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SYSTEMATIC REVIEW

Predictors of functional outcomes in adults with brain tumor undergoing rehabilitation treatment: a systematic review

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ABSTRACT

INTRODUCTION: The number of diagnosed brain tumors (BT) has increased in recent years. The results of treatment of patients with surgery, chemotherapy and radiotherapy are also improving and their survival rate has increased significantly. Symptoms of the disease and side effects of oncological treatment may reduce the functional performance of patients. It is so important to conduct rehabilitation in this group of patients. The aim of this systematic review is to identify predictors of effective rehabilitation in aspects of physical functioning of BT patients. The study was registered with health and social care, welfare, public health, education, crime, justice and international development departments, where there is a health-related interest outcome PROSPERO. We have received registration number is: CRD42021269398.
EVIDENCE ACQUISITION: To find relevant publications, the algorithm of keywords ("brain tumor") AND (rehabilitation OR "physical activity" OR exercise OR "physical therapy") was used. The search was conducted in PubMed, Web of Science, PEDro, ClinicalTrials.gov and Cochrane Library. Information was extracted using the PICO format (*i.e.*, participants, intervention, comparison, outcomes).
EVIDENCE SYNTHESIS: the initial search identified a total of 1122 results, and 21 articles met the criteria and were selected for analysis.
CONCLUSIONS: The results present that rehabilitation is an important and safe cancer encouraging therapy, brings functional benefits. The type of rehabilitation program, especially in BT patients, depends on many factors such as time and type of oncological treatment, general conditions which is strongly related to the general functioning of the patient. It still is a need for clinical research into the safety and effectiveness of rehabilitation interventions already during radio or chemotherapy in this group of cancer patients.

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KEY WORDS: Brain neoplasms; Neoplams; Rehabilitation; Occupational therapy; Exercise; Neoplasms.

Introduction

In 2018, a total of 296 851 cases of brain tumors (BT) and other types of central nervous system (CNS) tumors were reported worldwide.[1] In the years 2014-2018 in the US there were 83 029 deaths attributed to malignant BT and other CNS tumors. This means an average annual mortality of 4.43 per 100 000 and an average of 16 606 deaths per year.[2] More than 11.000 people are diagnosed with a primary brain tumor in the UK each year, of which about half are malignant in nature.[3] Treatment of patients with BT includes mainly surgical resection of the tumor as well as adjuvant treatment, chemo- and radiotherapy.[4-6] The tumor, and oncological treatment used, can cause several side effects, such as hemiparesis, sensory deficits, balance and mobility disorders, and cognitive dysfunctions.[7] Motor dysfunction in primary BT patients may be multifactorial, occurring as a result of direct effects of tumor location, swelling of the brain, as a result of treatments such as surgery, chemotherapy, radiation, steroids or other

pharmacotherapy.[8] All of this can deteriorate the patient's functional status and ability to activities of daily living.[9, 10] Due to the increasing survival of patients with BT,[1, 11-13] the need for rehabilitation is also increasing, which may help in the recovery or improvement of functional fitness. So far, the beneficial influence of rehabilitation on the condition of cancer patients,[14-16] especially those with breast cancer, has been studied.[17-20] Despite the high probability of clinical complications that result in disabilities, dysfunction, or neurological symptoms, functional and cognitive rehabilitation following cancer treatment in BT patients is still uncommon.[21]

Rehabilitation of patients with BT should be multidisciplinary and include issues such as: impairments in anatomical structures or function, the activity of daily living limitations, restriction in participation (*i.e.* employment, family life, social re-integration).[22]

Rehabilitation may take into account possible medical complications during and after oncological treatment in this group of patients, such as: venous thromboembolic disease, syndrome of inappropriate antidiuretic hormone (SIADH), dysphagia, and seizures, psychiatric symptoms such as depression, fatigue, mood changes, and personality changes have been noted in conjunction with other symptoms such as headaches, sleep changes, and cognitive disturbances.[23, 24] Although disability in the group of patients with primary BT are very common, patients are still referred to rehabilitation too seldom. In a study by Pace *et al.*[25] was confirmed that, only 12.8% of patients underwent inpatient rehabilitation, and only 14.9% outpatient rehabilitation.

Currently, there is no systematic review focusing solely on the functional aspects of rehabilitated BT patients in terms of oncological treatment. No one clearly defined the methods of assessing physical functioning in BT patients during comprehensive rehabilitation treatment. Previously published reviews cover only patients with glioblastoma (GBM),[26, 27] are not systematic,[28, 29] mainly concern cognitive rehabilitation,[30, 31] or do not include treatment methods.[22] Therefore, the aim of this systematic review is to identify predictors of functional outcomes in adult BT patients during effective rehabilitation treatment.

