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RESEARCH ARTICLES

Predicting compliance and survival in palliative whole-brain radiotherapy for brain metastases

Sebastià Sabater · Encarna Mur · Katrin Müller · Meritxell Arenas

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Abstract
Objective Brain radiotherapy is the main treatment for patients with brain metastases but its goal is just symptom control. Our aim was to study if different performance tools, used in geriatric practice, could improve patient selection for decision-making in the palliative brain radiotherapy setting.
Patients and methods Data from 61 consecutive patients were analysed. In addition to Karnofsky Performance Status (KPS) their physical activity was assessed by means of the activity of daily living (ADL) and instrumental ADL (IADL) scales. A neurocognitive evaluation was performed with the Pfeiffer Short Portable Mental Status Questionnaire (SPMSQ) and with the Mini-Mental Status Exam (MMSE). Radiotherapy compliance and short survival were the endpoints of the study.
Results High rates of cognitive impairment were found by both neurocognitive tools (Pfeiffer: 19.7% of patients; MMSE: 30%). Dependence was also highly prevalent, either measured by the ADL (50.8%) or by the IADL (43.3%). Nearly one third (27.9%) of patients died soon after radiotherapy evaluation. Longer survival was related to female, younger than 60 years, breast cancer primary tumour, steroid response, RPA class, and higher performance and neurocognitive score tools. A premature death was associated with neurocognitive tools, IADL and longer interval from brain metastatic diagnosis to radiotherapy. Twenty-three percent of patients were not able to finish the WBRT course due to clinical deterioration. The only variable related to compliance was a low MMSE score.
Conclusions Results suggest that the geriatric tools analysed could offer information on brain palliative radiotherapy complementary to that offered by the more usual tools. It will be interesting to study if our data could be extrapolated to the general palliative oncological field.

Keywords ADL · IADL · Neurocognitive evaluation · Performance status · Brain metastases

S. Sabater (✉)
Department of Radiation Oncology
Complejo Hospitalario Universitario
C/ Hermanos Falcó, 37
ES-02006 Albacete, Spain
e-mail: ssabater@tinet.org

E. Mur · K. Müller · M. Arenas
Department of Radiation Oncology
Sant Joan University Hospital
Reus, Tarragona, Spain

Introduction

Brain metastases are estimated to occur in approximately 10–30% of cancer patients. Their incidence will likely increase as treatment of tumours improves and patients survive longer [1]. Radiation therapy remains the main treatment for these patients. Their average median radiological response rate is 44%, with a median survival of 3–6 months [2]. No variation on radiation therapy regimens or radiosensitisers [3–7] has demonstrated a survival benefit. Thus, palliation is the expected goal for treatment. Recursive partitioning analysis (RPA) classes have emerged as a reliable tool to predict survival for brain metastatic patients, however survival in the most unfavourable class, III, is quite variable [2, 8–10]. Although predictive factors on survival and treatment response for patients with brain metastasis have been described, there is a lack of complete information on factors related to unfinished radiotherapy course treatments and early death after radiotherapy. The often inaccurate and systematic optimism of clinicians in

predicting survival time in terminally ill patients is well known [11, 12] and this influences radiotherapeutic treatment [13, 14]. A proper evaluation of these parameters could have consequences, not only when selecting patients for a palliative treatment, but also when planning resources in order to avoid overtreatment expenses.

Neurological focal injuries produce the same symptoms irrespective of the main illness. Brain metastasis patients usually have similar symptoms to cerebrovascular disease, which is more prevalent among elderly people. It is well known that dependency in activities of daily living (ADL) and instrumental ADL (IADL) are correlated with the risk of death in elderly patients [15], whether demented [16] or non-demented [17]. ADL describe the most basic activities involved in everyday independent function. IADL describe activities for adaptation to the environment and community, which are more cognitively influenced. The Karnofsky Performance Status, which is a validated oncological tool, is based on a physician's subjective evaluation of a patient's health. The remaining tools are designed and validated for use in elderly patients, but not specifically in cancer. Some of them have been tested in oncological settings and have included young patients (35–39).

