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Cognitive impairment and quality of life in long-term survivors of malignant brain tumors

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Thirtysix long-term survivors following the treatment of a malignant supratentorial brain tumor were examined for cognitive functions and global level of autonomy. Eighteen patients were symptom-free (SF) and 18 had clinical and neuroradiological recurrence (RE). The control group included 30 healthy subjects. All subjects underwent a neuropsychological battery for general and specific cognitive functions. The level of autonomy was assessed by means of the Karnofsky Performance Scale (KPS) for oncological patients. SF patients showed less impairment than RE patients both at the tests, as well as on the KPS. The cognitive deficits were subclinical in most SF patients, the tests for attention, memory and word fluency being the most sensitive in detecting subtle dysfunctions. The association between tumor location and specific cognitive deficits was inconstant in both patient groups. The results suggest that even subtle cognitive deficits can prevent SF long-term survivors from returning to premorbid autonomy and occupations, and that neuropsychological tests may be used as complementary routine indicators of their quality of life. Furthermore, our data show that, in selected patients, combined treatments and therapeutic insistence do not necessarily have the same deleterious effects.

Key Words: malignant brain tumor — long-term survival — symptom-free patients — cognitive impairment — quality of life.

Introduction

Quality of life in cancer patients has long been defined as a multidimensional concept that encompasses physical, psychosocial and spiritual components, as well as a subjective sense of well-being as a whole [13]. Cognitive disabilities may seriously compromise the recovery of personal autonomy and social functioning, and thus condition the quality of life of brain tumor patients who survive for a long time after diagnostic surgery. In long-term survivors, the late effects of radiotherapy and chemotherapy are a main cause of cognitive impairment [7, 8, 10, 15, 16, 17, 20, 23, 27]. Neuropsychological assessment has proved useful in weighing the neurotoxicity of radiotherapy and chemotherapy in long-term follow-up [8], but the poor survival prognosis of brain tumor patients has allowed only irregular evaluation of cognitive outcome. Although many neuropsychological investigations have been performed in the survivors of childhood brain tumors [24, 25], their results cannot be extrapolated to adult patients because of biological differences in brain maturity and treatment response. Few studies have evaluated neuropsychological changes

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in adult long-term survivors, and those which have been carried out have used different selection criteria in terms of both the duration and histological grading of the disease, and made inconstant reference to SF patients [15, 16, 21, 27].

With these studies as background, we evaluated adult patients who had survived for a long time after the surgical diagnosis of a malignant supratentorial tumor, and who presented different degrees of disease activity (i.e. SF or RE patients). The primary aim of this study was to assess the cognitive performance of long-term survivors who were symptom-free at the end of treatment. These patients had failed to return to their premorbid quality of life despite the absence of disabling physical deficits or clinically evident cognitive impairment. Neuropsychological assessment was performed to estimate general and specific cognitive functions in the dominant and non-dominant hemisphere (i.e. abstract reasoning, attention, verbal and non-verbal memory, language, visuospatial perception, constructional praxia and frontal lobe functions), and to delineate a patient's pattern of strenghts and weeknesses pointing to a dysfunctional area. The neuropsychological tests were chosen on the basis of their standardization in previous normative studies, and their proven sensitivity in detecting subclinical cognitive deficits. The level of autonomy was expressed by the KPS, chosen because of its routine clinical use in evaluating the impact of chemotherapy and radiotherapy on the quality of life [29], and because of its proven inter-rater reliability and construct validity in relation to the evidence of disease, daily activities, and working [26, 31]. This was a pilot study concerning particular dimensions of the quality of life at a late stage of the disease. The results are discussed in terms of the delayed effects of treatment.

Subjects

The study involved 36 patients who had survived a supratentorial malignant brain tumor following surgery, radiotherapy and chemotherapy; 18 were symptom-free and 18 had clinical and neuroradiological recurrence. This group was a selected sample (24%) of a total of 150 in-patients chemotherapeutically treated in our department between January 1989 and January 1993. Long-term survival was defined on the basis of the disease duration following a specific histological diagnosis (WHO grading). The patients were selected if they had survived diagnostic surgery for at least 18 (grade IV glioma) or 36 months (grade III glioma, neuroblastoma) but could not return to premorbid well-being and occupations. The SF patients did not show any physical disabilities or specific cognitive deficits at clinical examination, but many of them reported a subjective mild to moderate mental slowing and various memory difficulties.

