Specialty Topics in Pediatric Neuropsychology

Grace A. Mucci
Lilibeth R. Torno *Editors*

Handbook of Long Term Care of The Childhood Cancer Survivor

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Handbook of Long Term Care of The Childhood Cancer Survivor

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Foreword

A Survivor's Narrative: Not Just a Survivor, but Always Surviving

Living in Spain from the ages of 11 to 15 as an Asian Indian girl was the best part of my life. Through the company Bechtel, my father was offered a wonderful foreign assignment opportunity to Spain for 4 years. This allowed us to travel all over, taste, and experience the Spanish culture. In August of 1984, after a 15-day trip to Italy, my left knee began hurting and persisted until December. At school, I kept falling and found it strange, as I was not particularly clumsy as a child. After a fall down a flight of stairs, I ended up in the hospital. An X-ray was done and a doctor from my father's work was concerned that it may be bone cancer. He immediately wanted us to go to the Mayo Clinic in the United States for a second opinion. It was there at the age of 15 where I got the diagnosis of osteogenic sarcoma. What had started as simple pain just 4 months prior resulted in amputation of my left leg. At that time, the medical team informed us that I would not need chemotherapy before and after my amputation because the results of the CT scan had shown no metastasis.

Before my amputation, my orthopedic surgeon helped me decide to either amputate or have a stiff knee. He presented the pros and the cons of both options, and after directing me to a peer amputee mentor, I felt confident that amputation was the right choice. Following the amputation, the one thing I struggled with the most was phantom pain. At times I could feel as though my leg was still there and my toes curled up and dead. Other times, the phantom pain felt as if I was being shocked, causing the sensation of pins and needles. I remember the orthopedic surgeon, nurses, physical therapist, and the prosthetist constantly reassuring me that it would eventually go away. They all reminded me to be patient. I trusted my healthcare team. True enough, within six months, the intensity of the phantom pains subsided dramatically, even though to this day, I still experience phantom pains rarely.

Three weeks after surgery I was fitted with prosthesis and began intense physical therapy to learn how to walk again. In order to be a healthy amputee, the physical therapist and prosthetist educated me on some important aspects I needed to incorporate into my life. First was to maintain my weight, as a loss or gain of five pounds would make a difference in the fitting of my prosthesis. This would also prevent long-term wear and tear of the knee and

hip in the future. Second was to stretch the muscles and hip joint of my stump to prevent the formation of contractures. Contractures will limit the ability to fully extend my leg when walking with the prosthesis. I was also reminded that excessive hopping on the existing leg—a habit many amputees develop out of convenience—might result in a hip and/or knee replacement by the age of 40. Despite the medical team's advice, I did succumb to the habit of hopping around the house because it was just easier. With time, I was able to adapt to the prosthesis.

After two months of being in and out of the Mayo Clinic in Rochester, I was finally able to return to Spain. As an amputee, the challenge at that time was how my friends and school staff would receive me. I was excited to see everyone but was also very scared and worried about being accepted; it was not something I was prepared for despite all the advanced medical care I had received. I was not taught how to acclimate as a young teenage amputee. I learned quickly to use humor to deal with people's discomfort. Statements such as "having one leg up on them" or "tripod" would make them laugh. At this point I learned that humor and openness were the best medicine for the awkward moments. This attitude not only helped me cope with my amputation, but I was also able to see how others received me—with supportive hands and an open heart.

For the first few months after my amputation, I was able to adjust back into a routine. I still had monthly CT scans to monitor for recurrences and at that time do not recall suffering from overwhelming anxiety.

Five months after my amputation, I fell down while playing and suffered from bilateral pneumothoraces. Follow-up imaging confirmed that it was a relapse of osteogenic sarcoma, which caused my lungs to collapse. We returned to the Mayo Clinic where chemotherapy and surgical resection of the lung nodules were planned.

When I heard the word "chemotherapy" initially, I remember being frightened by the visual of another patient I had seen at the Ronald McDonald house who had no hair and was vomiting profusely. Even at that time, I remember hoping that I would never have to go through that, so the relapse and its treatment plan had actually turned into my worst nightmare. I did not want to look like a cancer patient. One month after my relapse and following initial chemotherapy, my family moved back to California and resumed my medical care at Jonathan Jaques Children's Cancer Center in Long Beach. I remember the oncologist educating me about the different types of chemotherapies and their long-term side effects such as infertility, neurocognitive difficulties, kidney dysfunction, and cardiac issues. At that time, however, I was more focused on getting through treatment. After 5 months of chemotherapy, the nodules shrunk enough to be surgically removed from both lungs.

I celebrated my Sweet 16th birthday before my first lung surgery and a month later I had the second lung surgery. Six months later, I had completed the full treatment protocol and was told that I was in remission. I was a survivor! Being a survivor meant that I would still need to be monitored closely for the next five years, and that I would always be reminded of the potential for recurrence.

Returning to reality was challenging. As a patient living with cancer, I had so much emotional support, but as a "cancer survivor," I felt abandoned and alone.

My life had gone from living in Spain as a teenager, with many friends, to being home schooled in the United States for what should have been my junior year. So at 17, returning to high school as a senior was even more challenging. I was entering a new school, not knowing anyone, with one leg, prosthesis, and the beginning stages of hair growth. Physically, this played on my insecurities making assimilation to a new school a continuous struggle. I always worried about how others would perceive me. Although it was hard at first, I resorted back to the humor and openness I used while I was in Spain. It worked!! Slowly, people came around and I was able to make friends. I decided to use my cancer experience as an opportunity to educate. By allowing people to ask questions, I noticed that they became more comfortable with my disability and me. I still carry this attitude with me today and I believe that it has contributed to the successes I've been able to maintain socially.

My senior year culminated with high school graduation and an acceptance to the California State University, Fullerton. In my "cancer world", I had also graduated by being cancer free for a year! It was at this time, I recall feeling anxiety with each approaching CT scan, fearing relapse with each blood work, oncology appointment, and CT scan results. For 5 years, I would need a monthly CT scan the first year, quarterly CT scans in year 2, semi-annual scans in year 3, and then yearly for the remaining two years.

At the age of 18, I had a year and a half of remission from cancer, a high school diploma, and one semester of college in my hands when the big "R" crushed my world—I had relapsed again. This time, there was a small nodule found in my heart. I would need open-heart surgery, another year of experimental chemotherapy, and stop attending college.

I felt as though my "survivor" medal was stripped from me as my remission dissipated, shattering my world in the process. I began chemotherapy in February of 1988, and by the summer, I was depressed, unable to see the light at the end of the tunnel. I had been battling cancer for three years on and off and never seemed to get a break. My oncologist realized the emotional difficulties I was suffering from and encouraged me to go back to college in the Fall to take two general education classes without hindering my chemotherapy regimen. This was the best remedy as it kept my mind going and helped me have some control in life. My oncologist taught me that although cancer can put life on hold, I must not succumb to cancer, but I should learn to move on. I was determined and it lifted my spirits as I found a new way to cope. It changed my focus and I was able to concentrate on school instead of "relapse" and "chemotherapy." Physically, however, I struggled once again as I lost my hair for the second time, this time during college. College is the height of socialization and experimentation, where many meet friends for life, boyfriends and girlfriends, college parties, dance clubs, experimentation with drugs, alcohol, and sex. For me, I did not personally engage in these natural college experimentations, partly because of my Asian culture and my 3-month oncology check-ups. I remember struggling with the feeling of being ugly. I had no hair, no eyebrows, no eyelashes, and was wearing a wig, while my peers came dressed up with make-up, high heels, and beautiful hairstyles. Adjusting to the college norm was challenging, especially as a cancer patient. I was embarrassed to wear short skirts because of the difference in color of my

limbs, and could not wear high-heeled shoes because of my prosthesis. Most of the time I felt that everyone was looking at my leg and not me. I struggled with body image and wondered whether men would find me attractive and desirable despite being legless. Unfortunately, psychotherapy was not necessarily an option for me at that time because being Asian-Indian, emotional distresses and psychological pathology both carried an associated stigma. Despite my initial struggles, I was able to create a social support system of friends who I met in college and knew as a child who were key in helping me through some of my insecurities.

Fast forward to 20 years later, at age 38, I was a cancer survivor, who received a master's degree in social work and my dream job as a pediatric oncology social worker at CHOC Children's Hospital in Orange, California. I was equipped with the hypervigilance that my cancer survivor mode granted me—any minute physical changes in my body (such as bumps, marks, blemishes, or any other ailments) triggered the initial thought of "is it cancer?"

Meanwhile, my gynecologist saw me annually to follow the potential infertility issues resulting from the chemotherapy I received as a teenager. I had known fibroids for many years and the gynecologist suggested to have the fibroids surgically resected from my uterus. A routine myomectomy had turned into a second cancer diagnosis—ovarian cancer—incidentally found during the fibroid resection.

The treatment for ovarian cancer involved surgical removal of my uterus and ovaries, followed by another six months of chemotherapy. This time the losses were much greater than they were at the age of 15. I went straight into surgically induced menopause with the inability to ever have children. In 24 h, I went from being a whole woman to feeling like an empty woman with an empty womb.

While still in the hospital recovering from my two surgeries, I started to notice that my back was hurting more than usual. Likely a side effect of being a survivor, but my hypervigilance led me to insist that my doctors order an MRI of my back. Unfortunately, the results of the MRI showed yet another tumor—a Schwannoma—beginning to wrap around my spine and needing immediate surgery to remove the tumor before I could begin chemotherapy.

Psychologically, I struggled with the thought of battling through central lines, chemotherapy, and hair loss *again*. Although I had some days where I coped poorly, somehow, I persevered and my fighting attitude to do this ONE more time kicked in. Emotionally, however, the thought of not having my own children was a long-term side effect, which was difficult to overcome. I felt angered when friends of mine would bring their children to the hospital for me to play with hoping it would make me feel better or being told "you can be an auntie to my baby." It took me about two years after diagnosis and treatment to finally hold a baby without becoming an emotional wreck.

When I began this cancer journey at 15, I remember my parents constantly telling me to take ownership of my medical care. As years went by, this sage advice not only helped me keep up on my medical needs but also take a proactive stance when medical problems arise. Today, I continue to attend long-term survivorship clinic every year.

Unfortunately, I have begun to experience many long-term side effects, but take the appropriate steps to avoid future problems. I am followed by four specialty doctors in addition to my Primary Care Doctor and my gynecologist: a cardiologist for possible cardiomyopathy, a gynecology oncologist for possible ovarian cancer relapse, a breast surgeon due to possible breast cancer following ovarian cancer, and an endocrinologist.

Being a Cancer Survivor is a hard balance. We have learned to protect the "ones we love as well as ourselves." Although we won the battle, the enemy, at times, is not too far behind us and one must learn to cope with those fears. The emotional spectrum of a cancer survivor can range from amazement and accomplishment to that of pure loneliness. We learn that cancer never really leaves us, but we also learn to become a light of hope for the oncology community and to others fighting the big "C."

The moral of this survivorship story is for cancer survivors to know themselves, continue to follow up with their physicians and specialists, attend yearly long-term clinic if available, and most importantly, be active participants in their medical care to allow for early intervention if needed. At times I feel it is harder to be a survivor than a patient. One must continuously adapt, cope, and find the courage within to move forward in life. My definition of a true "Survivor" is someone who shows a great will to live, with an enormous determination to overcome difficulties to carry on. Surviving is a constant battle and survivorship is a lifelong process.

This manuscript covers many of the myriad challenges facing survivors, but also the medical treatment team, families, and the community. It is important for all who work with individuals who have endured through cancer and its treatment to be ever mindful of the complex interplay of the unique physical, psychosocial, emotional, cultural, vocational, and financial challenges that affect one's journey.

I wanted to thank my cousin Regina Jacob, M.D., for giving me the guidance and support as I embarked on writing my personal story. Thanks for always reminding me the awesomeness of being a Survivor.

To my parents, Abraham and Leela Areeckal, words can't express how lucky and blessed I am to have you as my heroes, you both are amazing. YOU have taught me how to persevere, continue to love, laugh, fight, and most of all how to be a SURVIVOR. I love you both with all my heart and soul.

Orange, CA, USA Jenee Areeckal

Preface

We now live in the era of targeted therapies, pharmacogenomics, and molecular profiling. As science continues to evolve, the biology of cancer is being unraveled, albeit, slowly. Thanks to modern medicine, today, 80 % of children diagnosed with cancer will survive 10 or more years after therapy. However, the past three decades have also revealed the significant late effects of therapy that survivors live with. The lessons from past treatments help guide future treatment as we witnessed the effects of chemotherapy, radiation, and other intensive treatments given to children. Some of these survivors are now in their 30s and 40s; 60 % of whom experience chronic late effects, while 30 % have life-threatening conditions.

In our day-to-day experience in caring for survivors, we have been confronted with our own lack of knowledge and understanding as healthcare providers, the limitations of funding, as well as the lack of an organized system to transition adult survivors of childhood cancer. We have also seen firsthand the challenges of educating survivors, for various complex reasons some of whom seem to struggle with taking the necessary steps to understand their need for surveillance. Not only are the effects physical, the neurocognitive and psychosocial ramifications are just as significant.

It is for these reasons that this book is written. We decided to include comprehensive and in-depth discussions as well as integrate simple screening measures and road maps for the busy clinician. The road maps and screening tools are guidelines to help the clinician navigate a survivor's complex medical needs. The recommendations given in this book are the result of many hours of research and literature review done by brilliant contributing authors. However, as more research is done, these recommendations will also evolve. It is our hope that physicians, physicians-in-training, medical students, psychologists, therapists, and other providers caring for childhood cancer survivors may benefit from this book.

Finally, to the countless of childhood cancer survivors, we have shared times of sacred sorrow as you battled cancer, but now, we are privileged to share so many more sacred moments of joy as you journey through meaningful cancer survivorship.

Orange, CA, USA — Grace A. Mucci
Orange, CA, USA — Lilibeth R. Torno

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When we embarked on this project, we knew that it would require not only personal sacrifices, but sacrifices of those near and dear to us. It is for this reason that we would like to acknowledge everyone who has helped us along this journey.

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Second, our sincere gratitude is extended to our colleagues and friends who provided moral support and direction during the many phases of this project. Many professionals, including all contributing authors, have given much time, effort, and expertise in the creation of this book. We owe special thanks to Christine Marie Angeles, Edna Klinger, and Irma Padilla for their invaluable technical knowledge in layout, formatting, and graphics. Finally, words cannot express the sincere gratitude we feel for Janice Stern and her staff throughout this process. It is through all of them that we garnered professional and personal wisdom that helped to mold this manuscript.

Finally, we owe our deepest gratitude to our patients, who never cease to inspire us to be the best care providers we can. We are honored to be invited into their lives and help them through one, if not the, most difficult transition they face. It is amazing how much we have learned from their resiliency and tenacity to rise above their illness and become true survivors. While we are encouraged daily by advances in the medical and behavioral sciences as we seek a cure for cancer, we garner hope from our faith and our patients and feel truly blessed.

Grace A. Mucci
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Part I

Surveillance of the Survivor

The Long and Winding Road: Transitions in Care for the Childhood Cancer Survivor

1

Rajkumar Venkatramani and David R. Freyer

1.1 Introduction

For young people and their families, undergoing cancer treatment is an experience characterized by transition--"transition" being defined as passage from one state, stage, subject, or place to another [1]. The major transitions associated with cancer treatment are readily identifiable and familiar to clinicians. For most patients, these include the transition from development of symptoms to diagnosis of cancer, from diagnosis to the initiation of treatment, from completion of treatment to initial follow-up, and from initial follow-up to long-term cancer survivorship (Fig. 1.1).