We hypothesised that geriatric functional tools (ADL and IADL) could yield a more accurate prognosis, because they are self-assessments without a physician's subjective interpretation, than those habitually used in oncology (Karnofsky or ECOG Performance Scale). Since geriatric cancer patients' survival and tolerance to treatment may be predicted using the patient's ability to perform activities of daily living [17, 18] and cognitive function [16, 19], we studied whether brain metastatic patient life expectancy could be predicted using the same parameters, even if the sample included young patients.

Patients and methods

Patients

Files from patients treated between June 2001 and August 2003 for brain metastases were reviewed. Prognostic factors were examined and the demographic characteristics of the patients are listed in Table 1. All patients had a known diagnosis of cancer and neurological symptoms due to brain metastasis. At the time of the study, palliative brain metastasis treatment policy was a whole-brain radiotherapy (WBRT) palliative course which could be preceded by chemotherapy. No further aggressive options were considered because they were unavailable at our centre. Patients were referred from other units as well as units from other centres; consequently steroid schedules and dosages were not uniform. Palliative WBRT consisted of conventional external beam radiotherapy of 30 Gy delivered in ten fractions and was preceded by 2D planning. All patients underwent the test battery described below.

Table 1 Patient characteristics (n=61)

Gender	
Female	22
Male	40
Age (years)	
Median	60.0
Range	36–80
KPS	
≤70	28
≥80	33
Primary tumour	
Lung	37
Breast	13
Other	10
Primary tumour activity	
Yes	38
No	22
Number M1	
Simple	19
Multiple	39
Unknown	3
Median	3.3
Range	1–13
Extracranial M1	
Yes	33
No	28
Steroid response	
Yes	54
No	7
Chemotherapy	
Yes	14
No	45
RPA	
I	14
II	31
III	16

Assessment of performance status

The following evaluation tests were conducted before radiotherapy: (1) Karnofsky Performance Status (KPS); (2) Pfeiffer Short Portable Mental Status Questionnaire (SPMSQ); (3) Mini-Mental Status Exam (MMSE); (4) Barthel-index and (5) Lawton and Brody score. No subsequent determinations were done. KPS is a validated oncological tool based on the physician's subjective determination of the adjustment of the patient to the disease. Pfeiffer SPMSQ [20] is a very fast screening tool detecting cognitive impairment, which evaluates four parameters with only ten questions. Three or four mistakes means a clinically significant cognitive impairment, whereas five or more mistakes means a pathologic cognitive injury. MMSE is a wide screening tool for dementia. Two Spanish validated versions exist, one with 30 items, and the one used in this report with 35 items translated by Lobo [21, 22]. The maximum score is 35, and the lower the score, the higher the cognitive impairment (the 35-item version sets 26 as the cut-off for mild cognitive impairment). The Barthel Index [23] is used to assess the ability to conduct ADL, thus