The RE patients presented moderate to serious neurological deficits, but in no case did clinical deficits prevent a patient from cooperating with the neuropsychological test procedures.

The characteristics of the patients, and the location and histology of the tumors are shown in Table I.

There were no significant differences between SF and RE patients in terms of age at clinical onset ($p = 0.33$), age at evaluation ($p = 0.57$), schooling ($p = 0.61$) or disease duration ($p = 0.57$). Contrast-enhanced CT scans did not show any sign of tumor in 11 of the SF patients, who presented only the focal surgery outcome in the left ($n = 6$) or right ($n = 5$) hemisphere; the remaining SF patients showed static or reduced tumor bulk without mass effects (1 right- and 6 left-sided). Tumor and focal mass effects were left-sided in 12 RE patients, and right-sided in the remaining 6. Table II shows the treatment characteristics. Diagnostic surgery was performed by biopsy in 6 RE and 10 SF patients, and by resection in the others. Reoperation was performed in 13 RE (once in 9, twice in 3, and three times in 1 case) and in 10 SF patients (twice in 2, and once in 8 cases) with no significant difference between the two groups.

Radiotherapy was performed in all patients using standard radiation doses (mean 5000 rads); the present evaluation was performed between 5 and 360 months after radiotherapy, by which time both the acute the subacute side effects induced by this treatment had disappeared. Chemotherapy was administered after surgery and/or after radiotherapy in all of the patients by means of different associations of cisplatin, carbiplatin and etoposide; a single schedule of treatment lasted 3 days and each cycle was repeated at 4-5 week intervals up to 7-10 cycles. All of the patients had received a similar number of chemotherapeutic cycles, and had completed the last cycle between 1 and 37 months before testing. There were no significant between-group differences in terms of the time between the present evaluation and diagnostic surgery, radiotherapy or chemotherapy. Almost all of the RE patients were receiving desametazone (4-8 mg/day), and antiepileptics (phenobarbital, carbamazepine or dintoin) were being given to almost all patients. Thirty healthy subjects served as controls. One-way analysis of variance did not show any significant differences between the control and patient groups in terms of age ($F = 0.39$, $p = 0.67$) or schooling ($F = 1.87$, $p = 0.16$) (Table I).

TABLE I. *Subject characteristics, and the location and histology of tumors.*

	RE patients (n=18)	SF patients (n=18)	Controls (n=30)
Age at clinical onset	34.16±8.34 (19-49)	31.22±9.63 (17-51)	
Age at testing	40.33±8.32 (23-53)	38.61±9.9 (20-55)	37.73±10.61 (20-60)
Schooling	11.33±3.58 (5-19)	10.72±3.61 (5-17)	12.20±3.19 (5-19)
Disease duration (months)	74±33.75 (24-132)	87.27±93.17 (20-420)	
Histology			
glioma grade III	12	12	
glioma grade IV	6	5	
neuroblastoma		1	
Tumor location			
right			
frontal		3	
fronto-parietal	1		
fronto-temporal	3	1	
fronto-insular	1		
parietal	1		
temporal		1	
temporo-parietal		1	
left			
frontal	3	2	
fronto-callosal	1	1	
fronto-parietal	2	1	
fronto-parieto-callosal	1		
fronto-temporal	1	1	
temporal	1	1	
temporo-occipital	1		
temporo-parieto-occipital	1		
parietal	1	3	
occipital		1	
thalamic		2	

