Integrative Cancer Therapies
10(2) 119–126

DOI: 10.1177/1534735410392575
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Rehabilitation in Neuro-Oncology: A Meta-Analysis of Published Data and a Mono-Institutional Experience

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Abstract

Background. Rehabilitation for cancer patients with central nervous system (CNS) involvement is rarely considered and data on its use are limited. The purpose of the present study is to collect all available published data on neuro-oncology rehabilitation and perform a meta-analysis where results were presented in a comparable manner. Moreover, the authors report results on cancer patients with neurological disabilities undergoing rehabilitation at their unit. **Study design.** A PubMed search was performed to identify studies regarding cancer patients with CNS involvement undergoing inpatient physical rehabilitation. Studies with a complete functional evaluation at admission and discharge were selected. As the most common evaluation scales were Functional Independence Measure (FIM) and Barthel Index (BI), only articles with complete FIM and/or BI data were selected for the meta-analysis. Moreover, 23 cancer patients suffering from diverse neurological disabilities underwent standard rehabilitation program between April 2005 and December 2007 at the San Raffaele Pisana Rehabilitation Center. Patient demographics and relevant clinical data were collected. Motricity Index, Trunk Control Test score, and BI were monitored during rehabilitation to assess patient progresses. BI results of patients in this study were included in the meta-analysis. **Results.** The meta-analysis included results of a total of 994 patients. A statistically significant ($P < .05$) improvement of both BI and FIM scores was demonstrated after rehabilitation (standardized mean difference = 0.60 and 0.75, respectively). Functional status determined by either FIM or BI improved on average by 36%. **Conclusion.** Published data demonstrate that patients with brain tumors undergoing inpatient rehabilitation appear to make functional gains in line with those seen in similar patients with nonneoplastic conditions.

Keywords

neuro-oncology rehabilitation, meta-analysis, Functional Independence Motricity scale, Barthel Index

Introduction

Central nervous system (CNS) involvement is a negative prognostic feature in cancer.[1] Poor prognosis is in fact associated with both primary and secondary CNS tumors. If patients with CNS metastases are virtually incurable and likely to have short survival, primary CNS cancers can be surgically cured depending on disease stage and histotype.

Thanks to therapeutic advances, cancer patients with CNS involvement are living longer and rehabilitative issues are gaining increasing interest.

Approximately 70% of primary brain tumors are gliomas, with 75% of these being high-grade tumors (glioblastomas or anaplastic gliomas).[2] Whereas high-grade gliomas are virtually incurable even after optimal surgery and adjuvant chemoradiation with a reported median overall survival of 12 to 14 months,[2,3] rate of cure reaches 50% to 70% for low-grade gliomas.[4-8]

Whereas physical rehabilitation is a cornerstone for patients suffering from traumatic[9] or cerebrovascular[10] CNS lesions and is a fundamental part of the entire therapeutic process for complete patient recovery, rehabilitation for cancer patients with CNS involvement is rarely considered and data on its use and effectiveness are limited.[11]

Poor diffusion of rehabilitation in neuro-oncology is mainly due to the skepticism about its real benefit in patients with poor prognosis such as cancer patients, for whom

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it is difficult to ensure a "long-lasting" compliance as complex and laborious rehabilitation interventions are planned.[4]

The objective of the present study is to report our experience on 23 cancer patients with neurological disabilities due to CNS tumor or neurotoxicity from anticancer therapy. We also collected all available published data on neuro-oncology rehabilitation and performed a meta-analysis where results were presented in a comparable manner.

Basically the same approach as for nonneoplastic CNS diseases (traumatic brain injury, stroke, and traumatic spinal cord injury) is pursued.[11] These interventions include both prevention and treatment of medical complications such as pain, spasticity, and neuropathic bowel and bladder and the improvement of patients' mobility and activities of daily living, with the ultimate objective of improving quality of life.

Table 1. Patients' Characteristics

Type of disease, N (%)	
Meningiomas	12 (52%)
Astrocitomas	3 (13%)
Glioblastomas	2 (9%)
Iatrogenic neuropathy	6 (26%)
Total	23 (100%)
Age (year)	
Median	66
Range	26-87
Male–female ratio	11:12
Mean CIRS ± SD	1.43 ± 0.25
Mean LOS (range)	95 days (7-213)

Abbreviations: N, number of patients; CIRS, comorbidity index rating scale; SD, standard deviation; LOS, length of stay.