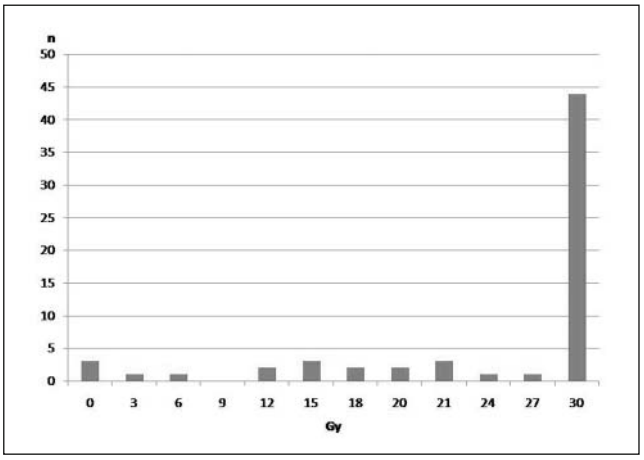

Fig. 1 Administered dose

evaluating ten basic functional capabilities. High scores indicate good functional independence. Results are grouped in five categories of dependence: total dependence, <20; severe dependence, 20–35; moderate dependence, 40–55; slight dependence, 60–99; total independence, 100. Lawton and Brody's Scale [24] is a self-reported assessment of abilities to interact with the community, which rates more sophisticated functions than ADL. It measures 8 IADL, more complex than the self-care activities. Low scores mean high dependence, whereas values under 4 mean a heavy dependence. The Lawton scale includes eight IADL for women and five of the eight for men. As we were studying not only a geriatric sample, but also younger people, more used to all kinds of housework, we asked all patients about female IADL questions. Later, scores were corrected to the male version (maximum score, 5 points) to avoid penalising elderly males with limited household skills.

Statistical analysis

The primary endpoints were poor radiotherapy compliance, defined as a treatment with an administered dose lower than prescribed, and early death, defined as death within 30 days after radiotherapy evaluation. The Chi-square statistics test was used to assess the association between categorical variables and means were compared with the t-test. Correlations among performance status parameters were assessed with Spearman's correlation coefficient test. Survival was calculated according to the Kaplan-Meier method and curves were compared with the Wilcoxon test.

Table 2 Characteristics of the patients that were unable to finish WBRT

Variable	Completed course	No start or early withdrawal	*p*
Gender			
Male	65.25%	62.5%	ns
Female	34.8%	37.5%	
Age			
Mean	57	65	0.009
Primary tumour activity			
Yes	32.6%	53.3%	ns
No	67.4%	46.7%	
Extracranial M1			
Yes	55.6%	46.7%	ns
No	44.4%	53.3%	
Primary tumour			
Breast	22.2%	18.8%	ns
Lung	62.2%	56.3%	
Other	15.6%	25%	
Steroid response			
Yes	88.6%	81.3%	ns
No	11.4%	18.8%	
Chemotherapy			
Yes	22.2%	26.7%	ns
No	77.8%	73.3%	
KPS			
≤70	43.5%	50%	ns
≥80	56.5%	50%	
Number M1			
Single	21.7%	56.3%	ns
Multiple	78.3%	43.8%	
Pfeiffer			
≤3	87%	62.5%	0.061
>3	13	37.5%	
MMSE			
≤26	42.5%	81.8%	0.038
≥27	57.5%	18.2%	
Barthel			
100	56.5%	37.5%	ns
≤99	43.5%	62.5%	
>55	89.1%	81.3%	ns
≤55	10.9%	18.8%	
Lawton			
≤4	62.2%	56.3%	ns
5	37.8%	43.8%	
RPA			
I	27.3%	20%	ns
II	45.5%	60%	
III	27.3%	20%	
M1 diagnosis–WBRT delay			
≤1 month	0%	18.8%	0.015
>1 month	100%	81.3%	1

Results

Patient characteristics

Sixty-one patients were included. At the time of analysis all patients had died and the date was known. Their median age was 59.6 years; male to female ratio was 2:1. The most common primary origin was the lung, 70% of men and 48% of women. In about 49% of all cases the histology was adenocarcinoma. The primary tumour location remained uncontrolled in 62.3% of patients; extracranial metastases were present in 50.8%. No patient had a previous cranial irradiation or a neurosurgical procedure.

Twenty-three percent of patients underwent chemotherapy due to brain metastasis prior to irradiation. All but nine of the patients clinically improved after corticosteroid administration.

The mean time delay from initial evaluation to start of treatment was 6.6 days (range 0–41). No correlation was observed between this delay and the radiotherapy dose administered. A positive significant correlation (rho=0.665, p=0.000) was found between delivered dose and time from radiotherapy evaluation to death.