Methods

The patients were rated on the KPS by a physician according to the original criteria [19].
The following neuropsychological tests were administered by another physician, who adopted the procedures and scoring described in the corresponding normative studies.
— The Raven Coloured Progressive Matrices are a test of abstract reasoning, which especially involves non-verbal abilities, and has proved sensitive to both right and left hemispheric damage [3].
— The Attentional Matrices allow attention to be measured in a simple digit cancellation task [28].
— The Trail Making test (parts A and B) gives a measure of the speed of visual exploration, recognition of numbers and letters, and visual-motor transposition, and is used to evaluate attentional functions, being sensitive to diffuse brain damage; the part B, reflecting the ability to shift attention to alternating stimuli, has proved sensitive to frontal lobe damage [6].
— The Design-Copying test needs the integrative functioning of the left and right hemispheres for correct spatial organization and reproduction of details, and reveals early signs of constructional apraxia in diffuse cortical impairment or posterior lesions [2, 11].
— The Token test is specific for receptive language disorders [12].
— The Word Fluency test on semantic cueing (colors, animals, fruits, towns) is a sensitive index in aphasic syndromes, and in cases of left frontal damage [28, 30].
— The Street test evaluates the ability to integrate biased visual information [28], and the Judgement of Line Orientation is a test for spatial exploration and perception: both of these tests have been proven sensitive to right posterior hemispheric damage [4, 5].
— Corsi Blocks Tapping is a test for the learning

TABLE II. *Treatment characteristics.*

	RE patients	SF patients	p
Number of operations	2±0.84 (1-4)	1.66±0.59 (1-3)	0.17
Interval between first surgery and testing (months)	43.83±24.69 (21-120)	72.16±82.21 (18-384)	0.17
Interval between radiotherapy and testing (months)	25±27.28 (5-120)	54.61±79.82 (6-360)	0.15
Cycles of chemotherapy	3.27±2.34 (1-8)	4.83±2.83 (1-10)	0.08
Interval between chemotherapy and testing (months)	6.66±9.52 (1-36)	8.38±11.12 (1-37)	0.62

of spatial positions, and can show right temporal dysfunctions [28].
— Story Recall evaluates the immediate and delayed retention of prose passages, and has been shown to be accurate in detecting left temporal dysfunctions [28].
T-statistics for unpaired samples were used to evaluate between group differences in the row scores produced by the cognitive tests and KPS ratings. A p value of ≤ 0.01 was considered to be significant. Furthermore, the patients' test scores were analysed according to the published norms and cut-off values in order to explore individual deficits and their association with tumor location. Spearman's coefficient was calculated in order to evaluate correlations between the KPS ratings and test scores.

Results

Table III shows the mean KPS ratings and test scores obtained in the subject groups. The KPS ratings were significantly higher in SF than in RE patients ($p = 0.01$).

TABLE III. *KPS ratings and neuropsychological test scores (mean±standard deviation) in patients and controls.*

	RE pts	SF pts	Controls	p*	p**	p***
KPS	77.77 ±14.37	88.88 ±11.82		0.01		
Raven Coloured Progr. Matrices	26.94 ±4.75	29.77 ±4.42	32.13 ±3.87	0.07	0.059	0.0002
Attentional Matrices	44.66 ±10.71	47.11 ±10.84	55.36 ±4.08	0.50	0.005	0.0005
Trail Making A	97.33 ±71.60	70.83 ±47.84	35.36 ±13.52	0.20	0.006	0.0019
Trail Making B	298.44 ±190.18	198.88 ±139.60	86.33 ±30.84	0.08	0.003	0.0002
Street	7.55 ±2.47	8.88 ±2.08	9.40 ±1.99	0.08	0.40	0.0109
Judgement of Line Orientation	20.77 ±5.85	22.11 ±5.13	22.96 ±5.02	0.47	0.57	0.17
Corsi Blocks Tapping	16.86 ±9.01	20.97 ±6.47	25.03 ±3.86	0.12	0.022	0.0013
Story Recall	7.84 ±5.68	11.99 ±4.12	13.87 ±1.85	0.01	0.081	0.0003
Word Fluency	13.91 ±8.12	17.06 ±4.15	23.64 ±3.30	0.15	0.0001	0.0001
Token	26.72 ±11.57	34.11 ±2.13	35.03 ±1.09	0.01	0.10	0.0074
Design-Copying	12.77 ±2.73	13.16 ±1.50	14 ±0	0.60	0.031	0.017

p*: RE vs DF patients. p**: DF vs controls. p***: RE vs controls.

