

ECOG or Karnofsky Performance Status to Assess Functionality in Glioblastoma Patients Among Different Observers

Claudia Panciroli^{1*}, Anna Estival², Giuseppe Lucente³, Jose Maria Velarde², Roser Garcia³, Laia Vilà², Sira Domenech⁴, Salvador Villà⁵, Carmen Balaña²

¹Clinical Investigation Unit, Institute Català d'Oncologia, University Hospital Germans Trias i Pujol, Spain

²Medical Oncology Service, Institute Català d'Oncologia, University Hospital Germans Trias i Pujol, Spain

³Department of Neuroscience, University Hospital Germans Trias i Pujol, Carretera del Canyet s/n, 08916 Badalona (Barcelona), Spain

⁴Institute Diagnostic per l'Imatge, University Hospital Germans Trias i Pujol, Carretera del Canyet s/n, Spain

⁵Radiation Oncology Service, Institute Català d'Oncologia University Hospital Germans Trias i Pujol, Spain

Abstract

Purpose: Glioblastoma (GB) patients usually have symptoms that affect their functional status, and medical staff, as well as the patients and their caregivers, might have different perceptions about it. The performance status is important to establish a patient's survival prediction and treatment decisions. This study was aimed to explore whether health care providers, patients, and caregivers have a common perception of patients' functional statuses and to investigate in further studies whether the functional scales used in oncology clinical practice are objective tools to evaluate brain tumour patients.

Methods: GB patients treated at our Neuro-Oncology Unit were evaluated once using Eastern Cooperative Oncology Group Performance Status (ECOG) and Karnofsky Performance Status (KPS) by a medical oncologist (MO), an independent investigator (II), the patient and the patient's main caregiver.

Results: Fifty patients were enrolled. Concordance in KPS evaluation among the four observers was low (Fleiss' Kappa=0.354; $p < 0.001$) and moderate in ECOG one (Fleiss' K=0.424; $p < 0.001$). Pairing the observers, the concordance between the MO and II was strong (KPS Cohen's Kappa=0.731; $p < 0.001$, ECOG Cohen's Kappa=0.741; $p = 0.001$), whereas it was poor between the patient and MO (KPS Cohen's Kappa=0.250; $p = 0.007$, ECOG Cohen's Kappa=0.241; $p = 0.009$) and between the caregiver and MO (KPS Cohen's Kappa=0.350; $p < 0.001$, ECOG Cohen's Kappa=0.346; $p = 0.000$).

Conclusion: Concordance among the observers was poor or moderate according to the functional scale used. Particularly, caregivers' perception of the patients' functional status was frequently worse than that of the professionals.

Keywords: Karnofsky performance status; ECOG performance status; Glioblastoma patients; Caregivers

Introduction

Patients with glioblastoma (GB) usually have symptoms at diagnosis that affect their daily life, and the natural history of the disease is marked by progressive neurological and functional deterioration [1,2]. Changes in behaviour, emotions, functional status and neurocognitive functions impact not only their daily life but also that of their families [3,4]. The family and, especially, the main caregiver play an important role in this process because they usually must take care of the patient constantly in most cases [5].

Evaluation of patients at oncological visits is usually performed using the functional cancer scales Karnofsky Performance Status (KPS) [1,6] or Eastern Cooperative Oncology Group Performance Status (ECOG), the Barthel Index (BI), functional scale for daily activities [7,8], and the Mini-Mental State Examination (MMSE). The latter scale is a quick and simple cognitive test first described for dementia and then used for gliomas to measure a patient's cognitive impairments [9,10], while KPS and ECOG represent widespread metric scores to determine physical functionality despite the tumour, both having predictive value for every cancer [11]. These scales have also shown their prognostic value in neuro-oncology when performed at the first patient assessment [12], as was described by the Radiation Oncology Group (RTOG) with the Recursive Partitioning Analysis (RPA) scale based on performance status, age, type of surgery and altered cognitive status, subsequently being replaced with the MMSE by the European Organization and Research on Cancer Treatment (EORTC) [13].

Thereafter, EORTC confirmed the value of these prognostic subclasses on the first-line trial that established temozolomide concurrent with radiotherapy and then as adjuvant treatment, as the standard treatment in newly diagnosed GB [14-17].