Nearly one third (27.9%) of patients died soon after radiotherapy evaluation and a similar percentage (23%) was unable to finish the WBRT course. Clinical neurological deterioration was the reason for removal or non-initiation of WBRT in every instance; 52.9% of such patients died during the following week and 35.3% died in the following two weeks; the remaining survived for more than one month. Considerable clinical deterioration, which precluded any radiotherapy session, was seen in 4.9% patients. An additional 16.4% of patients received less than half of the planned dose (Fig. 1). Significantly better treatment compliance was related to younger age, good neurological status assessed by the MMSE and early irradiation after brain metastases diagnosis. A borderline significance was related to the best Pfeiffer scores (Table 2).

Performance status

The baseline scores on the performance status tools administered are displayed in Table 2 and Fig. 2. A cognitive deficit was seen in 19.7% of patients when assessed by Pfeiffer SPMSQ. A MMSE score ≤26 was seen in 30% of patients. Some level of dependence was observed in 50.8% of patients when assessed by the Barthel index and in 43.3% when assessed by the corrected Lawton and Brody score. A KPS ≤60 was observed in 25.9% of patients and 10.3% of patients were disabled requiring considerable assistance (KPS≤50). A statistically significant correlation emerged between the different performance status tools; between ADL and IADL tools, r=0.774.

Survival analysis

The median survival time from radiotherapy evaluation was 81 days (95% CI 56–127). As expected, patients unfit to complete the WBRT course or to start it had lower median survival times (17.5 vs. 158.5 days, p<0.0001). Patients that did not achieve a neurological improvement with steroids were unable to get better with the later radiotherapy treatment, and this was a significant factor related to a lower median survival (Table 3). Significant prognostic factors for survival were gender, age, primary location, steroid response, RPA class, and performance status measured by KPS, Pfeiffer, Barthel, MMSE and Lawton scale. Breast cancer patients and, consequently, female patients had longer survival times. RPA classes I, II and III had median survival times of 102, 150 and 33 days, respectively. However up to 62.5% of class III patients survived more than 30 days. Similar results were seen for other variables when the same analysis was done for the poor prognosis groups. Thus 67.5% of male patients, 57.1% of patients with no steroid response, 33.3% of patients with more than 3 points on the Pfeiffer score, 50% of patients with fewer than 55 points on the Barthel index and 57.7% of patients with fewer than 4 points on the Lawton scale had survival times longer than 30 days.

Premature death

An early death defined as death within 30 days of the end of radiotherapy treatment accounted for 27.9% of patients. This was observed in 82.4% of patients treated with less than 30 Gy or unfit to start WBRT, but only in 6.8% of patients who finished their treatment (p=0.000). A negative correlation was seen between a delay to start radiotherapy from brain metastasis diagnosis and the final radiotherapy dose (rho=–0.262, p=0.041), but significance was lost when an extreme value was discarded. Despite that, only performance status-related variables were significant; KPS was the only performance status test that was not significant (Table 3). Table 4 shows the demographic characteristics related to an unfavourable prognosis.

Withdrawal from radiotherapy

The planned radiotherapy treatment was completed by 72.1% of patients. Early withdrawal was due to clinical deterioration; no deaths were seen during radiotherapy, but 85.7% of patients who became unfit to complete the radiotherapy course died during the following two weeks. Three patients (4.9%) could not start the prescribed treatment. When patients without any treatment fraction were excluded, analysis only showed a significance for the mini-mental score (p=0.045); no other variables were related to an early withdrawal.

Discussion

Survival of patients treated with WBRT is uniform between different studies, irrespective of the treatments tested [3–7, 25–28] and long-term survival is dismal. Our results, although modest, were obtained in a clinical setting and can be favourably compared to other, previously published, reports.

