15 Improving Patient's Functioning and Well-Being with Neurorehabilitation

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There are two main types of brain tumours: primary and secondary brain tumours [1]. Primary brain tumours originate from cellular abnormalities in brain tissue or in the tissues surrounding the brain. The most prevalent type of primary brain tumours in adults are meningiomas. Meningiomas are tumours that arise in the meninges, the layers of tissue that surround the outer part of the brain and spinal cord. Regarding tumours that originate in the brain itself, in childhood the majority of tumours that arise from brain tissue are neuronal tumours, while in adults the far majority originate from glial cells and are called gliomas, such as astrocytomas, oligodendrogliomas, glioblastomas and ependymomas [2]. Secondary brain tumours, also known as metastatic brain tumours or brain metastases, originate from tumours outside the central nervous system that have metastasized to the brain. In adults, metastatic brain tumours are even more common than primary brain tumours [2]. Brain tumours can be either malignant, including gliomas, primary central nervous system lymphomas (PCNSL) and brain metastases, or benign, such as the majority of meningiomas.

The overall symptom burden and disability in patients with brain tumours are significant [3–5]. Brain tumour patients may suffer from a variety of tumour-induced neurological symptoms including seizures, focal neurological deficits, cognitive deficits and behavioural and personality changes, in addition to more general cancer-related and treatment-induced symptoms such as nausea and vomiting, depression, anxiety and fatigue. These symptoms can have substantial negative

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impact on the patient's activities in daily life and his/her social interactions, as well as the patient's health-related quality of life (HRQoL) [6–10].

The prognosis of brain tumour patients may range from only several months (e.g. brain metastases) to more than 20 years (e.g. low-grade gliomas or meningiomas), and depends on tumour characteristics (histopathology and grade, cytogenetic abnormalities) and patient factors such as age and clinical condition [11]. There is a variety of treatment options for brain tumour patients. Currently, anti-tumour treatment consists of surgery (resection or biopsy for diagnostic reasons), radiotherapy and/or systemic chemotherapy, depending on the type and location of the tumour. Other more recently developed interventions include targeted treatment and immunotherapy [12–18]. In addition, supportive treatments (e.g. anti-epileptic drugs and corticosteroids) are administered to relieve symptoms [19–26].

Given the progressive and incurable nature of most gliomas and brain metastases, treatment is intended not merely to prolong life, but also to relieve the patient's symptoms and maintain or improve the patient's functioning, as well as to preserve patient's HRQoL as much and as long as possible. Apart from incurable brain tumours, also benign brain tumours may lead to longstanding decrease in functioning and well-being, be it due to the tumour or its treatment. Although anti-tumour treatment may result in improved functioning, neurorehabilitation can be seen as an additional supportive treatment option to maintain or improve functioning and well-being during the disease trajectory. Neurorehabilitation offers a variety of therapies that focus on helping patients with neurological diseases to overcome their disabilities by improving and/or preserving specific aspects of patients' functioning. These therapies include developing motor, communication and cognitive skills, coping with psychological problems and educating daily life functioning and community reintegration. By improving and/or preserving functional abilities and educating on how to cope and adjust to more permanent functional deficiencies, neurorehabilitation ultimately aims to improve the patient's HRQoL.

This chapter will focus on the role of neurorehabilitation in improving brain tumour patients' functioning. First, we will discuss how patients' functioning is defined and can be measured. Next, we will focus on neurorehabilitation treatment options, taking into account their impact on the different levels of functioning.

15.1 Levels of (Dys)function

Health is not only defined as physical well-being. In 1948, the World Health Organization (WHO) defined health as "*a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity*" [27]. The WHO International Classification of Functioning, Disability and Health (ICF) describes changes in health and health-related domains on three levels of human functioning: (1) body, (2) person and (3) society. For these three levels, respectively, changes in health can manifest as (a) impairments, (b) activity limitations and (c) participation restrictions.

Impairments are losses or abnormalities of body functions or structures and reflect the basic level of well-being [28]. As mentioned earlier, brain tumour patients may suffer from a wide range of impairments, including physical and cognitive impairments [6–10].

As a result of these *impairments,* persons might be constraint in their ability to perform activities of daily living (ADL). This is referred to as *activity limitations* [28–30]. ADL can be categorized in basic activities of daily living (BADL) and instrumental activities of daily living (IADL). BADL include basic skills such as walking and taking care of one's self [31]. IADL, on the other hand, include skills required for autonomous functioning like driving, handling finances and the ability to use a computer or smartphone [31, 32].

