Research Article

Validation of a Battery of Neuropsychological Tests for Patients With Metastatic Cancer

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Abstract

This study aimed to investigate the psychometric properties of Trail Making Test (TMT), Continuous Reaction Time (CRT), Finger Tapping Test (FTT), Digit Span Test (DST), and Mini-Mental State Examination (MMSE) in Brazilian patients with metastatic cancer. Cognitive performance of 178 patients with metastatic cancer and 79 controls was assessed using the TMT, CRT, FTT, DST, and MMSE. Discriminant validity, concurrent validity, and reliability (39 patients were retested after 3-7 days) were investigated. Discriminant validity between groups was observed in TMT, DST, and MMSE. Measures of concurrent validity and cognitive performance were positively correlated with physical performance, education level, and better performance on MMSE. Negative correlations were observed between cognitive function, pain, anxiety, and depression. All tests but FTT demonstrated very good reliability. Thus, all neuropsychological tests but FTT showed psychometric properties that permit their use in clinical and research purposes in patients with metastatic cancer.

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Introduction

There is substantial variation regarding the prevalence of cognitive dysfunction in patients with cancer ranging from 10% to 90% (Brant, 2010; Bruera et al., 1992; Centeno, Sanz, & Bruera, 2004; Kurita, Lundorff, de Mattos Pimenta, & Sjøgren, 2009; Kurita et al., 2011). These rates depend on sample characteristics, such as diagnoses, disease stage, tumor stage and site, comorbidities, treatments, measurement tools used, and cognitive domain assessed (Cohen & Armstrong, 2004; Kurita et al., 2011; Sjøgren, 1997). Cognitive dysfunction can interfere with daily living activities, treatment adherence, self-care, and social interaction, and tends to worsen near death (Bruera et al., 1992; Hjermstad, Loge, & Kaasa, 2004).

Generally, cognitive dysfunction is diffuse and includes different domains; however, typically, attention, concentration, visual memory, and mental processing speed dysfunctions occur during the initial phases of cancer (Arcuri, Palladini, Dumas, Lemoignan, & Gagnon, 2015; Kurita et al., 2011), while delirium and dementia are more prevalent at later stages (Cohen & Armstrong, 2004; Hjermstad et al., 2004). Thus, identification of cognitive dysfunction is difficult because it may be subtle. Furthermore, there is a paucity of validated instruments, lack of consensus regarding the best assessment tools, and insufficient professional cognitive assessment training (Arcuri et al., 2015; Kurita et al., 2009; Kurita et al., 2011).

Few studies of patients with metastatic cancer, with the exception of breast cancer, describe patients' cognitive function assessed by multiple, potentially relevant neuropsychological tests (Dutta, 2011; Taillibert, Voillery, & Bernard-Marty, 2007). Moreover, few studies describe these tests' psychometric properties in the population with cancer (Mystakidou, Tsilika, Parpa, Galanos, & Vlahos, 2007; Santos, de Mattos Pimenta, Kurita, Braga, & Sjøgren, 2014). The gold standard tool for evaluation of cognitive dysfunction is the Mini-Mental State Examination (MMSE); however, there are questions about its capacity to identify subtle cognitive dysfunction (Lange et al., 2014; Tombaugh & McIntyre, 1992).

Lack of assessment can result in poor management of cognitive dysfunction, increasing risk of patients' autonomy loss and caregiver burden (Hjermstad et al., 2004). Proper cognitive evaluation of patients with cancer requires a standardized and systematic approach and validated tools to provide easy follow-up and a common language for health care team communication. Patients with cancer may be more vulnerable to cognitive dysfunction due to

a variety of factors (comorbidities, treatment, anxiety, depression, disease stage, use of psychotropic drugs) besides the classical factors (age, schooling, metabolic disorders) that can interfere in several cognitive domains (Cohen & Armstrong, 2004; Kurita et al., 2009; Kurita et al., 2011; Sjøgren, 1997) and, therefore, a battery covering several functions would be useful.