Patients and Methods

San Raffaele Patients and Methods

Twenty-three cancer patients (12 meningiomas, 5 gliomas, and 6 nonbrain tumors with iatrogenic neuropathy) suffering from diverse neurological disabilities underwent a standard rehabilitation program between April 2005 and December 2007 at the San Raffaele Pisana Rehabilitation Center. Patient demographics and relevant clinical data were collected at admission. Motricity Index (MI),[12] Trunk Control Test (TCT) score,[12] and Barthel Index (BI)[13] were monitored during rehabilitation to assess patient progresses. Overall health status and comorbidities were evaluated using the Comorbidity Index Rating Scale and summarized by the Gravity Index (GI) score ranging from 1 to 5.[14]

All patients signed an informed consent form for the study. The research has been approved by the local institutional review board and ethics committee (San Raffaele Pisana Hospital).

Search Method for Meta-Analysis

A PubMed search was performed in November 2009 with the following key terms: "(metastatic) OR (neoplastic) OR (nontraumatic) OR (oncology) OR (cancer)" to select reports on cancer patients, "(rehabilitation) OR (functional outcome)" to select reports on rehabilitative interventions, "(Brain) OR (Myelopathy) OR (spinal cord)" to select reports on cancer patients with CNS involvement. The search had no restriction apart from English language.

Out of the retrieved articles, studies regarding cancer patients with CNS involvement undergoing inpatient physical rehabilitation with a complete functional evaluation at admission and discharge were selected.[15-27] A number of evaluation scales were applied in the studies; however, as the most common were Functional Independence Measure (FIM) and Barthel Index (BI) scales, only articles with complete FIM and/or BI data were selected for the meta-analysis. References of selected articles were used to identify further studies meeting the inclusion criteria. Reports with less than 11 patients were excluded.

Statistics

Overall TCT, MI, and BI scores are summarized by means and relative standard deviations for the entire cohort of San Raffaele patients before and at completion of rehabilitation. Changes in the score for each patient between entry and discharge were analyzed using the Wilcoxon test for paired samples as the data were considered not normally distributed. Efficiency, that is, (score at discharge − score at admission)/length of stay in days, was also calculated.

The effect of rehabilitation on FIM and BI scales were meta-analyzed for the studies responding to the aforementioned inclusion criteria.

The changes in the scores from baseline to the end of rehabilitation and 95% confidence intervals were measured in units of standardized mean difference (SMD), that is, SMD = difference in means/pooled standard deviation, and illustrated graphically using a forest plot.

Use of SMDs allows one to pool and compare measures of FIM and BI in different scales, as certain studies used only the motricity component of the FIM scale whereas others used the 5-point instead of 10-point Likert-type scale for the BI score. Since the meta-analysis was performed on a continuous measure (comparison of means between treated cases, ie, after rehabilitation, and controls, ie, before rehabilitation), the Hedges *g* statistic was used.

Both random-effects and fixed-effects models were applied using the *Q* test to assess for study heterogeneity. If

Table 2. Scales for Functional Status Assessment

Scale	Admission	Discharge	Difference	% Increase	Efficiency	*P* Value
Mean TCT (±SD)	63.78 (±30.3)	71.2 (±31.9)	+7.4 (±17.2)	+7% (±27%)	+0.08	.05
Mean MI (±SD)	286.0 (±83.5)	297.2 (±76.5)	+11.2 (±47.8)	+10% (±38%)	+0.12	.426
Mean BI (±SD)	69.7 (±27.1)	72.2 (±28.4)	+2.5 (±13.3)	+6% (±29%)	+0.03	.135

Note: TCT = Trunk Control Test; SD = standard deviation; MI = Motrcity Index; BI = Barthel Index.

the *Q* test showed a *P* value inferior to .05 (statistically significant), then the random-effects model was considered. Meta-analysis results were interpreted according to Cohen's rule of thumb for interpretation of the SMD statistic (a value of .2 indicates a small effect, a value of .5 indicates a medium effect, and a value of .8 or larger indicates a large effect). Statistical analyses were performed using MedCalc for Windows, version 9.5.0.0 (MedCalc Software, Mariakerke, Belgium).

