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Large variation in assessment and outcome definitions to describe the burden of long-term morbidity in childhood cancer survivors: A systematic review

Nina Streefkerk[1,2] Lisanne C.E. Fioole[1] Josien G.M. Beijer2 Elizabeth (Lieke) A.M. Feijen[1,2] Jop C. Teepen[2] Jeanette F. Winther[3] Cecile M. Ronckers[2] Jaqueline J. Loonen4 Eline van Dulmen-den Broeder[2,5] Rod Skinner[6] Melissa M. Hudson[7] Wim J.E. Tissing[2,8] Joke C. Korevaar[9] Renée L.Mulder[1,2] Leontine C.M. Kremer[1,2]

1 Department of PediatricOncology and Pediatrics, Emma Children's Hospital, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands
2 Princess Máxima Center for Pediatric Oncology, Utrecht, The Netherlands
3 Department of Clinical Sciences, PediatricOncology and Hematology, Skåne University Hospital, Lund University, Lund, Sweden
4 Department of Hematology, Radboud University Medical Center, Nijmegen, The Netherlands
5 Department of PediatricOncology/Hematology, Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands
6 Department of Paediatric and Adolescent Haematology and Oncology and Children's BMTUnit, Great North Children's Hospital, Newcastle upon Tyne Hospitals NHS Foundation Trust, and Northern Institute of Cancer Research, Newcastle University, Newcastle upon Tyne, UK
7 Department of Oncology, St Jude Children's Research Hospital, Memphis, Tennessee
8 Department of PediatricOncology/Hematology, Beatrix Children's Hospital/University of Groningen/University Medical Center Groningen, Groningen, The Netherlands
9 Netherlands Institute for Health Services Research, Utrecht, The Netherlands

Abstract

We systematically reviewed outcome assessment methods, outcome classification, and severity grading of reported outcomes in studies investigating the burden of physical long-term morbidity in childhood cancer survivors (CCS).

A MEDLINE and EMBASE search identified 56 studies reporting on three or more types of health conditions in 5-year CCS, for which information was extracted on outcome types and classification, methods of outcome ascertainment, and severity grading.
There was substantial variability in classification and types of health conditions reported and in methods of outcome ascertainment. Only 59% of the included studies applied severity grading, mainly the common terminology criteria of adverse events. This large variation in assessment and definition of the burden of physical long-term morbidity in CCS challenges interpretation, comparison, and pooling data across studies. Global collaboration is needed to standardize assessments and harmonize definitions of long-term physical morbidity and associated outcomes in childhood cancer survivorship research.

1. Introduction

Over the past decades, improvements in therapy for pediatric malignancies have led to increasing numbers of childhood cancer survivors (CCS).[1-3] Those individuals constitute a vulnerable group at risk of long-term morbidity related to their cancer and its treatment, such as subsequent neoplasms and organ dysfunction.[4-7]

Characterizing long-term morbidity in CCS is important to guide the development of less toxic treatment protocols for newly diagnosed children with cancer. This knowledge is also relevant to inform surveillance guidelines and resource allocation for implementation of survivorship care. Consequently, long-term morbidity in CCS represents an important well-studied area of research that has been the topic of several landmark publications. These studies demonstrate that CCS experience a substantial burden of physical morbidity.[4-7] However, an accurate interpretation of the overall physical burden of long-term morbidity in this population and its associated risk factors as well as comparison of results across research investigations requires better understanding of the diversity of outcome study methods that inform our current knowledge.

This study aimed to systematically review the outcome assessment methods, and outcome classification and severity grading of reported conditions in studies investigating the physical burden of long-term morbidity in childhood cancer survivors. The burden of morbidity in CCS can also be measured using data from national registries that include health outcomes (eg, hospitalizations).[8-11] Such studies, which enable comprehensive ascertainment of specific outcomes across populations, generally have limited patient-level data especially detailed information about cancer treatment, and are not considered in this review.