TABLE IV. *Neuropsychological deficits revealed by tests in symptom-free patients.*

Pts	Tumor location	Defective functions
	Right hemispheric	
PT*	frontal	attention
PG*	frontal	attention
LM	frontal	attention, spatial perception, spatial learning
BC*	fronto-temporal	attention
RV*	temporal	attention
CS*	temporo-parietal	attention
	Left hemispheric	
CC*	frontal	attention
MM*	frontal	attention
SA	fronto-callosal	attention
SG	fronto-parietal	none
CI	fronto-temporal	none
BR	temporal	attention, verbal memory
LG*	parietal	attention, spatial perception
OG*	parietal	attention, spatial perception
MC*	parietal	attention, visual perception, spatial learning, word fluency, verbal memory
FA*	occipital	attention, spatial perception
FG	thalamic	attention
BC	thalamic	attention, word fluency

* Contrast-enhanced CT scan did not reveal any sign of tumor.

SF patients performed better than RE patients at every cognitive test, t-statistics showing significant differences at the Story Recall and Token test ($p=0.01$).

In comparison with the control group, SF patients showed impairment at the Attentional Matrices, Trail Making and Word Fluency tests ($p<0.01$); differences at the Corsi Blocks Tapping and Design-Copying tests only approached significance. Comparisons between RE patients and controls showed significant differences at every test ($p\leq0.01$), except for the Judgement of Line Orientation.

Two SF patients had scores within the normal range at every cognitive test. None of the SF patients showed a pathological score at the Raven Coloured Progressive Matrices. The Trail Making test and the Attentional Matrices showed deficits in respectively 16 and 3 SF cases. Seven SF patients had deficits in specific cognitive functions which in only 1 case were strictly congruent with lesion location; in 5 cases the deficits could be associated with dysfunctions in adjacent or distant brain areas and, in 1 case, they were bi-hemispheric (Table IV).

None of the RE patients had a completely normal cognitive performance. The Raven Coloured Progressive Matrices, Attentional Matrices, and Trail Making test produced defective scores in respectively 1, 5 and 18 cases. Twelve patients also had deficit in specific functions which were homolateral to the lesion side in 5, controlateral in 1, and bi-hemispheric in 6 cases (Table V).

In SF patients, Spearman's coefficient revealed significant correlations between KPS ratings and the scores of the Word Fluency and Corsi Blocks Tapping tests ($p<0.01$) whereas, in RE patients, KPS ratings correlated with every test score, except for the part A of the Trail Making test. These correlations were good as far as the Corsi Blocks Tapping, Story Recall, Word Fluency, Design-Copying and Token tests were concerned ($p\leq0.01$), but less significant in the case of the other tests ($p\leq0.05$) (Table VI).

Discussion

Neuropsychological evaluation highlighted some differences between the patient groups in terms of both the frequency and degree of cognitive impairment, greater impairment being apparent in RE patients. SF long-term survivors had mild to moderate cognitive deficits, mainly relating to attention, memory and frontal lobe functions (i.e. shifting attitude and word fluency) and only revealed by tests in most cases. In this regard, the Trail Making test proved to be the most sensitive instrument. Most of the RE patients showed multiple cognitive deficits, which were consistent with the clinical background in most cases. Since there were no differences between the SF and RE patients in terms of histological grading, tumor location or treatment characteristics, the data indicate that disease recurrence is the main factor in determining cognitive worsening in long-term survivors.

TABLE V. *Neuropsychological deficits revealed by tests in patients with tumor recurrence.*

Pts	Tumor location	Defective functions
	Right hemispheric	
PS	fronto-parietal	attention
DNM	fronto-temporal	attention
CC	fronto-temporal	attention
BC	fronto-temporal	attention, visual perception
SA	fronto-insular	attention
PC	parietal	attention, spatial learning
	Left hemispheric	
PE	frontal	attention
SG	frontal	attention
RG	frontal	attention, spatial perception
SV	fronto-callosal	attention, verbal memory
SG	fronto-parietal	attention, constructional praxia, word fluency, verbal comprehension, spatial perception, spatial learning, verbal memory
GC	fronto-parietal	abstract reasoning, attention, verbal comprehension, word fluency, spatial learning, verbal memory, constructional praxia
GF	fronto-parieto-callosal	attention, word fluency, verbal memory
CM	fronto-temporal	attention, word fluency, verbal comprehension, verbal memory, spatial learning
SMG	temporal	attention, word fluency, verbal memory, spatial learning
AE	temporo-occipital	attention, word fluency, verbal comprehension, visual and spatial perception, spatial learning, verbal memory
GAM	temporo-parieto-occipital	attention, verbal memory, word fluency, verbal comprehension
FI	parietal	attention, spatial perception, verbal memory