Several factors, including age, performance status, tumour grade, histology and number of prior progressions, are strong predictors of survival in neuro-oncology [18,19]. Of these factors, the performance status score, either assessed by the KPS or ECOG scoring system, is consistently a robust prognostic factor to approach therapeutic decisions [20]. Thus, physical performance plays an integral role in the individualization of treatments and disease in malignant glioma [21]. However, these scoring systems fail to fully characterize physical functioning and lack sufficient sensitivity to accurately discriminate among individuals with good performance status (e.g., KPS>70; ECOG

***Corresponding author:** Claudia Panciroli, Clinical Investigation Unit, Institute Català d'Oncologia, University Hospital Germans Trias i Pujol, Spain, Tel: +34 93 497 8925; Fax: +34 93 497 8950; E-mail: cpanciroli@iconcologia.net; claudiapanciroli@gmail.com

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0 or 1) [6,22]. As a matter of fact, we believe that the performance status scales are not always fully precise to detect the complete range of symptoms due to a neuro-oncologic disease that impacts on the global functioning of patients and their families [23].

In our daily activity, we frequently observe considerable differences in disease perception among healthcare providers, patients, and caregivers concerning the patient’s functional status. These aspects have not yet been examined in depth. This leads to different values recorded for the same patient by different professionals at the same visit, creating confusion when establishing a patient’s survival prediction and treatment decision making.

This study was aimed to evaluate patients with the previously described scales to test their reproducibility when administered by two different trained professionals with a parallel evaluation also conducted by the patient and the main caregiver. The aim was to test the concordance of the patient’s functional status, as assessed by both KPS and ECOG, among the four observers, to investigate in further studies if the scales used in oncology practice are an effective tool to provide an objective evaluation of functionality in brain tumour patients [22], when establishing their survival prediction and oncology treatment.

Methods

Population

This prospective study was performed in patients who visited the Neuro-Oncology Unit (UNO) of Catalan Institute of Oncology (ICO)-Badalona. Patients were asked to participate in our study, and we informed them that the results would not interfere with medical treatments and clinical visits. Information about how to apply the KPS and ECOG assessments was also given to participants. Subjects were eligible for the study if they had a diagnosis of GB at any stage of the disease, were accompanied by the main caregiver and could perform a self-assessment of KPS/ECOG. The main caregiver was defined as the person taking care of the patient’s needs most of the time. The investigators were the medical oncologist (MO) taking care of the patient’s cancer treatment and a PhD student trained in neurocognitive impairments, as an independent investigator (II).

Study design

Patients were evaluated once with KPS/ECOG during the same oncological visit. MMSE, BI and a neurological examination were also performed. Both MMSE and BI were administered to every patient by the II, while KPS/ECOG was performed by the MO, II, patient and caregiver. We used the MMSE to evaluate neurocognitive impairments, the BI to identify patient’s grade of functional independency, and KPS/ECOG to assess the functional status (Table 1). The participants were asked to provide information about their socio-demographic background through an interview. We classified jobs as “qualified” if the work required higher skills or training previously acquired (i.e., journalist or engineer) and “non-qualified” if the work did not require a skill to be performed (i.e., maid or workman). We classified the educational level as high, middle or low if the participants attended university, secondary school or primary school, respectively. We registered the disease’s characteristics, tumour location, oncological treatment scheme and concomitant medications such as antiepileptics (AEDs), anxiolytics, antidepressants, opioids, and corticosteroids. All variables were recorded. To perform our analysis of the concordance between two observers, we compared the MO’s evaluation with that of the patient and caregiver because the MO is the professional who makes the final decisions about the patient’s care and because of the quite high concordance between the MO and II.

Karnofsky Performance Status (KPS)	Eastern Cooperative Oncology Group Performance Status (ECOG)	Description
100	0	Fully active, able to carry on all pre-disease performance without restrictions.
80-90	1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg., office work, house work.
60-70	2	Ambulatory and capable of all self-care but unable to carry out the previous job. Up and about more than 50% of waking hours.
40-50	3	Ambulatory and capable of all self-care but unable to carry out the previous job. Up and about more than 50% of waking hours.
20-30	4	Completely disabled. Cannot carry on self-care. Totally confined to bed or chair.

Table 1: Description of Karnofsky Performance Status (KPS) and Eastern Cooperative Oncology Group Performance Status (ECOG) scale measures.