Few studies have described the assessment of cognitive function using a battery of neuropsychological tests in patients with metastatic cancer and evaluated their psychometric properties. Thus, based on the most used tests (Kurita & de Mattos Pimenta, 2008; Kurita, de Mattos Pimenta, Oliveira Júnior, & Caponeiro, 2008; Kurita et al., 2009; Kurita et al., 2011; Sjøgren, 1997), we selected five instruments for cognition evaluation.

Aim

To analyze the psychometric properties of the following neuropsychological tests: Trail Making Test (TMT), Continuous Reaction Time (CRT), Digit Span Test (DST), Finger Tapping Test (FTT), and MMSE among patients with metastatic cancer.

Hypotheses

Hypothesis 1: Tests can discriminate between patients and controls (discriminant validity).

Hypothesis 2: MMSE, DST, and FTT (dominant and nondominant hand) scores are positively correlated with schooling and Karnofsky Performance Status (KPS), and TMT (A and B), CRT, and FTT (difference between hands) are positively correlated with age, pain intensity, anxiety, and depression (convergent validity).

Hypothesis 3: MMSE, DST, and FTT (dominant and nondominant hand) scores are negatively correlated with age, pain intensity, anxiety, and depression and TMT (A and B), CRT, and FTT (difference between hands) scores are negatively correlated with schooling and KPS (divergent validity).

Hypothesis 4: Test performance remains stable over a 3- to 7-day period (reliability).

Method

Sample, Settings, and Procedure

This study was conducted in the chemotherapy department of a São Paulo cancer center, Brazil, from October 2010 to June 2012. Patients were

identified from the chemotherapy appointment list and selected using patients' charts information. The patients were contacted via telephone, provided with information about the study, and asked if they were willing to participate. In case of an affirmative answer, they received additional details at a scheduled appointment. Those who met inclusion criteria and agreed to participate in the study signed an informed consent form.

The selection of the healthy group was independent from the selection of patients. Individuals accompanying patients (family, friends, coworkers, caregivers, or people from the same community or church member) in the ambulatory waiting room were invited to participate in the study as healthy controls. They were not necessarily related to the patients included in the study as they could be accompanying other patients who were not eligible to this study. Those who accepted and met inclusion criteria completed the tests.

Patient inclusion criteria were age between 18 and 65, schooling ≥ 6 years, metastatic cancer, score of $\geq 40\%$ on the KPS, and adequate comprehension and communication abilities in Portuguese language. Patients were excluded if they had central nervous system (CNS) cancer or metastases, upper limb impairments, and visual or hearing deficiencies, which could interfere with testing.

Inclusion criteria for healthy controls were age between 18 and 65, schooling ≥ 6 years, MMSE score >26, no alcohol or drug intake in the last 24 hr, and no history of cancer. Controls were excluded if they had upper limb impairment, visual/hearing deficiencies, psychiatric illness, or a Hospital Anxiety and Depression Scale (HADS) score of >8 for each subtest.

A total of 202 patients were contacted for participation, and 24 patients did not meet inclusion criteria. The final convenience sample consisted of 178 outpatients with metastatic cancer and 79 healthy controls. Participants received instructions, completed sociodemographic and clinical characteristics questionnaires, and were tested in a silent room. All clinical data were collected in the first assessment. The neuropsychological tests were explained and applied in the following order: TMT, CRT, DST, FTT, and MMSE. Average assessment time was approximately 60 min for patients and 40 min for controls. After the first assessment, patients were invited to retake the test within 3 to 7 days. If they accepted, a new appointment was scheduled.

Instruments

Interviews were used to obtain sociodemographic characteristics (age, sex, schooling, income, cohabiting partner), symptom characteristics (presence and intensity of pain rate on a visual numeric scale from 0 to 10; Kumar, 2011), and anxiety and depression (HADS; Botega, Bio, Zomignani, Garcia,

& Pereira, 1995). The researcher who was collecting the data classified patients' KPS (Karnofsky & Burchenal, 1949).

TMT. TMT consists of two parts that evaluate visual scanning speed, motor function, attention, and mental flexibility. In TMT-A, participants place random numbers in increasing order. In TMT-B, participants place numbers and letters in an alternating sequence also in increasing order. Scores are calculated based on the amount of time required to correctly complete each subtest and number of errors. Shorter time signifies better performance (Loring, 1999; Mitrushina, Boone, & D'Elia, 1999; Reitan, 1958; Spreen & Strauss, 1998).

