Rehabilitation in pediatric oncology

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Highlights

- Improving treatments in childhood cancer leads to an increasing number of survivors
- There is a need to reduce the risks of late effects due to cancer and therapy
- Physical and neuropsychological rehabilitation needs to start from diagnosis onwards

Introduction

The childhood cancer survivor population exponentially expands due to increasing survival rates (1). Current multimodal therapies result in five-year survival rates exceeding 80 % in Western European countries. Hence, possible late effects of the treatment increasingly require attention and have shifted the focus of research towards survivorship studies.

Survivors can be at risk of multiple physical as well as cognitive and mental health difficulties, which can be attributed to either the disease itself or its treatment. Such problems can subsequently lead to social or socioeconomic problems, and can ultimately largely affect their well-being and quality of life. In this narrative review article, we provide an overview of possible sequelae after childhood cancer and their challenges in daily life. We describe physical and psychological side effects, and possible impact later in life. For each domain, we also provide some guidelines and potential interventions. Throughout the review, we will follow the model provided by international classification of Functioning Disability and Health (ICF).

Health conditions

Cancer therapeutic regimens, such as chemotherapy, radiotherapy, surgery, stem cell transplantation, and more recently immunotherapy, targeted therapy are critical for achieving survival, but may have adverse effects on physical and psychosocial health later in life, e.g. the risk of subsequent neoplasms and organ dysfunction, fatigue and school problems. Systemic treatments such as chemotherapy could lead to acute and late effects including cardiovascular, endocrine, reproduction, renal and hepatic toxicity, hearing loss, which can have a large impact on daily life of survivors. Studies indicate childhood cancer patients to be more sedentary than healthy peers, there is an increased risk of developing inactivity-related diseases such as osteoporosis, diabetes, hypertension, and coronary artery disease (2). Of childhood cancer survivors, 50% reported being obese, 61% having dyslipidemia and 23% being hypertensive, which also lead to a higher risk of cardiovascular problems (3).

Body structure and function

Physical and motor functioning

The disease process and the therapy have a pronounced impact on the physical and motor functioning and these should be monitored during and after treatment.

A decrease in *cardiorespiratory function* can be present after each cancer treatment and is highly prevalent with exercise intolerance (peak oxygen uptake of <85% from maximal cardiopulmonary exercise testing) being present in 65% of survivors of childhood cancer (4).

A significant *decrease in strength of all muscles* compared to age and gender matched controls is reported at the beginning of cancer treatment and even 3 years after treatment (5). Moderate-to-severe *bone mineral density* (BMD) deficits were reported in 68% of childhood cancer survivors presented, and 46% had severe deficits (6). In case of leukemia, this decrease in BMD can directly be attributed to leukemic processes. Furthermore, in bone or soft tissue sarcoma patients, a prosthesis can complicate physical functioning. Finally, patients with tumors in the central nervous system, can present *motor problems related to damage of the spinal or cranial nerves*, or to cerebral damage in motor-related brain areas (e.g. primary and secondary motor area, cerebellum). Proper rehabilitation aimed at reaching healthy levels of physical capacity, is important and this not just for general health and ability to participate in physical activities, but also for social reintegration and better quality of life.

Fatigue & Pain

Both short- and long-term effects of childhood cancer treatments on the energy level of patients are evidenced. These studies increasingly demonstrate difficulties in sleep and altered sleep patterns, increased daytime sleepiness, resulting in chronic fatigue (7,8). Moreover, fatigue is significantly associated with experienced levels of pain, so they appear to be interdependent (9). Patients appear to be at higher risk than controls of experiencing chronic pain, which ranges between 4.3% and 75% of survivors across studies. Given that worse sleep could be associated with distress and decreased physical activity, these patients might benefit from stress reduction exercises or physical exercise, respectively (10).

Accelerated ageing & Neurocognitive functioning

Cancer treatments including cranial radiotherapy and systemic chemotherapy, have both been associated with acute neurotoxicity and neural damage. Hence the so-called concepts “chemobrain” and “accelerated ageing” have been posed, referring to the induced damage at cerebral level and the associated decreased neurocognitive outcomes of childhood cancer patients (11).