Results

San Raffaele Experience

We treated 23 patients (12 females, 11 males; median age and range in years = 66, 26-87, respectively) with brain tumors (n = 17) or other tumors with anticancer therapy–related neuropathy (n = 6) at the San Raffaele Rehabilitation Center with a tailored program of rehabilitation (see Table 1 for patients' characteristics). The 3 analytic score systems employed to test patient functional status were evaluated before and at completion of the rehabilitative intervention (Table 2). An improvement in the functional status was recorded for all the scales, with a 7%, 10%, and 6% increase in the TCT, MI, and BI scores, respectively. However, the increase was statistically significant only for the TCT score ($P = .05$), probably because of the small sample size. Figure 1 displays the dot-line diagram for TCT scores at admission and at discharge.

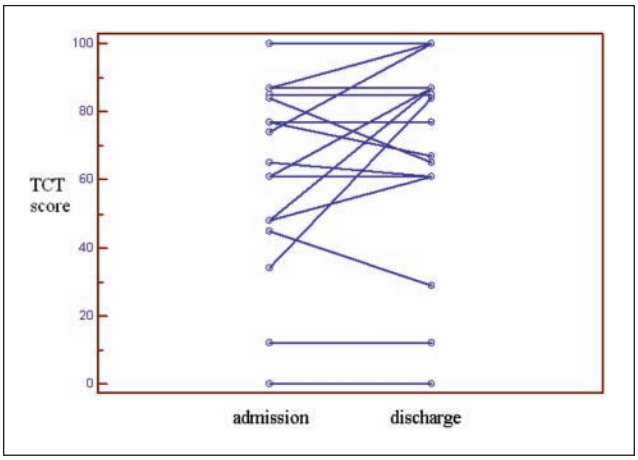


Figure 1. Dot and line diagram of Trunk Control Test (TCT) score changes

Meta-Analysis

Initial PubMed search retrieved 2568 publications. Of these, 11 retrospective trials (9 with complete FIM data and 2 with complete BI data) met the aforementioned inclusion criteria.[15,17-19,21-27] BI data of our patient cohort were also inserted in the BI meta-analysis (San Raffaele data). Table 3 summarizes results from the trials included.

Two studies reported FIM results not for the entire cohort of patients but for specific patient subgroups: the Greenberg et al[26] study divided patients into meningiomas (n = 128) and gliomas (n = 40), and the Tang et al[17] study divided patients into 3 groups—gliomas (n = 18), metastatic brain tumors (n = 25), and other primary brain tumors (n = 20). Moreover, in the Marciniak et al[24] study, results of the motor and cognitive FIM components were reported separately. These patient subgroups were analyzed in the meta-analysis as distinct study subpopulations. In the Geler-Kulcu et al[23] study, only the motor component of FIM scale was used.

A total of 994 patients were included in the meta-analysis (Table 3). Seventy-seven percent of the patients had primary or metastatic malignant tumor (717 out of 931 patients with available data), and 23% had benign tumors, mainly meningioma. Sex was equally represented (49.6% male, 50.4% female); the weighted average age was 59 years.

Mean length of stay in the rehabilitation facilities was 38 days (based on 683 patients with available data); 76% of patients were discharged to home (511 out of 671 patients with available data on discharge disposition).

