Review

Cancer Epidemiology, Biomarkers & Prevention

Approach for Classification and Severity Grading of Long-term and Late-Onset Health Events among Childhood Cancer Survivors in the St. Jude Lifetime Cohort

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Abstract

Characterization of toxicity associated with cancer and its treatment is essential to quantify risk, inform optimization of therapeutic approaches for newly diagnosed patients, and guide health surveillance recommendations for long-term survivors. The NCI Common Terminology Criteria for Adverse Events (CTCAE) provides a common rubric for grading severity of adverse outcomes in cancer patients that is widely used in clinical trials. The CTCAE has also been used to assess late cancer treatment-related morbidity but is not fully representative of the spectrum of events experienced by pediatric and aging adult survivors of childhood cancer. Also, CTCAE characterization does not routinely integrate detailed patient-reported and medical outcomes data available from clinically assessed cohorts. To address these deficiencies, we standardized the severity grading of long-term and late-onset health events applicable to childhood cancer survivors across their lifespan by modifying the existing CTCAE v4.03 criteria and aligning grading rubrics from other sources for chronic conditions not included or optimally addressed in the CTCAE v4.03. This article describes the methods of late toxicity assessment used in the St. Jude Lifetime Cohort Study, a clinically assessed cohort in which data from multiple diagnostic modalities and patient-reported outcomes are ascertained. *Cancer Epidemiol Biomarkers Prev; 26(5); 666–74. ©2016 AACR.*

Introduction

Investigators, having achieved remarkable progress in developing curative therapy for pediatric malignancies, now have a responsibility to evaluate cancer-related morbidity and its impact on long-term survivor health and quality of life (1, 2). Previous research has established that childhood cancer survivors commonly experience long-term (persistent) health problems following diagnosis and treatment and are at risk for late-onset health events occurring at rates exceeding those of sibling and population comparison groups (3–9). The morbidity associated with childhood cancer survival is multifactorial, with patient, treatment, and health care circumstances influencing outcomes (2). The reported prevalence estimates of specific complications vary by data collection methods (e.g., patient report, registry/administrative data, clinical assessment) as well as time (e.g., from diagnosis, attained age) of assessment. These disparities complicate comparison of research outcomes across studies and challenge the characterization of high-risk survivors who may benefit from alternate treatment strategies, heightened surveillance, and preventive or remedial interventions.

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Essential to the characterization of high-risk morbidity profiles associated with cancer treatment is the use of a common rubric for classifying and grading adverse outcomes. The NCI Common Terminology Criteria for Adverse Events (CTCAE) provides a descriptive terminology that is widely used for grading severity of adverse events observed in clinical trials (10–12). However, despite significant revisions over time, the current CTCAE v4.03 (10) is still not fully representative of the spectrum of outcomes experienced by pediatric and aging adult survivors of childhood cancer. Moreover, CTCAE v4.03 does not routinely integrate detailed patient-reported and medical outcomes data available from clinically assessed cohorts, which may increase the likelihood of inconsistent assessments among research investigators in long-term follow-up settings. To address these deficiencies, we adopted a standardized severity grading of long-term and late-onset health events to utilize in the St. Jude Lifetime Cohort (SJLIFE) Study population. Specifically, we developed an approach that is applicable to childhood cancer survivors across the lifespan by modifying the existing CTCAE v4.03 criteria and aligning grading rubrics from other sources for conditions not included or optimally addressed in the CTCAE v4.03. The purpose of this article is to describe the methods of long-term and late-onset adverse event assessment used in the SJLIFE study, where data from multiple diagnostic modalities and patient-reported outcomes are ascertained.

Materials and Methods

Study population

The ongoing institutional review board (IRB)–approved SJLIFE study was initiated in late 2007, with the aim of facilitating longitudinal evaluation of health outcomes among individuals surviving pediatric cancer (13). Eligibility criteria for participation in SJLIFE initially included diagnosis of pediatric cancer treated or followed at St. Jude Children's Research Hospital (SJCRH, Memphis, TN), attained age of 18 years or older, and survival of 10 or more years from diagnosis. In 2015, eligibility criteria were expanded to include 5-year survivors of any age. The SJLIFE study design involves a retrospective cohort with prospective follow-up and ongoing accrual (Fig. 1). The retrospective component of SJLIFE utilizes (3–9) data from surviving cancer patients treated at SJCRH since its opening in 1962. During and following treatment of pediatric malignancy, cancer remission status and treatment-related toxicities are routinely monitored by the primary oncology team and/or the long-term follow-up (After Completion of Therapy) clinic until the survivor is 10 years from diagnosis and at least 18 years of age. Data obtained from medical record review of all participants include demographic details, the cumulative doses of specific chemotherapeutic agents, the fields and doses of radiation, information on surgical interventions, primary cancer recurrences and subsequent neoplasms, and acute and late organ-specific toxicity.