For some patients, transition may also include development of relapse, and, for too many, end-of-life care. Effective management of these cancer-related transitions requires strong communication skills and anticipatory guidance born of familiarity with the underlying cancer and treatment regimen, as well as the typical clinical course.

In pediatric and adolescent oncology, however, these transitions do not occur in isolation, but rather against a backdrop of the patient's normal physical, emotional and social development. The successive transitions of developmental maturation that begin during infancy and continue through older adolescence not only influence each patient's response to cancer-related transitions, but also cause patients to require support during the cancer experience in order for healthy adulthood to be achieved.

One additional transition of survivorship, which arguably represents a unique convergence of both cancer-related and normal developmental components, is the one which occurs between older adolescence and young adulthood. In no other transition do we encounter the simultaneous complexities of established treatment-related health problems, emerging risks, need for ongoing medical surveillance, change from pediatric to adult-focused health care services, threats to maintaining health insurance, completion of

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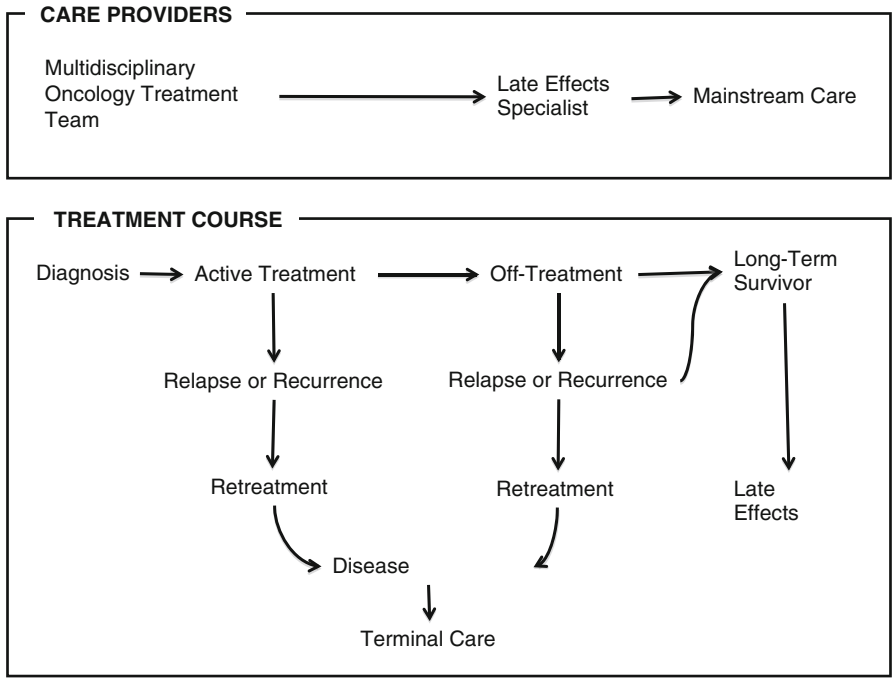

Fig. 1.1 Major transitions associated with cancer treatment. Reproduced with permission from MacLean et al. Cancer 1996; 78(6)

formal education, entrance to the work force, the achievement of personal independence, and redefinition of familial and societal roles, to name a few. With more and more young people surviving childhood cancer than ever before, the need for workable approaches to health care transition in young adulthood has never been greater.

The purpose of this chapter is to provide an overview of the major transitions experienced by children and adolescents undergoing management of their cancer, especially during the long-term follow-up phase. Key issues and potential interventions for each are discussed. The principles and practice of health care transition for young adult survivors of childhood and adolescent cancer are emphasized.

1.2 Developmental Aspects of Transition

Cancer commonly affects growth and development, either directly in physical changes or through parenting and peer experiences. Physicians and other health care professionals taking care of childhood cancer survivors should have an understanding of major developmental tasks of childhood in order to normalize the cancer experience in an age-appropriate way [2, 3]. Providing appropriate support for those tasks differs somewhat according to the type of transition. As summarized in Table 1.1, during transitions associated with diagnosis and treatment, the focus for all age groups is to support patients and families through crises characterized by sudden and dramatic change, unfamiliar situations, uncertain outcomes and frightening possibilities.

In contrast, during transitions associated with survivorship, especially during late long-term follow-up, the focus switches to assisting patients and families with understanding and coming to terms with the persisting health problems and/or future risks resulting from cancer treatment. In both transitions, explanations should become more detailed, commensurate with the patient's and the family's cognitive capacity and degree of involvement in medical decision-making. In pediatric oncology, clinicians are faced with the interesting challenge

Table 1.1 Developmental stages of childhood and their correlates for transitional care

Developmental stage	Selected developmental features [3]	Correlates for transitional care	
		Diagnosis and treatment phase	Survivorship phase
Preschool (2–5 years)	Acquisition of language and motor skills	Arrange child life interventions to minimize procedure-related anxiety	Child too young to understand the need for long-term follow-up
	Formation of simple concepts of reality	Facilitate child's understanding that illness is not a punishment	Direct anticipatory guidance about late effects towards the parents
	Emotional connection with other people Cognitive features of magical thinking, egocentrism and dominance of perception	Advise parents that being calm may be more comforting than explanations like "this will make you better"	Mention eventual transition to adult-focused providers
Middle childhood (6–12 years)	Expansion of child's world outside the home	Provide simple explanations to child regarding diagnosis and necessary treatments	Provide simple explanation to child relating prior illness to the need for continued follow-up
	Ability to get along with other children	Maintain educational progress through hospital-based school activities and school reentry programs	Continue to educate parents on late effects, health and wellness
	Development of concrete operational thinking	Encourage child's involvement in simple treatment choices (e.g., flavor of medications)	Mention eventual transition to adult-focused providers
	Acquisition of adult concepts and communication (writing, reading, calculating)	Advise parents against over protectiveness and encourage normal disciplining	Advise parents against over protectiveness and encourage normal disciplining Encourage parents to allow children to have increasing responsibilities at home and an increasing role in decisions
Early adolescence (10–13 years)	Development of formal logical operations	Provide straightforward but more detailed explanations of diagnosis and treatment	Provide straightforward but more detailed explanations about follow-up care
	Awareness of changing body and interest in opposite sex	Provide support to reduce social isolation and depression through interventions such as child life therapy	Encourage increased participation in medical decision making and personal health choices
	Reduced interest in family-centric activities Increasing peer-identification	Supplement parental support with organized peer-support activities	Initiate discussions about eventual transition to adult providers

(continued)

Table 1.1 (continued)

Developmental stage	Selected developmental features [3]	Correlates for transitional care	
		Diagnosis and treatment phase	Survivorship phase
Middle adolescence (14–16 years)	Importance of physical attractiveness, popularity and self-esteem	Direct conversations towards the adolescent with active involvement in decision-making	Direct the conversation towards the adolescent with active involvement in decision-making
	New understanding of abstract concepts and consequences	Provide support for body image issues, self esteem	Reserve 1-on-1 time with teen for a portion of each clinic visit
	Reorientation of primary relationships from family to peer groups	Provide support to reduce social isolation and depression through adolescent support groups and teen-friendly facilities	Discuss prevention of high risk behaviors (smoking, alcohol, drug use, unprotected sex)
	Start of dating	Stress importance of adherence to therapy	Discuss targets for transition readiness and provide rationale for transition to adult focused providers
Late adolescence (17–20 years and beyond)	Development of personal independence, core values, ethical principles and philosophy of life	When feasible, offer flexibility in treatment schedule to accommodate important social events, e.g., graduation	Encourage a primary role for older adolescent during clinic visits
	Attainment of emotional independence	Offer internet access in hospital rooms for social networking	Provide information related to reproductive health and sexuality
	Development of intimate relationships	If desired by patient, include significant other during clinic visits	Continue education about importance and rationale for life long follow-up
	Emerging importance of career decisions as related to self-concept and emerging societal role	Help parents realize the need for adolescent's privacy and developing autonomy	Encourage pursuit of higher education and provide information on survivor focused scholarships and resources
	Preparation for occupation	Stress importance of adherence to therapy	Emphasize importance of preparing for employment with insurance benefits to cover continued follow-up care Help them understand insurance options available for cancer survivors Assess transition readiness (see Fig. 1.2) and coordinate transition to adult setting

of caring for older long-term survivors who were treated as young children, yet never developed insight into and understanding of their cancer and its treatment. They return year after year with little knowledge as to why they are in the cancer clinic. As these survivors mature into adolescence, it is essential they receive sufficient information about their cancer, its treatment, and the resulting health implications, in order to prepare them properly for health care transition.

1.3 The Transition from Completion of Cancer Treatment to Initial Follow-Up

This period encompasses the end of treatment until approximately 24 months after completion of treatment, during which most survivors are at the highest risk for relapse. The primary focus during this transition is to assist the patient in returning to baseline function. Ironically, toward the latter phases of treatment, many older patients develop a certain comfort level in receiving chemotherapy, especially if it is tolerated reasonably well and no relapse has occurred. The transition to end of therapy may elicit anxiety and fears related to relapse, for which many families feel unprepared [4].

One way to aid families in navigating this transition is to have a formal conference with them at the end of treatment [5]. This conference should involve at least the patient, parents and/ or significant others, the primary oncologist, and ideally the primary nurse and social worker. During this end of treatment conference, the team should briefly summarize the cancer diagnosis, the treatment received, immediate plan for follow-up, surveillance and other health recommendations. Many families are relieved to discover that they are not now "on their own," but that cancer treatment is followed by a formal phase of surveillance with systematic monitoring initially for relapse, and then later for long-term health and well-being. Straightforward conversation about the risk and typical patterns, the timing and symptoms of relapse, when to call the oncology clinic and the specific plan for surveillance will help reduce anxiety. Parents and patients should be briefly re-educated about the relevant, major long-term effects of treatment and need for continued follow-up. This presents an excellent opportunity to introduce the concept of lifelong survivorship care and the long-term follow-up program, if such a program exists in the institution. Parents should be encouraged to re-establish their child's care with the child's primary care provider, whom they should now contact for any health issues except those clearly related to the cancer. Specifying when to resume childhood immunizations and normal activity should be discussed. A copy of the treatment summary and follow-up plans should be provided to the older patient, parents and the primary care provider as a roadmap or guideline for future healthcare. Names and updated contact information for organizations providing further information and support to survivors may be provided.

1.4 The Transition from Initial to Long-Term Follow-Up Care

The transition period begins approximately 2 years post-cessation of cancer treatment and continues onwards. This transition is, for most patients, open-ended in the sense that life-long surveillance is recommended for most childhood cancer survivors. The separation between initial and subsequent periods of follow-up care is not uniformly distinct, as the risk for late relapse differs by cancer diagnosis. Indeed, for institutions where referral to cancer survivorship programs occurs relatively early, long-term follow-up services can overlap and should continue parallel with disease-directed surveillance for some period of time. The primary focus of this transition is to establish the practices for risk-based monitoring and to provide related health education to the survivor and family. Whereas the major risk during the initial period of follow-up is relapse, the major risk during this later period is disengagement from medical care and failure to remain in structured follow-up.

1.4.1 Late Effects and the Need for Survivorship Care

While the incidence of childhood cancer has increased gradually over the past three decades, mortality due to childhood cancer has steadily decreased [6]. In 2005, an estimated 328, 652 childhood cancer survivors were alive in the United States [7]. The prevalence of childhood cancer survivors has been estimated to be

approximately 1 in 640 among Americans aged 20–39 years [8]. These figures will undoubtedly increase in the future as survival continues to improve.

Many survivors remain at increased, life-long risk for clinically significant complications of their cancer therapy. These are commonly referred to as "late effects," defined as any chronic or late-occurring outcome, physical or psychosocial, that persists or develops 5 years after the cancer diagnosis [8]. In an analysis of self-reported data from 10,397 survivors and 3,034 siblings, investigators from the Childhood Cancer Survivor Study (CCSS) found that the risk for a chronic or life-threatening health problem was 3.3 and 8.2 times higher, respectively, in survivors compared with their siblings. The cumulative incidence of one or more chronic health conditions reached 73.4 % 30 years after the cancer diagnosis, with a cumulative incidence of 42.4 % for conditions graded as severe, disabling, or life-threatening [9]. A study involving 1,315 survivors from the Netherlands reported similar findings [10]. The excess risk does not appear to reach a plateau with time [9, 10]. Data from the CCSS indicate that all-cause mortality is 8.4 times higher among survivors compared with the United States (US) population 25 years following cancer diagnosis [11]. Although recurrent/progressive disease accounted for most deaths, second or subsequent cancers and cardio-pulmonary late effects were noted to become important contributors over time [11]. Selected late effects by organ system, their risk factors and recommended surveillance tests are outlined in Table 1.2.

There is expert consensus that most childhood cancer survivors should remain in structured, lifelong follow-up due to increased risk for late effects, impaired health status, and premature death. To assist in this task, the Children's Oncology Group (COG) has developed risk-based, exposure-indexed clinical practice guidelines for late effects surveillance [12]. The guidelines are intended to increase awareness about the potential late effects and to standardize the follow-up care of survivors provided by pediatric oncology, subspecialty, and primary care clinicians. Individual guidelines are updated regularly and, along with corresponding patient/family educational materials, may be downloaded from the COG website [13]. Research is underway to validate these guidelines and determine their clinical utility. Similar guidelines have been developed by other international cooperative pediatric oncology groups [14–16].

1.4.2 Role of the Cancer Survivorship (Long-Term Follow-Up) Clinic

The American Academy of Pediatrics (AAP) has recommended that pediatric cancer treatment centers offer a mechanism for the long-term follow-up (LTFU) care of successfully treated patients, either at the original treatment center or with a specialist familiar with the potential adverse effects of cancer treatment [17]. The main goals of LTFU clinic are to provide surveillance for late effects, identify and address medical and psychosocial issues, provide health education and health promotion interventions to modify risk, and conduct longitudinal research (Table 1.3).

Various effective models exist for delivering LTFU care [18]. Most LTFU clinics are staffed by nurse practitioners, a social worker, and a physician with expertise in childhood cancer survivorship. LTFU clinic staff should also have referral access to other specialists such as psychologists, nutritionists, genetic counselors, cardiologists, endocrinologists, fertility specialists, and orthopedic surgeons. However, given that a recent survey of COG centers found that only 59 % have a dedicated LTFU clinic, many institutions provide survivorship care by the same treating oncologist [19]. In programs offering an LTFU clinic, comprehensive survivorship evaluation is resource-intensive, beginning with generating a detailed cancer treatment history, performing a complete physical assessment, preparing a treatment summary and survivorship care plan, and educating the survivor and family about health risks, behavior and promotion.

Referral to LTFU clinic generally represents the "official" transition to long-term follow-up care.