Evidence acquisition

The literature review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyzes (PRISMA) guidelines.[32] This study did not require the approval of the bioethics committee. The study was registered in health and social care, welfare, public health, education, crime, justice, and international development, where there is a health-related outcome PROSPERO. The registration number is: CRD42021269398.

Search strategy

To find relevant publications, the algorithm of keywords ("brain tumor") AND (rehabilitation OR "physical activity" OR exercise OR "physical therapy") was used. The search was conducted in PubMed, Web of Science, PEDro, ClinicalTrials.gov and Cochrane Library. Reference lists were also searched for additional publications. The search was performed simultaneously and independently by the two authors AP and KH. The searches were completed on September 2, 2021. The search terms were formulated using the PICO structure. Subjects (P) were adults (> 18 years of age) with a known brain tumor. Intervention (I) included rehabilitation aimed at improving physical function. Comparisons (C) widely referred to exercise interventions versus no, supervised or unsupervised, variable frequency and duration of motor interventions, and comparisons of different types of exercise. Outcomes (O) included functional improvement and quality of life.

Inclusion and exclusion criteria

The following inclusion criteria were used: 1) original studies published in English; 2) studies conducted on a group of adult patients diagnosed with a BT who underwent rehabilitation aimed at improving physical functions.

The exclusion criteria were: 1) an intervention consisting only of cognitive rehabilitation; 2) no assessment of the patients' physical function.

Quality assessment

To assess the methodological quality of the included studies used the Quality Assessment Tool for Quantitative Studies (QATQS).[33] The evaluation was carried out by two authors, AP and AP.[1] Any conflicts were resolved by the third author, KH. This tool evaluates eight areas: selection bias, study design, confounders, blinding, data collection methods, withdrawals and dropouts, intervention integrity, and analysis. In the case of one time surveys, the withdrawals and drop-outs section was rated as 1. Individual sections can be rated *weak*, *moderate*, or *strong* according to the Dictionary. The whole study is classified as *strong*, when no section is rated as *weak*, the assessment of one section as *weak* results in the overall assessment of the study as *moderate*. The study is *weak* if two or more sections are rated as *weak*.

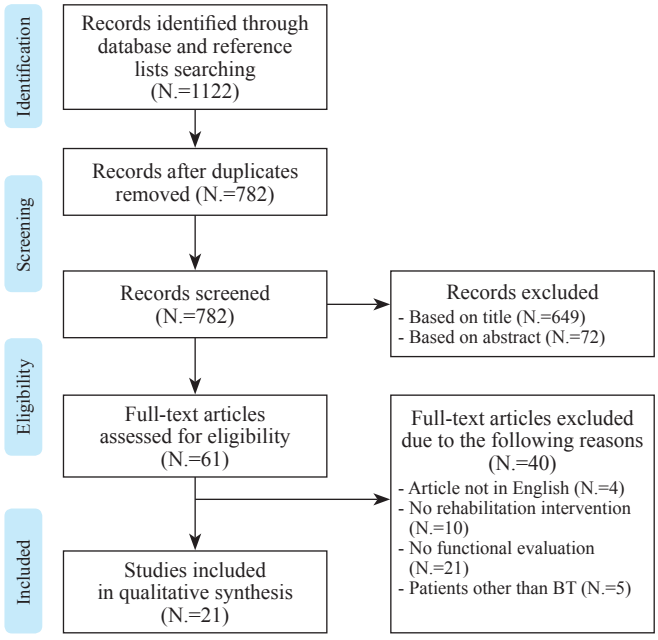

Figure 1.—PRISMA flow diagram of the search strategy process.

Data collection and analysis

Authors Anna Pieczyńska and Agnieszka Pilarska[1] conducted an independent review and analysis of the articles. First, duplicates were removed, then the publications were checked for inclusion and exclusion criteria. The following data was extracted from the included articles: first author, year of publication, study population characteristics, study design, inclusion/exclusion criteria, intervention characteristics, assessment of the outcome, and results.

Evidence synthesis

After searching the databases and considering additional records, a total of 1122 studies were identified. Ultimately 21[34-54] results were included in this study. The flow diagram according to PRISMA guidelines is presented in Figure 1.