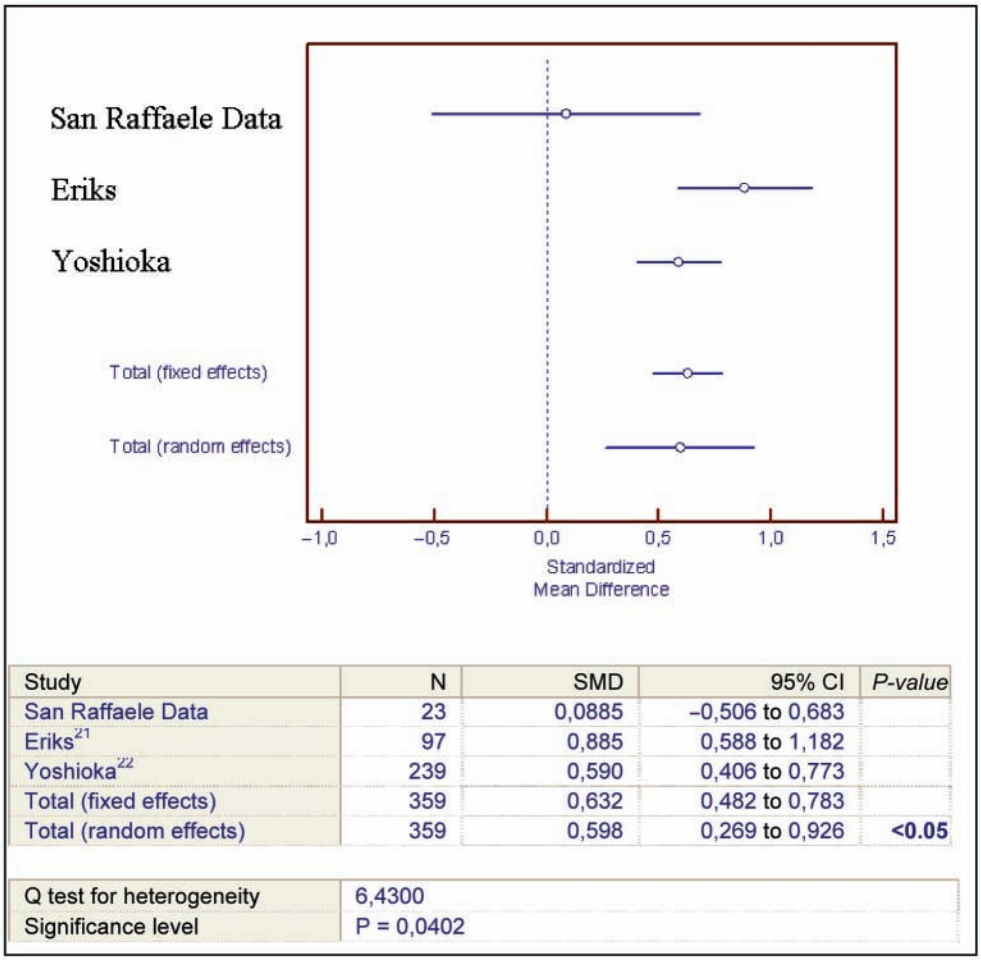
After rehabilitation, the functional status improved on average by 36% (weighted average of percentage improvement of either BI or FIM score).

The meta-analysis revealed a statistically significant ($P < .05$) effect of rehabilitation on both BI and FIM scores, with a SMD of 0.60 and 0.75, respectively. These results correspond, according to the Cohen's rule of thumb, to

Table 3. Summary of Data From Selected Studies

Study	N	Setting	Malignancy	Benign	Male	Female	Mean Age (Years)	Functional Assessment	Mean Score at Admission	Mean Score at Discharge	Score Change	Mean LOS (Days)	Distance to Home
San Raffaele data	23	Metastatic and nonmetastatic patients	15	8	11	12	66	BI	69.7	72.2	+6%	95	23
Eriks et al[21]	97	Metastatic spinal cord lesion	97	0	51	46	59	BI	7.2	12	+67%	103	59
Yoshioka[22]	239	Metastatic and nonmetastatic patients	239	0	96	143	62	BI	12.4	19.9	+60%	NA	NA
Geler-Kulcu et al[23]	21	Benign or malignant brain tumor, all resected	15	6	14	7	52	FIM	Mot = 17.7	Mot = 26.6	+50%	NA	NA
Huang et al[15]	63	Primary/metastatic benign/ malignant brain tumors	NA	NA	31	32	60	FIM	61	84.7	+39%	25	54
Marciniak et al[24]	132	Primary/metastatic benign/ malignant brain tumors	88	44	67	65	58	FIM	Mot = 42.0, cogn = 19.5	Mot = 59.1, cogn = 22.6	Mot = +41%, cogn = +16%	25	85
O'Dell et al[25]	40	Primary/metastatic benign/ malignant brain tumors	32	8	16	24	53	FIM	71.5	96.9	+42%	18	33
Tang et al[17]	63	Primary/metastatic benign/ malignant brain tumors	Glio = 18, met = 25, others = 20	0	28	35	Glio = 61, met = 61, others = 62	FIM	Glio = 84, met = 94, others = 71	Glio = 102, met = 107, others = 86	Glio = +21%, met = +14%, others = +21%	Glio = 28, met = 20, others = 37	46
Tang et al[18]	63	Metastatic spinal cord compression	63	0	30	33	62	FIM	83	102	+23%	23	NA
Greenberg[26]	168	Only primary brain tumors, both benign and malignant	40	128	99	69	Mening = 60, glio = 54	FIM	Mening = 80.1, glio = 68.2	Mening = 90.3, glio = 80.7	Mening = +13%, glio = +18%	Mening = 24, glio = 23	150
Mukand et al[27]	51	Primary or metastatic brain tumors. Only malignant included	38	13	33	18	58	FIM	67.2	87.1	+30%	NA	35
McKinley et al[19]	34	Neoplastic spinal cord compression	30	4	17	17	58	FIM	65.7	81.3	+24%	23	26
Total	994	—	77%	23%	49.6%	50.4%	59	—	—	—	+36%	38	75%