Table 1.2 Overview of selected late effects in childhood cancer survivors

Organ system	Late effect	Risk factors	Surveillance
Neurologic	Neurocognitive delay	Methotrexate, cytarabine, RT	Neuropsychological testing
	Leukoencephalopathy	Methotrexate, cytarabine, RT	Neurologic examination, MRI
	Peripheral neuropathy	Vincristine, vinblastine	Neurologic examination
Endocrine	Hypothyroidism	RT	TSH, free T4
	Growth hormone deficiency	RT	Growth chart
	Gonadal failure	RT, alkylators	Testosterone, estradiol, FSH, LH
Cardiovascular	Cardiomyopathy	Anthracyclines, RT	Serial echocardiography
	Coronary artery disease	RT	Clinical history
	Carotid artery narrowing	RT	Carotid artery ultrasound
Pulmonary	Pulmonary fibrosis, restrictive or obstructive lung disease	Bleomycin, busulphan, lomustine, carmustine, RT	Chest X-ray, pulmonary function testing
Genitourinary	Reduced GFR	Cisplatin, RT	Serum creatinine
	Tubular dysfunction	Cisplatin, ifosfamide	Serum electrolytes, Mg, Phos
	Hemorrhagic cystitis, bladder fibrosis	Cyclophosphamide, ifosfamide, RT	Urinalysis
Reproductive	Infertility	Alkylators, RT	Clinical history, specialty assessment
Gastrointestinal	Cirrhosis	RT	Liver function test
	Chronic enterocolitis	RT	Clinical history
	Strictures	Surgery	Clinical history
Musculoskeletal	Osteopenia/osteoporosis	Corticosteroids, methotrexate	Bone density measurement
	Osteonecrosis (AVN)	Corticosteroids	Clinical examination, MRI
	Altered bone growth	RT	Clinical examination
Eyes	Cataract	Corticosteroids, RT	Regular eye examination
Auditory	Hearing loss, tinnitus	Cisplatin, RT	Audiological evaluation
Oral	Dental caries, dry mouth, dental maldevelopment	RT	Regular dental examination
Psychosocial	Post-traumatic stress syndrome, interpersonal difficulties, special educational needs, career and vocational challenges, insurance deficits	The cancer experience; functional disabilities arising from specific late effects	Clinical history, psychological evaluation, social work assessment
Secondary neoplasms	Melanoma, breast carcinoma, thyroid carcinoma, sarcoma, bowel cancer, brain tumor	RT	Site specific surveillance
	Acute myeloid leukemia/ myelodysplastic syndrome	Etoposide, anthracyclines, RT	CBC

Adapted from Freyer DR. J Clin Oncol 2010;28:4810–4818
RT radiation therapy, *MRI* magnetic resonance imaging, *TSH* thyroid stimulating hormone, *FSH* follicle-stimulating hormone, *LH* luteinizing hormone, *GFR* glomerular filtration rate, *AVN* avascular necrosis, *CBC* complete blood count

When this should be initiated is a matter of varying practice and some debate. A survey of 24 comprehensive pediatric survivorship programs found that most patients were referred to LTFU clinics when they reached 5 years post-diagnosis and 2 years off therapy, whichever was later [20]. The rationale for this relatively late time point is that the risk for relapse is minimal for most

Table 1.3 Components and tasks of survivorship care [8]

Components of ideal system of survivorship care
1. Provide a range of direct services to survivors to identify, prevent, treat and manage late effects
2. Bridge the realms of primary and specialty health care with education and outreach
3. Coordinate medical care with educational and occupational services
4. Conduct research to better understand late effects and their prevention
Specific tasks of survivorship program
1. Educating and counseling survivors regarding the specific conditions to which they are susceptible and guidance of self-monitoring of late effects
2. Applying preventive approaches known to be effective for the general population, including encouragement of abstinence from tobacco, limited exposure to alcohol, sun protection, physical activity, maintenance of a healthy weight, consumption of fruits and vegetables
3. Providing psychosocial support services to survivors and their families
4. Providing reproductive and sexuality counseling
5. Providing genetic counseling for individuals with a hereditary cancer and their family members
6. Assistance with identifying and meeting financial challenges

pediatric cancers. One concern about such a late time point is that for cancers treated with relatively brief therapy (e.g., Wilms' tumor and Burkitt lymphoma), the period of elapsed time between end of therapy and referral for LTFU is relatively long, during which patients/families lose motivation to remain in surveillance. Consequently, this traditional time point is being reconsidered by some programs in favor of something earlier while patients are still engaged in disease-directed follow-up.

The transition to LTFU care is neither as predictable nor as automatic as might be assumed. Even well-established pediatric survivorship clinics within large cancer treatment programs at prominent hospitals do not necessarily capture all eligible survivors. The reasons for this have not been studied extensively, but one survey of survivorship programs suggests many factors. Institutional factors include inadequate resources and finances to sustain programs, low institutional commitment toward the provision of survivorship care, and a lack of capacity to care for the growing population of survivors. Factors arising from the survivor include lack of both interest and awareness of cancer-related risks [20]. Patients/families may also be reluctant to relinquish their relationship with their treating oncologist in order to see a new physician in LTFU clinic. In preparing them, physicians may well need to confront their own reluctance to "let go" of patients with whom they have bonded during treatment. Some patients may find it difficult to come to the same clinic where they experienced the trauma of cancer treatment. Because of this, it is ideal to hold LTFU clinic in a setting separate from the acute oncology clinic. Survivors and their families may lack financial resources or have to travel long distances to the LTFU clinics, as these are often located far from their local communities. Lack of health insurance coverage for surveillance tests may be an issue, although most states provide catastrophic health insurance programs that cover follow-up services up to 21 years of age.

1.5 The Transition from Child-Oriented to Adult-Focused Care

As promulgated by the Society for Adolescent Medicine, the now-classic definition of health care transition is the planned movement of adolescents and young adults with chronic physical and medical conditions from child- centered to adult-oriented health care systems [21]. Its overarching purpose is to provide continuous, well-coordinated care that is both medically and developmentally appropriate. As mentioned previously, the medical rationale for health care transition of childhood cancer survivors is the need for late effects surveillance. While health care transition is a concept now being applied broadly across most chronic diseases or conditions originating in childhood [22–24], cancer survivorship is different in that patients are considered cured, and may not have developed symptoms of late effects yet. This can cause many survivors to wonder why continued medical

care is necessary. From a developmental perspective, while pediatric care tends to be nurturing and prescriptive, adult care is typically collaborative and empowering, perhaps more supportive of the emerging autonomy of an older adolescent/young adult. Communication should be directed toward the adolescent/young adult rather than the parent in order to address important issues such as sexuality, reproductive health, substance abuse and other risk-taking behaviors [21]. Most adolescent cancer survivors undergo the same developmentally appropriate shifts as their peers, including educational advancement, change in residence, re-orientation of primary relationships, need for employment and health insurance, and switch to an adult-focused health care provider [25]. It is important for health care transition to address these needs in a way that is relevant for childhood cancer survivors. Of particular importance is their understanding of the non-intuitive relationship linking education, employment and health insurance—the "survivorship triad." Adolescent survivors should be counseled to stay in school to reach the highest educational degree they can, which will assist them in securing employment that hopefully offers the health insurance necessary for them to obtain the life-long survivorship care they need.

Health care transition generally occurs in the age range of 18–21 years. This is also the age when most pediatric hospitals begin to have difficulty serving the needs of adult patients, due to child-oriented facilities and lack of convenient access to adult-focused specialists. Recent surveys reveal considerable variation in timing of transition among pediatric centers [19]. Some have drawn support for delaying transition until the mid- to late-twenties, derived from recent evidence that neurobiological maturation in brain regions responsible for risk-assessment, motivation and choice is not complete until that time [26]. Relatively little is known about what factors contribute to successful health care transition, particularly for childhood cancer survivors. Through focus group interviews of adolescents with special health care needs, their parents and providers, Reiss and Gibson identified the following factors as being important: (1) having a future-focused orientation throughout care; (2) viewing transition positively as a normal milestone of late adolescence; (3) starting the transition process early; (4) fostering personal and medical independence by promoting early involvement of the child in medical decision making; and (5) maintaining continuous, uninterrupted health care insurance if possible [27]. Inasmuch as most children with cancer become long-term survivors, it is appropriate to make first mention of health care transition even as early as the initial family conference at diagnosis, and to revisit the topic at end of therapy and upon referral to LTFU clinic.

Although health care transition is best conceived as a gradual process, eventually care must be transferred to the new provider and setting. At this "transition visit," at least four broad goals must be accomplished: (1) assessment of readiness for transition; (2) education of the survivor/family on essential skills needed in the adult health care system; (3) preparation of an updated health care summary, including past cancer treatment, current and potential health problems, and recommended late effects surveillance (Survivorship Care Plan); and (4) communication with the new adult-focused provider(s) including a clear transfer of responsibility for follow-up.

1.5.1 Transitional Care Models for Young Adult Survivors

A variety of models are in use for care of young adult survivors. No single care model is "best" for all settings. In designing a transitional care program, institutions should consider models that make the most of their strengths and resources while adapting best to limitations. More research is needed to define "best practices" in this area. In general, existing programs fall into three broad categories: (1) Cancer Center-based; (2) Community-based; or (3) Hybrid [18].

Cancer Center-Based Model. In this model, adult-focused care continues to be provided within the same cancer center or health system

where treatment was given. This model is more prevalent in institutions where both children and adults are treated. In a recent survey of COG institutions, this was the most common model used for care of adult survivors [19]. In this model, the post-transition team includes an adult-focused primary care provider (internist, family medicine, medicine/pediatrics), and/or medical oncologist, plus pediatric survivorship specialists. Thus, this model involves transition to adult services but not transfer of care. An advantage of this model is continuity of providers and medical records. A disadvantage is that survivors may be required to travel long distances. Further, survivors at low risk of developing late effects may not need this degree of resource intensity.

Community-Based Model. In this model, survivorship care is provided by a community-based primary care provider [18]. Here, there is both transition and transfer of care. When properly executed, this model involves the treatment center providing an identified primary care provider with a formal Survivorship Care Plan (as described above). Advantages of this model include geographic convenience, an emphasis on wellness/prevention that characterizes primary care, and integration of cancer survivorship into routine health care. The chief disadvantage is that the primary care provider may have a relative lack of medical expertise in late effects.

Hybrid Model. In this model, a combined approach is used that involves both the community-based primary care provider and the cancer treatment center. Survivors undergo transition and transfer of care, but in this case a robust linkage is maintained between the pediatric survivorship center and the primary care provider. A formal Survivorship Care Plan is provided to the primary care provider who assumes responsibility over late effects monitoring. Ideally in this model, the primary care provider maintains regular interactions with the survivorship center to report on the survivor's status and receive updates on changing follow-up guidelines. In theory, the Hybrid Model offers the advantages of both the Cancer Center-based and Community-based Models but offsets the disadvantages of each. Delivery of survivorship care by the primary care provider is appealing because CCSS data have shown better utilization of general medical care than cancer center care among young adult survivors [28]. Additionally, a recent study from the Netherlands showed that a coordinated program involving the childhood cancer treatment center and family physicians resulted in good outcomes and provider satisfaction [29].

A variant of the Hybrid Model, called the Risk-Stratified Model, is utilized in the LIFE Cancer Survivorship and Transition Program at Children's Hospital Los Angeles (CHLA). In this model, the site of post-transitional survivorship care is determined by the classification of survivors according to risk for developing clinically significant late effects. As shown in Fig. 1.2, transition-ready survivors are classified as either Lower or Higher Risk using adapted criteria [30, 31].

At 21 years of age, Lower Risk survivors undergo transition to their primary care providers to continue life-long follow-up as specified in their Survivorship Care Plan. Lower Risk survivors are contacted annually by the LIFE Program to ascertain current health status and adherence to recommended surveillance ("virtual follow-up"). Those deemed to be Higher Risk return annually to the LIFE Clinic for Adult Survivors of Childhood Cancer, a collaborative pilot initiative involving adult-focused providers held at a community-based adult cancer center. In this model, all survivors undergo transition, but full transfer of care occurs only for those classified as Lower Risk. Transition-related outcomes data are now being collected to evaluate the efficacy and satisfaction with this model. One anticipated benefit is rational, risk-based utilization of valuable survivorship resources.

1.5.2 Barriers to Transition of Young Adult Survivors

No discussion of health care transition for young adult survivors of childhood cancer is complete without mention of the sometimes formidable

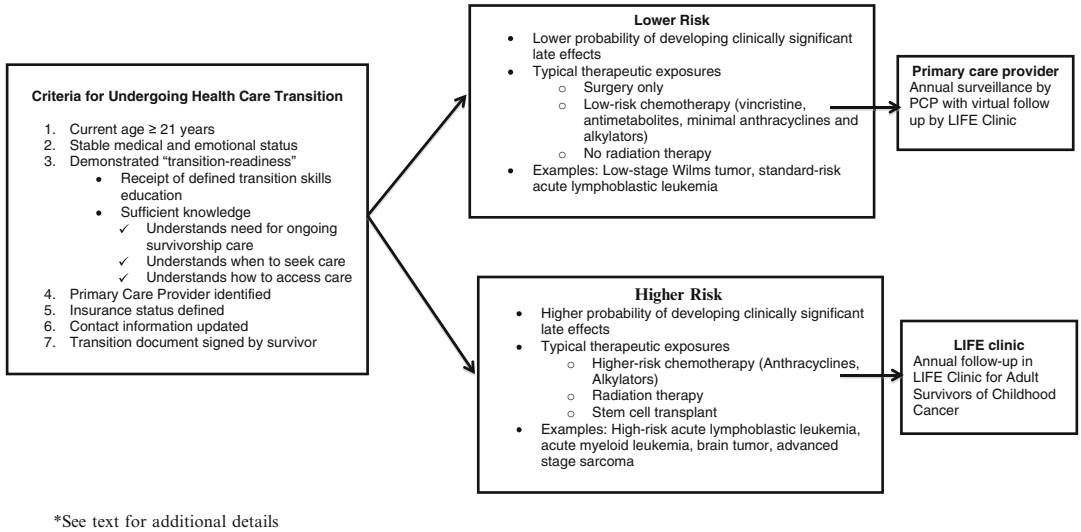

Fig. 1.2 Risk-stratified model for transition of young adult survivors used by the LIFE Cancer Survivorship and Transition Program at Children's Hospital Los Angeles

barriers encountered at the level of the survivor, health care provider and medical systems (Table 1.4). While some have been the subject of research, others remain clinical observations and impressions.

Barriers Related to the Survivor. Certain negative perceptions and lack of relevant health-related knowledge may interfere with follow-up. These factors include a lack of awareness about long term risks and need for continued monitoring [32, 33], reluctance to terminate long-standing relationships with their pediatric oncology providers, and the challenge of building relationships in new health care settings [27]. Additionally, the perceived stigma of a cancer history and the emotional difficulty of continuing to discuss the cancer experience may contribute [34]. There is some evidence to suggest that targeted interventions aimed at improving survivor knowledge might result in improved adherence to recommended late effects screening. Seventy-two survivors of Hodgkin lymphoma who were at increased risk of breast cancer or cardiomyopathy but had not undergone recommended screening during the previous 2 years were mailed a one-page survivorship care plan containing applicable surveillance recommendations [35].

Table 1.4 Barriers to transition of survivorship care

Survivor-related	Complex cancer treatment history
	Multiple long-term health risks
	Failure or inability to assume personal responsibility for health
	Lack of personal support systems
	Lack of trust in new health care provider
Survivor/family related	Over-protectiveness
	Fear of loss of control
	Emotional dependency on child survivor
	Lack of trust in new health care provider
Adult-focused provider related	Lack of knowledge or experience in post-transitional care and survivor's underlying medical condition and health risks
	No preexisting emotional bond with survivor/family
	Burden of assuming care for unfamiliar, occasionally complex survivors
Health system-related	Lack of seamless referral networks linking pediatric and adult-oriented providers
	Lack of systemic training of health care professionals in post-translational health care
	Loss of health insurance needed for continuation of survivorship care in young adulthood and beyond

Adapted from Freyer DR. J Clin Oncol 2010;28:4810–4818

Their primary physicians were given patient-specific information. Within 6 months, 41 % of survivors completed the recommended mammogram and 20 % completed the echocardiogram. However, providing written directives may not be enough, as they can be easily misplaced or lost [36]. Electronic health records accessible by survivors or their care providers through secure internet portals, such as the innovative Passport For Care initiative [37], may address some of these issues.