Although experienced clinicians are able to integrate supplementary information into the existing scores, the choice of radiotherapy dose and fractionation is often

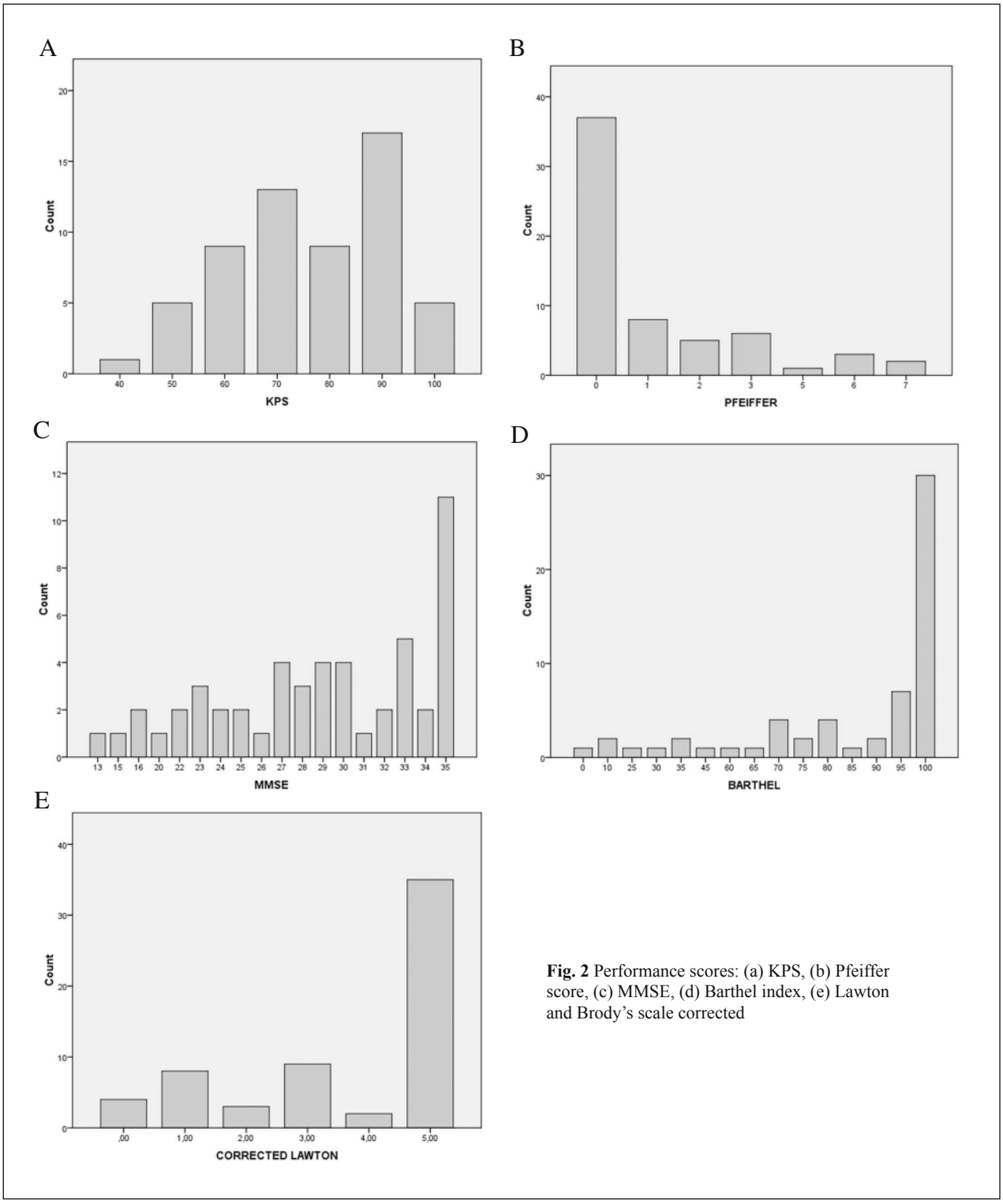

Fig. 2 Performance scores: (a) KPS, (b) Pfeiffer score, (c) MMSE, (d) Barthel index, (e) Lawton and Brody's scale corrected

based on the radiation oncologist's estimation of a patient's survival, and clinicians are often inaccurate and systematically optimistic in their survival predictions [11–13, 29]. Moreover, disease evolves unpredictably, with some patients doing better than predicted, while others do worse.