Activity limitations, in turn, may result in problems at the highest level, the societal level. Dysfunction on this level is referred to as *participation restrictions* [28–30]. Whereas *activity limitations* refer to problems with specific activities, *participation restrictions* reflect the interference the bodily *impairments* and *activity limitations* have on a person's ability to fulfil a certain role at work or school, in the home or during community or leisure activities. The WHO ICF states: "*Activity limitations are difficulties an individual may have in executing activities. Participation restrictions are problems an individual may have in involvement in life situations*" [29, 30].

As an example, a brain tumour patient with severe memory and concentration problems (*impairment*) is no longer able to work (*activity limitations*), and is therefore restricted in his/her ability to be an active member of the working society (*participation restriction*). Therefore, functional decline or disabilities on a basic level of functioning can have an extensive negative impact on higher levels of functioning and well-being.

15.2 Value of Functional Assessments in Research and Clinical Practice

Assessing patients' level of functioning is valuable in both clinical research and clinical practice. In clinical drug trials, outcome measures reflecting the patients' functioning are used to determine the net clinical benefit of a treatment strategy, in conjunction with traditional outcome measures such as overall and progression-free survival and objective response rate on imaging. The net clinical benefit is determined by how a patient "feels, functions, or survives" [33, 34]. Historically, overall survival has been the favoured primary endpoint in clinical trials, as it is generally viewed as the ultimate objective and a reliable measurement of treatment effect. However, patient-centred outcome measures are increasingly implemented as secondary outcome measures to determine the net clinical benefit [33, 34]. In contrast to clinical drug trials, outcome measures in neurorehabilitation trials reflecting the patients' functioning are usually the primary endpoint. The focus of rehabilitative treatment could be on a single or multiple domains, such as physical, cognitive or emotional functioning, activities of daily living, or social or vocational skills.

In clinical practice, assessing the level of functioning is particularly useful. Foremost, functional assessments are implemented to assess individual patient's present level of functioning and at multiple intervals to monitor for potentially foreseen and unforeseen functional decline during the course of disease and/or treatments [35]. Outcomes on functional assessments can have several applications. Functional outcomes may be used, for example, to determine if the patient's physical state is well enough to undergo or continue certain treatments (e.g. patients with Karnofsky performance status (KPS) scores >70 [36]), if measures need to be undertaken to avoid any (further) decline (e.g. physical therapy to avoid muscle atrophy), if alterations need to be made to the treatment regimen to better manage symptoms (e.g. adjusting anti-epileptic drug or dose) or if treatment has been or continues to be effective (e.g. functional improvements due to tumour response). Furthermore, functional outcomes on each level of well-being can facilitate the patient–physician communication and can be applied in shared decision-making regarding treatment options. Especially the functional assessments of the higher-order level of functioning (i.e. participation restrictions) can make the physician aware of potential problems beyond the purely physical or cognitive symptoms and may improve the patient's overall functioning and well-being [35].

15.3 Measuring (Dys)function

The US Food and Drug Administration (FDA) categorized patient-centred outcome measures, referred to as clinical outcome assessments (COAs), into four subtypes based on the source of information: patient-reported outcome (PRO) measures, observer-reported outcome (ObsRO) measures, clinician-reported outcome (ClinRO) measures and performance outcome (PerfO) measures [37]. ClinRO measures are measurements based on the evaluation of health care professionals, while PROs directly reflect the patient's perspective [38]. Although the consensus is that patients are the best source to rate their functioning and well-being [39], there are situations where patients may not be the most reliable source. In that case, ObsRO measures may be useful. Proxy ratings should be considered as a potentially appropriate alternative in neuro-oncology because proxies might better judge the patients' functioning in those situations where patients are cognitively impaired or have a very poor health status. Lastly, PerfO measures assess patient's (physical or neurocognitive) functioning based on their performance on a task and are, unlike the other outcome measures, objective measurements. PerfOs have the benefit of having good face validity and reproducibility, are sensitive to change over time and may detect functional limitations before it is reflected in the self-reported questionnaires (PROs) [40]. However, they are typically more expensive, time consuming and burdensome for patients. Furthermore, a recent systematic review found moderate to large correlation coefficients between the self-reported and performance-based assessment within the same domain of disability [41].

The development of measurement tools evaluating levels of functioning mirrors the evolution of the concept of dysfunction. At first, measurement tools were developed that mainly focused on assessing impairments (physical capabilities and sensory abilities), shifting to an increase in the development of tools assessing self-care abilities (e.g. BADL and IADL) and more recently towards social participation (fulfilment of social roles) [42–44]. Since (dys)function is a broad multi-dimensional concept, it can be challenging to measure this entire concept accurately.