Barriers Related to the Health Care Provider. Barriers related to the health care provider involve both the pediatric cancer specialist and the adult-focused physician. Among both pediatric oncology providers and survivors, there are concerns that adult-focused providers lack survivorship expertise [19, 32, 33]. A factor likely contributing to this is the current paucity of survivorship-related content in medical school curricula and primary care residency training, whereas pediatric oncology fellowship training in survivorship is improving [38]. At the same time, it is unclear how diligent pediatric cancer specialists have been in reaching out to develop collaborative relationships with those primary care providers due to their own reluctance to "let go" of survivors. The extent to which these factors actually are operative is not well understood, but the perceptions are pervasive [19].

This lack of survivorship expertise might be addressed in several ways. Fundamentally, clinical survivorship and health care transition must be addressed at multiple levels of education for health care professionals, particularly during residency training in the primary care specialties of family medicine, internal medicine and medicine-pediatrics. It also needs to be included as a topic in continuing medical education conferences and on-line courses, such as the "Focus Under Forty" series recently launched by the American Society of Clinical Oncology [39]. At the same time, it may be unrealistic to expect primary care providers to have sufficient expertise in caring for higher-risk survivors. As discussed earlier, one response might be for pediatric survivorship programs to stratify young adult survivors at the time of transition such that only those deemed to be at lowest risk for developing late effects are transitioned to primary care providers. Another is to make patient-specific surveillance recommendations available to both survivors and their primary care providers through a secure, interactive on-line resource that can be accessed in real time at the point-of-care, the prototype for this being Passport For Care [37]. Passport For Care could prove helpful even for some pediatric oncologists [40].

Barriers Related to Systems of Care. At least two important system-based issues serve as barriers to effective survivorship care. The first is a lack of survivorship care networks linking pediatric and adult-focused providers. A key element for facilitating this is a shared electronic medical record (EMR) containing relevant clinical detail for each patient. Since the type of EMR that bridges treatment centers and outpatient practices is usually provided by hospitals or health systems, its availability is dependent upon their strategic commitment in this area. As a partial or interim alternative, the Passport For Care initiative may be utilized [37].

The second issue, particularly pertinent in the US, is the lack of continuous health insurance coverage over the transitional age period. Data from the CCSS have documented that, compared with siblings, young adult survivors have less health insurance coverage and are more likely to report difficulties obtaining it [41]. This is, by no means a survivorship-specific issue, as young adults in general are the most under-insured segment of the US population [42]. For childhood cancer survivors, this may result in not receiving appropriate monitoring or management for late effects despite increasing risk. Typically, children with cancer are covered by Medicaid-funded state programs for catastrophic illness, but this coverage usually ends at 21 years of age, resulting in the "aging out" phenomenon commonly mentioned in transitional care literature from the US. For young adult survivors fortunate enough to qualify for coverage on their parents' private health insurance policy, a provision of the Patient Protection and Affordable Care Act passed in 2010 by the US Congress permits them to remain covered until 26 years of age [43].

1.6 Conclusion

The transitions during childhood cancer treatment take place against a backdrop of each patient's normal physical, emotional and social development. Understanding the major developmental tasks of childhood is essential in order to normalize the cancer experience in an age-appropriate way. Families often feel unprepared for end of cancer treatment and are relieved to discover that they will be systematically followed for relapse initially and long-term health and well-being later. Many survivors remain at increased life-long risk for clinically significant complications of their cancer therapy. The primary focus of long term follow up care is risk-based monitoring for late effects and provision of health information to the survivor and family. Transition of young adult survivors from the pediatric to adult-focused setting is a major challenge. Multiple transitional care models exist but formidable barriers may be encountered at the level of survivor, health care provider and medical systems. Understanding these barriers and developing strategies to overcome them are essential for successful health care transition of the young adult survivor of childhood cancer.

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2 Developmental Considerations in the Transition from Child and Adolescent to Adult Survivorship

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2.1 Introduction

As a growing number of childhood cancer survivors mature into adults, they have given us a better understanding of the evolving and lasting impact of cancer on the developing child. Because the needs of survivors are ongoing and complex, interdisciplinary care can be optimized when considered within a lifespan developmental approach. A developmental perspective requires sensitivity to the dynamic context of the child and family's illness experience over time [1, 2]. More broadly, development is seen as a function of interactions between an individual and the environment, such that the individual, environment, and interactions shift over a temporal course [3]. Transitions between developmental periods are also important, as major changes in social roles and contexts can significantly alter the course of physical and psychosocial well-being.

Applied to childhood cancer, a lifespan developmental perspective is integral to planning long-term care. As noted in subsequent chapters of this book, the child's age or the timing of diagnosis and treatment, as well as his or her current developmental status during survivorship, are important with respect to evaluating risk for late effects and providing appropriate medical and supportive care. The developmental context of cancer has particular relevance for the child's concept of illness and death, medical knowledge, and involvement in self-care and decision making into survivorship. Furthermore, the timing of any stressor, such as a cancer diagnosis and treatment, may have implications for the emergence of psychopathology and successful coping strategies in children. Finally, there is evidence that childhood cancer can affect the transition between developmental periods after diagnosis, including the attainment of socially-valued milestones (e.g., graduation, employment) and the survivor's future orientation or goals (e.g., desire to marry or have children).

Thus, we begin this chapter by defining childhood, adolescence, and emerging adulthood and by highlighting the primary tasks of each developmental period [1]. Because limited work has examined the cancer experience of infants and toddlers, we focus on later years, particularly the transition from adolescence into emerging

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adulthood when survivors begin taking greater responsibility for their healthcare and often transfer from pediatric to adult providers. Attention is paid to the consequences of a child's diagnosis and treatment for cancer with respect to medical, psychosocial, and socially-valued outcomes. Clinical implications for the assessment and care of the childhood cancer survivor are discussed within a developmental context. Finally, directions for future research are summarized at the conclusion of this chapter.

2.2 Childhood, Adolescence, and Emerging Adulthood

Early childhood (e.g., infancy and preschool years) is a peak period for diagnosis of the two most common childhood cancers, leukemia and brain tumors, but it is the least studied developmental period in psycho-oncology [4]. The intersection of rapid biological development and treatment toxicities can set the stage for later morbidity and late effects, such as neurocognitive, sensorimotor, or psychosocial problems. Foundational skills are established such as forming a secure attachment, eating, and toileting. Greater communication skills, physical mobility, and socialization occur through parallel play and exploration of the world outside of the primary attachment. Although toddlers are relatively egocentric, they develop the ability to conceive of unobserved objects, events, or feelings that allow for fantasy or imaginative play. During middle and later childhood (i.e., ages 5–10 or 12 years old), entry into formal education coincides with the acquisition of academic skills and concrete operational thought, such as elemental logic and conservation. Children become more self-sufficient and engage in new relationships outside of the family. As they begin to learn and conform to social rules, peer relationships are established, and there is a growing importance of group acceptance and same sex friendship. The development of self-esteem is also notable as youth engage in social comparison with peers.

Adolescence is defined in many ways based on chronological age, biological indicators (e.g., pubertal timing or maturation), or simply as the second decade of life. It primarily encompasses the teenage years and is characterized by numerous biological, psychological, and social changes [5]. Neurobiological changes occur, such as synaptic pruning of the prefrontal cortex and ongoing myelination of intracortical regions [6]. The development of formal operational thinking marks a greater capacity for abstract thought and higher order reasoning. Executive functions, such as perspective taking and emotion regulation, evolve. Socially, adolescents develop greater autonomy from parents and gravitate more toward the peer group. With puberty and hormonal changes, psychosexual development begins to include dating, sexual exploration, and more intimate emotional connections with various romantic partners. At the same time, adolescents are also at higher risk for psychopathology, risky health behaviors, and non-adherence to medical regimens [3, 7, 8]. Despite expectations to increase self-management and responsibility for their healthcare, many health behaviors (e.g., adequate nutrition, exercise) are known to decline markedly in adolescence [9, 10]. In addition, experimentation in risk-taking behaviors (e.g., alcohol use, unprotected sex) is common, further blurring the distinction between normative and abnormal functioning during this time [3].

During emerging adulthood (i.e., ages 18–25) one gains increasing independence, acquires more responsibility, and forms an identity that will likely endure throughout adulthood [11]. The decisions and actions that occur during this time can affect education levels, occupational attainment, and social status across the lifespan [12]. Neurobiological changes continue [6]. Primary developmental tasks include formulating one's own identity or self-concept, establishing independence from parents, and exploring educational, career, and romantic options [11]. Typically, parent-child relationships improve in early adulthood as children become more independent, more geographically distant (e.g., away at college), and more similar to their parents with

regard to roles and responsibilities (e.g., adult work or spousal roles) [13]. Additionally, friendships and peer acceptance remain important in emerging adulthood, and romantic relationships become more serious and intimate [11, 14]. However, there is significant variability among youth in these domains. A hallmark characteristic of the late teens and early 20s is the experience of multiple life changes, such as dating different partners, moving frequently, seeking temporary or part-time employment, and pursuing various educational alternatives. Because of the inherent instability during this time, it is often challenging to assess developmental outcomes and then extrapolate or predict future adult well-being. For example, occupational status as an unemployed student or a part-time, hourly employee during emerging adulthood is often temporary and may not be indicative of later economic success.

2.3 Medical Knowledge and Health Behaviors

When a child or adolescent is diagnosed with cancer, there is potential to disrupt development in many areas, which can lead to subsequent difficulties in adulthood. The transition to emerging adulthood is particularly important as they begin taking primary responsibility for their healthcare, experience changes in health insurance, and often "outgrow" their pediatric providers [11, 15]. Unfortunately, the inherent instability in residence and employment during this developmental period may increase the risk that survivors are lost to follow-up and fail to engage in appropriate surveillance for relapse and late effects. Furthermore, Kadan-Lottick et al. (2002) found that nearly 30% of 635 survivors over the age of 18 could not accurately report their diagnosis, and many were unaware of specific treatments they received [16]. Thus, attention to these issues is crucial for adequate care.

With respect to early cancer communication, parents often act as gatekeepers, managing what and how their child is told about the illness and treatment [17]. Unfortunately, health literacy and lay understanding of cancer is often poor [18], and several studies suggest that parents may not fully understand important aspects of their child's diagnosis, which can complicate communication with the child [19, 20]. Although older children often receive more information about their illness relative to younger children [21, 22], it is typically focused on treatment and procedural details, rather than severity and long-term outcomes. In one study, only 30% of parents talked to their children about all or almost all aspects of their child's cancer [21]. Claflin and Barbarin (1991) found that of 43 children with cancer, only 50% of children under the age of 9 knew the name of their illness, compared with 87% of 9 to 14-year-olds, and 70% of those over 14 years [23]. Even among adolescents with a long history of disease-free survival, confusion about their disease and treatment is common [24, 25].

Despite ongoing improvements in survivor education and greater availability of comprehensive long-term follow-up care, lack of knowledge has significant implications in multiple domains, including decision making, healthcare utilization, and monitoring of late effects. Although knowledge is critical, it is often not sufficient in producing adherence to medical regimens. Health behavior models suggest other factors are also important, such as adolescent's risk perceptions, self-efficacy, and perceived barriers (e.g., lack of health insurance, transportation) or benefits (e.g., improved quality of life, prevention of late effects) of action [7]. Furthermore, it is important to consider these within a socio-ecological framework. As the desire for autonomy grows throughout childhood and adolescence, independence may be disrupted by the diagnosis and treatment demands [8]. During survivorship, adolescents and emerging adults may wish to be independent not only of parents but also from other authority figures (e.g., physicians or others offering advice), resulting in poorer adherence to healthcare recommendations.

Many lifelong health behaviors are established in childhood, yet significant declines in health promoting behaviors, such as nutrition and exercise, occur in adolescence [9, 10]. Adequate

nutrition, exercise, sun protection, and self-examination/screening are important for all youth, but especially for optimizing the well-being of survivors. The extent to which the diagnosis or treatment caused physical limitations or disrupted the development of healthy habits will affect health in survivorship. Nutritional problems are common during treatment, and parents may be unaware of specific needs, such as the importance of calcium to prevent osteopenia in survivorship [26]. Children with cancer also demonstrate reduced physical activity and a lower capacity for exercise both during treatment and long-term [27, 28]. Adherence to sun protection has been noted as the least frequent health behavior practiced by survivors [29]. Furthermore, screening behaviors, such as breast or testicular self-examination, have been suboptimal among survivors [30].

Testing limits and experimenting in high risk or health compromising behaviors, for example sexual activity and substance use, is normative in adolescence [31]. Unfortunately, involvement in these behaviors, even at an experimental level, can have significant long-term consequences for physical and psychosocial health (e.g., sexually transmitted diseases, drunk driving accidents). This is especially problematic for survivors of childhood cancer and may increase vulnerability to further health problems or secondary malignancies. Although children and adolescents with cancer may be protected from some high risk or health compromising behaviors, participation in these behaviors is generally similar to peers [32–34].

2.4 Psychosocial Functioning

Early psychopathology and social difficulties in children are concerning as they can increase risk for comorbid or future problems [35]. Generally, survivors are not at risk for severe psychopathology over the long-term, but there is some risk for internalizing (e.g., depressed mood, post-traumatic stress symptoms) and social (e.g., peer rejection) problems, particularly among children with brain tumors or those who received central nervous system (CNS) directed therapies [36]. While many individual and family factors can contribute to the development of psychopathology in childhood, often proximal factors, such as parental depression, and family conflict are the most common contributors to a child's risk in the context of cancer [37, 38]. This mirrors the developmental literature indicating that the two primary factors that buffer the impact of stress on children are intelligence and having a warm and consistent caregiver [39].

Stress and coping research also suggests that cumulative stressors and disengagement coping strategies, such as denial and wishful thinking increase risk for difficulties, while active engagement coping strategies tend to be associated with resilience in youth [40, 41]. It is important to note that parents and children may cope similarly, as parents often provide direct instruction or model coping strategies for their children. While young children may not be capable of more complex coping strategies (e.g., cognitive restructuring) to manage stress, they acquire a more sophisticated repertoire as they mature, and intervention studies suggest many of these effective strategies can be introduced to children as young as 9 [42, 43].

2.5 Developmental Milestones

Because survivors appear to have limited psychopathology, research has focused on more subtle indicators of functioning, such as the attainment of socially-valued outcomes or developmental milestones (e.g., graduation rates, employment, parenthood). Given the significant risk for cognitive and functional deficits following treatment, it is not surprising that research has found survivors of childhood cancer may not reach certain developmental milestones, or they may have delays in achieving life goals, such as completing their education and finding employment [44–46]. A growing area of interest has been the social development (e.g., family and peer relationships) of cancer survivors. For example, there is some evidence that survivors of childhood cancer may experience early social difficulties, as well as delays in marriage and parenthood relative to peers [44–46]. Difficulty

achieving developmental milestones may be evident particularly for survivors who are female, had a brain tumor, or received CNS-directed therapies [44, 45].

It is important to note that early difficulties or delays in developmental milestones may have a cascading effect on other outcomes, whether developmental, social, emotional, or behavioral [35]. This may include continuity of early difficulties, a higher risk for concurrent problems, as well as a risk for future problems in multiple domains. For example, early academic difficulties during or after treatment may indicate the extent to which survivors will continue struggling with educational demands in the future. Furthermore, a child who falls behind academically or has cognitive deficits due to treatment may later experience peer victimization at school or internalizing problems, which in turn may decrease the chances of graduating from school, securing gainful employment, finding a mate, and supporting a family in adulthood [35, 45].