CRT. CRT uses computer software to evaluate sustained attention and vigilance. Auditory signals are randomly provided to participants at random intervals (2-5 s) via headphones. Participants press a button immediately after hearing the signal. Scores are calculated in milliseconds on 10th, 50th, and 90th percentiles. The 10th percentile represents the fastest and best responses and the 90th the slowest and worst times (Elsass, 1986).

DST. DST consists of two subtests and evaluates attention, concentration, and working memory. In the forward test, participants' orally repeat a number sequence in the same order as presented by the researcher. In the backward test, participants repeat the sequence in reverse order. If two subsequent errors occur, the test is stopped. Scores are based on the number of correct answers and range from 0 to 14 (Mitrushina et al., 1999; Nitrini et al., 1994). Fewer errors are considered better.

FTT. FTT evaluates psychomotor speed and requires the individual to tap a key as many times as possible using the index finger of each hand, and the number of taps is recorded. Participants complete five trials of 10 s, with brief resting periods between trials. Scores are calculated using the mean number of taps for each hand and the difference between hands (Lezak, Howieson, & Loring, 2004; Mitrushina et al., 1999; Spreen & Strauss, 1998). Higher means and lower differences between hands indicate better performance.

MMSE. MMSE is a general measure of cognitive function that consists of 30 questions assessing the domains orientation to time and place, registration of words, attention and calculation, word recall, language, and visual construction. The score is based on the number of correct answers and ranges from 0

to 30 (Folstein, Folstein, & McHugh, 1975; Nitrini, 2004). As our sample had at least 6 years of schooling, we adopted a cutoff point of >26 for good cognitive function (Brucki, Nitrini, Caramelli, Bertolucci, & Okamoto, 2003; Lourenço & Veras, 2008).

Data Analysis

Psychometric properties of the neuropsychological test were assessed to confirm our hypotheses. Statistical analyses were performed by SPSS v. 22.0 (IBM, Armonk, NY) with a significance level of 5%. The groups (patients and controls) were compared regarding sociodemographic characteristics by Pearson's correlations, chi-square test, and *t* test. Observed differences in sex, age, and schooling were subjected to an ANCOVA adjusted for these variables. Pearson's correlation was used to assess convergent and divergent validity between patients' scores in the tests and age, schooling, KPS, pain intensity, anxiety, and depression. Considering that MMSE is a gold standard instrument for general cognitive assessment, correlations between this instrument and the other tests were also analyzed. Tests' reliability was investigated using ICC to analyze test–retest agreement for the patient group. The strength of reference value agreement is classified as follows: almost perfect (0.81-1.00), substantial (0.61-0.80), moderate (0.41-0.60), fair (0.21-0.40), slight (0.00-0.20), and poor (<0.00; Landis & Koch, 1977).

Ethical Considerations

This study was approved by the institution's ethics committee and all participants signed informed consent forms.

Results

Sample Characteristics

Patients and controls did not differ in cohabitation status, monthly income, and presence and intensity of pain. Patients had markedly low pain intensity ($M = 1.1$, median = 0). Most participants were females, with a higher proportion in the control group. Patients were almost 10 years older than controls. The sample's schooling corresponded to a high school degree (median = 11 years), although controls' average was 1 year higher (12.8, $SD = 3.2$) than patients (11.3, $SD = 3.4$; Table 1). Considering the differences observed, statistical analysis was adjusted for these variables in discriminant validity, as described in the "Method" section.

Table 1. Sample Characteristics.