Note: N = number of patients; malig = malignant; LOS = length of stay; BI = Barthel Index; NA = not available; FIM = Functional Independence Measure; Mot = motricity component of FIM; cogn = cognitive component of FIM; glio = glioblastoma; met = metastatic tumor; mening = meningioma.



Study	N	SMD	95% CI	*P-value*
San Raffaele Data	23	0,0885	−0,506 to 0,683	
Eriks[21]	97	0,885	0,588 to 1,182	
Yoshioka[22]	239	0,590	0,406 to 0,773	
Total (fixed effects)	359	0,632	0,482 to 0,783	
Total (random effects)	359	0,598	0,269 to 0,926	**<0.05**

Q test for heterogeneity	6,4300
Significance level	P = 0,0402

Figure 2. Meta-analysis of Barthel Index (BI) data
Note: N = number of patients; SMD = standardized mean difference; CI = confidence interval.

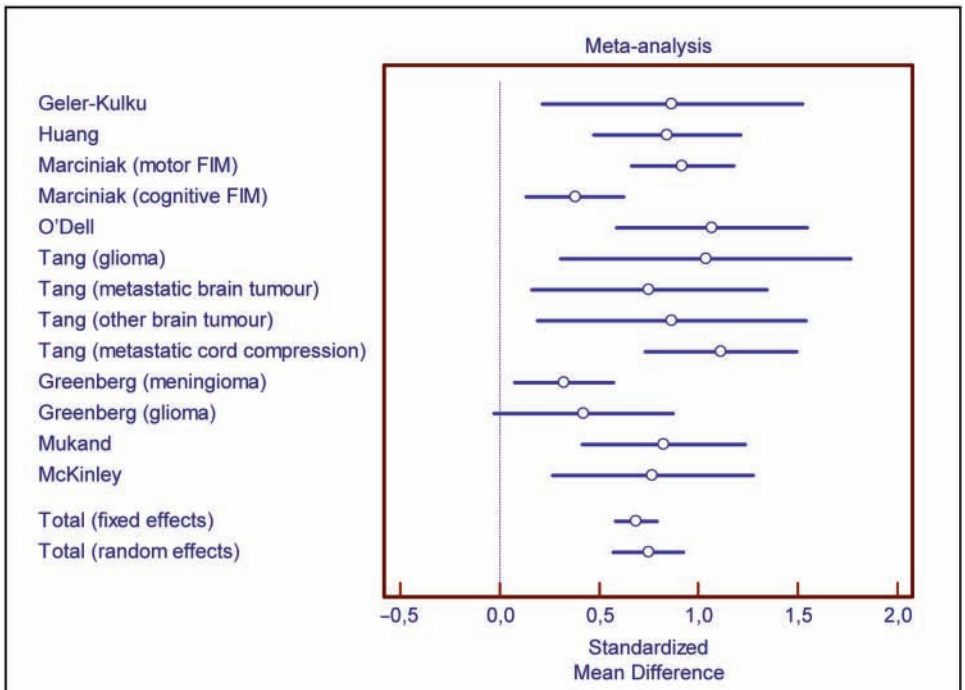
medium and large effects, respectively. Since the *Q* test for heterogeneity was statistically significant for both BI and FIM meta-analyses, the random effects model was considered (Figures 2 and 3).

Discussion

Referral to a rehabilitative facility remains low for cancer patients with CNS involvement. Results of a survey by Boake and Meyers[28] showed that a relevant number of rehabilitation hospitals treat no more than 10 patients with brain tumors each year. Rehabilitation is often considered of no potential benefit for patients with brain tumor because of the poor prognosis related to the underlying cancer disease. However, data from our experience and from 11 selected retrospective trials showed that inpatient rehabilitation may provide a functional improvement similar to that seen for nonneoplastic disease with an overall increase in independence of 36%. This gain is statistically significant and is a result of a meta-analysis on nearly a thousand patients. Improvement is demonstrated for both malignant and benign cancer patients and for both brain and spinal cord tumors. The median length of stay in hospital is also encouraging (approximately 1.5 month) with three quarter of the patients able to go back home after discharge.