In addition to longitudinal evaluations undertaken as part of SJLIFE, all oncology patients transitioned from SJCRH long-term follow-up care to community providers are followed by the IRB-approved St. Jude Long-Term Follow-Up (SJLTFU) study. All SJCRH patients are invited to participate in the SJLTFU study at diagnosis. Health and vital status of SJLTFU participants are monitored by the St. Jude Cancer Registry and supplemented by periodic National Death Index searches.

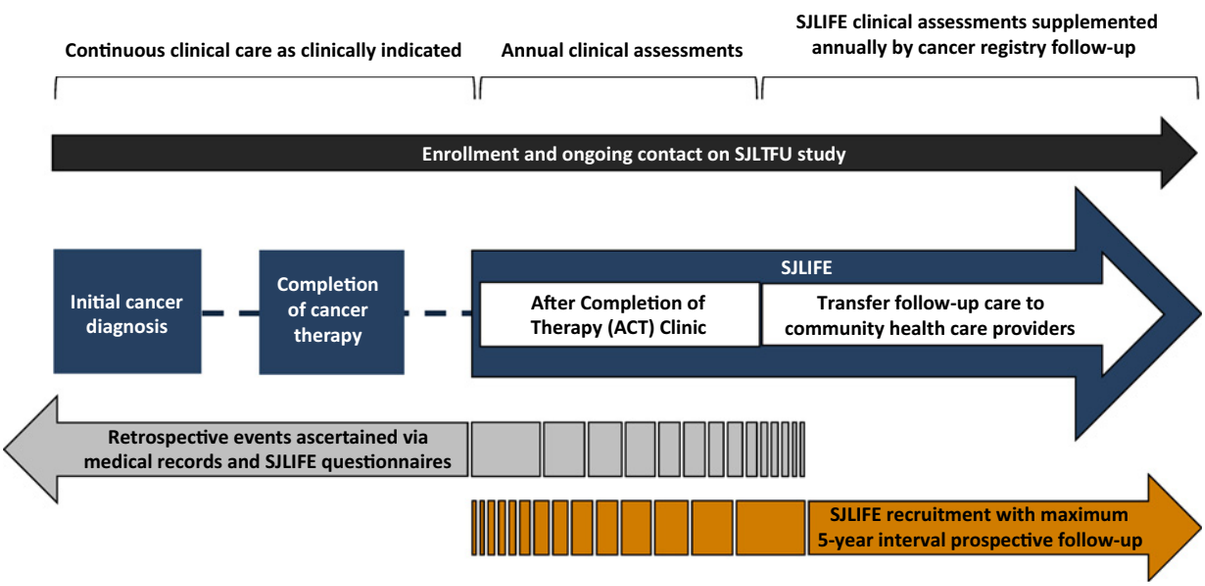

Figure 1.

Sources of health outcomes data used in the SJLIFE study where severity grading criteria of long-term and late-onset health events were applied. During and following treatment of pediatric cancer, cancer remission status and treatment-related toxicities are routinely monitored by the primary oncology team and/or the long-term follow-up (After Completion of Therapy) clinic until the survivor is 10 years from diagnosis and at least 18 years of age. Participants in the SJLIFE cohort are invited to return to SJCRH at least once every 5 years for follow-up using protocol-based medical evaluations and assessments of patient-reported outcomes, neurocognitive function, and physical performance status. In addition to longitudinal evaluations undertaken as part of SJLIFE, all oncology patients transitioned from SJCRH long-term follow-up care to community providers are followed by the IRB-approved SJLTFU study. All SJCRH patients are invited to participate in the SJLTFU study at diagnosis. Health and vital status of SJLTFU participants are monitored by the St. Jude Cancer Registry and supplemented by periodic National Death Index searches.