In neuro-oncology, several COAs are used to assess the different levels of functioning. First, dysfunction on the *impairment* level is commonly assessed using PROs. This includes assessment of physical symptoms (e.g. visual analogue scale (VAS) for pain and fatigue), subjective cognitive complaints (e.g. functional assessment of cancer therapy-cognition (FACT-Cog)) and psychological problems (e.g. hospital anxiety and depression scale (HADS)). In addition, many HRQoL questionnaires comprise items on impairments, including items on sensory disorders, trouble sleeping, appetite loss, constipation, motor dysfunction, dyspnoea and seizures (e.g. European Organization for Research and Treatment for Cancer (EORTC), Quality of Life Questionnaire Core 30 (QLQ-C30) and the brain cancer module, the QLQ-BN20). Although more common in paediatric brain tumour patient research [45–47], proxy ratings (ObsRO) are also used to assess symptoms, cognitive functioning or behavioural changes in adults with brain tumours [48]. There are also several ClinROs that measure on the *impairment* level. The neurologic assessment in neuro-oncology (NANO) scale [49], for instance, evaluates brain tumour patients on nine relevant neurologic domains (symptoms and cognitive skills). Although performance status scales, such as the Eastern Cooperative Oncology Group Performance Status (ECOG), WHO performance status and the KPS scale, are often seen as measures of *impairment*, they also reflect aspects of *activity limitations*. PerfO measures assessing on the *impairment* level can focus on physical impairment, such as a neurological examination (i.e. physical and sensory tests to examine physical or sensory impairments) or cognition, typically assessed with a neuropsychological test battery. Neuropsychological tests assess impairments regarding many different cognitive domains, for example, memory (e.g. Hopkins verbal learning test-revised (HVLT-R); assessing direct free recall, delayed free recall and recognition), attention (e.g. D2 test of attention, selective and sustained attention and visual scanning speed), executive functioning (e.g. Delis-Kaplan executive function system (D-KEFS)), visuospatial constructional ability (e.g. Rey complex figure test and recognition trial (RCFT)) or language (e.g. Boston naming test).

Dysfunction on the level of *activity limitations* is typically assessed with BADL and IADL scales. Most commonly used BADL scales in neuro-oncology are the Barthel index (BI) and the Katz index of activities of daily living (Katz ADL). The BI and Katz ADL were originally developed as ClinROs [50–53]. However, nowadays BADL as well as IADLs can be assessed either by a health care professional, a proxy or by the patients themselves [32, 44, 54–57]. The functional independence measure and functional activity measure (FIM–FAM) is also commonly implemented as an ADL scoring system to assess the effectiveness of a rehabilitation program. This measure includes items with regard to both BADL and IADL, and is administered as a ClinRO. Assessing IADL can be particularly valuable in brain tumour patients, since cognitive decline is presumed to negatively impact their abilities to perform IADL. IADL involves higher-order activities "*with little automated skills for which multiple cognitive processes are necessary*" [58] and is therefore more sensitive to early effects of cognitive decline when compared to BADL [56, 59, 60]. However, unlike BADL, IADL is not commonly measured as a separate construct in neuro-oncological research. In some rare cases, the Lawton and Brody instrumental activities of daily living scale is used to assess IADL [61, 62]. Currently, a brain tumour-specific instrumental ADL measure is being developed as a PRO as well as an ObsRO [63], facilitating use in clinical trials and clinical practice. BADL and IADL can also be measured using PerfOs, such as the physical performance test (PPT) [64] and direct assessment of functional status (DAFS) [56], yet these are not commonly used in neuro-oncology.

To the best of our knowledge, there are no measures available for use in neuro-oncology that assesses functioning at the level of *participation restriction* only. HRQOL questionnaires cover some items on *participation restriction*, but they do not capture the full extent of potential issues on this level of functioning. The EORTC QLQ-C30 and QLQ-BN20 questionnaires, for example, contain items on the interference of the patient's physical condition or medical treatment with their family life or social activities. The FACT-general and brain module contains similar items, such as having trouble meeting the needs of the family, and being bothered by the drop in contribution to the family. A questionnaire such as the social role participation questionnaire (SRPQ) [65] (developed for patients with arthritis), focusing on participation restrictions only, could perhaps be useful in neuro-oncology to better assess functioning on this level. The SRPQ is a broad instrument assessing the influence of health on 11 specific social role domains and one "general participation" item. Patients rate (a) how important the social roles are to them, (b) their satisfaction with the amount time spent in that particular social role and (c) their ability to participate in that role in the way they want (i.e. role performance) on a 5-point Likert scale. As with the brain tumour-specific IADL, the development of a brain tumour-specific questionnaire on participation restrictions or social roles should be considered.