The need for more accurate evaluation to improve patient selection for treatment has led to the investigation of additional tools. It is well known that KPS predicts outcome in patients with cancer [30, 31]; even for brain metastases it is a recognised independent prognostic factor [26, 32–34]. But while the more commonly used KPS

Table 3 Survival, early death and early withdrawal analysis

Variable	Median survival (days)	*p* value	Early death	Early withdrawal
Gender				
Male	116	0.00283	ns	ns
Female	258			
Age				
≤60	125.5	ns	ns	ns
>60	47.5			
Primary tumour activity				
Yes	137.5	ns	ns	ns
No	71			
Extracranial M1				
Yes	97	ns	ns	ns
No	70.5			
Primary tumour				
Breast	234	0.00245	ns	ns
Other	67			
Steroid response				
Yes	107.5	0.0349	ns	ns
no	44.5			
Chemotherapy				
Yes	135	ns	ns	ns
No	82			
KPS				
≤70	59	0.0049	ns	ns
≥80	184			
Number M1				
Single	48.5	ns	ns	ns
Multiple	87.5			
Pfeiffer				
≤3	104	<0.0001	0.046	ns
>3	11			
MMSE				
≤26	32	0.0019	0.027	0.045
≥27	185			
Barthel				
100	145	0.0078	0.02	ns
≤99	48			
>55	104	0.0057	ns	ns
≤55	28			
Lawton				
≤4	48	0.0085	0.046	ns
5	145			
RPA				
I	102	0.0218	ns	ns
II	150			
III	33			
M1 diagnosis-WBRT delay				
≤1 month	117	ns	0.02	ns
>1 month	48.5			

Table 4 Percentage of patients with unfavourable characteristics and a survival time longer than 1 month

Variable	% survival >1 month
Gender, male	67.5
Age, >60 years	63.3
Steroid response, no	57.1
KPS, <70	63.0
Pfeifer, >3	33.3
MMSE, <26	53.3
Barthel, ≤55	50.0
≤99	56.7
Lawton, <4	57.7

is a physician's subjective determination, the tools tested here are patient self-evaluation and thus, we think, a more reliable patient performance status assessment. MMSE has already been demonstrated to have value in studies involving brain metastases [35] or brain gliomas [36], and it is accepted that sustained cognitive impairment is a poor prognosticator in patients with terminal cancer [37]. The other tools have been tested in the oncological setting, but not evaluating brain metastasis. Meyers et al. [38] found a modest correlation between ability to perform basic ADL and survival. Maione et al. [39] found a significant prognostic value for IADL but not for ADL. We cannot forget that ADL and IADL tools measure different aspects of the same problem and thus explain the correlation found.

Our study has several limitations. In the first place, no information about mood state was available and depression has an influence on survival in terminally ill patients [40]. Secondly, we did not assess patients with a formal quality of life tool or with a battery test of cognitive functions, which could add extra information and more sensitive results [41]. We deliberately did not use these tools because they are time-consuming, precluding their application in a clinical setting, and could be hard to administer to very ill patients. Our study only includes patients treated with WBRT, so results cannot be extrapolated to more favourable patients selected for aggressive therapies such as surgery or radiosurgery [42, 43]. The last limitation of our study is related to the limited number of patients involved and the lack of a validation group.

Despite the limitations above, the present analysis supports the hypothesis that self-assessment tools could improve KPS prognostic significance, especially showing the better behaviour for the MMSE.

In summary, the results suggest that alternative methods to evaluate function add independent information to the widely used Karnofsky score. Our results warrant investigating the value of these performance tools in a large prospective study. If results become validated, they could be used in oncological clinical practice because they are inexpensive and easy to perform and not time-consuming.

Conflict of interest The authors declare that they have no conflict of interest relating to the publication of this manuscript.