Quality assessment

The methodological quality of the included studies is presented in Supplementary Digital Material 1, Supplementary Table I.[34-54] 15 studies[34, 41-54] were assessed as strong and 6 studies[35-40] as moderate. The highest rated section was the data collection, and the worst withdrawals and dropouts. A detailed assessment of the individual sections is presented in Figure 2.

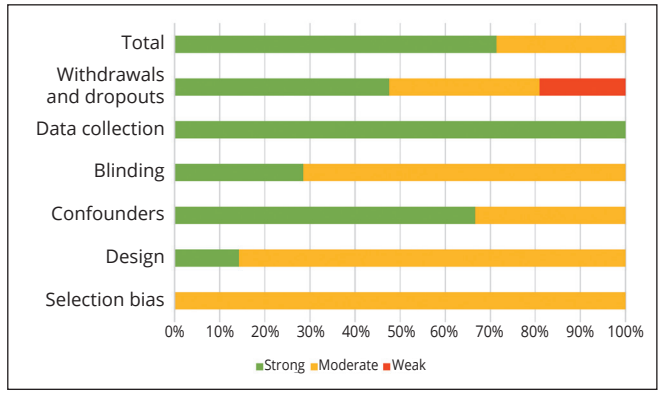

Figure 2.—Detailed assessment of individual sections expressed as a percentage.

Characteristics of study participants

The total number of participants in all studies was 3582. The participants who have diagnosed a BT were 1514 people. The remaining patients were control groups diagnosed with stroke – 1953 and brain injury – 115.

The type of BT in patients was classified according to the 2016 World Health Organization (WHO) Classification of Tumors of the Central Nervous System grade in 3 studies.[34, 35, 44] Most studies mentioned individual types of tumors diagnosed in patients, such as: meningioma, glioma, GBM, astrocytoma, schwannoma, oligodendroglioma.[36-38, 40, 42, 45-52] In the study, Huang *et al.*[41, 43] divides tumors into benign and malignant. In three articles,[36, 40, 42] the authors also mention metastatic tumor. Fu *et al.*[53] conducted research only on a group of patients with leptomeningeal cancer (LMD).

Patients in the analyzed studies were subjected to surgical resection of a BT as well as adjuvant therapy (radio and chemotherapy). 3 articles did not describe adjuvant treatment during the study.[36, 41, 43] Detailed characteristics of the participants are presented in Supplementary Digital Material 2, Supplementary Table II, Supplementary Digital Material 3, Supplementary Table III.[34-54]

Eleven of the analyzed studies are retrospective.[34, 38, 39, 41-43, 46-49, 53] Detailed characteristics of study design and results are presented in Supplementary Table III.[34-54]

Yu *et al.*,[34] Huang *et al.* 2000[43] and Greenberg *et al.*[38] compare the results of rehabilitation of patients with BT with patients after stroke. O'Dell *et al.*,[49] Bilgin *et al.*[39] and Huang *et al.* 2000[41] as a control group recruited patients with traumatic brain injury. The publications by Marciniak *et al.*[48] and Mukland *et al.*[42] compare the functional results of patients with a BT before and after rehabilitation,

and Roberts *et al.*[46] additionally checks whether there are differences in the results of patients participating in and not participating in rehabilitation. Reilly *et al.*[47] compares the functional outcomes of patients participating in acute inpatient rehabilitation after initial diagnosis of GBM and after diagnosis of recurrent GBM. The functional outcomes in LMD patients undergoing acute rehabilitation were assessed by Fu *et al.*[53]

The remaining 10 studies are prospective.[35-37, 40, 44, 45, 50-52, 54] Hojan *et al.*[35] study compared the functional outcomes of BT patients participating in 12-week outpatient and inpatient rehabilitation. Shahpar with co-authors[51] investigated the influence of rehabilitation on functional outcomes in BT patients undergoing outpatient rehabilitation. Han *et al.*[36] compared the functional outcomes of BT and stroke patients who participated in a 4-week rehabilitation program. In their studies, Geler-Kulcu *et al.*[37] and Bartolo *et al.*[52] also compared the effects of rehabilitation of patients with BT and after stroke. The effectiveness of a 3-week-long rehabilitation based on virtual reality in patients with BT was performed by Yoon *et al.*[40] Khan *et al.*[54] assessed the effectiveness of a multidisciplinary 6-8 week rehabilitation program. Hansen *et al.*[44] used a 12-week rehabilitation program for patients with GBM in his research. Baima *et al.*[45] included high-grade BT patients who did home training for 1 month. The use of 6 weeks of aerobic training in a group of people with BT was studied by Ayotte *et al.*[50]