Following provision of informed consent, participants in the SJLIFE cohort are invited to return to SJCRH at least once every 5 years for follow-up using protocol-based medical evaluations and assessments of patient-reported outcomes, neurocognitive function, and physical performance status. Permission for release of medical records is requested at each evaluation to validate interim, survivor-reported medical events. Data available through both retrospective health record review and prospective, standardized clinical assessment provide detailed information about symptoms, physical findings, laboratory/diagnostic study results, and clinical interventions to consider in the severity grading of chronic and late health events experienced by cohort members.

Grading of chronic and late-onset health events

A large and diverse multidisciplinary team reviewed data regarding health events routinely collected as part of the SJLIFE and SJLTFU studies, focusing on persistent health conditions present from diagnosis or developing during or shortly after therapy (long term) and those developing 5 or more years after diagnosis (late onset); congenital conditions and acute cancer- and treatment-related toxicities that subsequently resolved were excluded. The compiled health events were then compared with those in CTCAE v4.03.

The grading criteria for each late effect featured in CTCAE v4.03 were reviewed by the multidisciplinary team. Minor modifications were made to the CTCAE grading schema for some conditions to integrate specific diagnostic findings, clinical management, surgical interventions, and patient-reported outcomes, with the goal of creating a more transparent and uniformly replicable grading rubric (Table 1). Clinical management was incorporated into the grading criteria to account for the treatment burden and intervention risks among survivors whose adherence to clinical management resulted in normal laboratory and diagnostic testing results.

In addition, pediatric-specific criteria (e.g., bone mineral density deficit; ref. 14) and more conservative diagnostic ranges were used to revise definitions of certain CTCAE v4.03 conditions (e.g., bradycardia and tachycardia) to avoid overdiagnosis based on assessments that fell marginally outside the standard reference ranges. Grading criteria for CTCAE v4.03 events originally designed to capture acute toxicities (e.g., seizures) were modified to facilitate chronic event grading that coincided with the traditional categories [mild (grade 1), moderate (grade 2), severe/disabling (grade 3), life-threatening (grade 4), or death (grade 5)].

Chronic and late health events perceived to be relevant to pediatric cancer survivors that were not included or optimally addressed in CTCAE v4.03 were also identified (e.g., liver fibrosis/cirrhosis; Table 2). Metrics for severity grading of newly identified events were derived from established standards (e.g., body mass index for overweight and underweight pediatric survivors) or developed by multidisciplinary team consensus using a rubric similar to that of the CTCAE. Detailed grading criteria for neuropsychologic outcomes were outlined by psychologists, incorporating patient-reported outcomes and the results of validated cognitive and psychologic measures and comprehensive psychosocial evaluations by study social workers (Supplementary Table S1). Proxy parent report was used when patient self-report was not appropriate (i.e., young age of participant, severe cognitive impairment). Novel (compared with CTCAE) grading procedures were outlined for the spectrum of benign and malignant subsequent neoplasms experienced by childhood cancer survivors and mapped using histology-based *International Classification of Diseases for Oncology*, Third Edition (ICD-O-3; ref. 15), in combination with lesion site and surgical *International Classification of Diseases*, 9th Revision, Clinical Modification (ICD-9-CM; ref.16) codes (Table 3). With the exception of amputation, surgical interventions were not graded as a chronic health condition; instead, the clinical or functional consequences of the procedure were graded (e.g., chronic kidney disease following nephrectomy).

Results

Using organ system–based categories, 190 medical and 18 neuropsychologic conditions were selected for late effects grading (Fig. 2; Supplementary Tables S1 and S2). In all, categories were used as published in CTCAE v4.03 for 91 conditions/events (44%) and modified from those of CTCAE v4.03 categories in 94 (45%). Another 23 (11%) required development of new grading criteria for late effects not included in CTCAE v4.03 or for events with CTCAE v4.03 grading not suitable for pediatric or chronic (vs. acute) health conditions.

Discussion

The majority of individuals treated for cancer during childhood, adolescence, and young adulthood will experience extended survival after reaching the 5-year milestone from diagnosis (1, 2). An accurate characterization of cancer-related morbidity is essential to optimize therapeutic approaches for newly diagnosed patients and guide health surveillance recommendations for long-term survivors. The ability to compare outcomes from multiple cohorts requires the use of a common language for the assessment of adverse health events. Historically, CTCAE has provided comprehensive guidelines that enable consistent evaluations of treatment-related toxicity, but its application to cancer survivor cohorts has been limited by a primary focus on acute toxicities and lack of consideration of pediatric-specific reference ranges and developmental health risks (17).