First, regarding non-CNS cancers, most evidence on neurocognitive decline exists for leukemia patients, since these patients received cranial radiotherapy until the 80’s, and are treated with CNS-directed chemotherapy nowadays. Our previous imaging studies have demonstrated microstructural neurological changes in long-term leukemia as well as sarcoma survivors after high-dose intravenous chemotherapy which mostly correlated with subtle decreases in processing speed (12,13). So, regarding chemotherapy-induced neural changes, the neurobehavioral outcomes seem relatively stable, with only subtle changes in attention. Consequently, most of these patients do not experience observable problems or do not demonstrate clearly decreased performance at school. Of course, the cancer treatment can still challenge them in other ways to reintegrate at school again.

Second, pediatric brain tumors are the second most common type of pediatric cancers (after leukemia). These children are at high risk to experience neurocognitive problems. It is estimated that 40%, up to 100%, of survivors, depending on specific sample and type of cognitive functions assessed, are developing one or more neurocognitive problems (14). These problems are often associated with worse academic or professional functioning. Multiple factors are found to play a role in the development of neurocognitive deficits: size and location of tumor, surgical intervention, chemotherapy and radiotherapy or a combination.

Activities: rehabilitation approaches at the level of functioning and activities

Physical rehabilitation

As survivors often experience lower cardiovascular fitness, muscle weakness and osteopenia, this in combination with decreased physical activity and a sedentary lifestyle may also lead to early development of diseases such as hypertension, diabetes, osteoporosis. For these patients, physical activity is important and is suggested to elevate strength, cardiovascular functioning, health-related quality of life (HRQoL), which is even more important for inactive patients who are at higher risk of secondary cancers and relapse (15).

In adult cancer, evidence is available showing that specific doses of physical activity (aerobic and or resistance training) can improve many cancer-related side effects, including physical function, quality of life (QoL), anxiety, depression, and fatigue (Campbell 2019). In children however, similar literature remains scarce. A few systematic reviews on the effects of physical exercise intervention in childhood cancer survivors conclude that most likely there is a beneficial effect of activity on cardiovascular fitness, on strength, and on bone marrow density, with no clear evidence yet on fatigue and QoL (3). The current evidence suggests that mild-moderate intensity exercise is safe and feasible and an active lifestyle throughout the paediatric cancer experience should be promoted (16). Klika et al. suggest hereby a 3 phase exercise rehabilitation plan: Phase 1: in-hospital exercises aimed at being fun and moving from sedentary behaviour to any movement and emphasis on motor skill acquisition where physical therapists work together with the medical oncology team (3). Phase 2: transition to home-based training (under parental supervision): aimed at return to normal activities and sport and thus a shift towards aerobic, strength, flexibility and skill refinement. Phase 3: home-based and independent training. Behavioral change towards a life-long active lifestyle is required, with techniques such as goal setting, self-monitoring, problem solving and feedback, modelling (17). To give an example, in UZ Leuven, a group exercise program is implemented on top of the individual physical therapy sessions during the intensive chemotherapy, called the KIKFIT program. This program helps motivating children to be involved in group sessions and to be physically active (phase 1).

However, exercise guidelines for children with cancer remain inconclusive and the optimal physical training program is not known yet. Currently we perform studies to determine what the suitable “dose” (=type, intensity, duration and frequency) of exercise is in this group to obtain benefits on specific side effects following treatment. For example, a child with major strength decrease following treatment will benefit most likely from resistance training, while a child who is at risk for osteopenia after treatment, will need exercises aimed at loading the bone and stimulate bone formation at a to be defined intensity. A child hindered by fatigue might benefit more from short bouts of aerobic training at a light intensity (18). Consequently, we need to move away from a one-size-fits-all program design to an exercise program tailored to the specific physical and psychosocial profile of each survivor and thus approach exercise oncology as precision medicine.