The lack of any consistent relationship between tumor location and the extension and degree of cognitive impairment has long been recognized: tumoral growth may allow the maintenance of some measure of residual neuronal function and induce fewer deficits than acute vascular lesions [1], but it may also have distant effects [9]. The pathophysiological characteristics of the tumor may partially explain the lack of relationship between lesion location and neuropsychological profile in tumor subjects. However, these findings may also be an example of the limitations of one of the main dogmas of neuropsychology, i.e. the correlation between locus of lesion and type of deficit. The data may be in agreement with the Lashley's classic principle of mass action and equipotentiality. Otherwise, it may be argued that the effects induced by the tumor involve areas connected with the lesion site, so that cognitive deficits may express the dysfunction of extended circuits rather than a dysfunction strictly related to the site of the tumor. Previous neuropsychological investigations in long-term brain tumor survivors have shown variable cognitive impairment, ranging

TABLE VI. *Spearman's correlation coefficients between KPS ratings and cognitive test scores in patient groups.*

	RE patients		SF patients	
	r	p	r	p
Raven Coloured Progressive Matrices	0.51	0.02	0.13	0.59
Attentional Matrices	0.51	0.02	0.09	0.70
Trail Making A	−0.34	0.16	−0.23	0.35
Trail Making B	−0.53	0.02	−0.23	0.34
Street	0.45	0.05	0.15	0.55
Judgement of Line Orientation	0.48	0.04	0.17	0.49
Corsi Blocks Tapping	0.75	0.0001	0.57	0.01
Story Recall	0.72	0.0004	0.13	0.60
Token	0.69	0.001	0.40	0.09
Word Fluency	0.56	0.01	0.61	0.005
Design-Copying	0.59	0.007	0.39	0.10

from mild attention and memory deficits to profound dementia [15, 16, 21, 27]. In previous SF cases, no clear effect of the tumor type and location has been documented, whereas the late effects of radiotherapy and chemotherapy have been indicated as the main causes of cognitive impairment [15, 23, 27]. The cognitive impairment observed in our SF patients may also be explained by the long-term effects of treatment, as a wide range of cognitive risk has been reported after both radio and chemotherapy. Late dementia [10], and attention and memory disorders [17], have been described after radiotherapy; and memory loss, disorientation and difficulty in abstract reasoning may follow leucoencephalopathy after treatment with carmustine, cisplatin, methotrexate and cytosine-arabinoside added to radiation [20]. Furthermore, chemotherapy itself may directly cause deficits in general cognitive functions [16]. However, other studies have underlined the safety of radiotherapy or chemotherapy in unradiated patients by showing the absence of cognitive risk [8], or a lower morbidity in patients treated with primary radiotherapy [7]. Our findings, concerning normal to moderately defective performance in SF long-term survivors, are also in contrast with a high level of treatment-related cognitive risk. The data suggest that the late toxic effects of therapeutic insistence, in selected patients, may be acceptable.

In analogy with their cognitive performance, SF patients had satisfactory KPS ratings which were significantly higher than those of the RE patients. This finding is in line with the absence of physical disabilities or evidence of disease in these patients, and is consistent with the construct validity of the KPS in discriminating disease recurrence. The different level of correlation between the KPS ratings and the test scores of SF and RE patients needs further consideration. In the original studies [18, 19], the KPS emphasized physical over psychosocial changes; recently, a relationship has been shown with patients' self-reports of everyday cognitive problems [22]. Our findings suggest that the KPS may be an indicator of cognitive impairment in patients with serious illness conditions, but that the correlation becomes poor in patients who are reasonably well. In SF patients who do not show any other disabling condition, subclinical to moderate cognitive deficits may be a main cause in preventing the recovery of full autonomy and well-being. In accordance with previous studies [8, 14], our data support the routine use of neuropsychological tests as indicators of subtle brain dysfunctions, and as complementary instruments for assessing particular aspects of the quality of life in SF patients. In any case, the present pilot study concentrated on a late disease stage; further longitudinal investigations are needed to examine cognitive changes during different periods of the disease and treatment. In addition, the assessment of the quality of life requires specific instruments capable of covering emotional and social dimensions.