Challenged with defining the long-term impact of cancer and its treatment in a large cohort of clinically assessed cancer survivors who developed health events across an age spectrum, we modified the CTCAE v4.03 to facilitate consistent and transparent late effects assessment by research team members. Age-appropriate reference ranges were incorporated in the grading criteria for a variety of conditions. Rather than relying on the organ system–specific "other" category for many events, clinically relevant data were added in an effort to augment the grading criteria. Our approach to grading the severity of subsequent neoplasms illustrates how histologic subtype and clinical management were integrated into the assessment of the generic category of "neoplasms, benign, malignant, and unspecified" (Table 3). Inclusion of details about conditions represented within a generic category, diagnostic parameters, and surgical and medical management in grading criteria was perceived by research staff as particularly helpful in improving accuracy and uniformity of assessments. In this regard, we noted that several categories in the proposed CTCAE v5.0 include similar specifications.

As highlighted by previous investigators, guidelines for evaluating adverse events impacting physical and intellectual growth and development in pediatric cancer survivors are not

Table 1. Examples of modifications of CTCAE v4.03 and rationale

Example	Rationale for modification	CTCAE v4.03	Modified CTCAE v4.03
CTCAE v4.03 Eye disorders: Other, specify Visual field deficit	"Visual field deficit" is not specifically included as an adverse event in CTCAE v4.03. Option of "other" eye disorders is not specific without incorporating patient-reported outcomes relative to performance of ADLs. Grade 4 is eliminated, because visual field deficits represented persistent (as opposed to acute) events in long-term survivor cohort.	1. Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated 2. Moderate; minimal, local, or noninvasive intervention indicated; limiting age appropriate instrumental ADL 3. Severe or medically significant, but not immediately sight threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL 4. Sight-threatening consequences; urgent intervention indicated; blindness (20/200 or worse) in affected eye	1. Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated 2. Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADL (unable to drive) 3. Severe or medically significant, but not immediately sight threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL (unable to ambulate/navigate) 4. Not applicable
CTCAE v4.03 Infections and infestations: Hepatitis viral	With availability of more effective therapy for chronic hepatitis, "Grade 1: asymptomatic; treatment not indicated" was perceived to be inappropriate, as symptoms are not the only indication driving treatment decisions. Grade 2 category developed to reflect common presentation with asymptomatic hepatitis and variceal hemorrhage to reflect decompensated liver function. Additional text added to Grade 3 to align with proposed CTCAE v5.0.	1. Asymptomatic, treatment not indicated 2. Not applicable 3. Symptomatic liver dysfunction; fibrosis by biopsy; compensated cirrhosis 4. Decompensated liver function (e.g., coagulopathy, encephalopathy, coma) 5. Death	1. Asymptomatic 2. Asymptomatic but treated with antiviral therapy 3. Symptomatic liver dysfunction; fibrosis by biopsy; compensated cirrhosis: hospitalization or prolongation of existing hospitalization indicated 4. Decompensated liver function (e.g., coagulopathy, encephalopathy, coma, variceal hemorrhage) 5. Death
CTCAE v4.03 Nervous system disorders: Intracranial hemorrhage	Text added to clarify neuroimaging findings consistent with intracranial bleeding in asymptomatic survivors.	1. Asymptomatic; clinical or diagnostic observations only; intervention not indicated 2. Moderate symptoms; medical intervention indicated 3. Ventriculostomy, ICP monitoring, intraventricular thrombolysis, or operative intervention indicated 4. Life-threatening consequences; urgent intervention indicated 5. Death	1. Asymptomatic; clinical or diagnostic observations only; intervention not indicated (MRI evidence of microhemorrhage, e.g., hemosiderin) 2. Moderate symptoms; medical intervention indicated 3. Ventriculostomy, ICP monitoring, intraventricular thrombolysis, or operative intervention indicated 4. Life-threatening consequences; urgent intervention indicated 5. Death
CTCAE v4.03 Respiratory, thoracic, and mediastinal disorders: Bronchospasm	Text added to clarify integration of routine clinical management into severity grading.	1. Mild symptoms; intervention not indicated 2. Symptomatic; medical intervention indicated; limiting instrumental ADL 3. Limiting self-care ADL; oxygen saturation decreased 4. Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated 5. Death	1. Mild symptoms; intervention not Indicated 2. Symptomatic; medical intervention indicated; limiting instrumental ADL; intermittent asthma requiring short-acting beta agonists as needed 3. Limiting self-care ADL; oxygen saturation decreased; persistent asthma requiring daily controller medication (oral or inhaled) 4. Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated 5. Death
CTCAE v4.03 Investigations: Ejection fraction decreased	Ejection fraction parameters specified to denote subnormal range and clinically significant decline from baseline. Text added to clarify integration of routine clinical management into severity grading.	1. Not applicable 2. Resting EF 50%–40%; 10%–19% drop from baseline 3. Resting EF 39%–20%; >20% drop from baseline 4. Resting EF <20% 5. Death	1. Not applicable 2. Resting EF less than 50%–40%; 10%–19% absolute drop from baseline 3. Resting EF 39%–20%; >20% absolute drop from baseline; medication indicated or initiated 4. Resting EF <20%; refractory or poorly controlled heart failure due to drop in ejection fraction; intervention such as ventricular assist device, intravenous vasopressor support, or heart transplant indicated 5. Death