Variables	Patients ($N = 178$)	Controls ($N = 79$)	p value*
Sex			
Female	102 (57.3%)	62 (85%)	**.001**
Male	76 (42.7%)	17 (15%)	
Total	178 (100%)	79 (100%)	
Age (years)			
M (*SD*)	50.5 (9.9)	41.4 (13.3)	**<.001**
Median (min-max)	52.0 (23.0-65.0)	40.0 (18.0-65.0)	
Total	178 (100%)	79 (100%)	
Schooling (years)			
M (*SD*)	11.3 (3.4)	12.8 (3.2)	**<.001**
Median (min-max)	11 (6.0-29)	11.0 (7.0-27.0)	
Total	178 (100%)	79 (100%)	
Cohabiting partner			
Yes	110 (62.5%)	48 (67.7%)	.540
No	66 (37.5%)	29 (33.3%)	
Total	176 (100%)	77 (100%)	
Monthly income			
M (*SD*)	1,446.21 (1,627.02)	1,632.04 (1,228.10)	.375
Median (min-max)	957.45 (0-12,765.96)	1,276.60 (229.79-6,806.51)	
Total	174 (100%)	79 (100%)	
Karnofsky performance status index (KPS)			
M (*SD*)	88.25 (9.25)	—	—
Median (min-max)	90 (40-100)	—	
Total	178 (100%)	—	
Pain			
Yes	42 (23.6%)	14 (17.7%)	.238
No	136 (76.4%)	65 (82.3%)	
M (*SD*)	1.1 (2.2)	0.7 (1.7)	
Median (min-max)	0 (0-10)	0 (1-7)	

*p values <.05 were statitically significant.

Most frequent types of primary tumor among the patients were colorectal, breast, and stomach cancers, and was most frequently metastasized to the liver, the lungs, and the bones.

Psychometric Properties

Discriminant validity (Hypothesis 1). Discriminant validity analyses indicated differences between patient and control performance on TMT-A (number of errors), TMT-B (number of errors and test time completion), forward and

Table 2. Performance on Neuropsychological Tests and Discriminant Validity Between Cancer Patients and Controls (ANCOVA).

Neuropsychological test	Patients	Controls	*p* value
TMT-A	104 (100%)	62 (100%)	
Time: *M* (*SD*); median (min-max)	52.2 (30.7); 46 (21-221)	40.2 (13.4); 37 (15-98)	.089
Errors: *M* (*SD*); median (min-max)	0.33 (0.63); 0 (0-2) (34 errors)	0.15 (0.70); 0 (0-3) (9 errors)	**.032**
TMT-B	178 (100%)	79 (100%)	
Time: *M* (*SD*); median (min-max); *N* (%)	138.9 (87.7); 113 (29-509)	96.6 (43.2); 92 (38-274)	**.008**
Errors: *M* (*SD*); median (min-max); *n* (%)	178 (100%)	79 (100%)	**.020**
	1.2 (1.28); 1 (0-7)	0.53 (0.78); 0 (0-3)	
	104 (100%)	62 (100%)	
DST forward	178 (100%)	79 (100%)	
M (*SD*); median (min-max)	6.0 (2.3); 6 (2-13)	6.8 (2.3); 6 (2-12)	**.037**
DST backward	178 (100%)	79 (100%)	
M (*SD*); median (min-max)	4.7 (1.9); 5 (1-11)	5.3 (1.9); 5 (2-11)	**.049**
FTT dominant hand	178 (100%)	79 (100%)	
M (*SD*); median (min-max)	36.4 (12.9); 38.2 (9.6-62.2)	37.9 (12.11); 38.4 (2.0-61.0)	.529
FTT nondominant hand	178 (100%)	79 (100%)	
M (*SD*); median (min-max)	35.5 (10.6); 37.2 (6.4-61.2)	37.1 (9.6); 36.6 (13.4-54.4)	.47
FTT difference	178 (100%)	79 (100%)	
M (*SD*); median (min-max)	3.06 (30.08); −1 (−89-69)	5.09 (28.88); 4 (−8469)	.336
CRT 10th percentile	173 (100%)	78 (100%)	
M (*SD*); Median (min-max)	192.3 (100.1); 166.0 (17-698)	178.9 (46.9); 167.5 (127-456)	.262
CRT 50th percentile	173 (100%)	78 (100%)	
M (*SD*); median (min-max)	250.6 (145.5); 204 (55-970)	227.5 (79.0); 211.5 (152-758)	.189
CRT 90th percentile	173 (100%)	78 (100%)	
M (*SD*); median (min-max)	352.7 (198.7); 289.0 (92-1165)	312.0 (116.8); 288.0 (186-999)	.094
MMSE	178 (100%)	79 (100%)	
M (*SD*); median (min-max)	27.3 (2.0); 28 (21-30)	28.4 (1.0); 28.0 (27-30)	**<.001**
Score < = 26[a]	31 (17.4%)	—**	
Score > 26	147 (82.6%)	79 (100%)	

Note. TMT = Trail Making Test; DST = Digit Span Test; FTT = Finger Tapping Test; CRT = Continuous Reaction Time; MMSE = Mini-Mental State Examination.