Types of rehabilitation treatment

Various types of rehabilitation were used in the analyzed articles. In 8 cases,[38, 41-43, 47-49] rehabilitation was not described in detail, it is only known that it was inpatient. Additionally, occupational therapy was part of the improvement process in 7 research articles (Yoon *et al.* in a control group).[34-36, 40, 44, 46, 51] Only in one study was used virtual reality (VR) therapy.[40] The home exercise program was performed used in the Baima *et al.*[45] study. Methods such as proprioceptive neuromuscular facilitation (PNF) and Bobath method were used in 4 studies.[35-37, 39] Most often, the exercise program involved training the range of motion in the joints, strength training, improving balance and coordination, and gait training. In 6 studies,[34-36, 44, 45, 50] patients undertook aerobic and endurance training.

Functional assessment

The Functional Independence Measure (FIM) was the most frequently used tool for assessing functional fitness and rehabilitation progress in BT patients in 14 articles.[35, 38, 41, 42, 46-50, 52-54] Five authors[34-36, 39, 40] used the Barthel Index to asses activities of daily living. Yu *et al.*[34] and Yoon *et al.*[40] used Fugl-Meyer Assessment to assess motor functions. Hansen *et al.*[44] and Ayotte *et al.*[50] used 6 and 10 minute walk test. In most articles Berg Balance Scale was used to assess the balance in study group. In three studies, the authors used the FACT questionnaire.[35, 45, 50]

The results of all analyzed studies confirm the effectiveness of rehabilitation in improving physical fitness and coping with activities of daily living. The improvement after rehabilitation in patients with BT is comparable to the results achieved in the group of patients with stroke and traumatic brain injury.

In the analyzed articles, rehabilitation was carried out both before[37, 49, 51] and after oncological treatment.[35, 40, 42] In several studies, patients underwent rehabilitation during radio and chemotherapy.[44-46, 48, 49, 51]

Time of rehabilitation

The time of rehabilitation intervention was also varied in the analyzed studies. Some articles mention specific timeframes: 12 weeks,[35, 44] 4[36, 45, 52] and 3[40] weeks. Other authors give the average time of patients' rehabilitation, most often related to the length of stay in the ward. This time varies from 2 to even 22 weeks.

Most often, the therapy was carried out at the intensity of 5 times a week[34, 37, 40, 44, 50] for 1 hour.[34, 36, 37, 40, 52] Some authors recommended rehabilitation 6 times a week[35, 54] or every day.[45] The shortest duration was 30 minutes,[39] the longest is 3 to 6 hours a day.[51]

Discussion

The aim of our systematic review was to evaluate predictors of functional outcomes in adults patients with brain tumor who were received rehabilitation treatment. Based on the literature review, we distinguished the following factors: types of rehabilitation treatment, types of functional assessment, and time of rehabilitation. Currently, there are no clear guidelines for carrying out rehabilitation and functional assessment in the group of BT patients.

Contemporary comprehensive rehabilitation of patients with BT can be multidisciplinary.[22, 55] The cancer rehab-team includes specialists such as physiatrist, oncologist, physiotherapist, psychologist, speech therapist, rehabilitation nurse, and social worker.[22] In our review, we focused on assessing patients' physical functions in terms of performing their daily activities in BT patients. Articles that covered exclusively or mainly cognitive rehabilitation were not included in this analysis.

Most of the analyzed studies were conducted on relatively small groups of patients. This may be since patients with BT suffer from many psychological disorders such as depression, fatigue syndrome, and emotional instability.[56, 57] This makes patients reluctant to undertake additional activities. The short time of patients' survival also makes it difficult to gather a large group of subjects. In the case of the most common BT, GBM, the median life expectancy of patients is 12-15 months, with less than 25% surviving to 2 years and less than 10% surviving to 5 years.[58]

The clinical studies in our review most often included patients with various types of BT, frequently they were GBM, meningioma, astrocytoma, leptomeningeal cancer, oligodendroglioma and metastatic tumor. Few studies[46, 47, 53] have only looked at patients with one type of tumor. The current classification of nervous system tumors is *The 2021* World Health Organization Classification of Tumors of the Central Nervous System, which should be used in all future articles in order to standardize the nomenclature and classification of BT. WHO classification of CNS tumors uses molecular parameters in addition to histology to define many tumor entities, thus formulating a concept for how CNS tumor diagnoses should be structured in the molecular era.[59] This classification was used in three analyzed articles.[34, 35, 44]