(Continued on the following page)

Table 1. Examples of modifications of CTCAE v4.03 and rationale (Cont'd)

Example	Rationale for modification	CTCAE v4.03	Modified CTCAE v4.03
CTCAE v4.03 Metabolism and nutrition disorders: Glucose intolerance (includes impaired fasting glucose, insulin resistance with impaired glucose tolerance, diabetes mellitus)	Text added to clarify integration of routine clinical management into severity grading.	1. Asymptomatic; clinical or diagnostic observations only; intervention not indicated 2. Symptomatic; oral agent indicated 3. Severe symptoms; insulin indicated 4. Life-threatening consequences; urgent intervention indicated 5. Death	1. Asymptomatic; clinical or diagnostic observations only; pharmacologic intervention not indicated or initiated (e.g., dietary modification) 2. Symptomatic; oral agent indicated or initiated 3. Severe symptoms; insulin indicated or initiated 4. Life-threatening consequences; urgent intervention indicated or initiated 5. Death

Abbreviations: ADL, activities of daily living; ICP, intracranial pressure.

Table 2. Examples of new grading criteria developed to supplement CTCAE v4.03

Condition	Rationale for addition/change	New grading criteria	Grading source
Amputation	CTCAE does not include this adverse event.	1. Partial ostectomy or other bone repair 2. Amputation below ankle or below elbow/revision of amputation 3. Total ostectomy/upper extremity amputation above elbow or higher/lower extremity amputation above ankle or higher 4. Not applicable 5. Not applicable	ICD-9-CM diagnosis and procedure codes
Bone mineral density deficit	CTCAE does not have pediatric-specific criteria for bone mineral density deficits.	1. Radiologic evidence of low BMD with z-score of ≤ -2.0 and no history of significant fractures 2. Low BMD (z-score ≤ -2.0) and significant fracture history (defined as a long bone fracture of the lower extremity, vertebral compression, 2 or more long bone fracture of the upper extremities); therapy to improve BMD indicated or initiated 3. Limiting self-care ADL 4. Not applicable 5. Not applicable	International Society of Clinical Densitometry
Overweight Obesity	CTCAE categories do not provide pediatric-specific reference ranges.	For age 2–<20 years 1. Not applicable 2. BMI $\geq$85th percentile <95th percentile 3. BMI $\geq$95th percentile 4. Not applicable 5. Not applicable	Centers for Disease Control and Prevention
Seizures	CTCAE categories are more appropriate for acute event versus chronic seizure disorder/epilepsy.	1. Seizures not requiring medication 2. Seizures requiring 1 non-PRN medication 3. Seizures requiring 2 or more non-PRN medications; poorly controlled seizures with prescribed medications 4. Seizures requiring evaluation for surgical intervention 5. Death	Multidisciplinary team consensus
Executive function deficit	CTCAE does not include this adverse event.	1. Performance on a task is >1 but <2 SD below the mean and no functional impairment 2. Performance on a task is >2 but <3 SD below the mean or performance on a task is >1 but <2 SD below the mean and functional impact on instrumental activities. Examples include, but are not limited to, special education services at school (IEP, 504 plan, not self-contained), unable to reach educational/occupational goals secondary to cognitive impairment, assistance needed completing tasks at home, scheduling/attending appointments 3. Performance on a task is >3 SD below the mean or performance on a task is >1 but <3 SD below the mean and functional impact in self-care activities. Examples include, but are not limited to, unable to live independently, unable to work, self-contained classroom 4. Not applicable 5. Not applicable	Performance on neuropsychologic testing of executive functions, including measures of cognitive flexibility/shifting, verbal fluency/initiation, working memory, and self-monitoring
Posttraumatic stress[a]	CTCAE does not include this adverse event.	1. Meet criterion for >2 but <4 PTSD symptom clusters (intrusion, avoidance, cognition and mood, arousal and reactivity); mental health intervention not indicated 2. One cluster B symptom (intrusion) rated as "moderately" or higher, 2 cluster C symptoms (avoidance) rated as "moderately" or higher, 2 cluster D symptoms (cognition and mood) rated as "moderately" or higher, 2 cluster E symptoms (arousal and reactivity) rated as "moderately" or higher and treatment limited to 1 initiated or indicated mental health intervention; symptoms interfere with social or occupational functioning 3. One cluster B symptom (avoidance) rated as "moderately" or higher, 2 cluster C symptoms (avoidance) rated as "moderately" or higher, 2 cluster D symptoms (cognition and mood) rated as "moderately" or higher, 2 cluster E symptoms (arousal and reactivity) rated as "moderately" or higher and >1 mental health intervention initiated or indicated; symptoms interfere with self-care 4. Hospitalization indicated due to extreme symptoms of posttraumatic stress 5. Death	Validated patient reported outcome measure. Threshold of clinical intervention and impact on ADL