References

1. Clayton A, Danson S, Jolly S et al (2004) Incidence of cerebral metastases in patients treated with trastuzumab for metastatic breast cancer. Br J Cancer 91:639–643
2. Gaspar L, Scott C, Rotman M et al (1997) Recursive partitioning analysis (RPA) of prognostic factors in three Radiation Therapy Oncology Group (RTOG) brain metastases trials. Int J Radiat Oncol Bio Phys 37:745–751
3. Langer C, Mehta M (2005) Current management of brain metastases, with a focus on systemic options. J Clin Oncol 23:6207–6219
4. Soffietti R, Costanza A, Laguzzi E et al (2005) Radiotherapy and chemotherapy of brain metastases. J Neurooncol 75:31–42
5. Mehta M, Rodrigus P, Terhaard C et al (2003) Survival and neurologic outcomes in a randomized trial of motexafin gadolinium and whole-brain radiation therapy in brain metastases. J Clin Oncol 21:2529–2536
6. Tsao M, Lloyd N, Wong R et al (2005) Radiotherapeutic management of brain metastases: a systematic review and meta-analysis. Cancer Treat Rev 31:256–273
7. Rades D, Bohlen G, Dunst J et al (2008) Comparison of short-course versus long-course whole-brain radiotherapy in the treatment of brain metastases. Strahlenther Onkol 184:30–35
8. Nieder C, Nestle U, Motaref B et al (2000) Prognostic factors in brain metastases: should patients be selected for aggressive treatment according to recursive partitioning analysis (RPA) classes? Int J Radiat Oncol Biol Phys 46:297–302
9. Rades D, Dunst J, Schild SE (2008) A new scoring system to predicting the survival of patients treated with whole-brain radiotherapy for brain metastases. Strahlenther Onkol 184:251–255
10. Nieder C (2008) Two new prognostic indices for brain metastases: where do we go from here? Strahlenther Onkol 184:488–489
11. Glare P, Virik K, Jones M et al (2005) A systematic review of physicians' survival predictions in terminally ill cancer patients. BMJ 327:195–200
12. Christakis N, Lamont E (2000) Extent and determinants of error in doctors' prognoses in terminally ill patients: prospective cohort study. BMJ 320:469–473
13. Chow E, Davis L, Panzarella T et al (2005) Accuracy of survival prediction by palliative radiation oncologists. Int J Radiat Oncol Biol Phys 61: 870–873
14. Barnes EA, Chow E, Tsao MN et al (2010) Physician expectations of treatment outcomes for patients with brain metastases referred for whole brain radiotherapy. Int J Radiat Oncol Biol Phys 76:187–192
15. Repetto L, Comandini D, Mammoliti S (2001) Life expectancy, comorbidity and quality of life: the treatment equation in the older cancer patients. Crit Rev Oncol Hematol 37:147–152
16. Larson EB, Shadlen MF, Wang L et al (2004) Survival after initial diagnosis of Alzheimer disease. Ann Intern Med 140:501–509
17. Schupf N, Tang MX, Albert SM et al (2005) Decline in cognitive and functional skills increases mortality risk in nondemented elderly. Neurology 65:1218–1226
18. Neale R, Brayne C, Johnson AL (2001) Cognition and survival: an exploration in a large multicentre study of the population aged 65 years and over. Int J Epidemiol 30:1383–1388
19. Nguyen HT, Black SA, Ray LA et al (2003) Cognitive impairment and mortality in older Mexican Americans. J Am Geriatr Soc 51:178–183
20. Pfeiffer E (1975) A short portable mental status questionnaire for the assessment of organic brain deficit in elderly patients. J Am Geriatr Soc 23:433–441
21. Lobo A, Saz P, Marcos G et al (1999) Revalidation and standardization of the cognition mini-exam (first Spanish version of the Mini-Mental Status Examination) in the general geriatric population [in Spanish]. Med Clin 112:767–774
22. Folstein M, Folstein S, McHugh P (1975) Mini-Mental State: a practical method for grading the cognitive state of patients for the clinician. J Psiquiatr Res 12:189–198
