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REVIEW PAPER

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Challenges of rehabilitation for patients with primary malignant glioma – a review of recent literature

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ABSTRACT

Primary malignant glioma is one of the greatest challenges in contemporary rehabilitation. Due to the introduction of newer and newer methods of oncological treatment the overall survival in this group of patients retrospectively increased. This article is a review of the scientific literature of recent years concerning the principles of clinical assessment of patients with primary glioblastoma and the selection of methods in rehabilitation programs based on general condition. In the last years, there has been an increase in the results of clinical studies on the implementation of rehabilitation treatment in primary malignant glioma patients after oncological treatment. Thus, identification of accurate functional performance, behavior changes, evaluation of cognitive function, and cancer markers and oncological treatment as well as quality of life outcomes in this population are of major clinical importance. Primary malignant glioma patients represent a unique patient population with distinctive functional impairments and limitations to physical exercise. Therefore, individual comprehensive rehabilitation treatment may be useful in improving the physical and cognitive functioning as well as decreasing the fatigue syndrome. Such a therapy allows this group of patients to participate in society despite the consequences of cancer treatment.

Keywords: brain tumor, exercise, oncology.

Introduction

Malignant glioma (glioblastoma) is a major challenge in the oncology setting, with median survival nearly 100% of glioblastomas recur, usually within 6–8 months. However the median survival duration of glioblastoma patients in the last years was 14.9 months [1]. Several factors, including age, performance status, tumor grade and histology, and the number of prior progressions, molecular genetic factors, and therapy administered are strong independent predictors of survival in this population [2,3]. The current standard treatment for glioblastoma is surgical resection followed by 6 weeks of conventional fractioned radiotherapy or/and chemotherapy, followed by 12 months of adjuvant chemotherapy [4], although the use of off-label anti-angiogenic agents and other targeted therapies is not uncommon [5]. In a clinical trial setting, the current standard of care for patients with newly diagnosed glioblastoma multiforme (radiotherapy plus temozolomide followed by 6 cycles of adjuvant temozolomide) provided 2- and 5-year survival rates of 27% and 10% [6]. An additional treatment mainstay is the use of high-dose corticosteroids to control intracranial oedema. The use of such aggressive combination therapy together with tumour-related impairments can simultaneously directly (i.e., direct cytotoxic injury) or indirectly (i.e., effects secondary to therapy such as physical inactivity) deleteriously impact the organ components (i.e., the pulmonary-cardiac-muscle axis) that govern exercise tolerance [6]. Poor exercise tolerance leads to a vicious downward cycle characterized by deconditioning (physical inactivity), fatigue, and other functional limitations e.g. body composition changes, muscle atrophy, quality of life (QoL), and depression. Glioblastoma patients represent a unique patient population with distinctive functional impairments and limitations to physical exercise and they have been one of the greatest challenges for rehabilitation in the last years.

Therefore this paper is a review of recent scientific literature concerning the principles of functional assessment and the selection of methods in rehabilitation programs based on general condition in primary malignant glioma patients across the cancer trajectory.

Clinical assessment

Performance status assessment

Physical functioning plays an integral role in modulation of treatment and disease pathophysiology in malignant glioma [2,6,7]. In the current clinical practice, oncologists rely exclusively on the use of subjective performance status scoring systems (e.g., Karnofsky Performance Status (KPS), and the Modified Barthel Index (MBI) or Eastern Cooperative Oncology Group (ECOG) to evaluate functional status in primary malignant glioma patients [8,9]. Study findings show [8–10] that higher KPS and ECOG correlate with improved outcomes. The size, location, and infiltration of a malignant brain tumor may impair the autonomic nervous system response causing dysregulated peripheral sympathetic activation which, in turn, leads to decreased skeletal muscle blood flow and early acidosis. Several methods are available to clinicians that provide objective determinations of physical functioning in the oncology setting [7]. Of these, a 6-minute walk test (6MWT) is a simple and clinically feasible method to evaluate functional capacity and is a robust predictor of mortality in numerous clinical settings [6]. According to the Jones study [11] in 171 patients (70% were diagnosed with glioblastoma multiforme – WHO grade IV, and 85% were undergoing therapy), the 6MWT distance is a clinically feasible tool that provides an objective measure of physical functioning in selection of patients with recurrent glioma. Opposite results of the Ruden et al. study [12] indicate that the clinical utility of the 6MWT may not extend to glioma. A potential explanation is that patients with recurrent glioma may display neurologic impairment that limits their ability to adequately perform a walking test. Other important finding was that functional capacity, as measured by a 6MWT, was not associated with survival in patients with recurrent glioma [12]. On the other hand, Activity Daily Livings scales (ADLs) and exercise behavior are often considered to be synonymous. However, these measures evaluate different aspects of physical functioning [13]. ADLs evaluate the patient's ability to bathe, feed etc., whereas exercise is defined as a planned, structured, and repetitive physical activity performed in leisure time. Together, these results indicate that basic ADLs appear to be well preserved in patients with malignant glioma and, as a result, do not provide prognostic value, whereas exercise behavior successfully discriminates mortality risk. The functional independence measurement and functional activity measurement system (Functional Independence Measures – FIM and Functional Assessment Measures – FAM) may be used to objectively determine impairments in different domains [14]. Therefore, they are recommended for assessment in rehabilitation of glioma patients.