2 Methods

2.1 Search

The electronic databases of MEDLINE/Pubmed (from 1945) and EMBASE/Ovid (from 1980) were searched to December 5, 2017. Search terms for childhood cancer, survivors, and late effects/burden of disease were combined in our search in these databases (Table S1).

2.2 Inclusion and exclusion criteria

We included original research reports written in English and without restrictions on publication dates that used data from self-report or clinical assessment to describe the occurrence of long-term morbidity in CCS. Childhood cancer survivors were defined as being treated for a malignancy before the age of 21 and having survived at least 5 years after the primary cancer diagnosis. Studies including survivors of Langerhans cell histiocytosis,myelodysplasia syndrome, and/or benign

brain tumors were included if the patients received treatment with chemotherapy and/or radiotherapy.

Because we aimed to only include studies that focused on longterm physical multi-morbidity in CCS, we defined studies describing the physical burden of morbidity as those reporting outcomes of at least three distinct organ systems (including subsequent neoplasms as a separate system) as a primary outcome. Metabolic syndrome and cardiovascular risk factors were considered as a single organ system. Case reports, case series, reviews, conference abstracts, commentaries, and editorials were excluded, as were studies that relied solely on data via record linkage and studies that reported hospitalizations, mortality, or psychosocial outcomes only.

2.3 Study selection and data extraction

Two authors (Nina Streefkerk and [Lisanne C.E. Fioole or Josien G.M. Beijer]) independently identified articles meeting the inclusion criteria from abstract and full text selection and independently performed data extraction. Discrepancies between authors were resolved by consensus or by consulting a third author (Renée L. Mulder or Leontine C.M. Kremer). Data on study characteristics, outcomes ascertainment methods, types of reported outcomes, and outcome grading were extracted using standardized forms. Because the aim of this review is to describe the methods of the included studies, no risk of bias assessmentwas performed.

3 Results

3.1 Results of the search

A total of 2978 unique articles were retrieved for title/abstract selection after the MEDLINE and EMBASE search (Figure 1). We excluded 2602 articles in this phase, of which 414 articles based on study type: 292 reviews and 122 conference abstracts. During full text screening of the remaining 376 articles, 320 articles were excluded, primarily because the study population did not include 5-year CCS or because the outcomes studied in the respective articles concerned fewer than three distinct organ systems. Fifty-six articles met all inclusion criteria for this review.

[Figure 1]

3.2 Characteristics of the included articles

Table S2 provides an overview of baseline characteristics of the 56 included articles. The number of survivors in the included articles varied from 13[8] to 13 841.[9] Multiple articles featuring results of the investigations of long-term physical morbidity from four survivorship consortia were included. Thirteen articles from the Childhood Cancer Survivor Study (CCSS) were included,[4,9-20] as were four from the St Jude Lifetime cohort,7,21-23 three from the Amsterdam-based Emma Children's Hospital cohort,[5,24,25] and two from the Swiss Pediatric Oncology group.[26,27] In 34 articles, reports focused on survivors with a specific diagnosis, for example central nervous system tumors,[10,14,28-35] infant leukemia,[21] or Ewing sarcoma.[13,16,36] Three articles were limited to survivors who had received specific treatment modalities (eg, cranial irradiation),[24] and nine articles specified both, for example survivors of a specific diagnosis type who had received specific treatment modalities such as high-risk neuroblastoma survivors treated with stem cell transplantation.[8] Authors of 20 articles compared scores among CCS to those of a control group, mainly siblings (n = 13[4,10,11,13-15,17-20,37-39]), the general population (n = [27,40]), or a group of survivors defined by inclusion criteria other than the survivor study population of main interest (n = 2[12,24]). Three articles used a combination of the above

mentioned control groups.[41-43] One study compared survivors' results to population-based normative data.[44]