Sommario

Trentasei pazienti, lungosopravviventi dopo il trattamento per un tumore sopratentoriale maligno, sono stati sottoposti ad una valutazione delle funzioni cognitive e del livello globale di autonomia. Diciotto pazienti erano asintomatici e 18 presentavano recidiva clinica e radiologica. Come gruppo di controllo sono stati esaminati 30 soggetti sani. Tutti i soggetti sono stati sottoposti ad una batteria neuropsicologica per la valutazione di funzioni cognitive generali e specifiche. Il livello di autonomia è stato definito mediante la scala di Karnofsky per pazienti oncologici. I pazienti asintomatici hanno mostrato una minore compromissione sia delle funzioni cognitive che del livello di autonomia rispetto a quelli con recidiva. I deficit cognitivi sono risultati modesti nella maggior parte dei pazienti asintomatici ed i test di attenzione, fluenza verbale e memoria sono apparsi i più sensibili nel rilievo di disfunzioni subcliniche. L'associazione tra sede del tumore e deficit cognitivi specifici è risultata incostante in entrambi i gruppi di pazienti. I risultati suggeriscono che deficit cognitivi anche lievi possono impedire il completo recupero dell'autonomia e delle attività premorbose nei lungosopravviventi asintomatici e che i test neuropsicologici possono fornire indici complementari nella valutazione routinaria della qualità di vita. I nostri dati inoltre mostrano che, in pazienti selezionati, l'insistenza terapeutica non induce necessariamente effetti deleteri.

References

[1] Anderson S.W., Damasio H., Tranel D.: *Neuropsychological impairments associated with lesions caused by tumor or stroke.* Arch. Neurol. 47:397-405, 1990.

[2] Arrigoni C., De Renzi E.: *Constructional aprax-*

ia and hemisphere locus of lesion. Cortex 1:170-197, 1964.

[3] BASSO A., CAPITANI E., LAIACONA M.: *Raven's coloured progressive matrices: normative values on 305 adult normal controls.* Funct. Neurol. 2:189-194, 1987.

[4] BENTON L.A., HAMSHER K., VERNEY N.R.: *Judgement of line orientation.* In: Benton L.A., Hamsher K., Verney N.R. (Eds.): Contribution to neuropsychological assessment, Otfried Spreen, pp. 44-54, 1983.

[5] BENTON L.A.: *Some problems associated with neuropsychological assessment.* Bull. Clin. Neurosci. 50:11-15, 1985.

[6] BORNSTEIN R.A.: *Classification rates obtained with standard cut-off scores on selected neuropsychological measures.* J. Clin. Exper. Neuropsychol. 8:413-420, 1986.

[7] CAVAZZUTI V., FISHER E.G., WELCH K., BELLI J.A., WINSTON K.R.: *Neurological and psychological sequaele following different treatments of craniopharyngioma in children.* J. Neurosurg. 59:409-417, 1983.

[8] CROSSEN J.R., GOLDMAN D.L., DAHLBORG S.A.N., NEUWELT E.A.: *Neuropsychological assessment outcomes of nonaquired immunodeficiency syndrome patients with primary central nervous system lymphoma before and after blood-brain barrier disruption chemotherapy.* Neurosurgery 30:23-29, 1992.

[9] DAMASIO A.R., GESHWIND N.: *Anatomical localization in clinical neuropsychology.* In: Vinken P.J., Bruyn G.W., Klawans H.L. (Eds.): Handbook of clinical neurology, vol. 45: Clinical neuropsychology, Elsevier Publishers, pp. 7-22, 1985.

[10] DE ANGELIS L.M., DELATTRE J.K., POSNER J.B.: *Radiation-induced dementia in patients cured of brain metastases.* Neurology 39:789-796, 1989.

[11] DE RENZI E.: *Disorders of space exploration and cognition.* New York: John Wiley and Sons 1982.