Abbreviation: ADL, activities of daily living; BMI, body mass index; PTSD, posttraumatic stress disorder.
[a]All grades require exposure to a traumatic event.

Table 3. Severity grading for benign and malignant neoplasms

Subsequent neoplasms	CTCAE v4.03 grading rubric	Grading rubric for SJLIFE				
		Grade 1	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Benign neoplasms	Neoplasms benign, malignant, and unspecified (including cysts and polyps) Other, specified 1. Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated 2. Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADL 3. Severe or medically significant but not immediately life threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL 4. Life-threatening consequences; urgent intervention indicated 5. Death	Low-grade or benign neoplasms where surgical intervention is not indicated; observation or minimally invasive biopsy only (e.g., meningioma followed by MRI only or gastrointestinal polyps diagnosed and resected during colonoscopy)	Any low-grade or benign neoplasm requiring surgical intervention more than a minimally invasive biopsy. Excludes CNS or cardiothoracic surgical interventions (e.g., fibroadenomas, thyroid adenomas, gastrointestinal polyps requiring surgical resection)	Any low-grade or benign neoplasm requiring CNS or cardiothoracic surgical intervention (e.g., meningioma or myxoma requiring intervention)	Life-threatening consequences; urgent intervention indicated	Death
Malignant neoplasms		Asymptomatic or mild symptoms; clinical or diagnostic observations only; low-grade neoplasms where intervention is not indicated (e.g., cervical dysplasia/CIN and teratoma incidentally identified on imaging)	Moderate symptoms; minimal, local, or noninvasive intervention indicated; limiting age appropriate instrumental ADL; low-grade, non-metastatic neoplasms (e.g., cervical carcinoma *in situ*, cervical lymph node paraganglioma, basal cell carcinoma, squamous cell carcinoma, parotid carcinoma)	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL; high-grade neoplasms where single-treatment therapy required (surgery, radiation with or without chemotherapeutic agent; e.g., breast cancer if *in situ*, prostate cancer, meningioma requiring intervention, bladder carcinoma, thyroid cancer, carcinoid, squamous cell carcinoma cervix, glioma, astrocytoma, GIST)	Life-threatening consequences; urgent intervention indicated; high-grade neoplasms where multimodal therapy required or more than one chemotherapy agent used (e.g., MDS, AML, ALL, Hodgkin lymphoma, non-Hodgkin lymphoma, non–*in situ*/invasive breast cancer, osteosarcoma, Ewing sarcoma, primitive neuroectodermal tumor/PNET, soft tissue sarcoma, renal cancer, anaplastic CNS tumor, glioblastoma, carcinoma of head/neck, liver cancer, lung cancer, mesothelioma, melanoma)	Death

Abbreviations: ADL, activities of daily living; ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; CIN, cervical intraepithelial neoplasia; CNS, central nervous system; GIST, gastrointestinal stromal tumor; MDS, myelodysplastic syndrome; PNET, primitive neuroectodermal tumor.