3.3 Outcome assessment methods

Most articles were based on self-reported outcome data (n = 23 articles, 41%) collected via questionnaires[4,9-11,13-20,34,37,41,42,45-47] or phone interviews[38,39,48,49] (Table S2, Figure 2 . All 13 articles from the CCSS cohort were based on serial multi-outcome questionnaires. This CCSS questionnaire was adapted by several authors in subsequent studies.[34,37,38] Other authors affiliated with other study cohorts developed novel questionnaires.[5,14,24,25,28,41-43,46,47,49-51]

In 10 reports (18%), data were obtained solely by clinical evaluation[26,27,32,35,40,52-56] (Table S2, Figure 2 . This generally included a medical history, physical examination, and additional testing, which varied per study, but could include laboratory evaluations, diagnostic imaging, and organ function tests (data not shown). Ten (18%) reports included outcome data obtained solely by retrospective medical record abstraction.[8,22,23,29,30,36,57-59] In 10 articles (18%), a combination of methods of data ascertainment was used[5,7,21,24,25,28,43,50,51,60] (Figure 2), either using a combination of those methods for obtaining and validating health outcome data in one individual, or using different outcome ascertainment methods for different subgroups of survivors (eg, for questionnaire responders and nonresponders). Additionally, in one investigation questionnaires were sent to survivors' treating pediatricians,[44] in one investigation record linkage was used in combination with questionnaires to the family physician and the pediatrician,[61] and in one investigation self-reported data obtained from questionnaires were combined with data on vital status and cause of death obtained by record linkage.[12]

[Figure 2]

3.4 Outcome classification and reported outcome types

Outcomes in the studies were reported as specific health conditions (eg, heart failure or asthma) or as aggregated outcomes across organ systems (eg, cardiac or endocrine conditions). In all, 14% of the studies reported on incidence or prevalence calculations without mention of the underlying definitions for health conditions and/or organ systems.The results presented below do not consider these reports.

A rubric for classification of outcomes was specified in 48 investigations (82.8%, Table S2). Outcomes were classified according to an existing system in the majority of these reports, either any version of the common terminology criteria for adverse events (CTCAE; n = 23, 48%[4,5,7-13,16-19,23-25,37,40,42,46,51,54,58]), the international classification of diseases-10 (ICD-10; n = 1, 2%[61]), or the late effects normal tissues (LENT; n = 1, 2%[48]). In 22 investigations (46%), a custom-made outcome classification was used to categorize multimorbidity.[14,15,21,22,26-28,30,32,33,41,43-45,47,50,52,53,56,57,59,60]

The categories of specific organ systems outcomes were reported in 40 of the included investigations (71%). The number of organ system categories varied to a maximum of 24[24] (Table S2). Table 1 summarizes the organ system categories reported in the 12 investigations without formal restrictions on tumor type or treatment modality. In three of those investigations, the organ system categories were not reported but instead prevalence, (cumulative) incidence, or relative risks of one, multiple, any, or selected health conditions were reported.[4,38,45]

There were considerable differences in the number of organ system categories reported (from three[9] to 19[5]), and also in the organ system categories (Table 1 . Various descriptions were used to report health conditions in additional organ system categories, such as "organ systems,"[60] "constitutional symptoms,"[54] "organ toxicity,"[47] or the phrase "coded only in late radiation morbidity

scoring."[54] Table 2 shows that fewer and variable number and types of organ system categories were described in reports of long-term morbidity burden in survivors of central nervous system tumors.

Following more detailed evaluation of the classification of specific health conditions into organ system categories, we noted major differences. For example, cardiovascular conditions reported by Mulrooney et al included heart failure, myocardial infarction, cardiomyopathy, stroke, dysrhythmia, and coronary artery disease,[18] whereas Hamilton et al reported acute myocardial infarction, pericardial disease, cardiomyopathy, and heart transplant.[36] Other investigations reported "any heart disease" without further specification.[43] Publications describing respiratory conditions often included thromboembolic disease, not only in the lungs but also in other parts of the body.[16-18] Dental conditions were variably classified as diseases of the digestive system, as in the CTCAE[62] or as musculoskeletal conditions, as in the ICD-[10.9,21,22,44,50,63] Although according to the CTCAE, headache is part of "general symptoms and signs"[62] and in the ICD-10 it is part of "nervous system disorders,"[63] the condition was also classified under a separate category "pain" in some studies.[24,25] Moreover, although hypertension is usually classified as a circulatory or (cardio)vascular condition,[62,63] one study reported hypertension as a renal condition.[22]