[a]A cutoff point of 26 was adopted for schooling > 6 years and a score of >26 was inclusion criteria for controls.

**As per inclusion criteria, controls with MMSE scores <= 26 were not included in the study.

Table 3. Convergent and Divergent Validity of Neuropsychological Tests in Cancer Patients Using Pearson Correlation Analysis.

	Variable						
Neuropsychological test	Age	Schooling	KPS	Pain	Anxiety	Depression	MMSE
MMSE	$r = .160$	$r = .264$	$r = .072$	$r = -.110$	$r = -.195$	$r = -.162$	—
	p **= .033**	$p <$ **.001**	$p = .340$	$p = .143$	p **= .009**	p **= .031**	
CRT 10th percentile	$r = -.058$	$r = -.116$	$r = -.029$	$r = .045$	$r = .123$	$r = .161$	$r = -.227$
	$p = .448$	$p = .130$	$p = .703$	$p = .558$	$p = .108$	p **= .034**	p **= .003**
CRT 50th percentile	$r = -.053$	$r = -.142$	$r = -.038$	$r = .058$	$r = .106$	r **= .170**	r **= –.245**
	$p = .487$	$p = .062$	$p = .618$	$p = .447$	$p = .166$	p **= .026**	p **= .001**
CRT 90th percentile	$r = -.093$	$r = -.153$	r =–.054	$r = .088$	r **= .161**	r **= .236**	r **= –.251**
	$p = .225$	p **= .044**	$p = .484$	$p = .250$	p **= .035**	p **= .002**	p **= .001**
TMT A	$r = .063$	$r = -.399$	$r = -.281$	$r = .152$	$r = .285$	$r = .356$	$r = -.527$
	p =.524	$p <$ **.001**	p **= .004**	$p = .123$	p **= .003**	$p <$ **.001**	$p <$ **.001**
TMT B	$r = .111$	$r = -.344$	$r = -.139$	$r = .090$	$r = .157$	$r = .161$	$r = -.474$
	$p = .141$	$p <$ **.001**	$p = .065$	$p = .231$	p **= .036**	p **= .032**	$p <$ **.001**
Digit Span forward	$r = .118$	$r = .209$	$r = -.028$	$r = -.167$	$r = -.124$	$r = -.203$	$r = .193$
	$p = .116$	p **= .005**	$p = .707$	p **= .026**	$p = .098$	p **= .007**	p **= .010**
Digit Span backward	$r = .022$	$r = .259$	$r = .015$	$r = -.008$	$r = -.037$	$r = -.140$	$r = .385$
	$p = .772$	$p <$ **.001**	$p = .843$	$p = .913$	$p = .626$	$p = .062$	$p <$ **.001**
FTT dominant hand	$r = -.076$	$r = .161$	$r = .089$	$r = -.050$	$r = -.122$	$r = -.126$	$r = .192$
	$p = .314$	p **= .032**	$p = .237$	$p = .510$	$p = .104$	$p = .093$	p **= .010**
FTT nondominant hand	r =–.085	$r = .212$	$r = .108$	$r = -.113$	$r = -.132$	$r = -.080$	$r = .171$
	$p = .260$	p **= .004**	$p = .153$	$p = .131$	$p = .078$	$p = .290$	p **= .022**
FTT difference	$r = -.229$	$r = .045$	$r = -.024$	$r = .109$	$r = -.018$	$r = -.102$	$r = .119$
	$p = .703$	$p = .552$	$p = .756$	$p = .150$	$p = .816$	$p = .177$	$p = .114$

Note. KPS = Karnofsky Performance Status; MMSE = Mini-Mental State Examination; CRT = Continuous Reaction Time; TMT = Trail Making Test; FTT = Finger Tapping Test.

backward DST, and MMSE. No differences occurred for TMT-A (test time completion), FTT, and CRT (Table 2).