Concluding, physical rehabilitation/exercise referrals should be a standard practice for all children with cancer. To succeed in this mission in oncology, communication of clinicians, health care providers and the patient’s parents appear to be key, and they should *assess* physical activity at regular intervals, *advise* and educate patients and their parents on the message that moving matters and that the parents should show this as example, modelling behaviour, and *refer* them to appropriate exercise programs (22).

Psychosocial support

Besides support for physical recovery, patients are strongly challenged mentally throughout their cancer disease. They can be at risk for developing internalizing or externalizing problems, for which professional psychosocial support by a psychologist is highly recommended (19). There is consensus that personalized psychological care should be an essential part during and after the treatment for every child and family. The Pediatric Medical Traumatic Stress model of Kazak provides a clinical framework to establish psychosocial interventions, including three levels of psychosocial risk profiles: Universal, Targeted and Clinical (20). The largest group consists of ‘Universal’ families. These families are found to be adaptive and resilient when being confronted with health-related stressors. The ‘Targeted’ families are prone to psychosocial difficulties as a result of acute distress or pre-existing risk factors. The smallest group is the ‘Clinical’ group. These families have multiple psychosocial risk factors. The Psychosocial Assessment Tool (PAT) is a brief, parent report screener and can be used to identify these risk profiles (20). A Flemish version is currently investigated in some centers and the first results are in line with the general distribution of these groups. Based on the individual risk profile, appropriate interventions can be installed during and after the treatment. A recent meta-analysis demonstrated that a wide variety of psychosocial interventions, such as individual counselling of the families, targeted interventions of anxiety and depression within families, group sessions for parents or patients, acceptance and commitment therapy, can be effective in pediatric cancer survivors to reduce the psychological burden and to improve social skills (21).

Neurological rehabilitation

Ideally, prevention of neurological problems by reducing treatment exposure, while maintaining the best prognosis, should be the ultimate goal. Especially, children with brain tumors are at highest risk. In 2015, a set of standards of psychosocial care for children with cancer was published, including monitoring of neurocognitive functioning of children with a pediatric brain tumor during and after treatment (22). A wide variety of neurocognitive problems can occur: overall intellectual decline, slow processing speed, attentional, memory and visuomotor difficulties, executive dysfunctioning, but also learning problems. Since 2010, a neurocognitive follow-up program in UZ Leuven has been established for all these children. Irrespective of the treatment, all children with a pediatric brain tumor are invited to perform a comprehensive neurocognitive battery shortly after diagnosis, which is repeated every two years. A longitudinal follow-up of children treated for a pediatric brain tumor is crucial because the effects of the tumor and its treatments take place in a developing brain. It is well established that children treated with radiotherapy are at high risk to develop neurocognitive problems months after the treatment. Several studies demonstrated growing discrepancies between survivors and controls in intellectual functioning, processing speed, attention and working memory over time (23). Age at diagnosis, amount of irradiation and use of chemotherapy are other important risk factors that can increase the degree of impairment (23–25). A comprehensive neurocognitive assessment is time-consuming, but should be considered in standard care, as supported by several international initiatives, e.g. The workgroup Quality of Survival of the SIOPE-Brain Tumor and International Guideline Harmonization Group (www.ighg.com) (26–28). Our experience of the neurocognitive follow-up in UZ Leuven is positive, as it helps to understand the problems that many survivors experience in daily and school life. Such a comprehensive neurocognitive assessment of the impact of the disease and its treatment is a crucial step to understand the problems, provide psycho-education and to detect the needs for support and rehabilitation. Psychoeducation is a crucial element in the long-term follow-up. Not only the child and parents, but also schools need to be involved, during (if available also hospital schools) and after treatment. The strength/weakness profile of neurocognitive functioning provides directions for 1) specific interventions at home or school and 2) referral to specialized rehabilitation services.