However, these findings have a number of shortcomings.

1. Type and duration of rehabilitation programs may be different across the studies and can affect the outcome. A standardized therapeutic approach seems still far away, and a major effort should be made in this direction to make data consistent and comparable.
2. Patient cohorts were heterogeneous as benign and malignant and brain and spinal cord tumors are often pooled together in the studies.



Study	N	SMD	95% CI	*P-value*
Geler-Kulku[23]	21	0,868	0,213 to 1,523	
Huang[15]	63	0,844	0,476 to 1,213	
Marciniak (motor FIM)[24]	132	0,919	0,664 to 1,174	
Marciniak (cognitive FIM)[24]	132	0,379	0,134 to 0,623	
O'Dell[25]	40	1,068	0,591 to 1,546	
Tang (glioma)[17]	18	1,035	0,309 to 1,762	
Tang (metastatic brain tumour)[17]	25	0,753	0,163 to 1,343	
Tang (other brain tumour)[17]	20	0,865	0,192 to 1,537	
Tang (metastatic cord compression)[18]	63	1,111	0,731 to 1,491	
Greenberg (meningioma)[26]	128	0,324	0,0759 to 0,571	
Greenberg (glioma)[26]	40	0,423	−0,0276 to 0,873	
Mukand[27]	51	0,823	0,413 to 1,233	
McKinley[19]	34	0,770	0,267 to 1,273	
Total (fixed effects)	767	0,686	0,582 to 0,790	
Total (random effects)	767	0,748	0,573 to 0,922	**<0.05**

Q Test for heterogeneity	29,3220
Significance level	P = 0,0035

Figure 3. Meta-analysis of Functional Independence Measure (FIM) data
Note: N = number of patients; SMD = standardized mean difference; CI = confidence interval.

3. Scales employed for the functional assessment during rehabilitation varied across the studies and this renders the results difficult to meta-analyze.
4. A selection bias may be present as it is plausible that only patients with a good performance status and good prognosis were chosen for the rehabilitation treatment.
5. The retrospective nature of the trials conducted so far is also itself a major concern.
6. The benefit of rehabilitation has to be counterbalanced against a major ethical issue, as the time spent in the rehabilitative facility can be excessively long, especially when considering the relative short remaining time of life. In this respect, a

compromise between time spent at home with relatives and caregivers and time spent in the facility should be pursued.

All these biases and concerns are difficult to overcome; however, the present meta-analysis provides encouraging results that warrant further investigation in controlled prospective trials.

Furthermore, a randomized trial comparing nonneoplastic brain injuries to brain tumors could be designed in the near future. Among the articles selected, 5 studies have retrospectively compared effectiveness of rehabilitation in brain tumor patients with outcomes in nonneoplastic patients suffering from either ischemic or traumatic brain inj ury.[15,19,23,25,26] Patients were matched according to sex, age, and disease location within the brain and treated with a similar rehabilitation program. According to these studies patients with brain tumors are suitable for standard rehabilitation protocols as functional gains are comparable with that seen in nonneoplastic patients (20% to 50% improvement). Length of hospital stay was shorter for cancer patients with an average of 2 to 3 weeks time of admission and a high discharge to community rate (70% to 80%).

Conclusions

In conclusion, rehabilitation in cancer patients is a complex challenge as not just the physical impairment must be taken into account but social, vocational, and emotional issues are also raised. However, published data demonstrate that, thanks to tailored rehabilitation programs, patients with brain tumors might make functional gains in line with those seen in patients with nonneoplastic conditions.

Authors' Note

The present research was been carried out within the Experimental Physiopathology—Oncology Rehabilitation PhD program, "Tor Vergata" University of Rome.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interests with respect to the authorship and/or publication of this article.

Funding

The present research has been partially funded by the Italian Ministry of Health as a part of the national project RO 2006 titled "Quality of Life in Oncological Frail Patients. The Role of Oncological Rehabilitation: From Care to Take Care.

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