Variables	Patients	Caregivers
	n=50	n=50
Sex		
Male	25 (50%)	23 (46%)
Female	25 (50%)	27 (54%)
Age		
<50	12 (24%)	16 (32%)
≥ 50	38 (76%)	34 (68%)
Handedness		
Right	48 (96%)	50 (100%)
Left	2 (4%)	0 (0%)
Educational level		
None	3 (6%)	2 (4%)
Low	30 (60%)	34 (68%)
Middle	9 (18%)	5 (10%)
High	7 (14%)	9 (18%)
Not reported	1 (2%)	0 (0%)
Job		
Non-qualified	41 (82%)	35 (70%)
Qualified	8 (16%)	15 (30%)
Not reported	1 (2%)	0 (0%)
Tumor characteristics		
Location		
Right	25 (50%)	NA
Left	24 (48%)	
Bilateral	1 (2%)	
Lobe		
Frontal	28 (56%)	NA
Others	22 (44%)	
One	38 (76%)	
More	10 (20%)	
Central	2 (4%)	
Treatment		
Active	40 (80%)	NA
Non-active	10 (20%)	
Support		
Yes	47 (94%)	NA
No	3 (6%)	
Medications		
AEDs	33 (66%)	0 (0%)
Dexamethasone	20(40%)	0 (0%)
<4 mg	9(45%)	--

≥ 4 mg to <8 mg	5(25%)	--
≥ 8 mg	6(30%)	--
Antidepressants drugs	9 (18%)	5 (10%)
Anxiolytic drugs	10 (20%)	8 (16%)
Psycho-stimulants	1 (2%)	0 (0%)
Opioids	2 (4%)	0 (0%)

Note: Abbreviation: AEDs: Anti-Epileptic Drugs; NA: Not Applicable.

Table 2: Patients and care givers characteristics.

n=50	Min	Max	Median	IQR
BI	15	100	95	25
MMSE	4	30	25	7
Patients' KPS	40	100	70	30
Caregivers' KPS	30	100	70	40
MO's KPS	40	100	80	30
II's KPS	40	90	70	30
Patients' ECOG	0	3	2	1
Caregivers' ECOG	0	3	2	2
MO's ECOG	0	3	1	1
II's ECOG	1	3	2	1

Note: Abbreviations: BI: Barthel Index; MMSE: Mini Mental State Examination; KPS: Karnofsky Performance Status; ECOG: Eastern Cooperative Oncology Group Performance Status; MO: Medical Oncologist; II: Independent Investigator; IQR: Interquartile Range.

Table 3: Scales' summary descriptive statistics.

n=50	K	p
KPS	0.354	<0.001
ECOG	0.424	<0.001

Note: Abbreviations: KPS: Karnofsky Performance Status; ECOG: Eastern Cooperative Oncology Group Performance Status; K=Fleiss' Kappa; p=p-value.

a) Among the observers.

n=50	K	p
MO vs. II KPS scores	0.731	<0.001
Patient vs. MO KPS scores	0.25	0.007
Caregiver vs. MO KPS scores	0.35	<0.001
MO vs. II ECOG scores	0.741	0
Patient vs. MO ECOG scores	0.241	0.009
Caregiver vs. MO ECOG scores	0.346	0

Note: Abbreviations: KPS: Karnofsky Performance Status; ECOG: Eastern Cooperative Oncology Group; MO: Medical Oncologist; II: Independent Investigator; K=Cohen' Kappa; p=p value.

b) Pairing the observers.

	KPS	100	90	80	70	60	50	40	30
n=50	ECOG	0	1	2	3	4			
	MO's scores	1	15	12	4	10	5	3	0
	II's scores	0	13	11	7	10	5	4	0
	Patient's score	4	10	10	6	11	8	1	0
	Caregivers' score	3	10	8	8	8	8	3	2

c) Distribution of KPS and ECOG scores.

Table 4: Concordance of KPS and ECOG scores **a)** among the observers, and **b)** pairing the observers. **c)** shows the distribution of KPS and ECOG scores.

Statistical Analysis

Statistical analysis was performed using the “Statistical Package for Social Science” (SPSS), version 21.0 and the “R Statistical Programming Language” (R), version 3.1.1. The concordance on the patients' functional status among the four observers was analyzed with

Fleiss' Kappa, using R; while pairing the observers, it was tested with Cohen's Kappa, using SPSS. Cohen's Kappa assesses the concordance only between two raters, whereas Fleiss' weighted Kappa is a robust measure to assess the reliability of agreement between a fixed number of observers, even more than two [24]. That's why in our analysis we used both systems. We considered an almost perfect concordance if Kappa (K) ≥ 0.81, a substantial/strong concordance if K=(0.80-0.61), a moderate concordance if K=(0.60-0.41), a fair/poor concordance if K=(0.40-0.21), a slight agreement if K=(0.20-0.01) and no concordance if K ≤ 0.00 [25]. We also reported the MO's and caregiver's KPS score distribution estimated using chi-squared test. A p value<0.05 was considered significant.