Convergent and divergent validity (Hypotheses 2 and 3). To confirm the hypotheses about convergent and divergent validity, we performed tests investigating the relationship between sociodemographic and clinical characteristics on the neuropsychological tests scores. They revealed that all cognitive tests correlated with schooling and MMSE. In addition, MMSE, CRT, TMT (A and B), and DST (forward) correlated with depression. MMSE, CRT 90th percentile, and TMT (A and B) were weakly correlated with anxiety. A significant correlation was found between MMSE and age (Table 3).

Reliability (Hypothesis 4). To examine the reliability and stability of the neuropsychological tools, all patients have been invited to be retested on all cognitive tests during a 3- to 7-day period. Only 39 patients (21.9%) accepted and underwent retesting ($M = 5.96$ days). For most of the tests, performances showed moderate, substantial, or almost perfect agreement between the first and second assessments, meaning the results were similar over the period considered, with the exception of FTT difference between hands, which was fair. The results regarding the reliability of the tests are presented in Table 4.

Discussion

The cognitive performance of patients with cancer regarding attention, vigilance, memory, motor function, and mental flexibility is poorly investigated, except for patients with breast cancer (Dutta, 2011; Taillibert et al., 2007). Although the gold standard for measurement of cognitive function is MMSE, its ability to identify minor and subtle cognitive deficits is questionable (Lange et al., 2014; Tombaugh & McIntyre, 1992). There is no doubt that more domain-specific tools can be useful for research and clinical purposes, but only few have undergone psychometric investigation in patients with cancer (Mystakidou et al., 2007a; Santos et al., 2014).

Nonvalidated tools may produce uncertain results and provide poor support for clinical decision making and research outcomes. Thus, this study analyzed the psychometric properties (discriminant validity, convergent and divergent validity, and reliability) of five neuropsychological tests. With the exception of TMT-B (Santos et al., 2014) and MMSE (Mystakidou et al., 2007a), these tools have never been validated in patients with metastatic cancer.

Despite the use of a convenience sample, its size (178 patients, 79 healthy controls) is noteworthy compared with smaller sample sizes in validation studies. To our knowledge, this was the first study to evaluate the

Table 4. Reliability of Neuropsychological Tests Between Cancer Patients Using the ICC.

Neuropsychological test	ICC ($n = 39$)	*p* value	Classification[a]
MMSE	0.707	**<.001**	Substantial
CRT 10	0.944	**<.001**	Almost perfect
CRT 50	0.931	**<.001**	Almost perfect
CRT 90	0.893	**<.001**	Almost perfect
TMT A	0.715	**.025**	Substantial
TMT B	0.535	.089	Moderate
DST forward	0.722	**<.001**	Substantial
DST backward	0.515	**<.001**	Moderate
FTT—Dominant hand	0.768	**<.001**	Substantial
FTT—Nondominant hand	0.699	**<.001**	Substantial
FTT—Difference	0.305	**.023**	Fair

Note. ICC = Intraclass Correlation Coefficient; MMSE = Mini-Mental State Examination; CRT = Continuous Reaction Time; TMT = Trail Making Test; DST = Digit Span Test; FTT = Finger Tapping Test.

[a]Range of the strength of agreement (almost perfect: 0.81-1.00, substantial: 0.61-0.80, moderate: 0.41-0.60, fair: 0.21-0.410, slight: 0.00-0.20, poor: <0.00).

psychometric properties of a battery of neuropsychological tests in metastatic cancer patients.

As in the "Results" section, the discussion is presented according to the hypotheses of this study. As expected, most tests (three of five) discriminated patients from controls, and patients performed worse than controls in all tests. MMSE, TMT-A (number of errors), TMT-B (time and number of errors), and DST discriminated patients from controls, but CRT and FTT did not.

MMSE mean scores of patients and controls were within the normal range. In partial support of our findings, a former validation study reported that MMSE could discriminate between patients with cancer according to disease severity; however, this study lacked comparison with healthy controls (Mystakidou et al., 2007a). There are several factors related to the cancer disease like general health status, comorbidities, and treatment, which may interfere with patients' concentration ability and disturb performance on associated tests (e.g., math or word recall).