Regarding interventions, first some pharmacological treatments exist that could be used for cognitive improvements, including methylphenidate (MPH), a mixed dopaminergic-noradrenergic agonist which is often used with a good response rate of 75-80% in children with ADHD. A large multisite and multiphase trial with MPH demonstrated beneficial effects in attention regulation and social and academic competence in children with a pediatric brain tumor or acute lymphoblastic leukemia (29). Currently, the use of MPH in the clinical setting should be monitored very carefully for the occurrence of side effects (e.g. weight loss), and not all survivors and parents are willing to use it. Contra-indications are uncontrolled seizures and uncorrected hypothyroidism. Several other drugs could also have potential beneficial effects (e.g. Modafinil, Donezepil, Metformin), but are still to be investigated.

Second, cognitive remediation and computerized cognitive training are other non-pharmacological avenues to target deficient functions, which also impact activities in daily living. It is found that cognitive remediation can positively impact metacognitive and academic skills, but has little impact on improving the deficient functions. Also, the beneficial effects are modest (with effect sizes ranging from 0.1-0.5). The labor- and time-intensiveness complicate implementation in daily life. Computerized cognitive training can additionally have a positive impact on the specific functions that are trained, but the low ecological validity and generalizability are a significant limitation. Currently, rehabilitation trajectories focus on training of activities in daily living and participation. Additional, training of strategies to deal with and to compensate for cognitive problems are common part of the rehabilitation process. Parents, other caregivers, teachers should be involved, who need to be a coach by providing instructions, giving cues to stay attentive, eliminate distractors, provide positive feedback.

Personal factors

Demographic factors

Not all patients develop similar daily life complaints. Besides physical and clinical risk factors as described in section 3, also pre-existing patient- and family-related factors play an important role in coping with the situation, and long-term physical and psychological quality of life. In addition, different childhood cancers and their treatment can differently interact with physiological functioning of the body, brain and psychological processes of the child, depending on their age, gender and socioeconomic status. More specifically, for some processes, younger age can be a risk factor. For instance, lower levels of growth hormone at younger ages is known to result in a shorter adult height. Also neurotoxic processes could affect brain development to a larger extent in younger children (which is associated with the "Growing into deficit" concept). On the other hand, older patients might be more at risk for some mental health issues and difficulties in socializing or reintegration at school (30). However, the directions of these risk factors still need more validation in future studies.

Socio-emotional functioning & resilience (e.g. post-traumatic stress/growth)

Some patients are specifically vulnerable to be challenged emotionally, if there are already pre-existing emotional and social difficulties within the family of the patient. By contrast, resilience and post-traumatic growth has also been observed in patients who were longer out of treatment, who had more social support, and who showed optimism during treatment (31). In addition, a more positive experience of the illness severity predicted higher chances of posttraumatic growth (32). Such positive factors as well as personal growth can explain why some studies demonstrate improved HRQoL in survivors many years after treatment.

Motivation and adherence

Successful adherence to follow-up is very important to monitor a healthy lifestyle, risk factors for relapse as well as long-term mental well-being. Whether childhood cancer patients adhere to their follow-up and transition to adult care, depends on their own self-management skills, education, empowerment, social environment, personal feelings and emotions, the clinical settings, financial issues and insurance and good communication (33). In other words, patients ideally receive sufficient information and empowerment, not only by the clinical setting, but also strongly supported by their families.

Environmental factors

Family, social & school support

As previously mentioned, adherence to treatments and empowerment strongly relies on social support by family members and friends (33). Adherence is of course important for the long-term physical functioning of the patient, while the empowerment of the patient is very predictive for their long-term mental functioning. Also after treatment, fulfilling the patient's wish of having a "normal life" as much as possible, requires sufficient social support and understanding of the environment. Additional psychosocial programs (e.g. yoga, psychoeducation, sport activities,…) could also help with the reintegration process (21).

Inpatient / survivorship (time since treatment)

Although long-term survivors more often live more independently than their siblings, some subpopulations are at increased risk to be able to live independently (34). More specifically, cranial radiation, use of psychopharmaceutics (antiepileptics, psychostimulants), attention problems, poor physical functioning, depression and racial/ethnic minority status are significant predictors of a smaller chance to be able to live independently.