The effectiveness of rehabilitation in the group of patients with BT is often tested in comparison with the control group such as people after stroke or traumatic brain injury. Many dysfunctions such as hemiparesis, aphasia, cognitive deficits, and visual disturbances that are seen in the BT population are also common in other neurological conditions such as traumatic brain injury or stroke.[22] There is strong evidence to support multidisciplinary rehabilitation in these neurological disorders.[60, 61] However, compared to other neurological disorders, the time limits for intervention in people with BT are shorter due to the high mortality rate or side effects of oncological treatment which decrease exercises ability.[22] Therefore, it is necessary to define appropriate, well-defined functional objective of rehabilitation in BT patients.

Functional assessment in BT patients

FIM was most often used to assess the patient's function. The tool is designed to assess areas of dysfunction in activities that commonly occur in subjects with any progressive, reversible or stable neurologic, musculoskeletal, or other disorder *i.e.* patients with functional mobility impairments.[62] The FIM is used by healthcare practitioners to assess and grade the functional status of a person based on the level of assistance he or she requires. Inter-Rater Reliability of FIM has been established at an acceptable psychometric performance (Intraclass co-relation coefficients ranging from 0.86 to 0.88. The concurrent validity with Barthel Index (ICC>0.83) have shown strong construct validity between items on Barthel Index and items on the FIM the measure functional limitations.[63] Although the FIM is not a specific scale for cancer patients, it is one of the most widely used tools for assessing disability in patients with many neurological diseases.[64] Giga *et al.*[64] shown in their review list the nine most frequently scales for assessing patients with BT. The most common instrument in their study is the Karnofsky scale, which is specific to oncological patients.[65] It is used as a criterion for the selection of participants by measuring their functional status. This scoping review[64] did not identify one unique assessment instrument for BT patients group. These patients are specific in a way that there is no unifying patient-specific clinical set of symptoms and their symptoms depend on various other factors. Both FIM and Karnofsky scale cover all components of the International Classification of Functioning, Disability and Health. However, the assessment tools that are not diagnosis-specific, still must be validated for the BT population. Many authors also use the Berg Balance Scale. It was originally developed to measure balance in patients with many neurological diseases and symptoms (such as stroke, MS, Parkinson diseases, ataxia), it is now commonly used to measure static and dynamic balance abilities in people with varying conditions *e.g.* respiratory and cardiac and disabilities also with BT.[66-68]

Three of the studies in our review mention the FACT questionnaire for patient function assessment.[35, 45, 50] This tool provides information on cancer-related quality of life.[69] A dedicated version for patients with brain tumor included specific symptoms in this disease is FACT-BR.[70] Also in the review by Giga *et al.*[64] The FACT-Br questionnaire has been used less although has as good properties in terms of intra-rater reliability and structural validity as other function measurements. It contains problems that have not been included in any of the remaining tools listed, and can clearly be important for this population, such as handling stress or driving a car.

Another group of tests used in the assessment of patients with BT were physical endurance tests. The studies included in this review mention the walk tests - 6 or 10 minutes which are used for the objective assessment of functional exercise capacity.[71] According to reports by Schmidt *et al.*[72] 6 minute walk test- 6MWT in cancer patient seems to

be as valid in relation to objective and subjective measures of physical function and exercise capacity as in healthy older and patients with cardiac or pulmonary disease. Measurement of exercise capacity in cancer patients may be especially useful when cancer-related fatigue (CRF) develops. Up to 40% of patients report fatigue at cancer diagnosis, 80%–90% during chemotherapy and/or radiotherapy. Aerobic exercise can help relieve CRF symptoms, so it is important to monitor the level of exercise capacity in cancer patients.[73]

Time of rehabilitation

The analyzed articles concern both inpatient and outpatient rehabilitation, undertaken during, before or after the completion of oncological treatment after surgery resection. Patients who have undergone tumor resection, depending on their current needs, may be referred to oncological treatment if their functional status allows it. In case of insufficient functional results, they may be referred to inpatient rehabilitation. Patients with BT often have a disability similar to that of a stroke, many of these patients benefit from acute inpatient neurorehabilitation. Most studies[35, 38, 41, 42, 46-49, 53] shown benefits of inpatient rehabilitation for the functional status of BT patients, and some studies have even correlated participation in rehabilitation with increased survival.[74, 75]

Rehabilitation can also be carried out during oncological treatment - radio and chemotherapy, which can have a significant impact on the functioning of patients. Radiation can have significant long-term consequences, either episodic or static, and may influences on functional status this patients group.[76] Acute radiation encephalopathy has onset days to weeks after initiation of therapy, corresponding to a time frame in which the patient may be receiving rehabilitation. Symptoms include headaches, lethargy, and worsening of existing focal symptoms, and respond to increase in corticosteroid dosing.[77, 78] All of this may contribute to the deterioration of the functioning of patients and problems in the area of daily activities.[79] Therefore, rehabilitation should be indispensable during oncological treatment, whether inpatient or outpatient.