3.5 Outcome grading

In more than half of the included publications (n = 33, 59%), the outcome severity was graded, most often according to the CTCAE (n = 27, Figure 3 . Additionally, Geenen et al developed a scoring system for burden of disease, which incorporated both number and CTCAE-based severity of reported outcomes.[5] Six articles described another method of severity grading, either an established method such as the LENT[48,64] or late effects severity score (LESS)[33,65] scoring system, or a grading method that was specifically developed for the study (n = 4[26,27,53, 56]). In one investigation, only hearing loss was graded according to the CTCAE and other outcomes were not graded for severity.[34] Fifteen of the 26 (57.7%) investigations that used the CTCAE to grade severity relied solely on self-reported data.[4,9-13,16-20,37,41,42,46] The other 11 studies utilized outcome data obtained by clinical evaluation solely,[40,54] medical record abstraction solely,[8,58] or either in combination with self-reported data.[5,7,23-25,43,51]

[Table 1] [Table 2] [Figure 3]

4 Discussion

This systematic review highlights the large variation in outcome ascertainment methods, classification, and severity grading identified among studies using self-reported or clinically ascertained data to evaluate the burden of long-term morbidity in CCS. First, a variety of methods have been used to assess long-term morbidity in CCS. Second, the classification of specific health conditions into organ system categories and types of organ systems reported is very diverse. Third, nearly half of the investigations identified in our search did not apply a method of severity grading. This lack of uniformity in long-term morbidity assessment challenges interpretation, comparability, and potential pooling of data across late effects studies.

The use of different outcome assessment methods as found in this study, all with individual advantages and disadvantages, can lead to disparate characterization of long-term morbidity. For example, in studies relying on clinical evaluation, asymptomatic health conditions can be included as an outcome of screening, while in studies relying solely on self-reported data, often symptomatic conditions that have prompted clinical intervention are represented.

We noticed that there were considerable differences in both the reported number of organ system categories as well as in the types of reported organ systems across studies. For example,

authors describing cardiovascular outcomes generally report on heart failure, myocardial infarction, and hypertension, but some also included stroke in this category.[9,13,17,18] A possible explanation could be that authors did not investigate all possible specific health conditions within one organ system system category or that certain health conditions had not occurred in the study cohorts. Furthermore, we observed inconsistency in the classification of specific health conditions into organ system categories. For example, thromboembolic events extremities were considered a pulmonary condition by some authors, which is inconsistent with both the ICD-10 and the CTCAE where it is classified as a cardiovascular condition.[62,63]

Regarding the grading of long-term morbidity in childhood cancer survivors, the CTCAE was used in 27 investigations. This system is mandatory for reporting acute adverse events in cancer trials funded by the USA-based National Cancer Institute,[66] but is not optimally designed to address long-term morbidity in survivors of childhood cancer. Other investigations have adapted the CTCAE to include outcomes relevant to pediatric cancer treatment late effects.[7,67,68] We identified that the majority of investigations in which the CTCAE was used relied solely on self-reported data, although adequate CTCAE grading often requires detailed additional diagnostic information. For example, in several endocrine conditions laboratory results are required to distinguish between grades 2 and 3,[62] which are not commonly available in self-reported data sources. To overcome the limitations of the CTCAE, St Jude Lifetime Cohort Study investigators developed a modified version for severity grading of late-onset health events among CCS.[67] So far, efforts to internationally standardize and harmonize long-term morbidity outcomes for survivors of childhood cancer have not yet been undertaken. In 2010, the International Late Effects of Childhood Cancer Guideline Harmonization Group (IGHG) was established, which aims to harmonize long-term follow-up guidelines for CCS.[69] Recently, the IGHG initiated a harmonization initiative for long-term outcomes for CCS. This endeavor includes a Delphi method in which experts in long-term morbidity research worldwide collaborate to establish a standardized core outcome set for clinically relevant self-reported physical long-term morbidity in CCS, including outcome classification and definitions. It is important that future harmonized outcomes can be assessed and graded when using different data assessment methods.