Finances

As childhood cancer treatment have high financial costs, the economic burden to the family should ideally be limited. In Europe, insurance systems for standard care are mostly sufficient. However, for rare diseases only expensive experimental treatments are an option, which are not covered by their insurance. Besides these short-term costs, also financial outcomes of survivors highly depend on their employment opportunities. Given the abovementioned sequelae, their employment rates and socioeconomic status can be decreased, which are highly associated with task efficiency, somatization and depression (35,36). Hence, early neurorehabilitation is mostly important for neuro-oncological patients, suffering from neural damage, in order to maximize their job opportunities later in life. Additionally, physically impaired patients, e.g. due to a prosthesis, should start rehabilitation as early as possible to maximize their chances of obtaining a career which requires physical performance.

Participation

After cancer treatment, patients are confronted with new challenges in their lives. Physical, neurological and mental difficulties can arise, which could complicate their reintegration in society. It is very important to soon engage again in their hobbies and sport activities. This engagement is not only important to re-establish a healthy lifestyle and to repair physical functioning, also for their social engagement and support. Such engagement highly depends on their bodily functioning (e.g. organ toxicity), physical capacity, levels of fatigue, neurocognitive and mental functioning, as well as personal and environmental factors. Specific attention should be provided for neurocognitive impaired or socially isolated patients, to motivate them for stimulating activities as well as to support them in accepting the existing complications.

Conclusion: long-term quality of life

Childhood cancer survivors might have to deal with long-term consequences of their treatment with impact, with large variability between survivors, on their health and physical function, social and emotional well-being and cognitive functioning. Therefore, these patients are in need of adapted follow-up care and specific rehabilitation approaches, focused on their individual physical, psychosocial and cognitive problems and aimed at improving their functioning, activities and participation .

As physical activity has beneficial effects on the musculoskeletal and cardiovascular system as well as on psychosocial variables such as anxiety and depression in childhood cancer patients, motivating them to be (lifelong) physically active should be standard practice. In addition, abovementioned psychosocial and neurocognitive interventions, as well as the protective factors can help improve anxiety for relapse or reintegration, depressive mood, fatigue, pain and quality of life. Early physical and psychological interventions could therefore help in increasing benefit finding and personal growth in order to improve the patients' daily life quality. All of these interventions increasingly receive attention for international guideline constructions and will be integrated in a new EU-funded PanCareFollowUp project (www.pancarefollowup.eu) initiated in four clinics in Belgium, Czech Republic, Italy and Sweden with the objective to standardize survivorship care.

Conflict of interest: the authors have no conflict of interest to declare.

REFERENCES:

1. Erdmann F, Frederiksen LE, Bonaventure A, Mader L, Hasle H, Robison LL, et al. Childhood cancer: Survival, treatment modalities, late effects and improvements over time. Cancer Epidemiol. 2020 May 24:1010733. doi:10.1016/jcanep.2020.101733. Epub ahed of print.
2. Ness KK, Leisenring WM, Huang S, Hudson MM, Gurney JG, Whelan K, et al. Predictors of inactive lifestyle among adult survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. Cancer. 2009;115(9):1984-94.
3. Klika R, Tamburini A, Galanti G, Mascherini G, Stefani L. The role of exercise in pediatric and adolescent cancers: A review of assessments and suggestions for clinical implementation. J Funct Morphol and Kinesiol. 2018:3(1):7.
4. Ness KK, Plana JC, Joshi VM, Luepker R V., Durand JB, Green DM, et al. Exercise intolerance, mortality, and organ system impairment in adult survivors of childhood cancer. J Clin Oncol. 2020;38(1):29-42.
5. Hartman A, Van Den Bos C, Stijnen T, Pieters R. Decrease in peripheral muscle strength and ankle dorsiflexion as long-term side effects of treatment for childhood cancer. Pediatr Blood Cancer. 2008;50(4):833-37.
6. Wilson CL, Ness KK. Bone mineral density deficits and fractures in survivors of childhood cancer. Curr Osteoporos Rep. 2013;11(4):329-37.
7. Daniel LC, van Litsenburg RRL, Rogers VE, Zhou ES, Ellis SJ, Wakefield CE, et al. A call to action for expanded sleep research in pediatric oncology: A position paper on behalf of the International Psycho-Oncology Society Pediatrics Special Interest Group. Psychooncology. 2020;29(3):465-74.
8. Christen S, Roser K, Mulder RL, Ilic A, Lie HC, Loonen JJ, et al. Recommendations for the surveillance of cancer-related fatigue in childhood, adolescent, and young adult cancer survivors: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group. J Cancer Surviv. 2020;14(6):923-38.
9. Schulte FSM, Patton M, Alberts NM, Kunin-Batson A, Olson-Bullis BA, Forbes C, et al. Pain in long-term survivors of childhood cancer: A systematic review of the current state of knowledge and a call to action from the Children's Oncology Group. Cancer. 2020;127(1):35-44.
10. Van Dijk-Lokkart EM, Steur LMH, Braam KI, Veening MA, Huisman J, Takken T, et al. Longitudinal development of cancer-related fatigue and physical activity in childhood cancer patients. Pediatr Blood Cancer. 2019;66(12):e27949.
11. Krull KR, Hardy KK, Kahalley LS, Schuitema I, Kesler SR. Neurocognitive Outcomes and Interventions in Long-Term Survivors of Childhood Cancer. J Clin Oncol. 2018;36(21):2181-89.
12. Schuitema I, Deprez S, Van Hecke W, Daams M, Uyttebroeck A, Sunaert S, et al. Accelerated aging, decreased white matter integrity, and associated neuropsychological dysfunction 25 years after pediatric lymphoid malignancies. J Clin Oncol. 2013;31(27):3378–88.
13. Sleurs C, Lemiere J, Christiaens D, Billiet T, Peeters R, Sunaert S, et al. Advanced MR diffusion imaging and chemotherapy-related changes in cerebral white matter microstructure of survivors of childhood bone and soft tissue sarcoma ? Hum Barin Mapp 2018;39(8):3375-87.
14. Castellino SM, Ullrich NJ, Whelen MJ, Lange BJ. Developing interventions for cancer-related cognitive dysfunction in childhood cancer survivors. J Natl Cancer Inst. 2014;106(8):dju186.
15. Viña CC, Wurz AJ, Nicole Culos-Reed S. Promoting physical activity in pediatric oncology. Where do we go from here? Front Oncol. 2013; 3:173 doi:10.2289/fonc2013.00173.
16. Baumann FT, Bloch W, Beulertz J. Clinical exercise interventions in pediatric oncology: A systematic review. Pediatr Res. 2013;74(4):366-74.
17. Schmitz KH, Campbell AM, Stuiver MM, Pinto BM, Schwartz AL, Morris GS, et al. Exercise is medicine in oncology: Engaging clinicians to help patients move through cancer. CA Cancer J Clin. 2019;69(6):468-84.
18. Schmitz KH, Stout NL, Maitin-Shepard M, Campbell A, Schwartz AL, Grimmett C, et al. Moving through cancer: Setting the agenda to make exercise standard in oncology practice. Cancer. 2020;127(3):476-84.