15.4 Neurorehabilitative Interventions

Neurorehabilitation can be implemented to address patients' various dysfunctions associated with the treatment or disease, and may contribute to maintaining and improving HRQoL. Neurorehabilitation considers physical, psychological and social aspects of the patient's well-being and, therefore, requires a multidisciplinary team care, including psychologists, nurses and rehabilitation specialists, to obtain optimal results. Despite the fact that rehabilitation is commonly being practiced in clinical settings, it has not been extensively recognized in cancer care. In recent years, however, the increase in the number of long-term survivors due to advances in cancer care has led to an increased interest in cancer rehabilitation [66]. The type of neurorehabilitative treatment is often determined by several factors, including the patient's diagnosis, received treatment and their anticipated survival. Although this suggests that neurorehabilitation programs should be different for the various types of brain tumour patients, several studies have indicated that rehabilitation provides significant functional gains in patients with

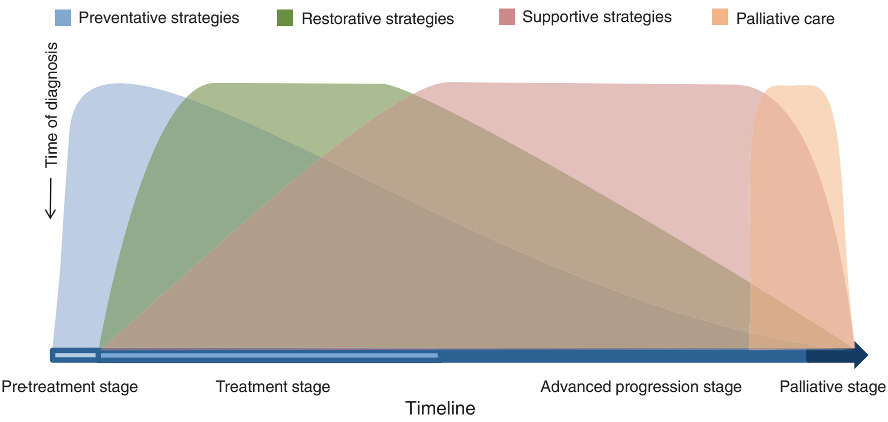

Fig. 15.1 Schematic depiction of the adaptive rehabilitation strategies during the stages of functional progression

brain tumours irrespective of tumour type, location of lesion or the presence of metastases during inpatient rehabilitation [67–73].

Several neurorehabilitative interventions are available for brain tumour patients. However, the potential effects of rehabilitation on the patients functioning may vary in the different phases of the disease. Therefore, the so-called adaptive rehabilitation program for patients with cancer described by Dietz may also be useful for brain tumour patients. This program consists of four categories: prevention, restoration, support and palliation [74]. Adaptive rehabilitation reflects the stages of functional progression, from the time of diagnosis until end of life, and introduces the relevant intervention strategies for these stages (Fig. 15.1).

Neurorehabilitation at the time of diagnosis and prior to treatment mainly consists of preventative strategies. In this phase, the focus lies on education and early intervention to abate the effects of the tumour and prevent functional loss [75]. As mentioned earlier, baseline levels of function (i.e. impairments, activity limitations and participation restrictions) can be assessed prior to treatment and monitored during the course of the disease. Preventative strategies can be implemented to retain patients' functioning and to prevent occurrence of impairments during the course of disease or during treatment [74, 76, 77]. For example, rehabilitation could be focused on maintaining a good physical condition [78] and making certain decisions to change lifestyle prior to treatment (e.g. quit smoking [79]) that may decrease the impact of potential adverse outcomes of treatment. Physical therapy can be implemented to prevent (further) physical decline. Another form of a preventative strategy is psychological support, which can be introduced after receiving the diagnosis or prior to or during treatment. By informing (newly) diagnosed patients about what may be expected with regard to the effects (e.g. physical, emotional, cognitive, behavioural) of having a brain tumour and undergoing treatment, and addressing patients' present and future concerns, (further) psychological distress may be reduced or prevented.