[12] DE RENZI, VIGNOLO L.A.: *The Token test: a sensitive test to detect receptive disturbances in aphasia.* Brain 85:665-678, 1962.

[13] DONOVAN K., SAMSON-FISHER R.W., REDMAN S.: *Measuring quality of life in cancer patients.* J. Clin. Oncol. 7: 959-968, 1989.

[14] FLECK J.F., EINHORN L.J., LAUER R.C., SCHULTZ S.M., MILLER M.R.: *Is prophylactic cranial irradiation in small-cell lung cancer?* J. Clin. Oncol. 8:209-214, 1990.

[15] HOCHBERG F.H., SLOTNICK B.: *Neuropsychological impairment in astrocytoma survivors.* Neurology 30:172-177, 1980.

[16] IIMPERATO J.P., PALEOLOGOS N.A., VICH N.A.: *Effects of treatment on long-term survivors with malignant astrocytomas.* Ann. Neurol. 28:818-822, 1990.

[17] JOHNSON B.E., BECKER B., GOFF W.B., ET AL.: *Neurologic, neuropsychologic and computed cranial tomography scan abnormalities in 2- to 10-year survivors of small-cell lung cancer.* J. Clin. Oncol. 3:1659-1667, 1985.

[18] KARNOFSKY D.A., ABELMANN W.H., CRAVER L.F., ET AL.: *The use of nitrogen mustards in the palliative treatment of carcinoma.* Cancer 1:634-656, 1948.

[19] KARNOFSKY D.A., BURCHENAL J.H.: *The clinical evaluation of chemotherapeutic agents in cancer.* In: MacLeod C.M. (Ed.): Evaluation of chemotherapeutic agents, New York: Columbia University Press, pp. 191-205, 1949.

[20] LEE Y.Y., NANERT C., GLASS J.P.: *Treatment-related white matter changes in cancer patients.* Cancer 57:1473-1482, 1986.

[21] LIEBERMAN A.N., FOO S.H., RANSHOFF J., ET AL.: *Long-term survival among patients with malignant brain tumors.* Neurosurgery 10:450-453, 1982.

[22] MACKWORTH N., FOBAIR P., PRADOS M.D.: *Quality of life self-reports from 200 brain tumor patients: comparisons with Karnofsky performance scores.* J. Clin. Oncol. 14:243-253, 1992.

[23] MARIE J., COUDIN B., GUERIN J., CAUDRY M.: *Neuropsychological impairment in adults with brain tumors.* Am. J. Clin. Oncol. 10:156-162, 1987.

[24] MOSTOW E.N., BYRNE J., CONNELLY R.R., MULVIHILL J.J.: *Quality of life in long-term survivors of CNS tumors of childhood and adolescence.* J. Clin. Oncol. 9:592-599, 1991.

[25] MULHERN R.H., KUN E.: *Neuropsychological functions in children with brain tumors: III. Interval changes in the six months following treatment.* Med. Ped. Oncol. 13:318-324, 1985.

[26] SCHAG C.C., HEINRICH R.L., GANZ P.A.: *Karnofsky performance scale revisited: reliability, validity and guidlines.* J. Clin. Oncol. 2:187-193, 1984.

[27] SICHEZ N., FAUCHON F., CHANTELARD J.V., ET AL.: *Quality of life in long term survivors of astrocytomas treated with surgery and radiation therapy: a neuropsychological study.* Abstract II Meeting European Neurological Society, p. S2, 1990.

[28] SPINNLER H., TOGNONI G.: *Standardizzazione e taratura italiana di test neuropsicologici.* It. J. Neurol. Sci., suppl. 8, 1987.

[29] TANNOCK I., MURPHEY K.: *Reflection on medical oncology: an appeal for better clinical trials and improved reporting of their results.* J. Clin. Oncol. 1:66-70, 1983.

[30] VILKKI J.: *Differential perseverations in verbal retrieval related to anterior and posterior left hemisphere lesions.* Brain Language 36:543-554, 1989.

[31] YATES J.W., CHALMER B., MCKEGNEY F.P.: *Evaluation of patients with advanced cancer using the Karnofsky performance status.* Cancer 40:2220-2224, 1980.

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