In this review, we investigated burden of morbidity studies. We decided not to focus on the burden of hospitalizations, because hospitalizations represent health conditions for which survivors need intensive medical care and thus important, less severe conditions managed in the outpatient setting might be missed. As a result, several important papers on hospitalizations in survivors, for example, from the Adult Life after Childhood Cancer in Scandinavia study and from the DCOGLATER study were not included.[70-72] A future systematic review should investigate the methods featured in publications reporting hospitalizations in long-term childhood cancer survivors. The aim of this study was to describe the landscape of long-term morbidity studies in CCS, and not to evaluate the incidence or prevalence of long-term morbidity. The large heterogeneity would also have limited the pooling of data.

In conclusion, this descriptive systematic review identified substantial variability in methods used to assess the burden of long-term morbidity in CCS. Diverse outcome assessment methods, organ system classifications, and severity grading rubrics may hinder optimal characterization of long-term morbidity in CCS. Harmonization and standardization of outcome classifications and severity grading for a minimal set of core outcomes is important to facilitate interpretation, comparison, and pooling of data across long-term morbidity studies. A worldwide collaboration is needed to define this core outcome set to ensure uniformity in morbidity assessment of children with cancer, which will guide survivorship care. The IGHG is poised to pursue this initiative.[69]

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CONFLICT OF INTEREST
The authors declare that there is no conflict of interest.

ORCID
Nina Streefkerk https://orcid.org/0000-0003-3758-7434
JopC. Teepen https://orcid.org/0000-0002-2647-2677

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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Tables and figures