During the treatment stage, preventative, restorative and supportive strategies can be implemented. One such preventative strategy is part of physical therapy, and includes early postoperative ambulation and improving physical functions. It is known that physical strength tends to diminish during treatment due to fatigue and other adverse effects. However, physical and muscle strength can be enhanced by physical therapy to prevent disuse syndrome (e.g. contractures, muscle atrophy, loss of muscle strength and decubitus due to decline in mobility) [66]. Directly after treatment, restorative strategies may be implemented to maximize the recovery of patients' level of functioning either to levels prior to treatment or regaining maximal functional recovery in patients with more extensive impairments of functioning or decreased abilities [74, 76, 77].

There are various restorative strategies that can be implemented during the treatment stage, both physical and cognitive. The physical restorative strategy during this stage aims to restore the patient's balance, walking ability and general mobility. One study showed that brain tumour patients receiving comprehensive individualized multidisciplinary rehabilitation significantly improved on the FIM-mobility subscale (i.e. 13 out of 18 FIM items, excluding the items on communication and social cognition) at 3 months post-treatment follow-up compared to the waitlist control group; however, this effect was no longer present after 6-month follow-up [80]. Another study showed that brain tumour patients made significant improvements in their FIM scores from admission to discharge [81]. Although the length of rehabilitation was not a significant independent predictor of high or low FIM gain for patients with brain tumours, patients with brain metastases and glioblastoma who had the highest increase in functional gains were also the ones who had the longest survival time.

An example of a restorative strategy with regard to cognition is cognitive rehabilitation. Cognitive rehabilitation depends on the principles of neural plasticity of the brain. Neural plasticity refers to the brains capability to reorganize itself by neurons changing in structure and function and forming new neural connections [82]. It allows neurons to compensate for brain injuries and diseases, and mediates in the acquisition of knowledge and skills. Cognitive rehabilitation offers exercises aimed at improving various domains of cognition such as attention, memory, language and executive/control functions. Although cognitive deficits are characteristic for brain tumour patients, only few published studies have examined the potential benefits of cognitive rehabilitation in this patient population. One of these studies evaluated a multifaceted cognitive rehabilitation program (CRP), a computer-based attention retraining and compensatory skills training of attention, memory and executive functioning in patients with different types of brain tumours [83]. Patients were randomized to the intervention group or the waiting-list control group. The effect of CRP was evaluated by administering a battery of neuropsychological tests and self-report questionnaires at baseline, which was directly after the cognitive rehabilitation for the intervention group and at an equivalent time point for the control group, and at the 6-month follow-up. The study revealed less cognitive complaints immediately post-treatment and significant better scores on several neuropsychological tests in the intervention group: on four out of the seven individual attention tests (effect sizes ranged from 0.23 to 0.55) and two of the three individual verbal memory tests (effect sizes, 0.48 and 0.43). Moreover, patients in the intervention group reported less mental fatigue at the 6-month follow-up measurement. Although few studies have been conducted to evaluate the effects of neurocognitive rehabilitation, and though it is usually not integrated into the routine care of patients with brain tumours, neurocognitive training is feasible and might be able to induce improvements in cognitive skills. To help patients to manage the effects of their neurocognitive impairments better, neurocognitive rehabilitation should occur in parallel with medical management to treat fatigue, behaviour, memory, mood and the management of drugs that may be associated with neurocognitive side effects (e.g. anti-epileptic drugs) [84].

Although preventative and restorative strategies predominantly focus on the improvements gained on the *impairment* level of functioning, it is expected that this has an indirect positive impact on activities in everyday life. This is evident from a meta-analysis revealing a statistically significant effect of inpatient physical rehabilitation on functional improvement for both the Barthel index (an average of +44% score change from admission until discharge) and the functional independence measurement (FIM) scores (an average of +23% score change from admission until discharge), resulting in an overall average increase of 36% in independence [85]. In a recent study by Han et al. [86] brain tumour patients received conventional rehabilitation. This conventional rehabilitation therapy included physical therapy by neuro-developmental treatment (NDT)-certified therapists for one hour per day, neuromuscular electrical stimulation therapy, aerobic exercise, occupational therapy for stretching and strengthening of the upper extremity, and task-oriented therapy for ADL, fine motor training and sensory motor recovery. Computerized or focused cognitive training of neuropsychological deficits was not included. The combination of the physical restorative strategies and supportive strategies in this conventional therapy induced significant physical and cognitive (Korean versions of the motricity index (K-MI) and mini mental status examination (K-MMSE)) improvements in both benign and malignant brain tumour patients, as well as improved functioning in activities of daily living (Korean version of the modified BI (K-MBI)). In addition, results demonstrated that aspects of motor and cognitive dysfunction predicted lower levels of ADL function, before and after rehabilitation [86].