Categories of system-based chronic and late medical and neuropsychologic health events graded in the SJLIFE study

Unchanged from CTCAE v4.03 ($n = 91$) | Novel as compared with CTCAE v4.03 ($n = 23$) | Modified from CTCAE v4.03 ($n = 94$)

AUDITORY-HEARING	ENDOCRINE (CONT.)	HEMATOLOGIC	MUSCULOSKELETAL (CONT.)	NEUROCOGNITIVE	PSYCHOLOGICAL
Cerumen impaction	Adult GH deficiency	Thrombocytopenia	SCFE	Attention deficit	Suicide attempt
Cholesteatoma	Childhood GH deficiency	Thrombocytosis	TMJ disorder	Executive function deficit	Suicide ideation
Tinnitus	Hyperparathyroidism	Iron overload	Amputation	Fine motor dexterity deficit	Agitation
Vertigo	Hyperthyroidism	Anemia	BMD deficit (pediatric)	Memory deficit	Anxiety
Hearing loss	Hypoparathyroidism	Coagulopathy	BMD deficit (adult)	Processing speed deficit	Depression
CARDIOVASCULAR	Hypothyroidism	Neutropenia	Kyphosis	**OCULAR/VISUAL**	Hyperactivity
Arteriovenous malformation	**GASTROINTESTINAL**	Polycythemia	Limb length discrepancy	Dry eye syndrome	Oppositionality
Atrioventricular block	Bowel perforation	**IMMUNOLOGIC**	Osteonecrosis	Eyelid function disorder	Post-traumatic stress
Cor pulmonale	Celiac disease	Autoimmune disorders	Scoliosis	Glaucoma	Anorgasmia
Dysrhythmia	Dysphagia	Graft-versus-host disease	**NEUROLOGIC**	Ocular disease, noninfectious	Delayed orgasm
Pulmonary hypertension	Enterocolitis	Immunodeficiency	Autonomic dysfunction	Ocular surface disease	Insomnia
Raynaud phenomenon	Esophageal varices	**INFECTIOUS**	Cavernoma	Photophobia	Libido decreased
Thrombus	Esophagitis	Bronchial/lung infection*	Cerebellar dysfunction	Phthisis bulbi	Other psychiatric disorders
Vascular disease	Fecal incontinence	Endocarditis	Cerebral necrosis	Retinopathy	**RENAL/URINARY**
Aortic root aneurysm	Gastritis/duodenitis	Gastrointestinal infection	Cerebrovascular accident	Strabismus	Incontinence
Bradycardia, sinus	Gastrointestinal reflux disease	Genitourinary infection	Cerebrovascular disease	Cataract	Vesicoureteral reflux, acquired
Conduction abnormality	Gastrointestinal fistula	Hepatitis B, chronic	Hydrocephalus	Diplopia	Acute kidney injury
Congestive heart failure	Gastrointestinal necrosis	Hepatitis C, chronic	Hydrosyringomyelia	Orbital prosthetic complication	Chronic hematuria
Coronary artery disease	Gastrointestinal obstruction	HIV infection	Multiple sclerosis	Retinal detachment	Chronic kidney disease
Heart valve disorder	Gastrointestinal strictures	Lymphatic infection	Nerve root disorder	Visual acuity, reduced (OD)	Obstructive uropathy
High total cholesterol	Gastroparesis syndrome	Meningoencephalitis	Neuromuscular disorders	Visual acuity, reduced (OS)	Urinary bladder dysfunction
Hypertension	Malabsorption syndrome	Osteomyelitis	Peripheral motor neuropathy	Visual field deficit	Urinary tract calculi
Hypertriglyceridemia	Pancreatic insufficiency	Otitis media*	Peripheral sensory neuropathy	**PULMONARY**	**REPRODUCTIVE/GENITAL**
LV systolic dysfunction	Pancreatitis	Pelvic inflammatory disease	Pseudomeningocele	Epistaxis	Dysfunctional uterine bleeding
Pericarditis	Proctitis	Pharyngitis/tonsillitis*	Shunt malfunction	Respiratory tract hemorrhage	Dyspareunia
Prolonged QTc interval	Sialoadenitis	Sinusitis*	Seizures	Tracheal aspiration	Erectile dysfunction
RV systolic dysfunction	Gastrointestinal hemorrhage	Soft tissue infection	Cranial nerve disorder	Tracheal stenosis	Genitourinary adhesions
Tachycardia, sinus	Gastrointestinal ulcer		Dysarthria	Obstructive sleep apnea	Primary ovarian insufficiency
ENDOCRINE	**HEPATOBILIARY**	**MUSCULOSKELETAL**	Headaches*	Obstructive ventilatory defect	Prostatic hypertrophy, benign
Diabetes insipidus	Veno-occlusive disease	Arthralgia	Intracranial hemorrhage	Pulmonary diffusion defect	Retrograde ejaculation
GH excess	Hepatopathy	Arthritis	Movement disorders	Restrictive ventilatory defect	Vaginal fistula
Hyperprolactinemia	Portal hypertension	Dental maldevelopment	Narcolepsy	Asthma	Abnormal sperm concentration
SIADH secretion	Fibrosis/cirrhosis	Hernia	Neurogenic bladder	COPD	Cervical dysplasia
Overweight/obesity	Cholecystitis/cholelithiasis	Intervertebral disc disorder	Neurogenic bowel	Pleural space disorder	Endometriosis
Underweight	Constipation	Palatal defects, acquired	Paralytic disorder	Pneumonitis	Hypogonadism, central
Abnormal glucose metabolism	Hepatic failure	Prosthetic malfunction	Pseudotumor cerebri	Pulmonary embolism	Leydig cell insufficiency
Adrenal insufficiency		Skeletal spine disorder			Polycystic ovarian syndrome
					Precocious puberty
					Vaginal stenosis