23. Mahoney F, Barthel D (1965) Functional evaluation: the Barthel Index. Md State Med J 14:61–65
24. Lawton M, Brody E (1969) Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontologist 9:179–186
25. Rades D, Kueter JD, Hornung D et al (2008) Comparison of stereotactic radiosurgery (SRS) alone and whole brain radiotherapy (WBRT) plus a stereotactic boost (WBRT+SRS) for one to three brain metastases. Strahlenther Onkol 184:655–662
26. Lagerwaard F, Levendag P, Nowak P et al (1999) Identification of prognostic factors in patients with brain metastases: a review of 1292 patients. Int J Radiat Oncol Biol Phys 43:795–803
27. Rades D, Dunst J, Schild SE (2008) A new scoring system to predicting the survival of patients treated with whole-brain radiotherapy for brain metastases. Strahlenther Onkol 184:251–255
28. Rades D, Pluemer A, Veninga T et al (2008) Comparison of different treatment approaches for one to two brain metastases in elderly patients. Strahlenther Onkol 184:565–571
29. Maher E (1994) How long have I got doctor? Eur J Cancer 3:283–284
30. Hwang SS, Scott CB, Chang VT et al (2004) Prediction of survival for advanced cancer patients by recursive partitioning analysis: role of Karnofsky performance status, quality of life, and symptom distress. Cancer Invest 22:678–687
31. Vigano A, Dorgan M, Buckingham J et al (2000) Survival prediction in terminal cancer patients: a systematic review of the medical literature. Palliat Med 14:363–374
32. Kaal EC, Taphoorn MJ, Vecht CJ (2005) Symptomatic management and imaging of brain metastases. J Neurooncol 75:15–20
33. Meyers C, Smith J, Bezjak A et al (2004) Neurocognitive function and progression in patients with brain metastases treated with whole-brain radiation and motexafin gadolinium: results of a randomized phase III trial. J Clin Oncol 22:157–165
34. Broadbent A, Hruby G, Tin M et al (2004) Survival following whole brain radiation treatment for cerebral metastases: an audit of 474 patients. Radiother Oncol 71:259–265
35. Murray K, Scott C, Zachariah B et al (2000) Importance of the mini-mental status examination in the treatment of patients with brain metastases: a report from the Radiation Therapy Oncology Group protocol 91-04. Int J Radiat Oncol Biol Phys 48:59–64
36. Brown P, Buckner J, O'Fallon J et al (2004) Importance of baseline mini-mental state examination as a prognostic factor for patients with low-grade glioma. Int J Radiat Oncol Biol Phys 59:117–125
37. Pereira J, Hanson J, Bruera E (1997) The frequency and clinical course of cognitive impairment in patients with terminal cancer. Cancer 79:835–842
38. Meyers C, Hess K, Yung A et al (2000) Cognitive function as a predictor of survival in patients with recurrent malignant glioma. J Clin Oncol 18: 646–650
39. Maione P, Perrone F, Gallo C et al (2005) Pretreatment quality of life and functional status assessment significantly predict survival of elderly patients with advanced non-small-cell lung cancer receiving chemotherapy: a prognostic analysis of the multicenter Italian lung cancer in the elderly study. J Clin Oncol 23:6865–6872
40. Meyer HA, Sinnott C, Seed PT (2003) Depressive symptoms in advanced cancer. Part 2. Depression over time; the role of the palliative care professional. Palliat Med 17:604–607
41. Meyers C (2003) The use of the mini-mental state examination to assess cognitive functioning in cancer trials: no ifs, ands, buts, or sensitivity. J Clin Oncol 21:3557–3558
42. Patchell RA, Tibbs PA, Walsh JW et al (1990) A randomized trial of surgery in the treatment of single metastases to the brain. N Engl J Med 322: 494–500
43. Andrews DW, Scott CB, Sperduto PW et al (2004) Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial. Lancet 363:1665–1672