19. Brinkman TM, Li C, Vannatta K, Marchak JG, Lai JS, Prasad PK, et al. Behavioral, social, and emotional symptom comorbidities and profiles in adolescent survivors of childhood cancer: A report from the childhood cancer survivor study. J Clin Oncol. 2016;34(28):3417-25.
20. Kazak AE, Schneider S, Didonato S, Pai ALH. Family psychosocial risk screening guided by the Pediatric Psychosocial Preventative Health Model (PPPHM) using the Psychosocial Assessment Tool (PAT). Acta Oncol. 2015;54(5):574-80.
21. Peikert ML, Inhestern L, Bergelt C. Psychosocial interventions for rehabilitation and reintegration into daily life of pediatric cancer survivors and their families: A systematic review. PLoS ONE. 2018;13(4):e0196151.
22. Jones B, Currin-Mcculloch J, Pelletier W, Sardi-Brown V, Brown P, Wiener L. Psychosocial standards of care for children with cancer and their families: A national survey of pediatric oncology social workers. Soc Work Health Care. 2018;57(4):221-49.
23. Palmer SL, Armstrong C, Onar-Thomas A, Wu S, Wallace D, Bonner MJ, et al. Processing speed, attention, and working memory after treatment for medulloblastoma: an international, prospective, and longitudinal study. J Clin Oncol. 2013;31(28):3494–500.
24. Hanzlik E, Woodrome SE, Abdel-Baki M, Geller TJ, Elbabaa SK. A systematic review of neuropsychological outcomes following posterior fossa tumor surgery in children. Childs Nerv Syst. 2015;31(10):1869–75.
25. de Ruiter MA, van Mourik R, Schouten-van Meeteren AYN, Grootenhuis MA, Oosterlaan J. Neurocognitive consequences of a paediatric brain tumour and its treatment: a meta-analysis. Dev Med Child Neurol. 2013;55(5):408–17.
26. Limond JA, Bull KS, Calaminus G, Kennedy CR, Spoudeas HA, Chevignard MP. Quality of survival assessment in European childhood brain tumour trials, for children aged 5 years and over. Eur J Paediatr Neurol. 2015;19(2):202–10.
27. Limond J, Thomas S, Bull KS, Calaminus G, Lemiere J, Traunwieser T, et al. Quality of survival assessment in European childhood brain tumour trials, for children below the age of 5 years. Eur J Paediatr Neurol. 2020; 25:59-67.
28. Jacola LM, Partanen M, Lemiere J, Hudson MM TS. Assessment and monitoring of cognitive function in pediatric cancer. J Clin Oncol. 2021;Accepted.
29. Conklin HM, Helton S, Ashford J, Mulhern RK, Reddick WE, Brown R, et al. Predicting methylphenidate response in long-term survivors of childhood cancer: a randomized, double-blind, placebo-controlled, crossover trial. J Pediatr Psychol. 2010;35(2):144–55.
30. Chan SF, Hoag JA, Karst JS, Bingen KM. Social adjustment of adolescent cancer patients transitioning off active treatment: A short-term prospective mixed methods study. Pediatr Blood Cancer. 2019;66(3):e27530.
31. Turner JK, Hutchinson A, Wilson C. Correlates of post-traumatic growth following childhood and adolescent cancer: A systematic review and meta-analysis. Psychooncology. 2018;27(4):1100-109.
32. Barakat LP, Alderfer MA, Kazak AE. Posttraumatic growth in adolescent survivors of cancer and their mothers and fathers. J Pediatr Psychol. 2006;31(4):413-19.
33. Freyer DR. Transition of care for young adult survivors of childhood and adolescent cancer: Rationale and approaches. J Clin Oncol. 2010;28(32):4810-18.
34. Kunin-Batson A, Kadan-Lottick N, Zhu L, Cox C, Bordes-Edgar V, Srivastava DK, et al. Predictors of independent living status in adult survivors of childhood cancer: A report from the Childhood Cancer Survivor Study. Pediatr Blood Cancer. 2011;15(7):1197-203.
35. Guy GP, Berkowitz Z, Ekwueme DU, Rim SH, Yabroff KR. Annual economic burden of productivity losses among adult survivors of childhood cancers. Pediatrics. 2016;138(Suppl 1):S15-S21.
36. Prasad PK, Hardy KK, Zhang N, Edelstein K, Srivastava D, Zeltzer L, et al. Psychosocial and Neurocognitive Outcomes in Adult Survivors of Adolescent and Early Young Adult Cancer: A Report From the Childhood Cancer Survivor Study. J Clin Oncol. 2015;33(23):2545–52.