A study by Warren *et al.*[80] presented results of time to initial oncological treatment in patients with high-grade glioma and shown that group who are discharged to rehabilitation centers after surgery wait longer for oncological treatment than those who are discharged at home. In addition, they have longer hospital stays and worse outcomes than those who go home. However, the authors do not analyze the functional status of the patient, which is crucial in further patient referral. Patients who were discharged home very often have better functional results than those referred to rehabilitation wards. It should be noted that rehabilitation is aimed at improving the functional state of the patient so that can be referred for further oncological treatment. If it is possible they should use outpatient rehabilitation treatment, but with important disabilities and worse functional status patients should be admitted as inpatient. Rehabilitation of patients with BT have to also be continued after the completion of oncological treatment and discharge from the hospital.

BT may have dynamic changes, and depending on the aggressiveness of the tumor, they may recur. Also, the effects of cancer treatment, especially due to radiation necrosis, which may be delayed, can lead to new neurological symptoms months or years after initial diagnosis. Recurrence or progression of BT may lead to the reappearance or worsening of neurological symptoms requiring further rehabilitation. It is strongly recommended to continue treatment after discharge from the rehabilitation hospital due to the high probability of future neurological deterioration.[21]

Rehabilitation interventions

In the studies included in this review, in which we found a detailed description of rehabilitation interventions, exercises methods such as Bobath and PNF are often mentioned.[35-37, 39] These methods are used in physiotherapy with a group of neurological patients, especially after stroke, MS etc.[81-83] Patients with BT can also undertake aerobic and strength training. Many studies have confirmed the beneficial effects of exercise on cancer patients.[84-88] Exercise can reduce the side effects of oncological treatments. Fatigue, muscle wasting, and reduced physical performance can lead to limitation daily activities and a deterioration in health-related quality of life. The latest Exercise Guidelines for Cancer Survivors of the American College of Sports Medicine show that both aerobic and strength training, and combinations of these forms of training, are safe and should be undertaken by cancer survivors.[89] An interesting approach may be home rehabilitation and the use of VR technology, so that patients can continue the therapy after leaving the hospital. These types of rehabilitation programs have been found in studies to be effective, feasible and safe.[40, 45]Important part of rehabilitation treatment in people with BT is also occupational therapy, which often is used in the people after brain trauma, stroke, Parkinson disease, etc.[90, 91] Occupational therapy makes an important contribution in neuro-

rehabilitation, which ought to also apply to patients with BT with important influences on functional status in daily activity.[34-36, 40, 44, 46, 51]

BT patients are large group of patients who need supportive treatment to improve functional status. Rehabilitation is an important and safe cancer encouraging therapy, brings functional benefits. The type of rehabilitation program, especially in BT patients, depends of many factors such as time and type of oncological treatment, general conditions which is strongly related to the general functioning of the patient.

Limitations of the study

There are some limitations to this study. We included articles only on adults in the review and we did not analyze the predictors of effective rehabilitation and its effects in various age groups. We also do not analyze studies on psychological factors, that may affect physical functions. Additionally, the analysis of predictors of successful rehabilitation could be divided according to the type of cancer therapy used to investigate the impact of radio and chemotherapy on the effects of rehabilitation. However, the analyzed studies lack clear divisions into patients undergoing selected forms of oncological treatment. Most often, patients with radio- and chemotherapy are analyzed together.

Conclusions

Currently, there are no clear guidelines as to when rehabilitation should be carried out in the BT group. The type of rehabilitation program used should be strongly related to the general functioning of the patient. It still is a need for clinical research into the safety and effectiveness of rehabilitation interventions already during radio or chemotherapy in this group of cancer patients. There is also a shortage of research on various types of rehabilitation interventions – inpatient, outpatient at home rehabilitation or using VR. Measurement instruments should also be standardized to be able to compare the effectiveness of the therapy in improving the daily functioning of BT patients in the future.

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