Figure 1 Flow chart of the included articles

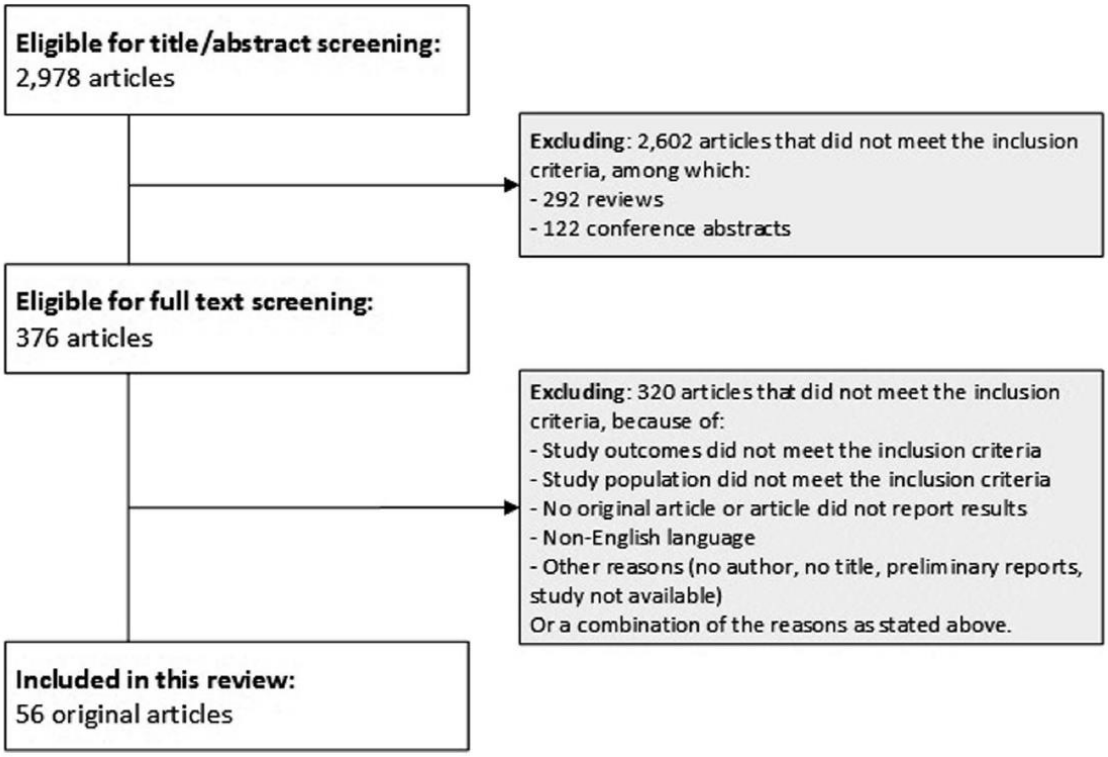

Figure 2 Overview of used data assessment methods in the included articles. In this Venn diagram, the number of reports using the stated data assessment methods are displayed. It also shows how many articles use multiple data assessment methods, and if so which methods are combined. This figure includes 53 reports and excludes three reports: (a) using data obtained from questionnaires to be completed by the responsible pediatrician44; (b) using data obtained from medical record abstraction, questionnaires to be completed by family, questionnaire to be completed by the responsible pediatrician61; (c) using self-reported data obtained from questionnaires, combined with data on vital status and cause of death obtained by record linkage12

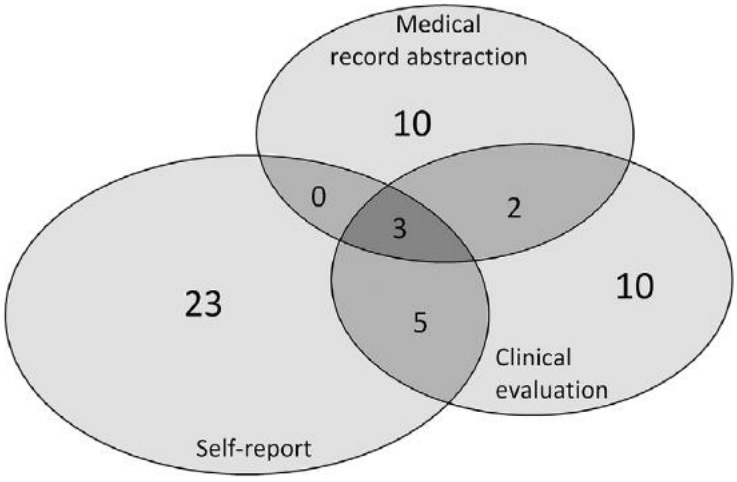

Table 1: Content of disease burden in all the articles describing the total burden of morbidity in childhood cancer survivors (n = 12) regardless of tumor type and/or treatment modality

Study	Prevalence		Outcomes																																						
Author, year	Prevalence of any health condition	No. of organ systems according to study	Alopecia	(Subsequent) neoplasms/malignancy	Ear, nose throat	Audiovisual problems	Auditory	Ophthalmologic	Sensory	Gastroenterology	Liver	Cardiovascular	Endocrine	"Growth/endocrine"	Pulmonary/respiratory	Metabolic	Nephrologic/renal	Urinary problems	Fertility/reproductive/sexual	Urology	Orthopedic/musculoskeletal	Problems in the extremities	Mobility	Spinal disease	Neurologic	Neuromuscular problems	Hematological, blood/bone marrow	Dermatology	Fatigue	Pain	(Neuro)psychosocial	"Intellectual/psychological"	Infections	Tissue hypoplasia	Miscellaneous	Cosmetic (effects)	"Organ systems"[b]	"Special sense/dental"	Constitutional symptoms	Coded only in late radiation morbidity scoring	Organ toxicity/other
Von Der Weid, 1996[26]	43%	6										X	X		X						X				X																X
Michel, 2009[45]	55.5%	Not reported[a]																																							
Ozono, 2014[43]	56%	10				X				X		X	X		X			X	X			X		X		X															
Stevens, 1997[47]	58%	7							X										X				X	X							X					X					X
Curry, 2006[60]	61%	7												X							X				X							X				X	X	X			
Oeffinger, 2006[4]	62.3%	Not reported[a]																																							
Oeffinger, 2000[54]	69%	15		X			X			X		X	X				X		X		X				X		X	X		X			X						X	X	
Geenen, 2007[5]	74.5%	19	X	X	X			X		X		X	X		X	X	X		X	X	X				X				X	X	X			X	X						
Bhakta, 2017[7]	99.9%[c]	13		X			X	X		X		X	X		X		X		X		X				X		X						X								
Liu, 2016[9]	Not reported[a]	3		X								X	X																												
Kenney, 2010[38]	Not reported[a]	Not reported[a]																																							