We could not find studies regarding DST validation for patients with cancer, but the MMSE findings regarding memory and attention corroborate with the notion that patients with cancer have more disease-related factors that may interfere with the domains evaluated by DST—attention, concentration, and working memory (Mystakidou, 2007a).

The differences on three out of four measures of TMT indicate that Part B may be more sensitive to cognitive dysfunction due to the higher complexity of this subtest involving mental flexibility. Results of the present study differ from a preliminary study of our group with a smaller number of participants (patients with cancer = 94, controls = 39) in which TMT-B discriminated patients from controls in time spent on the test but not in number of errors (Santos et al., 2014). The larger sample size in the current study could explain our finding.

The TMT, DST, and MMSE involve tasks that require efforts from multiple cognitive domains. Likely, this characteristic explains between-group differences. Conversely, the CRT and FTT tests are instinctive and require less complex cognitive process (hear a sound and press a button). The lower complexity of these tasks may have facilitated good performance in both groups, which could explain the similarity of performance between patients and controls. Only one study has verified CRT psychometric properties in patients with hepatic encephalopathy, traumatic brain injury, and healthy controls. Its purpose was to determine cutoff points for each percentile that could effectively differentiate between etiologies, but the study was performed in 1986 with one of the first versions of this test (Elsass, 1986).

MMSE is a broad neuropsychological tool that assesses cognitive aspects included in the other tests (Folstein et al., 1975; Tombaugh & McIntyre, 1992); thus, correlations were expected. Although there is some doubt on MMSE's ability to detect minor deficits (Lange et al., 2014; Tombaugh & McIntyre, 1992), the current study found correlations with all specific cognitive tests, which suggests that MMSE is an acceptable tool to assess cognition in metastatic cancer patients, considering that MMSE also showed a good performance in discriminant validity and reliability. MMSE and age were positively but weakly correlated ($r = .16$). However, patients were not older adults and the mean and median were very close; therefore, this unexpected correlation could be due to a confounding factor (e.g., schooling).

Schooling, depression, and anxiety are the most studied and recognized factors influencing cognitive performance (Alcalar, Ozkan, Kucucuk, Aslay, & Ozkan, 2012; Arsdale et al., 2016; Brucki et al., 2003; Cruzado et al., 2014; Hermelink et al., 2007; Kurita et al., 2008b; Llinas-Reglà et al., 2015; Lourenço & Veras, 2008; Scheibel, Valentine, & O'Brien, 2004; Vearncombe et al., 2009). As learning requires difficult and complex mental processes, cognitive skill development is a key element of education. It was expected and confirmed that individuals with higher schooling would achieve better scores on neuropsychological tests.

Consistently, a study of colon cancer patients reported correlations between TMT and education, among other tests (Cruzado et al., 2014). A population-based cohort study revealed a correlation between TMT A and B and schooling (Llinas-Reglà et al., 2015). Also, previous studies showed that MMSE has

different cutoffs contingent upon education level (Brucki et al., 2003). Depression results in poorer mental processing such as loss of attention, memory, and elements required for intellectual tasks. Thus, we expected and found that depression was accompanied by worse performance on neuropsychological tests. Consistently, other studies have showed that depression was negatively correlated with MMSE performance in advanced cancer patients (Mystakidou et al., 2007b), and that there was a negative correlation between depression, attention, and executive function among breast cancer patients (Vearncombe et al., 2009). Furthermore, chronic pain patients with higher depression scores performed worse on CRT (Kurita et al., 2008b), and there were correlations between TMT-B and depression among chronic myelogenous leukemia patients (Scheibel et al., 2004). However, other studies did not find correlation between depression, TMT, and FTT in breast cancer patients (Hermelink et al., 2007) and, similarly to results from patients with advanced cancer (Kurita & de Mattos Pimenta, 2008), there was no correlation between TMT and depression in colon cancer patients (Cruzado et al., 2014).