* chronic/recurrent, BMD=bone mineral density; COPD=chronic obstructive pulmonary disease; GH=growth hormone; HIV=human immunodeficiency virus; LV=left ventricular; RV=right ventricular; SCFE=slipped capital femoral epiphysis; SIADH = syndrome of inappropriate antidiuretic hormone; TMJ=temporomandibular joint

Figure 2.

Categories of system-based chronic and late medical and neuropsychologic health events graded in the SJLIFE study. Among 208 chronic and late-onset medical and neuropsychologic conditions, the severity grading was assessed by unmodified categories published in CTCAE v4.03 ($n = 91$, white), modified CTCAEv4.03 categories ($n = 94$, pink), or newly developed grading criteria ($n = 23$, yellow).

adequately represented in CTCAE v4.03 (17). This deficiency is particularly problematic in the long-term follow-up setting given the high prevalence of endocrine and cognitive late effects associated with specific pediatric cancer therapies (18–25). Children also experience emotional and psychosocial challenges that are unique from those of adults, necessitating addition of novel categories of pediatric-focused neuropsychiatric outcomes (20, 23, 26). Incorporating developmentally sensitive patient-reported outcomes into the grading criteria for many outcomes, especially neuropsychologic outcomes (Supplementary Table S1), enhanced our ability to assure that toxicity assessment considered the patient's perspective and chronic symptoms, which has been reported to be lacking in clinician-based assessments (27, 28).

Our efforts to standardize late effects toxicity assessments for the SJLIFE study should be considered in the context of several limitations. We focused on the assessment of late health outcomes and recognize a more thorough consideration of acute toxicity grading criteria in children is also needed. Although comprehensive in our attempts to be inclusive of the wide range of cancer- and treatment-related late effects, it is possible that we have overlooked other adverse events experienced by childhood cancer survivors. Finally, the modifications and additions to the CTCAE v4.03 reflect the opinions of investigators from a single institution. Broader, multi-institutional collaboration will be required to achieve the goal of a common language for the assessment of late effects of pediatric cancer and its treatment across an age spectrum.

Standardized measures for assessing the severity of long-term and late-occurring health conditions in childhood cancer survivors are needed. We believe that the approach adopted for the SJLIFE cohort augments the existing CTCAE rubric to allow uniform assessment and grading of toxicities across a wide spectrum of clinical and research environments. This mechanism provides a platform upon which to further develop and harmonize a system that facilitates future collaborative investigations.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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