Results

Patient characteristics

Fifty patients with GB and a caregiver for each one was enrolled in the study. The demographic and clinical characteristics are shown in Table 2. Seventy-six percent of patients were aged ≥ 50 years, 50% were males, and 50% were females. The age cut-off was determined according to RPA. Almost all patients were right-handed (96%), and most chose to receive family care (94%). Eighty-two percent of patients had a non-qualified job, and 60% had a low level of education. The predominant location of the tumour lesion was the frontal lobe (56%), and the GB was limited usually to only one lobe (76%).

Concerning GB involving more than one lobe (20%), 69% of patients had a frontal lobe lesion. There were no important differences in terms of the dominant hemisphere involvement (right, 50%; left, 48%), and a bilateral affection was present in one patient (2%). Ongoing cancer treatments (80%) were the first line of treatment in 46% of patients (temozolomide concomitant with radiation or as adjuvant treatment), the second line in 10% and the third line in 24% (bevacizumab, irinotecan or fotemustine). The remaining patients (20%) received the control (without treatment). Concomitant medications were AEDs in 66% of patients, corticosteroids in 40%, antidepressants in 18%, anxiolytics in 20%, psycho-stimulants in 2%, and opioids in 4%.

Statistical results of performance status' concordance

The different summary descriptive statistics are reported in Table 3 (n=50). We analysed the four observers' report measures using KPS (Tables 4a-4c) (Figures 1a and 1b), we found a fair concordance (Fleiss' K=0.354; p<0.001), while moderate when analyzing ECOG scores (Fleiss' K=0.424; p<0.001). Furthermore, the concordance between health care providers (MO and II) was strong (KPS Cohen's Kappa=0.731; p<0.001. ECOG Cohen's Kappa=0.741; p=0.001), whereas it was poor between the patient and the MO (KPS Cohen's Kappa=0.250; p=0.007. ECOG Cohen's Kappa=0.241; p=0.009) and between the caregiver and the MO (KPS Cohen's Kappa=0.350; p<0.001. ECOG Cohen's Kappa=0.346; p=0.000). Especially, the caregiver's perception of patients' functionality was mostly worse than the one perceived by the MO (p=0.000). Figures 2a and 2b shows that in most cases, the MO scores are higher than the caregivers' scores.

Discussion

We tested the assumption of a discrepancy on the perception of patients' functional status among health care professionals, patients and their families in a cohort of GB patients in our daily clinical context. The variability in KPS/ECOG evaluations among the observers is an important issue, as they have a prognostic value in GB patients, and they could also determine the possibility to enroll subjects in clinical

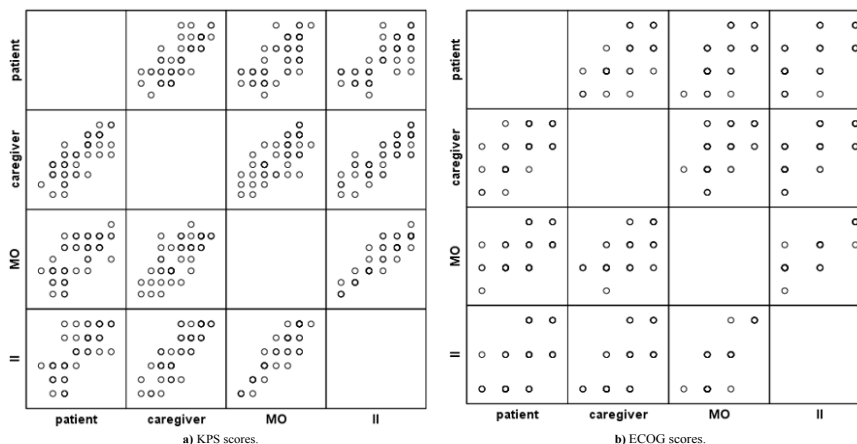


Figure 1: Concordance of a) Karnofsky Performance Status (KPS) scores and b) Eastern Cooperative Oncology Group Performance Status (ECOG) scores among the observers.

