor patients that were assessed with NANO Scale. Patients with stable RANO criteria may be able to demonstrate a low NANO Scale, and also, patients with a low NANO Scale have an increment in survival rate and could be predicting the tolerance to therapy. The finding in this study is in agreement with Nayak et al. study in 2017. NANO Scale provides an objective clinician-reported outcome of neurologic function with a high inter-observer agreement. The NANO Scale is designed to combine with a radiographic assessment to provide an overall assessment of outcome for neuro-oncology patients in clinical trials and daily practice.[16] This study has a certain limitation being retrospective in nature. However, the conclusion drawn from our study needs further validation through prospective and randomized clinical trials in multiple institutes. Continued research and development of specific planned next steps include incorporation of the NANO scale in conjunction with RANO criteria in a clinical trial to prospectively assess its validity and utility relative to radiographic and overall outcome are needed.

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Informed consent: No participant's informed consent was necessary for our retrospective study.

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