Cognitive dysfunction

Neuro-cognitive function is a very important determinant of QoL. It is well known that impairment of neuro-cognitive functioning, resulting in behavioral, emotional, and intellectual difficulties, occurs in nearly all patients with brain tumors and eventually compromises their independence. The medical factors and complications, including endocrine dysfunction, metabolic disturbances, infection, and pain can also contribute to cognitive and neuro-behavioural changes in this group of patients [15–18]. Psychological reaction such as anxiety, depression, and uncertainty about the future, and a combination of these factors is likely to contribute to cognitive impairment [15]. This impairment is related to a combination of various factors, including the tumor itself, tumor-related epilepsy, oncological treatment, and patient-related factors (e.g., age, psychological distress). Most studies on neuro-cognitive function in brain tumor patients pertain to those with low-grade glioma, and only a few studies have collected follow-up data in high-grade glioma patients [15, 17]. The published studies have generally used a retrospective design, or insensitive screening instruments for this patient population, such as the Mini-Mental State Examination [17]. Cognitive functioning was very often assessed by researchers and clinicians with a battery of standardized tests [19]. Meyers et al. [15] reported that cognitive function but not ADLs was an independent predictor of survival in patients with glioblastoma after adjustment for age, KPS, histology or time since diagnosis. Cognitive deficits, potentially compromising QoL, are commonly observed in glioblastoma patients in different stages of the disease [16, 20]. The neuro-cognitive deficit occurs during the oncological disease and so treatment is very important to patients and their caregivers, because these limitations interfere with QoL.

Quality of Life

As Dietz states, in fact, the goal of rehabilitation for people with cancer is to improve the QoL for maximum productivity with minimum dependence, regardless of life expectancy [20]. Porter's study results [21] showed that primary site was significantly associated with functional well-being. Shorter length of time from diagnosis to survey had a significant positive effect on several QoL domains and shorter length of time from completion of radiation to survey was associated with better physical well-being in glioma patients [21]. Common questionnaires, e.g., European Organization for Research and Treatment of Cancer (EORTC) Core Quality of Life Questionnaire, and Functional Assessment of Cancer Therapy (FACT) cancer-specific scales are used to assess health-related QoL in glioblastoma patients [22]. Interpretation of the impact of standard and new therapies on QoL in glioblastoma patients is consequently problematic, even when attempting to classify their effect into the three broad categories of negative, positive, or neutral. In agreement with some brain tumor studies [21, 23], but contradictory to another study [24], were findings of no association between QoL and lateralization of the tumor (left, right, or midline symmetry). The analysis of QoL data is challenging due to the high rates of non-random missing QoL values that may be linked to patients' QoL status, and if ignored may introduce bias in the interpretation of results [25]. Conversely, radiotherapy may decrease QoL in some patients due to adverse effects such as fatigue, somnolence, or cognitive problems. The effects of antiepileptic medication on QoL have been less extensively studied in patients with high-grade glioma, although some studies have reported a negative impact [26]. The effects of corticosteroid would be expected to decrease QoL [27]. Among newly diagnosed glioblastoma patients randomized to radiotherapy alone or radiotherapy plus temozolomide, the addition of temozolomide had no significant negative effect on QoL measures, except on social functioning ($p > 0.05$) [27]. Similarly, among first-relapse glioblastoma patients, temozolomide had no significant negative effect on QoL, although responders to temozolomide had improvement in most QoL scores, e.g., global, motor dysfunction, emotional function, future uncertainty, and communication deficit [28]. However, reliable serial measurement of QoL in patients with primary glioma patients is notoriously difficult, relating to many factors but particularly dropout bias or inability to repeatedly complete complex forms. It would appear that there is a progressive decrease in QoL during the course of high-grade glioma that substantially accelerates once the disease relapses. This is also expressed as deterioration peaks driven by the therapies administered (e.g., radiotherapy) or by the exacerbation of accompanying syndromes (e.g., brain edema, neurological symptoms, psychiatric disturbances).