Anxiety focuses patients' attention on personal thoughts, sensation, and behaviors, leading to poorer neuropsychological test performance (American Psychological Association, 2016). As expected, in this study, patients with higher anxiety scores had worse performance on the MMSE, CRT 90th percentile and TMT (A and B). However, these findings were not observed in other studies with breast cancer patients (Hermelink et al., 2007; Vearncombe et al., 2009).

In this study, FTT was only correlated with MMSE and schooling. Although no study of cancer patients analyzed the relationship between FTT and sociodemographic variables, investigations in other pathologies showed correlations with different ethnic groups, ages, education, handedness, or gender (Axelrod, Meyers, & Davis, 2014). Conversely, another study found correlations between FTT and age, dominant hand, and gender (Christianson & Leathem, 2004).

Symptoms such as pain, fatigue, sleep, and tiredness are frequently described as influencing cognitive performance; however, empirical data remain controversial (Arsdale et al., 2016; Kurita et al., 2008b). We observed few correlations between neuropsychological tests, pain, and KPS: As expected, TMT-A negatively correlated with KPS, and DST forward negatively correlated with pain. The rationale for weak correlations is likely related to patients' good clinical condition, demonstrated by mild pain and good KPS in a homogeneous sample.

Previous studies have reported relationships between pain and cognitive measures. MMSE was negatively correlated with pain (Tombaugh & McIntyre, 1992) and pain negatively affected working memory in samples of patients with cancer (Sjøgren, Olsen, Thomsen, & Dalberg, 2000). Contrary to our study, no correlation was observed between pain and TMT-A or B

(Kurita et al., 2008b) and neither type nor duration of pain was identified as being associated with neurocognitive measures in the sample of noncancer pain patients (Kurita et al., 2008a).

Previous studies identified contrasting findings about physical performance and cognition. Specifically, worse KPS correlated with poor CRT and FTT performance (Tchen et al., 2003).

Reliability measures for all cognitive tests varied from moderate to almost perfect in a 3- to 7-day period ($M = 5.96$ days), except for FTT difference. Consistent with several studies, MMSE reliability was substantial. In 1975, research revealed that the MMSE was reliable in both 24-hr and 28-day reassessment periods (Folstein et al., 1975). A Greek study evaluating the stability of MMSE for cancer patients reported reassessment stability during a 3-day period (Mystakidou et al., 2007a), supporting our findings that MMSE is reliable for cancer patients. DST reliability was substantial in the forward subtest and moderate in the backward, TMT reliability was substantial for TMT-A and moderate for TMT-B, CRT reliability was almost perfect in all percentiles, and FTT reliability was substantial for both hands in patients, and fair for the difference between both hands. We could not find studies that tested these tools' reliability in patients with cancer, strengthening the importance of the present work. Results indicate that they were adequate for test and retest assessment in the 3 to 7 days period and can be useful to monitor response to treatment. However, study with patients experiencing changes in cognitive status should be conducted to confirm the tests' ability to detect alterations.

Limitations of this study include the patients' good clinical condition, which could have interfered with results (e.g., absence of CRT and FTT discriminant validity and weak correlations between cognitive performance, pain, and KPS). In addition, future studies should evaluate individuals with more severe symptoms.

Conclusion

Discriminant validity between patients and controls was observed in three (TMT A and B, DST, and MMSE) of five tests. Measures of concurrent validity were as expected in that better cognitive performance correlated with better physical performance, less pain/anxiety/depression, higher education level of education, and better performance on MMSE. The tools demonstrated very good stability, except for FTT difference. Because of the scarcity of existing research, these findings contribute with new data related to cancer patients.

Objective cognitive assessment is not part of the clinical assessment routine in patients with metastatic cancer; however, treatment improvement and development of palliative care protocols may improve patients' life expectation, and maintenance of an adequate cognitive function is essential to good

quality of life. The mentioned cognitive tests may help to identify alterations due to disease progression and/or treatment effects and, consequently, they can assist the assessment/monitoring/management of impairment causes, especially those of transient nature. Therefore, further study to analyze predictive values of these cognitive tests in patients with cancer is necessary. Despite limitations, our results encourage increased research and clinical use of these tools to confirm their usefulness and adequacy.

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