2.6 Clinical Recommendations

Providing care that is sensitive to the context of child development is important throughout cancer treatment and survivorship. Pediatric providers should be aware of psychosocial issues, assess the unmet needs and concerns of their child and adolescent patients, determine the ongoing role of parents or significant others in care, and facilitate transitions to adult providers in advance of emerging adulthood. This is also an important time for preparing a diagnosis and treatment summary and providing education to survivors regarding the need for follow-up. Furthermore, adult healthcare providers should be aware of these concerns and the role cancer played in the child's early development. The dynamic and often unstable nature of emerging adulthood means that natural transitions in life roles and contexts (e.g., moving away from home, starting school) will likely affect financial stability, health insurance coverage, and access to care in survivorship. Attention to these factors will provide a foundation for determining the best approach to long-term follow-up.

As noted, healthcare providers should regularly assess medical knowledge and communication within the family, as well as screen for cognitive difficulties in the survivor, to tailor education accordingly. The Children's Oncology Group (COG) has created long-term follow-up guidelines, an educational web site, standardized patient treatment summaries, and psycho-educational materials individualized to specific late effects that may result from cancer treatments [47]. This website can be easily accessed by providers or families and offers teaching and educational materials that can be modified if needed to be developmentally appropriate. It is also important for healthcare providers to assess the survivor's social resources and network. Inclusion of primary caregivers or others who are aware in general of possible survivor challenges and offer significant social support to the survivor is crucial for effective teaching. These support providers can also be instrumental in helping the survivor adhere to recommendations for follow-up and screening.

Regular screening for psychosocial challenges and the assessment of strengths and available resources is also recommended to inform the allocation of services [48]. Referrals should be made for evidence-based treatments when warranted to reduce psychological problems [49, 50]. Although interventions to remediate social deficits or promote social skill development for survivors have shown modest results [51, 52], early intervention may help allay later social difficulties and increase independence in adulthood. As will be discussed in later chapters, the ability to provide ongoing support, such as educational accommodations, physical accessibility, or vocational rehabilitation, during treatment and later survivorship may help optimize the survivor's success at achieving developmental milestones in emerging adulthood.

2.7 Directions for Future Research

Arnett (2007) has argued success in emerging adulthood is not measured simply by the attainment of developmental milestones, but also by a

subjective sense of having reached adulthood [53]. Interestingly, most healthy emerging adults eventually get a job, marry, and have children, but expectations for happiness are high [53]. Contemporary views indicate that it is no longer simply about attaining these milestones, rather satisfaction in life should be high as well. In western countries, emerging adults now desire not just a mate, but a soul mate, and not just a job, but a career or "dream job". These are lofty goals for many as evidenced by current divorce and unemployment rates, but it remains unknown whether these idealistic goals are even more difficult to achieve for cancer survivors relative to their peers. While research has examined subjective sense of well-being and life satisfaction among adults with cancer, we know less about these concepts in pediatric cancer survivors. Do they have a sense of reaching adulthood at different ages than peers? Are they more or less happy in life? Are they more or less fulfilled, or do they just have different priorities after facing cancer?

These lingering questions provide new directions for research with long-term survivors of childhood cancer. While we are accumulating more knowledge about the impact of cancer and its treatment on individuals at different ages, there is more to learn. Much of our knowledge of psychosocial outcomes among survivors comes from seminal work through the Childhood Cancer Survivor Study [54]. Such epidemiological studies allow for screening of large cohorts, but longitudinal, outcome studies are also required for more in depth assessment of predictors and processes. Rarely have studies followed a large cohort of survivors prospectively from diagnosis into adulthood. Researchers must understand the explanatory factors that account for variation within the survivor population over time, as well as how their development differs from typical peers who have not experienced cancer.

Other methodological points for research include the need for diverse, multi-cultural cohorts and multiple informants to determine how perspectives and outcomes may differ in other countries or populations. Mixed method approaches that move beyond paper and pencil measures to include assessments such as lab-based tasks, "real world" observation, qualitative interviews, biological measures (e.g., actigraphy, psychoneuroimmunology), and functional imaging will enhance the quality of our science. Emerging work to examine unmet needs can be expanded to understanding how these needs evolve over the course of treatment and survivorship [55, 56]. Most importantly, research that can inform the development and evaluation of interventions to prevent difficulties and promote psychosocial resilience, as well as adherence to follow-up screening and care, is paramount. These interventions will be most effective if they can capitalize on innovative technologies or approaches that allow for wider dissemination and easy access to underserved populations.

We now expect that most children diagnosed with cancer will live long and hopefully full and happy lives. Thus, considering the long-term implications of their experience within a lifespan developmental context will help ensure optimal care and outcomes during survivorship. Ongoing research that is methodologically rigorous will advance our understanding of relevant issues for survivors. With each step forward, we are on a path to ensure that children with cancer are not only surviving, but thriving in adulthood.

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3 The European Experience of Establishing Guidelines for Surveillance of the Childhood Cancer Survivor

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3.1 Introduction

Continuing improvements in the treatment of childhood cancer have been observed across developed regions of the world during the last 50 years. However variations in survival persist between the different European regions. The Automated Childhood Cancer Information System (ACCIS) pooled data from most of the European population-based cancer registries and demonstrated that the improvements in 5- and 10-year probability of survival after a diagnosis of childhood cancer have been greater for children treated in Northern and Western Europe, or in the British Islands, than for those treated in Eastern or Southern Europe [1]. These differences in regional outcomes may reflect variations in access to medical care and in healthcare systems.

However, the gap between Eastern and Southern Europe and the other regions of the continent fell in magnitude during the 20 years covered by that study, and it is therefore reasonable to believe that in the coming decades survival rates close to 80 % will be observed in most children with newly diagnosed cancer in Europe [2].

There is no official aggregate data collection about the number of childhood cancer survivors (CCS) living in Europe, but there is some information from population-based national cancer registries such as those from the U.K. and the Nordic countries. For example, a Nordic study has estimated that 1 in every 1,000 individuals in the general population is a survivor of childhood cancer [3]. This figure might differ between European countries due to the above-mentioned differences in survival rates across Europe over time. Nevertheless, it is reasonable to estimate that there are now 300,000–500,000 CCS living in Europe. With a population of about 488 million inhabitants across the 27 European Union (EU) countries and assuming that 16 % are aged between 0 and 14 years, there are about 78.2 million children in Europe.

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Given an estimated average childhood cancer incidence in Europe of about 141 new cases/million/year [4], each year about 11,000 new childhood cancer cases will be diagnosed in the continent, and if a conservative overall 5 year survival of 75 % is assumed for these children over the next few years, it can be calculated that each year the European population of long-term CCS will increase by about 8,250.

At the same time that it is increasing in size, the population of CCS is also increasing in attained age and a significant number have reached or are entering adulthood. It is now estimated that the median age of CCS is between 20 and 29 years (depending on the country) with some of the oldest survivors already well beyond their 50th birthday. For example, data collected by the U.K. National Registry of Childhood Tumours since 1962 demonstrates that while in 2005 there were 25,989 CCS in the UK, with a median age between 20 and 24 years, in 2009 there were 30,174 survivors (a mean annual increase of about 1,000 survivors) with an older median age of 25–29 years (Stiller CA, personal communication, with permission).

Over the last three decades, increasing awareness has emerged amongst healthcare providers, as well as survivors and their families, that successful cancer treatment may cause late adverse effects in CCS, and in particular among those treated during childhood when the body is still developing. Moreover, it becomes evident that the national health systems in general and the pediatric cancer centers in particular need additional resources to address the emerging needs of survivors related to side effects of their previous treatment, and that transition programs need to be developed for CCS entering adulthood.

In 2008, PanCare (the Pan-European Network for Care of Survivors after Childhood and Adolescent Cancer) was founded in Lund, Sweden by a group of clinicians and epidemiologists with the ultimate aim of ensuring that every European survivor of childhood and adolescent cancer receives optimal long-term care. Subsequently, the network has grown to include more than 150 individuals including pediatric oncologists and hematologists, radiotherapists, other pediatric and adult medical sub-specialists, psychologists and nurses. It also now represents survivors and their families.

Recently, PanCare members were funded by the European Union (EU) to develop PanCareSurFup (PanCare Childhood and Adolescent Cancer Survivor Care and Follow-Up Studies) (www.pancaresurfup.eu), a project to undertake detailed large-scale epidemiological studies of late mortality and of risk factors for severe cardiovascular events and second malignant tumours, and which also has the ambitious objective to develop pan-European guidelines for long-term follow-up (LTFU) of CCS. This will include detailed recommendations for follow-up based on the treatment previously received, for models of care to facilitate LTFU and transition to adult care, and finally for promotion of optimal future health of survivors.

3.2 Clinical Practice Guidelines

The main aim of clinical practice guidelines is to improve healthcare processes and health outcomes. Their effective implementation will promote consistency in daily clinical practice and hence facilitate optimal utilization of healthcare resources. They are increasingly being used to assist both clinical and healthcare policy decision-making [5]. As defined by the US Institute of Medicine, clinical practice guidelines are "statements that include recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options" [6]. Guidelines are viewed as powerful tools to improve the quality of care. They can contribute to decreased variability in healthcare decisions between physicians, and stimulate effective care, communication and collaboration between different healthcare professionals, as well as between healthcare professionals and patients.

Before the wider use of guidelines, clinical practice was usually guided by non-systematic observations based on clinical experience. The knowledge of basic disease mechanisms and

pathophysiology was considered sufficient to guide clinical decision-making [7]. Systematic development of guidelines within a well-defined program started in the late 1970s. Guidelines were seen as tools to improve the quality of care, and were mainly consensus-based. The U.S. National Institutes of Health initiated the development of these so-called "consensus statements." The consensus conference had a central role within this process [8]. During the 1980s, various other organizations outside the USA adopted this program to develop their own consensus statements and standards for good medical care.

In the early 1990s, a shift emerged to more evidence-based clinical practice based on content-expertise and clinical experience-based decision-making. In 1992 evidence-based medicine (EBM) was introduced by the EBM Working Group. EBM is the process of integrating clinical expertise with the best research evidence to make high-quality decisions about the care of individual patients (Evidence-Based Medicine Working Group 1992). This emphasized the importance of systematic literature searches and evidence summaries in the development of guidelines. The Cochrane Collaboration was founded in 1993 to improve the availability of the best evidence in healthcare by facilitating the preparation and maintenance of systematic reviews. Cochrane systematic reviews help clinicians evaluate all the evidence addressing a particular clinical problem, using standardized methodology for searching and appraising the literature and for reporting the results [9].

In 1996 the second fundamental principle of EBM was presented. This principle suggested that decision makers must always balance the benefits and risks, inconvenience and costs associated with alternative management strategies in the decision making process, and also include consideration of the patients' values [10, 11].

The principles of EBM dominate contemporary guideline programs. The method of evidence-based guideline development has become the international standard by which contemporary clinical practice guidelines should integrate the best available evidence and clinical judgment, as well as the patients' perspectives.

3.3 Potential Advantages of Guidelines

Guidelines are a combination of a summary of evidence-based knowledge and recommendations. It is very challenging for a healthcare professional to remain up-to-date since more than two million new scientific papers are published each year. There is far too much information available and the conclusions of published work may be conflicting since all the accessible information is rarely summarized. Guidelines can facilitate in bridging the gap between research and clinical practice.

Clinical practice guidelines can improve the quality of clinical decisions. They are useful for clinicians who are uncertain about how to proceed, and also enable the patient to make well-informed healthcare decisions and to consider their personal needs and preferences in selecting the best option [5].

The greatest potential benefit of guidelines is the improvement of health outcomes. Guidelines recommending proven effective interventions and discouraging ineffective ones may reduce morbidity and mortality, and thus improve quality of life. Guidelines also make it more likely that patients receive uniform high-quality care, thereby reducing variability in daily healthcare practice. It has been shown that the consistency of healthcare is low—the frequency with which procedures are performed varies considerably between clinicians and geographical regions [5, 12]. Several international reviews have shown that the majority of implemented guidelines have resulted in significant improvements in the process and structure of care [13–15].

Finally, clinical practice guidelines can contribute to reduced healthcare costs by standardizing care and hence increasing the efficiency of care provision and reducing unnecessary or inefficient components of healthcare. Guidelines reduce expenses for hospitalization, drug prescriptions, surgery, and other procedures [5].

3.4 Evidence Based Guidelines

Many clinical practice guidelines have been developed by expert groups without complete appraisal of the evidence. This method relies on the group's knowledge of existing evidence and the clinical experience of its members. However, the knowledge of clinicians of published work is often incomplete due to poor presentation and dissemination of research findings and difficulties to keep fully up-to-date with the published literature. Guidelines developed without formal literature reviews and critical appraisal of the evidence may be biased towards supporting current practice rather than promoting newer and more evidence-based practice [16].

Traditionally, the incorporation of evidence into guideline development was achieved by providing narrative reviews of topic areas by experts in the field. However, the general methodology of this type of review is not transparent, since there are no explicit research strategies and inclusion criteria, and formal methods of synthesizing the evidence are lacking. Authors may cite studies selectively supporting their own opinion and fail to cite other studies providing alternative evidence. Therefore guidelines developed after non-systematic literature reviews may be prone to selection bias and provide false reassurance [16].

Evidence-based guidelines attempt to be as complete and focused as possible in summarizing the available evidence. The best way to summarize the evidence is a systematic review. However, since this is very time consuming and costly, a decision should be taken during the guideline process for which particular issues a systematic review should be performed. A systematic review aims to minimize the occurrence of bias through an explicit search strategy to identify all available evidence, selection and assessment of the methodological quality of the evidence, and reduction of random error by using quantitative methods (i.e., meta-analysis). The Cochrane Collaboration is the largest provider of systematic reviews for healthcare and includes approximately 6,000 systematic reviews in the Cochrane Library. The Cochrane Collaboration developed standardized methods to perform systematic reviews. The Cochrane Childhood Cancer Group (CCCG) in Amsterdam has been registered within the Cochrane Collaboration since 2006 (www.ccg.cochrane.org). The goal of the CCCG is to conduct and maintain systematic reviews on diagnosis of and interventions for cancer in children and young adults with respect to prevention, treatment, supportive care, psychosocial care, palliative and terminal care, nursing care, and late adverse effects of treatment.

However the translation of evidence into recommendations is not always straightforward since data can be interpreted in different ways depending on clinical experiences. In addition, one should keep in mind that evidence is only one component of the development of evidence-based guidelines and needs to be considered alongside clinical expertise and patient values. Transparency about the process is essential [9, 16].

3.5 General Methods for Guideline Development

To ensure that guidelines can be effective in improving healthcare they should meet specific quality criteria. Preferably, guidelines should be developed within a structured and coordinated guidelines program. The guideline process consists of the following steps:

1. Topic selection.
2. Composition of multidisciplinary working group.
3. Extensive search of literature.
4. Summary of the evidence, including quality assessment.
5. Formulation of recommendations (by combining the evidence with clinical expertise and the weighting of ethical, cultural and patient values. Reasons why specific choices have been made should be explicitly described).
6. Dissemination.
7. Publication.
8. Literature monitoring to identify needed updates.

It is important to note that developing evidence-based guidelines does not guarantee an

improvement in the quality of healthcare. The success of guidelines depends on many factors, including their clinical context, methodology, dissemination, and implementation strategies. Effective implementation should ensure guideline adherence in practice and hopefully subsequently lead to improved patient outcomes.