Fatigue syndrome

Cancer-related fatigue is defined by the National Comprehensive Cancer Network (NCCN) as a persistent, distressing, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning [29]. The average level of fatigue experienced by glioma patients is about 40–50% higher than normative levels for cancer patients, equating to approximately five times the clinically meaningful difference [7, 30, 31]. Powell with collegues' study [32] demonstrated that fatigue is a prominent pretreatment symptom in patients with newly diagnosed and operated glioblastoma, reaching a prevalence of 48% compared with only 11% among healthy controls. Fatigue in patients with primary brain tumors has repeatedly been reported in relation to radiotherapy [32]. The authors indicated that the contribution of toxicity from radio-chemotherapy to fatigue is probably only one factor among many. After Peters' study [33] the authors concluded that greater degree of fatigue was associated with poorer survival in high-degree glioma patients, and FACT scales are not independent predictors of prognosis. Fatigue was a strong independent predictor of survival that provides incremental prognostic value to the traditional markers of prognosis in recurrent glioma [33]. The authors concluded that pharmacological or non-pharmacological strategies (e.g. rehabilitation) are effective methods to decrease the fatigue syndrome.

Practical rehabilitation

Physical exercises

Increasing evidence suggests that exercise modulates a range of systemic factors (e.g., metabolic and sex-steroid hormone concentrations, immune surveillance/cytokine or angiogenic factors, and products of oxidation) that, in turn, may alter ligand availability in the tumor microenvironment with subsequent effects on relevant cell signaling pathways [34, 35]. Markedly reduced strength and fitness capabilities compared to age- and sex-matched norms have also been reported in glioblastoma patients [36]. For example, the maximal muscular strength was observed to be 57 ± 28% of predicted values and cardiorespiratory fitness reported to be 41 ± 10% of predicted values among clinically stable patients following surgery and unfavorable changes in body composition are also apparent with a loss of lean mass and gains in fat mass evident following surgery [36]. Many randomized trials demonstrate that structured physical training is a safe and well-tolerated therapy associated with significant improvements in several clinically relevant outcomes, such as cardiorespiratory fitness, QoL, and fatigue in patients with other cancer than brain tumors both during and after primary adjuvant therapy [34]. Actually, there have been no randomised clinical trials evaluating the efficacy of exercise in counteracting the physical impairments experienced by primary glioma patients. In the study by Schmitz et al. [37], an unexpected finding was the relatively high number of participants who reported meeting the American College of Sports Medicine exercise prescription guidelines for cancer survivors of achieving at least 150 min per week of strenuous/moderate exercise [38]. Physical exercise may represent a supportive intervention that may complement existing neuro-oncologic therapies and address a multitude of therapy-induced debilitating side effects in patients with brain tumours. In recent years, increased attention has focused on exercise as a rehabilitative intervention for cancer survivors both during and after the cessation of cancer therapy [34,39]. In the study by Hansen [40], the authors prepared exercise training for glioma patients which included individually tailored strength training of main muscle groups with increasing load ranging from 15 to 10 repetition maximum (RM) (leg press, arm flexion, arm extension, knee flexion and knee extension), cardio-training (20 min of cycling or treadmill with intensities ranging from 65% to 85% of the heart rate reserve), body awareness training or relaxation (training of proprioception, postural control or stability of the core muscles tailored to personal needs). The strength training workload was calculated based on baseline tests and included in patients' training diaries with progression instructions. The cardiovascular training was monitored by pulse by means of a wireless heart rate transmitter worn by the patients [38]. The authors [40] did not observe any side effects of this training during 6 weeks. Physical exercise in glioma patients may trigger processes facilitating neuroplasticity and, thereby, enhances an individual's capacity to respond to new demands with behavioral adaptations. A final and important potential mechanism is an abnormal neurohormonal response to exercise due to disease burden and surgical excision of normal brain tissue. The exercise response is governed by the interplay between central command and afferent information from the exercising muscles [40].