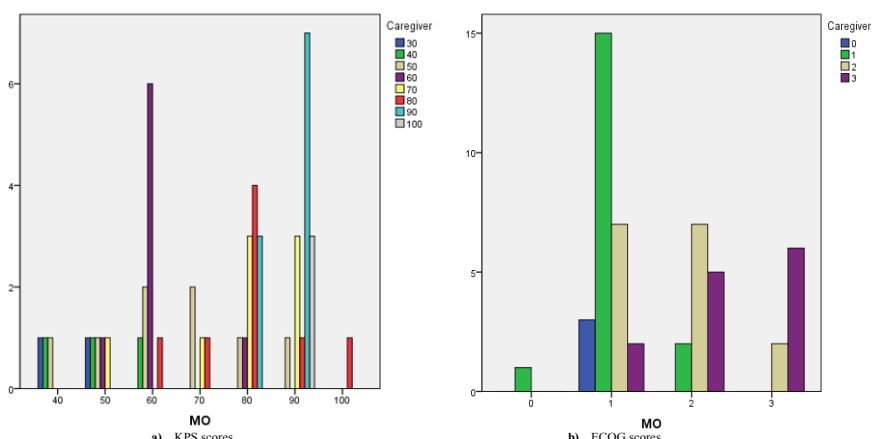


Figure 2: MO's and caregivers' scores regarding their perception of patient's functionality status, assessed by a) Karnofsky Performance Status (KPS) and b) Eastern Cooperative Oncology Group Performance Status (ECOG).

trials, as most of them require an ECOG ≤ 1 or ECOG ≤ 2 (KPS from 100 to 80 or 70) [1]. Further, the performance status is important to establish patients' survival prediction and treatment decisions.

Our study found a different concordance of KPS/ECOG scores depending on who performs the scales' evaluation. KPS' concordance among the four observers was poor. The agreement between the II and MO was strong but fair between MO and the patients. To support the latter finding, we suspect that patients' cognitive impairments or behavioural changes might cause a distorted functional self-perception [23,26]. Additionally, we found that caregivers had frequently a worse patient functional status perception than professionals, and we considered whether the family's overload or burnout aroused by the impaired patient and his/her health condition deterioration could cause the tendency to evaluate worse the patient's functionality [27,28]. The caregiver assessment can serve indeed as adequate proxies for patient reports [4]. Thus, we believe the importance that both assumptions might warrant further investigation.

Both ECOG and KPS assess the patients' ability to perform a job [1]. There is a percentage of cases in which patients do not show any physical impairment that affects their functionality (BI=100%); however, due to their low neurocognitive level, they are unable to carry out their previous job. Thus, their ECOG should be evaluated as

2 and the KPS as 70 rather than 0 and 100, respectively. Specifically, we acknowledge that KPS and ECOG do not consider the cognitive and neurological impairments that can affect, for example, the capacity to perform a qualified job but not a non-qualified job. As a matter of fact, neuro-cognitive impairments are important to consider in a job that requires attention and mental efforts. For this reason, we do believe that the fair concordance among the observers should also be explained by the inadequacy to fully evaluate brain tumour patients with KPS/ECOG, and we highlight that a functional scale adjusted for brain tumour patients is needed.

The main limitation of our study is the limited sample number, which is why concomitant medications, age, educational level, or the lesions' location were not tested as confounding factors. Additionally, we did not record some variables such as neurological impairments, pain severity, stress, burnout, anxiety and depression levels, and no control groups were included. Finally, exploring the agreement among all health care providers involved in patient care, such as radiation oncologists or neurosurgeons, would have also been important to be assessed.

Accordingly, our outcomes suggest that the agreement on the patients' functional status perception among the four observers is fair but higher when using ECOG because the latter scale is shorter

and easier to assess. Therefore, ECOG seems to encompass a wider spectrum of patients' symptoms and to have a better coverage of the caregivers' perception. The cause may be that, in ECOG, there are fewer options, making it easier to score the same.

Medical professionals should carefully screen for the capacity to make treatment decisions concerning brain patients' performance status [1]. Although the KPS was criticized concerning its psychometric characteristics, such as its reliability and insensitivity to neuro-cognitive impairments, it is still the standard functionality tool used in neuro-oncology practice [29]. However, we remark that none of the performance status' scales are perfect to fully evaluate the patient's functionality, as shown by the different concordance values found among patients/caregivers and professionals.

Conclusion

Notwithstanding, conclusion should be taken with caution. We did not perform a detailed study but a very preliminary attempt to explore not only professionals' but also caregivers' and patients' point of view regarding patients' functional status. With this aim, we provided additional information for both clinical practice and the planning of future studies. This is important to consider because the functional scales assume different values depending on who administers them.

Compliance with ethical standards All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

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