3.6 Existing European LTFU Guidelines

Over the last 10 years, several long-term follow-up (LTFU) guidelines have been developed. Those LTFU guidelines produced by European organizations are descibed in more detail below. In addition, the Children's Oncology Group (COG) from North America has published "Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers" which incorporate comprehensive recommendations for LTFU (Version 3.0, 2008) (www.survivorshipguidelines.org).

Two LTFU guidelines have been written independently in the U.K., namely the Scottish Intercollegiate Guidelines Network (SIGN) "Long term follow up of survivors of childhood cancer, A national clinical guideline" (2004) (www.sign.ac.uk/pdf/sign132.pdf) and the United Kingdom Children's Cancer Study Group (UKCCSG) Late Effects Group "Therapy-based Long-term Follow-up Practice Statement" (second edition, 2005) (http://www.cclg.org.uk/dynamic_files/LTFU-full.pdf). In addition, the Late Effects Taskforce of the Dutch Childhood Oncology Group (DCOG LATER) has developed the multidisciplinary "Guidelines for follow-up after childhood cancer more than 5 years after diagnosis" (http://later.skion.nl/). Furthermore, additional LTFU guidelines have been developed by national pediatric hematology/oncology late effects groups in several European countries, including France, Germany and Sweden. In contrast, some other European countries (e.g., Hungary, Italy) do not have any national LTFU guidelines, although a proportion of institutions performing LTFU may share follow-up protocols (e.g., the Person Prevention Oriented Approach developed in Genoa and Monza in Italy).

The UKCCSG and SIGN guidelines have both been published in written form and are also freely available on the internet. The Swedish SALUB "Follow-up after Childhood Cancer" guidelines are available on the internet in Swedish and in English (http://www.blf.net/onko/page6/page14/files/Salub_5_2010_Eng.pdf). Although the full DCOG LATER document is available on the internet only in Dutch, the cardiac guideline from this work has been published in English [17]. The LTFU guidelines produced by the German GPOH ("Care of children with cancer, adolescents and young adults—recognition, avoidance and treatment of late effects", http://www.awmf.org/leitlinien/detail/ll/025-003.html) are available in German with English translations for some sections. The other European LTFU guidelines are usually available only in their native language.

However, these guidelines have been produced using different methodologies by national groups working independently of each other, and therefore have diverse scopes and attributes. In the last 2 years, collaborative efforts have commenced to promote consistency between LTFU guidelines and standardization of their recommendations worldwide, but the magnitude of this task has required pragmatism in prioritizing those late effects most in need of harmonized recommendations. Meanwhile, recognition of the importance of developing new guidelines that will promote equity of access to optimal LTFU care across the whole of Europe is reflected in the award of EU programme funding to the PanCareSurFup project to develop pan-European LTFU guidelines.

3.6.1 Comparison of the Methodology and Content of the Published UKCCSG, SIGN and DCOG Later LTFU Guidelines

The three widely available European LTFU guidelines highlight the evolution of guideline development methodology over the last two decades. The UKCCSG Practice Statement was initially developed by a small working party from the Late

Effects Group (LEG) of UKCCSG (now known as CCLG, the Children's Cancer and Leukaemia Group). The first edition (then known as the UKCCSG Long Term Follow Up Therapy Based Guidelines) was introduced in 1995 as a booklet, but the second edition was published in both booklet format and on the internet in 2005. Both editions aimed to provide therapy-based guidelines to inform and guide all clinicians responsible for LTFU, including pediatric hematology/oncology and other medical staff and specialist nurses. The contributors, most of whom were members of the UKCCSG LEG, were chosen on the basis of their expertise and interest in the specific topics included within the guidelines. They used a range of information sources including their individual knowledge and searches of the published literature, as well as the clinical experience of, and expert opinions from, respected sources (including individuals, committees and reports) where available. However, there was no funding or systematic organizational support for the preparation of the guidelines and recommendations, and hence no formal critical appraisal of the evidence itself. In recognition of this, the second edition was described as a Practice Statement rather than as Guidelines. The cost of publication of each of the editions was supported by an educational grant from a pharmaceutical company, but these companies were not involved in the development of either of the documents.

The second edition updated and extended the information in the first, and added four new "late effects" sections as well as three new appendices providing specific guidance for LTFU of survivors of central nervous system (CNS) tumours and of bone marrow transplantation (BMT), and for immunization after completion of treatment. The Practice Statement is intended to be comprehensive, covering the full range of late adverse effects encountered by CCS. The statement is used by summarizing the treatment that the survivor has received previously, and using this to select appropriate follow-up protocols, which include clinical recommendations for assessment (history, examination and investigations as appropriate) and management (specialist referral and in some cases initial treatment).

The SIGN Clinical Guideline is an evidence-based guideline funded and developed using the well-established SIGN network and methodology. Over 120 SIGN guidelines have now been published since 1995, covering a wide range of medical, surgical and dental topics. The production of all SIGN guidelines is underpinned by a consistent and thorough evidence-based methodology centred on the use of a systematic review process to identify and critically appraise the evidence. Each guideline is developed by a representative multidisciplinary group. The resultant recommendations are explicitly linked to and graded according to the strength of the underlying evidence, thereby allowing clinicians to judge more easily the applicability and validity of the recommendations. Therefore, the recommendations of the SIGN Clinical Guideline have considerable strength given the rigorous process of their development. Unfortunately, the guideline is currently more limited in scope than the UKCCSG Practice Statement since it only covers issues related to growth, puberty/reproduction, cardiac, thyroid and cognitive/psychosocial function. Hence it omits many important late effects suffered by CCS (e.g., respiratory toxicity), although it is currently being updated and expanded to include second malignant neoplasms (SMNs), bone health, fertility issues, the metabolic syndrome and provision of information. Nevertheless, the recommendations may be used to identify CCS at risk of the categories of late effects included within the document and to guide their LTFU surveillance and care. In addition, the SIGN Clinical Guideline includes a very useful section on the practicalities of LTFU itself, and in particular on follow-up strategies with suggestions for different levels of care appropriate to the previous treatment received by the survivor.

In 2005, the need was recognized for national Dutch clinical practice guidelines for the follow-up care of CCS, resulting in a grant from the Netherlands Organisation for Health Research and Development (ZonMW). Consequently, in 2010 the evidence-based DCOG LATER guideline was published, with the aim of standardizing and improving survivor care in the Netherlands. Sixteen multidisciplinary working groups, including 81

participants with relevant professional expertise and survivors, contributed to the development of the guideline—each working group formulated relevant clinical questions, searched the literature and summarized the evidence, with regard to the etiology, prognosis, diagnosis and therapy of the important late adverse effects (LAEs) seen in survivors. Nationwide meetings were held to discuss the conclusions of the evidence summaries and to formulate recommendations based on the evidence, clinical expertise and patient values. The decision-making processes were clearly described. The DCOG LATER guideline covers the full range of LAEs experienced by CCS and gives recommendations about which CCS need surveillance, what surveillance modalities should be used, the frequency surveillance should be performed at, and what should be done when abnormalities are found. In addition, the guideline includes recommendations on employment and social consequences, and on the organization of LTFU care.

3.6.2 International Harmonization of Recommendations for LTFU Guidelines

The International Late Effects of Childhood Cancer Guideline Harmonization Group is a recently formed collaboration between representatives of the five international groups active in developing LTFU guidelines (CCLG, COG, DCOG LATER, SIGN and PanCareSurFup) as well as several individuals representing other international pediatric hematology/oncology and late effects organizations in North America, Europe, Japan, Australia and New Zealand. It seeks to achieve consensus concerning clinical practice guidelines for LTFU of major LAEs in CCS. Comparison of the published European and COG guidelines reveals areas both of concordance and discordance, resulting in the existence of many differing recommendations. Despite the potentially varied needs of different countries and healthcare settings, there is increasing recognition of the advantages and efficiencies of collaborative efforts to share evidence and the workload in LTFU guideline development. This leads to both complementary and beneficial outcomes such as harmonized recommendations. Recent work performed by the project has led to the development of surveillance recommendations for both secondary breast cancer and cardiomyopathy in CCS, identifying which survivors should be screened, how, when and how often [18, 19]. These recommendations have been developed in such a manner as to permit implementation in a variety of different healthcare and resource settings. Other future topics have recently been selected by a panel of experts in LTFU of CCS using a Delphi survey [20].

3.6.3 Pan European LTFU Guidelines

European concordant evidence-based LTFU guidelines are lacking at this current time; despite this, it has become clear that pan-European guidelines are urgently needed to tackle the issues that are most important for the future physical and psychosocial health of the rapidly-growing population of CCS. The overall goals of such guidelines should be to promote equity of access to optimal LTFU for each survivor in all European countries, and to facilitate rational and cost-efficient use of resources by national healthcare systems.

Pan-European LTFU guidelines will also offer the prospective opportunity to collect LTFU data homogenously throughout Europe, thereby not only providing important up-to-date information about the current burdens and nature of LAEs of childhood cancer treatment in Europe, but also permitting feedback to inform the planning of future clinical trials including those for primary prevention of late adverse effects in CCS.

3.6.4 PanCareSurFup Work Package 6 (Guidelines, Long-Term Follow-Up and Transition)

EU funding for the PanCareSurFup project, which will run until 2016, has provided the opportunity to develop pan-European evidence-based LTFU guidelines to meet these needs.

Particular care will be taken to avoid wasteful duplications of effort through collaboration with the other guideline-producing organizations aforementioned, including the European groups (CCLG, DCOG LATER and SIGN), COG and the International Harmonization group.

Work Package 6 (WP6) has been specifically tasked to perform this work. Evidence that has been gathered from a variety of sources will be summarized and used to develop the recommendations for clinical practice in the LTFU of CCS. These recommendations will be designed to optimize the prevention, early detection and treatment of physical or psychosocial LAEs, as well as the organization of LTFU care to achieve these aims. Particular attention will also be paid to developing specific recommendations for age-appropriate transitional LTFU care of CCS approaching adulthood, and to providing optimal general and individualized health-promotion advice for CCS and their families. The information sources utilized will include the published literature, existing clinical LTFU guidelines and research data accruing from the large-scale epidemiological studies of cardiovascular disease, SMNs, and late mortality that will be performed concurrently in PanCareSurFup itself. Since healthcare of long-term survivors involves both physical and psychosocial elements and is best achieved through active partnerships between both primary and more specialized health care providers from a wide range of disciplines, survivors and their families, input from representatives of all of these groups will be sought during the development of the PanCareSurFup LTFU guidelines.

In addition to the anticipated benefits of pan-European guidelines hereby mentioned, it is hoped that the PanCareSurFup guidelines will allow health service resources to be directed specifically to those most at risk, and most likely to benefit from surveillance and subsequent healthcare intervention, facilitating the development of health promotion initiatives in CCS and providing the finest evidence base for training healthcare professionals.

3.7 PanCareSurFup LTFU Guidelines: The Important Steps

The crucial stages during the production of the PanCareSurFup LTFU guidelines include the selection of appropriate topics, formulation of pertinent questions, acquisition and evaluation of relevant evidence leading to the development of evidence summaries to underpin the recommendations that will constitute the guidelines. The development of preliminary draft recommendations will allow the opportunity for feedback from a variety of sources that may then be incorporated into the final guidelines. These will then be disseminated widely amongst the target population (European CCS, their families and healthcare providers) and implementation strategies devised to ensure maximum reach and effectiveness. PanCareSurFup WP6 will also develop performance measures to facilitate subsequent audits to evaluate whether the aims of the guidelines are truly being achieved, although these audits will not be performed during the duration of PanCareSurFup itself.

3.8 PanCareSurFup LTFU Guidelines: The Methodology

The methodology for constructing the PanCareSurFup LTFU guidelines will be developed by the CCCG in conjunction with PanCareSurFup WP6. A Working Group of seven individuals has been set up to represent and lead WP6 in these and other tasks. An internet-based protocol developed by CCCG will be used to train all WP6 members in the standardized methods required to achieve internal consistency across all guideline components. This will be followed by a series of internet workshops to discuss the topics for LTFU recommendations to be included in the guidelines, and for which evidence summaries will be required. The final choices of topics will be selected at a workshop meeting attended by members of WP6 as well as

by other invited experts from a representative range of health-care disciplines (including primary care) and appropriate stakeholders (including CCS themselves and their families). In addition, the relevant questions to be asked in the evidence summaries will be formulated in the internet workshops and finalized in the workshop meeting, alongside the selection of topics.

As a broad outline, it is expected that the topics will cover models of provision of LTFU care (including transition to age-appropriate care in young adulthood and health promotion), major organ and system LAEs and their related issues, functional late effects, and SMNs. In addition, special attention will be devoted to ensuring that the needs of those groups of CCS at high-risk for late adverse effects, especially survivors of CNS tumours and of BMT, are adequately addressed during the processes of both topic selection and question formulation.

Once the topics and questions have been agreed, a sub-group will be selected for each topic, drawn from members of PanCareSurFup WP6 and invited experts within the topic in question. Each Topic sub-group will act as the focus of subsequent work for that particular topic, liaising with both the WP6 Working Group and the collaborating partners, and being responsible for the production of evidence summaries relevant to the agreed questions, followed by the development of draft recommendations.

The evidence summaries will be produced by the Topic Sub-groups following the methodology developed by CCCG and WP6, which will guide how the published literature will be used to answer specifically the questions. The exact phrasing of the questions will influence the manner in which the literature is searched and analysed, and will therefore be critical to the content of the evidence summaries and hence the nature of the recommendations. In this respect, it will be vital to enunciate clear, focused, and not overly complex questions relevant to practical issues faced by clinicians undertaking LTFU. For example, it is important to define risk groups precisely to allow surveillance strategies to be targeted appropriately. In the case of breast cancer surveillance, rather than simply stating that CCS who have previously received chest RT need yearly screening, it is very important for both clinicians and CCS to know whether this applies to all CCS receiving any dose of RT in a field including the breast, which could therefore, include, for example, the lower doses of total body irradiation (TBI) used as preparation for BMT, or just to CCS treated with higher doses of chest RT during, for example, the treatment of Hodgkin disease. By phrasing the questions appropriately, the literature was searched for studies that provided information on the magnitude of risk of breast cancer in CCS treated with different doses and fields, which therefore guided recommendations about the value of surveillance in these particular groups of CCS.

The initial draft practice recommendations will then be written by the Topic sub-Groups in collaboration with the Working Group, being constructed around the agreed questions and drawing on the conclusions of the evidence summaries. The methodology protocol will be used to guide the structure of the initial draft practice recommendations. A draft proposal for the overall combined practice recommendations will be then written by the Working Group and the chairs of the Topic Sub-Groups, facilitated by workshops held by each Topic Sub-Group and then completed at a final overarching workshop.

Liaison, collaboration, and multidisciplinary teamwork both within WP6, and with the other guideline bodies mentioned previously, will be extremely important at this stage of work. WP6 will seek feedback on the overall combined draft practice recommendations from multiple stakeholders including other national and international professional groups, selected expert individuals and specialist bodies, survivor and family organizations, and charities or other organizations involved in the care of children and adolescents undergoing LTFU after treatment of cancer. Formal written feedback will be requested using a structured feedback form.

By this stage, the outcomes of the epidemiological research performed in PanCareSurFup concerning cardiovascular disease, SMNs and late mortality will be available and any results with implications for the LTFU guidelines will be

incorporated into the practice recommendations alongside the feedback stage.

The final clinical practice guidelines will then be written by the Working Group during a further workshop in 2015, and will be based on the original draft practice recommendations and subsequent feedback received as well as the further research information described above.