Neuropsychological training

Cognitive impairment is one of the most common neurological disorders in brain cancer patients and exerts a deep negative impact on QoL interfering with family social and career-related activities. It is well known that oncological treatment may increase cognitive deficits. For example anaemia and fatigue, common symptoms in patients with glioblastoma, might affect cognitive function. Massa and et al. [41] investigated the effectiveness of erythropoietin during chemotherapy on cognitive function in ten elderly patients with cancer and anaemia, and their results supported the hypothesis that increases in haemoglobin concentrations are accompanied by significant improvement in cognitive performance as measured by the Mini-Mental State Examination. Pharmacologic interventions have not proven effective yet in the treatment of cognitive deficits in patients with glioblastoma. Cognitive rehabilitation interventions represent an alternative treatment approach. Zucchella et al. [42] in randomized controlled trial of cognitive training for glioma patients demonstrated a significant enhancement of cognitive performances after the 16 one-hour individual session of cognitive training (combining computer exercises and meta-cognitive training). In rehabilitation group the authors showed [42] a significant improvement of cognitive functions especially the visual attention and verbal memory. In a randomised controlled trial in 140 adult patients with low-grade and anaplastic gliomas after cognitive rehabilitation (individual two-hour sessions six times a week; conducted by one of neuropsychologists, incorporating both cognitive retraining and compensation training) Gehring with collegues [43] observed significant improvement in self-reported cognitive functioning at the immediate post-intervention assessment, and during the 6-month follow-up assessment – significantly better results than the control group tests of attention and verbal memory. The patients also reported less mental fatigue. The intervention incorporated both computer-based attention retraining and compensatory skills training of attention, memory, and executive functioning [43]. Alvares with colleagues [44] suggest that EEG biofeedback has potential for reducing the negative cognitive and emotional sequelae of cancer treatment as well as improving fatigue and sleep patterns. New evidence indicates that exercise exerts its effects on cognition by affecting molecular events related to the management of energy metabolism and synaptic plasticity [45]. Physical exercise has demonstrated an extraordinary aptitude to influence molecular pathways involved in synaptic function underlying learning and memory. An instigator in the molecular machinery stimulated by exercise is brain-derived neurotrophic factor, which has an influence on the interface of metabolism and plasticity [45].

Occupational therapy

Occupational therapy is a very important element of comprehensive rehabilitation. It comprises training in activities of daily living such as bathing, grooming, dressing, toileting, meal preparation, and homemaking. It is one of the most important exercises during oncological treatment [46]. In addition, occupational therapists evaluate home environments for potential modification, provide instruction in driving with adaptive devices, and implement interventions to promote upper extremity range of motion (ROM), strength, endurance, and coordination. The training focuses on bettering the patients' functional capacity, body, activity and participation level by adapting activities, regaining or developing activity abilities and/or rebuilding and developing patient skills [38]. In the study by Yoon et al. [45] conducted in 40 patients, the authors concluded that virtual reality-based rehabilitation combined with conventional occupational therapy may be more effective than conventional occupational therapy, especially for proximal upper-extremity function in patients with brain tumor.

Discussion

Because of the recent advances in surgical techniques, chemotherapy, and radiation therapy, survival times of patients with glioblastoma have increased and more of these patients require rehabilitation support and services [47, 48]. The International Classification of Functioning, Disability and Health (ICF) [49] framework defines a common language for describing the impact of disease at different levels. For example, brain tumour related 'impairments' (headaches, seizures, neuro-cognitive dysfunction, paresis, dysphasia), can limit 'activity' (decreased mobility, inability to self-care) and 'participation' (work, family, social reintegration), and reduce QoL [50]. FIM-FAM system is relatively simple, easy to perform in routine clinical practice and may be used as a tool for assessment of rehabilitation programs, especially in neurological disorders [14]. A close relationship between the medical and rehabilitation teams is necessary to maximize improvement because rehabilitation can be hampered by treatment side effects. It is plausible to assume that neuro-cognitive function, irrespective of clinical stage, may also have prognostic implications even after initiation of therapy and during the course of oncological treatment. Few studies have addressed the problem of methodology in glioblastoma patients in depth, and several limitations have to be mentioned. First, many groups have included patients with all sorts of primary brain tumors despite large differences in underlying neurobiology, treatment procedures, and prognosis. The majority of studies have reported statistically significant findings across a wide range of psychosocial (e.g., depression, anxiety, symptoms, etc.) and physiologic (e.g., muscle strength, immune and metabolic profiles, body composition) endpoints, culminating in clinically meaningful improvements in the patient's functional capacity and overall QoL in cancer patients [51, 52]. Many recent trials recommend comprehensive rehabilitation intervention in primary glioma patients in all stages of the disease for restoring function after cancer therapy, and in advanced stages of the disease as important part of palliative care with the aim to prevent complications, control the symptoms and maintain patients' independence and QoL [45, 47, 53–55].

To conclude, primary malignant glioma is one of the greatest challenges in contemporary rehabilitation. Identification of accurate functional performance, behaviour changes, evaluation of cognitive function, and markers of prognosis in oncological treatment may be useful in implementing individual comprehensive rehabilitation treatment. Such a therapy allows this group of patients to participate in society despite the consequences of cancer and oncological treatment.

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