Note. Summary of the characteristics of the reported disease burden in articles that included complete childhood cancer survivor (CCS) cohorts (ie, those articles that did not apply tumor- or treatment-related inclusion criteria). For those articles, the reported prevalence of having any outcome is displayed, as well as the number of organ systems for which outcomes were reported. Also, the specific organ systems, as defined in each individual article, were listed.

[a] Although the exact number of reported organ systems was not mentioned, the text of this article described that authors aimed to report the burden of morbidity of three or more organ systems in CCS; therefore, the study met the inclusion criteria.

[b] Organ systems included: respiratory, organ removal, cardiovascular, bladder problems, renal, hepatic, gastrointestinal.

[c] Cumulative incidence at age 50 years.

Table 2 Content of disease burden in all included articles (n = 10) describing the burden of morbidity in childhood central nervous system tumor survivors

Study	Prevalence		Outcomes																				
Author, year	Prevalence of any health condition	No. of organ systems according to study	Medical (neurological, endocrinological)	Subsequent neoplasm	Sensory/chronic neurosensory health conditions	Hearing, ocular, speech and taste	Vision/hearing	Ear/hearing	Eye/visual acuity	Endocrine	Neurological	Motor impairments	Cognitive (and developmental)	Memory impairment	General psychological distress	Psychiatric disorders/psychologic findings	Cardiovascular, pulmonary, gastrointestinal and renal	Circulatory	Pulmonary	Musculoskeletal/connective tissue	Kidney	Associated impairments[c]	Other (Alopecia, Second malignancies, VP shunt insertion)	Body mass index (BMI)	Dental	Kanofsky performance status
Armstrong, 2009[10]	82%[a]	4		X	X					X	X															
King, 2017[14]	Not reported[b]	5		X	X						X			X	X											
Armstrong, 2011[28]	Not reported[b]	4						X	X	X	X															
Edelstein, 2011[29]	100%	Not reported[b]																								
Ehrstedt, 2016[30]	Not reported[b]	2	X										X													
Lannering, 1990[32]	Not reported[b]	2										X											X			
Pillai, 2012[33]	Not reported[b]	5						X	X	X	X			X									X			
Saha, 2014[34]	Not reported[b]	7		X		X				X	X						X							X	X	
Spunberg, 1981[35]	Not reported[b]	4								X	X					X										X

Note. Summary of the characteristics of the reported disease burden in articles including childhood cancer survivors (CCS) who had a central nervous system tumor. For those articles, the reported prevalence of having any outcome is displayed, as well as the number of organ systems for which outcomes were reported. Also, the specific organ systems, as defined in each individual article, were listed.

[a]Prevalence does not include subsequent malignancies.

[b]Although the exact number of reported organ systems was not mentioned, the text of this article described that authors aimed to report the burden of morbidity of three or more organ systems in CCS; therefore, the study met the inclusion criteria.

[c]Associated impairments: visual impairments, hearing deficits, epilepsy, thyroid dysfunction.

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Figure 3 Overview of the grading systems as used in the included articles to address severity of outcomes. It shows the number of articles