Dissemination and implementation of the final clinical practice guidelines will be undertaken during 2015–2016 in collaboration with a wide range of healthcare professionals, regional and national organizations, professional bodies, survivors, families and other interested stakeholders including those already involved in the feedback process. This task will be performed in collaboration with Work Package 7 (Dissemination and Training) of PanCareSurFup. Subsequently, it will be extremely important to develop a reliable and effective mechanism to ensure regular review of the guidelines, with appropriate updating as required, although this will be outside the remit of PanCareSurFup itself since it will conclude its work in 2016.

3.9 Conclusion

Given the considerable differences between European nations and sometimes even within individual countries, the nature of LTFU after childhood cancer in Europe will probably include numerous and varied models of care. Therefore, guidelines will need to be diverse enough to accommodate many different needs while still setting a standard of excellence that all nations can aim for. Individual European countries are at different starting points with respect to existing facilities for LTFU, so the timescale for achieving these standards will not necessarily be the same across the continent. With increased awareness of and advocacy for equal access to treatment and care, improvements in and equity of access to LTFU will hopefully be facilitated across all of Europe.

As new drugs with novel modes of action become available for children with cancer, it will be very important to initiate systematic and timely surveillance for potential late complications of these agents, allowing recognition, evaluation and appropriate management of chronic toxicity as early as possible. Improving access to new drugs for children with cancer and the simplification of rules and regulations governing the performance of clinical trials are of utmost importance, as are defining strategies to facilitate other key issues that determine the overall success of treatment and care of childhood cancer patients and ultimately of survivors. The need for sustainable platforms for clinical trials and research in pediatric oncology in Europe cannot be emphasized enough.

Finally, the increased success rates for the treatment of cancer in children and the resulting awareness of late complications of the disease and its treatment makes international collaboration essential to capture these often rare events. It is extremely timely that such collaboration has now commenced within the International Late Effects of Childhood Cancer Harmonization Guideline Group mentioned above.

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Part II

Surveillance of Medical Late Effects

Long-Term Follow-Up Roadmaps by Disease and Treatment

4

Lilibeth R. Torno and Janet Hager

Abbreviations

ACS	American College of Surgeons
ALL	Acute lymphocytic leukemia
AML	Acute myelocytic leukemia
BCNU	1,3 Bis (chloroethyl-1 nitrosourea)
BUN	Blood urea nitrogen
CBC	Complete blood count
CCNU	Chloroethyl cyclohexyl nitrosourea
CRT	Creatinine
CXRT	Cranial radiation therapy
DOB	Date of birth
Dtap	Diphtheria, tetanus, pertussis vaccine
DXA	Dual X-ray absorptiometry scan
ECHO	Echocardiogram
EKG	Electrocardiogram
EWS	Ewing's sarcoma
FSH	Follicle stimulating hormone
HBV	Hepatitis B vaccine
HD CTX	High dose Cytoxan (cyclophosphamide)
HD MTX	High dose methotrexate
Hib	Hemophilus influenza type b
IGF-1	Insulin growth factor-1
IGFBP-3	Insulin growth factor binding protein-3
IT	Intrathecal
LFT	Liver function test
LH	Luteinizing hormone
LTFU	Long Term Follow-up
MMR	Measles Mumps Rubella
PCV	Pneumococcal conjugate
PFT	Pulmonary function test
PPV23	Polyvalent pneumococcal vaccine
S/Sx	Signs or symptoms
STS	Soft tissue sarcoma
Tdap	Tetanus, diphtheria, pertussis
TSH	Thyroid stimulating hormone
UA	Urinalysis
XRT	Radiation therapy

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4.1 Introduction

In today's world where clinicians are busy and practices are time-constrained, it has become challenging to provide comprehensive care to cancer survivors. This chapter provides a compendium of practice-management templates that will serve as a guide for busy medical providers. These guidelines, simplified and derived from the Children's Oncology Group (COG) Long Term Survivor Guidelines [1] (available in their entirety at http://www.survivorshipguidelines.org) are presented in table form. This format directs the clinician's attention to the essential elements of a

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patient's oncologic history. For example, the frequency of surveillance EKG/ECHO is based on total anthracycline dose received. These templates are scalable for each individual patient. They are also reproducible so that a copy of the table can be placed in patient charts to mark off future dates for surveillance tests or procedures. Undoubtedly, some patients may need more frequent monitoring while others may need less, depending on their risk factors. The hope is that these templates will have practical utility for the busy clinicians providing continuity of care to cancer patients post-treatment.

Some of the diseases, such as sarcomas (osteosarcoma, Ewing's sarcoma, rhabdomyosarcoma) have been grouped together to simplify follow-up. Since some of the patients are diagnosed during late adolescence (e.g. sarcomas, late recurrences or relapse), the guidelines can be adapted to accommodate early follow-up since these patients may have to be transitioned to adult healthcare soon after treatment ends. In these cases, disease evaluation needs to be incorporated into each patient's template for follow-up, per study protocol or institutional guidelines.

The post-hematopoietic cell transplant (HCT) immunization guidelines are based on recent consensus guidelines from the European Blood and Marrow Transplantation group (EBMT), American Society of Blood and Marrow Transplantation (ASBMT) consortium and other groups [2–5]. Timing to start immunizations varies between transplant centers, ranging from 6 to 12 months post-transplant. The immunization table has been designed following the 6-month schedule, which is currently utilized at CHOC Children's Hospital. The suggested 12-month immunization schedule as outlined in the HCT chapter is utilized in other centers in North America and Canada. The decision to immunize at 6 versus 12 months is often made by the transplant center, either one is acceptable based on current literature and practice.

It is always advantageous if the cancer survivor is equipped with knowledge and understanding of his cancer diagnosis and treatment. The treating institution should make it a point to provide a treatment summary and to educate the survivor of the need for surveillance. This will facilitate communication with the healthcare provider. However, as is most often the case, the survivor can only provide his or her cancer diagnosis and leave the clinician with many unanswered questions.

To help circumvent the lack of a treatment summary, this chapter also provides an overview of possible late effects associated with chemotherapy agents given to patients with leukemia and common solid tumors (Table 4.1). Included are cumulative dose ranges of chemotherapy known to cause potential late effects (Table 4.2). The clinician will then be able to cross-reference this information with current care guidelines. This additional information, in conjunction with the disease-specific Long Term Follow-up roadmaps (Tables 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, and 4.10) will help integrate care for the survivor from initial visit to future follow-up care. Since medical decision-making ultimately lies on the healthcare provider, these recommendations should only be used as guidelines.

Details of late effects will be discussed in individual chapters addressing each organ system.

Table 4.1 Common late effects associated with specific cumulative doses of chemotherapy

Chemotherapy	Dose	Late effect	Baseline screening
Anthracycline (Doxorubicin Daunorubicin Epirubicin Mitoxantrone Idarubicin)	≥300 mg/m^2 or >200 mg/m^2 + Chest XRT ≥30 Gy HD CTX (120–200 mg/kg)	Cardiomyopathy valvular, pericardial damage, coronary artery disease	EKG, ECHO
		Acute myeloid leukemia	CBC

(continued)

Table 4.1 (continued)

Chemotherapy	Dose	Late effect	Baseline screening
Cyclophosphamide (Cytoxan)	>7.5 gm/m^2	Gonadal failure	FSH, LH, estradiol/ testosterone
		Cardiomyopathy	EKG, ECHO
		Second cancers[a]	CBC, UA
		Nephropathy/bladder irritation	Serum electrolytes, UA
Ifosfamide	≥60 gm/m^2	Nephropathy	Serum electrolytes, UA
		Second cancers[a]	CBC, UA
		Gonadal failure	FSH, LH, estradiol/ testosterone
Etoposide	>3.5 gm/m^2	Leukemia	CBC
HD MTX[b] with IT chemo	>1 gm/m^2	Neurocognitive	Neurocognitive testing
		Deficits,	
		Leukoencephalopathy	
		Hepatic fibrosis (MTX)	LFTs, bilirubin
Bleomycin	>400 U	Pulmonary toxicity	PFT, CXR
Cisplatin	≥360 mg/m^2 or <360 mg/m^2 +CXRT	Ototoxicity	Audiogram
		Glomerular, tubular Dysfunction, Low Mg	UA, electrolytes
		Dyslipidemia	Fasting Lipid panel

[a]Leukemia, bladder CA
[b]*HD MTX* high dose methotrexate

Table 4.2 Cumulative dose ranges of common chemotherapy agents based on current COG protocols for each diagnosis

Chemotherapy	ALL	AML	STS	EWS	Osteosarcoma
Anthracycline Doxorubicin Daunorubicin Idarubicin Mitoxantrone	75–300 mg/m^2	450 mg/m^2	375–450 mg/m^2	375 mg/m^2	375–450 mg/m^2
Cyclophosphamide	1–4 gm/m^2		4.8–16.8 gm/m^2	8.4 gm/m^2	
Ifosfamide	9 gm/m^2 [a]			63 gm/m^2	48–51 gm/m^2
Etoposide	1 gm/m^2 [a]	1.5 gm/m^2	0–2.5 gm/m^2	3.5 gm/m^2	1.5 gm/m^2

[a]COG Very High Risk Protocol only [6]. Treatment protocols continue to evolve, hence, the above table serves only as a guideline

Table 4.3 Isotoxic dose conversion of anthracyclines based on current Children's Oncology Guidelines

Anthracycline	Conversion
Doxorubicin	Multiply by 1
Daunorubicin	Multiply by 0.833
Epirubicin	Multiply by 0.67
Mitoxantrone	Multiply by 4
Idarubicin	Multiply by 5

This table is a guide to determine the total anthracycline dose received based on equivalent dosing with doxorubicin. For example, if a survivor received 48 mg/m^2 of Mitoxantrone, multiply this by 4, to give a total anthracycline dose of 192 mg/m^2

Table 4.4 Leukemia follow-up

Evaluation	Baseline off therapy	LTFU 2 years	3 years	4 years	5 years	6 years	7 years	8 years	9 years	10 years	11 years	12 years
Date												
History, physical and exam	X	X	X	X	X	X	X	X	X	X	X	X
CBC, BUN, Crt, LFTs, UA, TSH, FT4, ferritin (baseline only)	X	X	X	X	X	X	X	X	X	X	X	X
Fasting glucose and lipid profile every 3–5 years and at entry to LTFU	X	X					X					X
Girls: FSH, LH, estradiol *Boys*: LH, FSH, testosterone *Baseline at age >13 and for delayed puberty, s/sx of estrogen/ testosterone deficiency*												
EKG, ECHO *Total anthracycline ≥300 mg/m2 (yearly) or <300 mg/m2 (every 3–5 years and at entry to LTFU)*	X	X					X					X
DEXA scan *Baseline at age 18 years, consider earlier if clinically indicated*												
Neuropsychological evaluation *Baseline and then PRN*	X											
Ophthalmology	X	X	X	X	X	X	X	X	X	X	X	X
Dentist every 6 months	X	X	X	X	X	X	X	X	X	X	X	X
If patient has sx of Osteonecrosis, MRI/orthopedic referral												
Monitor for obesity, second cancers												
Craniospinal XRT: monitor growth curve, IGF-1, IGFBP3, scoliosis												

Table 4.5 Hodgkin lymphoma follow-up

Evaluation	Baseline off therapy	LTFU 2 years	3 years	4 years	5 years	6 years	7 years	8 years	9 years	10 years	11 years	12 years	13 Years
Date													
History, physical and exam Chest XRT—include clinical breast exam	X	X	X	X	X	X	X	X	X	X	X	X	X
CBC, BUN, Crt, LFTs, TSH, FT4, ferritin (baseline only)	X	X	X	X	X	X	X	X	X	X	X	X	X
Fasting glucose and lipid profile every 3–5 years and at entry to LTFU	X	X					X					X	
Girls: FSH, LH, estradiol *Boys*: LH, FSH, testosterone, semen analysis PRN *Baseline at age >13 and for delayed puberty, s/sx of estrogen/ testosterone deficiency*													
CXR (*every 3–5 years to rule out fibrosis*)			X										
EKG, ECHO *Total anthracycline ≥300 mg/m2 (yearly) or <300 mg/m2 (every 3–5 years and at entry to LTFU)*	X	X					X					X	
Pulmonary function test (*every 3–5 years or more frequently if clinically indicated*)	X				X					X			
DEXA scan *Baseline at age 18 years, consider earlier if clinically indicated*													
Neuropsychological evaluation *Baseline and then PRN*	X												
Ophthalmology	X	X	X	X	X	X	X	X	X	X	X	X	X
Dentist every 6 months	X	X	X	X	X	X	X	X	X	X	X	X	X

(continued)

Table 4.5 (continued)

Evaluation	Baseline off therapy	LTFU 2 years	3 years	4 years	5 years	6 years	7 years	8 years	9 years	10 years	11 years	12 years	13 Years
If XRT to chest, mammogram/ breast MRI yearly (*begin 8 years after XRT or at age 25, whichever occurs last*). Breast ultrasound, if mass palpated. Breast self-exam every month													
If abdominal XRT, colonoscopy every 5 years (*begin 10 years after radiation or at age 35, whichever occurs last*). Stool guaiac per ACS													

Table 4.6 Intracranial tumor follow-up

Evaluation	Baseline off therapy	LTFU2 years	3 years	4 years	5 years	6 years	7 years	8 years	9 years	10 years	11 years	12 years
Date												
History, physical and exam	X	X	X	X	X	X	X	X	X	X	X	X
CBC, BUN, Crt, LFTs, Mg, UA, TSH, FT4, ferritin (baseline only), IGF-1/ IGFPB3(as indicated)	X	X	X	X	X	X	X	X	X	X	X	X
Fasting glucose and lipid profile every 3–5 years	X	X					X					X
Girls: FSH, LH, estradiol *Boys*: LH, FSH, testosterone *Baseline at age >13 and for delayed puberty, s/sx of estrogen/testosterone deficiency*												
CXR, PFTs (BCNU, CCNU) *Baseline, then every 3–5 years*	X				X					X		
DEXA scan *Baseline at age 18 years, consider earlier if clinically indicated*												
Neuropsychological evaluation *Baseline and then PRN*	X											
Audiogram (s/p Cisplatin)	X				X					X		
Dentist every 6 months	X	X	X	X	X	X	X	X	X	X	X	X
Ophthalmology	X	X	X	X	X	X	X	X	X	X	X	X
Endocrine evaluation	X											
Craniospinal XRT: monitor growth curve, scoliosis												

Table 4.7 Post hematopoietic cell transplant (HCT) follow-up

Evaluation	Baseline off therapy	LTFU 2 years	3 years	4 years	5 years	6 years	7 years	8 years	9 years	10 years	11 years	12 years	13 Years
Date													
History, physical and exam Chest XRT—include clinical breast exam	X	X	X	X	X	X	X	X	X	X	X	X	X
CBC, BUN, Crt, LFTs, UA, TSH, FT4, IGF-1/ IGFPB3 (as indicated), ferritin	X	X	X	X	X	X	X	X	X	X	X	X	X
Fasting glucose and lipid profile every 2 years		X		X		X		X		X		X	
Girls: FSH, LH, estradiol *Boys*: LH, FSH, testosterone *Baseline at age >12 and for delayed puberty, s/sx of estrogen/ testosterone deficiency*													
CXR (*every 3–5 years to rule out fibrosis*)					X					X			
EKG, ECHO (based on exposure)	X	X	X	X	X	X	X	X	X	X	X	X	X
Pulmonary function test (*every 1–2 years*)	X	X	X	X	X	X	X	X	X	X	X	X	X
DEXA scan *Baseline at age 18 years, consider earlier if clinically indicated*													
Neuropsychological evaluation *Baseline and then PRN*	X												
Ophthalmology	X	X	X	X	X	X	X	X	X	X	X	X	X
Dentist every 6 months	X	X	X	X	X	X	X	X	X	X	X	X	X