For some brain tumour patients, supportive care in the form of occupational therapy can be relevant in the treatment stage following initial treatment. One aspect of occupational therapy is professional integration, i.e., helping patients return to work to some extent. During prevocational therapy, the job reinstatement possibilities for brain tumour patients vary extremely depending on the tumour type and clinical condition. Even for brain tumour patients with more favourable prognosis, whom might benefit from this training, it is imperative to help develop a realistic view of their working potential. Some patients might have to come to grips with the realization that a return to work might not mean returning to their former employment position and/or not in the same capacity.

During prevocational training, work simulations can be implemented to teach and reinforce the use of compensatory strategies. These may include using a daily planner to maintain daily schedules or using written checklists for operating equipment (e.g. computers). In addition, education on the reorganization of the workspace and structuring/organizing the work day can allow successful completion of tasks which would otherwise be too challenging. The therapist could also encourage patients to resume or assume the role of homemaker or volunteer, or help develop a structured routine for leisure/avocational activities [87]. One study reported favourable participation outcomes (community independence and employment) after outpatient multidisciplinary rehabilitation in people with brain tumours [73].

However, most supportive interventions are designed to teach patients to accommodate to their disabilities and to minimize debilitating changes from ongoing disease. As the disease progresses and patients develop more permanent disabilities, the predominant focus shifts even more from the prevention and restoration of impairments towards higher levels of functioning in order to maintain a decent level of independence. In the advanced stage of the disease, the purpose of supportive strategies is to maintain a level self-care and independence using education and guidance (e.g. educating self-care strategies and skills and assisting with the use of supportive medical devices). Patients are assisted in learning how to cope and adjust to the disabilities, and are educated in the use of medical devices (e.g. learning to adjust to prosthetic devices or wheelchair) [74, 76, 77]. Occupational therapy may also focus on maximizing a person's independence with regard to daily functioning [87]. For example, *activity limitations* (i.e. BADL and IADL) could be improved by addressing problems regarding self-care, functional mobility, meal preparation, money management, driving and leisure activities due to physical and/or cognitive disabilities [87, 88]. Also, occupational therapy in the form of community reintegration training can be implemented to enhance the level of *participation restrictions,* by learning patients to reintegrate into the community despite their disabilities. Community living skills are essential to be a productive participant in society. Community reintegration training includes planning and participating in community-based activities. Tasks learned or re-learned in the clinic can be practiced in a more natural context during community reintegration activities.

Neuro-palliative rehabilitation is at the interface between rehabilitation and palliative care and focuses on symptom management and interventions to maximize HRQoL during the terminal stages of the disease. In this phase, the intent is to make patients feel as comfortable as possible, either physically, psychologically and/or socially, and respect their wishes. Palliative care may, for example, focus on symptom relieve (e.g. pain control), psychological support and reducing the chances of adverse effects of being bedridden, such as contractures and pressure ulcers, by using heat, (re-)positioning of the body, breathing assistance and relaxation, and with the use of low-frequency electromagnetic therapy equipment or with the use of assistive devices [74, 76, 77].

15.5 Conclusion and Future Perspectives

In conclusion, patients with brain tumours can have impairments on all levels of functioning, which may negatively affect their overall HRQoL. Neurorehabilitation can improve functioning on all levels of functioning, using different types of interventions which depend on the stage of the disease. Although several tools exist to assess functioning and well-being, there is still a need for brain tumour-specific tools on all levels of functioning, especially the higher-order levels of functioning. Moreover, there is a need for more empirical studies evaluating neurorehabilitative interventions in brain tumour patients using these functional assessment tools. By optimally assessing functioning and adequately addressing functional decline at the right moment with the right treatments and interventions, patient's HRQoL can subsequently be improved.

Developments have been made in the field of neurorehabilitation as a result of the emergence of new technological advances. In the past years, there has been a growing interest in e-health, i.e., digitized assessment tools and therapies. Several studies have been published recently regarding the development and testing of computerized neuropsychological test (CNT) batteries, virtual reality training tools and online/app-based rehabilitation [89–95]. However, the current emphasis is on preserving physical and cognitive functioning. Further well-designed studies in different brain tumour patient populations are needed to investigate how these e-health tools may help improve the patients' functioning and well-being on higher levels (I-ADL and societal participation).

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