Audiogram *Baseline and then as clinically indicated*						
Re-immunization to begin at 6 months post HCT	6 months	7 months	8 months	18 months	19 months	24 months
Date due	X	X	X	X		
Dtap/Tdap[a]—IPV—HPV/Hib	X	X	X			
PCV13				X		X
PPV23+ (give PCV if with GVHD)						X
MMR (only immunocompetent patients)						X
Optional immunizations at 18 months post HCT	Meningococcal type C conjugate—(MCV4) for ≥11 y/o (repeat after 5 years)			X		
	Hepatitis A virus for ≥1 y/o (two doses at 6 months apart)			X		X
	Human papillomavirus for ≥11 y/o (three doses at 18, 19 and 24 months)			X	X	X
	Varicella zoster virus ≥24 months (only immunocompetent patients)					X

[a]Tdap if > 7 years of age

Table 4.8 Neuroblastoma follow-up

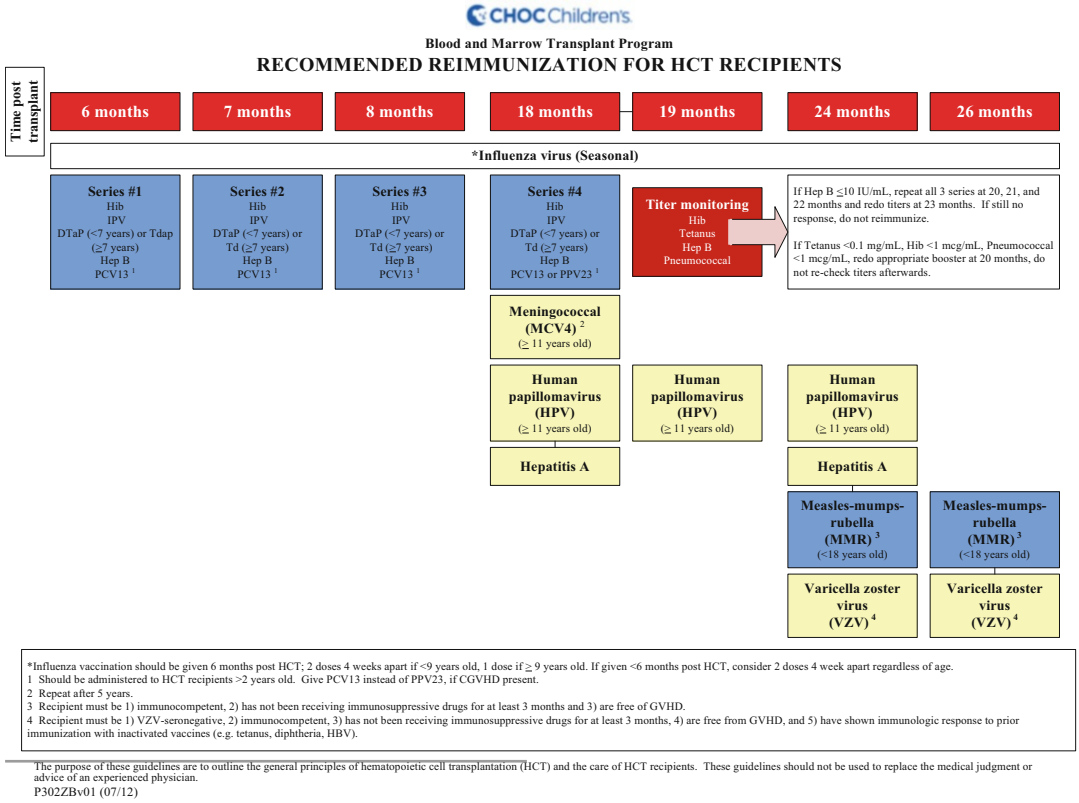
Evaluation	Baseline off therapy	LTFU 2 years	3 years	4 years	5 years	6 years	7 years	8 years	9 years	10 years	11 years	12 years	13 Years
Date													
History, physical and exam	X	X	X	X	X	X	X	X	X	X	X	X	X
CBC, BUN, Crt, LFTs, Mg, TSH, FT4, ferritin (*baseline only*)	X	X	X	X	X	X	X	X	X	X	X	X	X
Fasting glucose and lipid profile every 3–5 years and at entry to LTFU	X	X					X					X	
Girls: FSH, LH, estradiol *Boys*: LH, FSH, testosterone, semen analysis PRN *Baseline at age >13 and for delayed puberty, s/sx of estrogen/testosterone deficiency*													
EKG, ECHO *Total anthracycline ≥300 mg/m2 (yearly) or <300 mg/m2 (every 3–5 years and at entry to LTFU). More frequent surveillance with XRT to chest*	X	X					X					X	
DEXA scan *Baseline at age 18 years, consider earlier if clinically indicated*													
Ophthalmology *Baseline at entry into Long Term Follow Up, then PRN*		X											
Dentist every 6 months	X	X	X	X	X	X	X	X	X	X	X	X	X
Audiogram *Baseline and at 2 years, then PRN*	X	X											
If XRT given to spine/paraspinal/ abdomen, stool for guaiac, colonoscopy per ACS, monitor for scoliosis													

Table 4.9 Sarcoma follow-up

Evaluation	Baseline off therapy	LTFU 2 years	3 years	4 years	5 years	6 years	7 years	8 years	9 years	10 years	11 years	12 years
Date												
History, physical and exam	X	X	X	X	X	X	X	X	X	X	X	X
CBC, BUN, Crt, LFTs, Mg, UA, TSH, FT4	X	X	X	X	X	X	X	X	X	X	X	X
Fasting glucose and lipid profile every 3–5 years and at entry to LTFU	X	X					X					X
Girls: FSH, LH, estradiol *Boys*: LH, FSH, testosterone *Baseline at age >13 and for delayed puberty, s/sx of estrogen/ testosterone deficiency*												
EKG, ECHO *Total anthracycline ≥300 mg/m2 (yearly) or <300 mg/m2 (every 3–5 years and at entry to LTFU)*	X	X					X					X
DEXA scan *Baseline at age 18 years, consider earlier if clinically indicated*												
Neuropsychological evaluation *Baseline and then PRN*	X											
Audiogram (s/p Cisplatin)	X	X	X	X	X	X	X	X	X	X	X	X
Dentist every 6 months	X	X	X	X	X	X	X	X	X	X	X	X
Ophthalmology	X	X	X	X	X	X	X	X	X	X	X	X
Monitor limb length discrepancies	X											
If lung XRT, PFTs every 3–5 years or as clinically indicated. Clinical breast exam every year. Mammogram/breast MRI yearly (*age >25 years or 8 years post XRT*)												

Table 4.10 Wilms tumor follow-up

Evaluation	Baseline off therapy	LTFU 2 years	3 years	4 years	5 years	6 years	7 years	8 years	9 years	10 years	11 years	12 years	13 Years
Date													
History, physical and exam	X	X	X	X	X	X	X	X	X	X	X	X	X
CBC, BUN, Crt, LFTs,UA	X	X	X	X	X	X	X	X	X	X	X	X	X
Girls: FSH, LH, estradiol *Boys*: LH, FSH, testosterone, semen analysis PRN *Baseline at age >13 and for delayed puberty, s/sx of estrogen/testosterone deficiency*													
EKG, ECHO *Total anthracycline ≥300 mg/m2 (yearly) or <300 mg/m2 (every 3–5 years and at entry to LTFU)*	X	X					X					X	
Dentist every 6 months	X	X	X	X	X	X	X	X	X	X	X	X	X
If abdominal XRT, colonoscopy every 5 years (*begin 10 years after radiation or at age 35, whichever occurs last*). Stool guaiac test per ACS													
If lung XRT, CXR at baseline then every 5 years. Breast self-exam every month. Mammogram/breast MRI yearly (age >25 or 8 years post XRT)													
PFTs (*at baseline then every 3–5 years*)	X				X					X			



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Central Nervous System

5

Wei-Ping Violet Shen

5.1 Introduction

Acute lymphoblastic leukemia (ALL) and brain tumors are the two most common cancers occurring during childhood, accounting for more than half of all childhood malignancies. Advances in treatment over the last four decades have improved the 5-year survival rate to 73 % for children with central nervous system (CNS) malignancies and over 85 % for ALL [1, 2]. However, survivors of childhood leukemia and brain tumors are at a high risk of developing adverse effects from direct CNS insult by the tumor, surgery, radiation and chemotherapy. Adverse effects can be long lasting and debilitating, affecting neurological, neurocognitive, neuropsychological and endocrine functions, resulting in intellectual decline, learning disability, altered body images and poor social outcomes. Second malignancies in the central nervous system were also observed in survivors of ALL and brain tumors, which can be devastating and life threatening [3].

This chapter reviews CNS late effects in patients diagnosed with brain tumor or ALL during childhood. The effects of brain damage seen in childhood cancer survivors can be highly variable depending on the tumor location, types and degree of the insult and age of the patient when the insult occurred. It is also important to recognize that treatment of cancer evolves over time, which can influence the type and severity of the late effect. Surveillance of potential late effects in survivors may assist in early recognition and management of complications and improve the quality of life of survivors.

5.2 Risk Factors Affecting CNS Late Effects

5.2.1 Genetics

Patients with certain genetic syndromes are at increased risk of developing CNS tumors. Identification of genetic disorders among CNS tumor survivors will assist in disease specific monitoring and management.

Neurofibromatosis Type 1 (NF1) is the most common genetic syndrome predisposing to CNS tumors, with an estimated incidence of 1 in 3,000. Mutation in a tumor suppressor gene encoding neurofibromin is found in patients with NF1. Loss of neurofibromin leads to an increased risk of developing benign and malignant tumors in affected individuals [4]. Patients with neurofibromatosis are also at higher risk of developing moyamoya syndrome and secondary CNS malignancy following cranial radiation [5].

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Gorlin syndrome (GS), caused by mutations in the *PTCH1* tumor suppressor gene, affects many areas of the body and increases the risk of developing various tumors including basal cell carcinoma and medulloblastoma. The incidence of GS in medulloblastoma is probably between 1 % and 2 %. GS patients are at high risk of developing multiple invasive basal cell carcinomas particularly in the radiation field [6–9].

Li-Fraumeni syndrome (LFS) is linked to germ-line mutation of p53 tumor suppressor gene. Persons with LFS are at risk for a wide range of malignancies, with particularly high occurrences of breast cancer, brain tumors, acute leukemia, soft tissue sarcomas, bone sarcomas, and adrenal cortical carcinoma [10].

Von-Hippel Lindau syndrome (VHL) is an autosomal dominant disorder with an incidence of 1:40,000. The VHL gene maps to chromosome 3p25-26 and is a putative tumor suppressor. Patients with VHL are at risk of developing hemangioblastoma in the CNS and retina, renal cell carcinoma, pheochromocytoma and pancreatic neuroendocrine tumors [11].

5.2.2 Age

Of course, human brain development is not complete at birth. The cortical and subcortical white matter undergoes conspicuous growth during the first 2 years of life, but may not be fully mature before adolescence or even adulthood. Younger children, particularly those under three years of age at the time of cranial radiation are at very high risk of developing neurocognitive and other late effects due to immature white matter development [12]. These patients almost universally require special education services and are unlikely to live independently as adults [13].

5.2.3 Gender

Female survivors of brain tumor and ALL are at greater risk for neurocognitive and academic decline [14, 15]. Female ALL survivors who were treated with cranial radiation also had a significantly greater increase in Body Mass Index (BMI), earlier onset of puberty and reduced final height than their non-irradiated counterpart [16].

5.2.4 Social

Children raised in families with lower socioeconomic status may have less resources and support to intervene with neuropsychological late effects. Lack of insurance coverage can also impede screening and intervention of late effects [17].

5.2.5 Pre-existing Condition

Children with pre-existing learning or attention problems are at higher risk to have further decline of neurocognitive function [14].

5.3 Central Nervous System Insults

5.3.1 Tumors and Surgery

Brain tumors can infiltrate and disrupt the neurons and axonal pathways in the involved area and cause diminished function. Spinal cord tumors may cause weakness or paralysis of lower extremities, neurogenic bladder and/or bowel from cord compression. Leukemia can invade cerebral parenchyma or directly infiltrate the leptomeninges and subarachnoid space, sometimes even forming mass lesions (chloroma), which can cause seizures, altered mental status, headaches and cranial nerve deficits [18].

Peri-operative complications such as increased intracranial pressure, brain swelling, hydrocephalus, aseptic or bacterial meningitis, seizure and pseudomeningocele may result in lower visuospatial skill, memory, attention and performance IQ [19]. *Cerebellar mutism syndrome* (a.k.a. posterior fossa syndrome) (CMS) is a well-recognized complication of surgical removal of large midline posterior fossa tumors, manifested with diminished speech, emotional instability, hypotonia and ataxia. This develops in approximately a quarter of children with medulloblastoma post-operatively. Although most patients improve over time,

over half of patients suffer permanent neurologic dysfunction including cranial nerve deficits, hypotonia and ataxia [20]. Patients who develop CMS post-surgery were found to have significantly lower performance in processing speed, attention, working memory, executive processes, cognitive efficiency, reading, spelling and mathematics at 12 months post-diagnosis [21].

5.3.2 Radiation

Radiation therapy given after surgery can impose additional insult to the brain. The degree of insult is dependent on the age of the patient, the dose, field and location of radiation.

Neuropathological changes from cranial radiation include cerebral calcification, demyelination (*leukoencephalopathy*), mineralizing microangiopathy, white matter volume loss, vasculopathy and cerebral lacunes [22]. White matter volume is known to be associated with neurocognitive test performance, which shows deficiencies after cranial irradiation. A longitudinal study of survivors of medulloblastoma with serial MRIs revealed a significant loss of white matter volume in patients undergoing craniospinal irradiation (CSI). The white matter loss was more rapid among patients who received a CSI dose of 36 Gy versus CSI of 23.4 Gy [23]. Younger age at the time of irradiation and the need for a ventricular shunt was significantly associated with reduced white matter volume [24].

Cranial irradiation has also been linked to the development of *cerebral vasculopathy* years after treatment. Treatment related mineralizing microangiopathy has been related to the development of seizures [25]. Other cerebrovascular complications include strokes and moyamoya [5], which can cause hemiparesis, weakness, aphasia and result in poor physical health and activity limitations.

5.3.3 Neuroanatomical Regional Effects from Radiation

Radiation involving the *hypothalamic-pituitary axis* can result in neuroendocrine abnormalities. Growth hormone production is most prone to be disrupted by radiation therapy following doses as low as 12 Gy. Other hormones like thyroid stimulating hormone (TSH), adrenocorticotropic hormone (ACTH), follicle stimulating hormone (FSH), and luteinizing hormone (LH), appear to have a higher threshold above 40 Gy [26].

Radiation to *temporal regions* were associated with a higher risk for memory impairment and more social and general health problems, while radiation exposure to frontal regions were associated with general health problems and physical performance limitations [27]. Radiation to the *spine and spinal cord* can decrease growth of the vertebral body in young children and result in decreased sitting height. The incidence of spinal cord injury was reported at 1 % incidence at 42 Gy and 5 % at 45 Gy [28]. Chronic progressive radiation myelopathy can occur following spinal radiation [29]. Radiation damage to the *eyes* can lead to cataract, optic nerve damage, abnormal pupillary response, visual deficits, blindness (threshold 50 Gy), retinopathy-macular edema and neovascularization (threshold 50–60 Gy). Hearing loss can result in radiation doses greater than 40–50 Gy to the cochlea.

The newer radiation technologies such as conformal radiation, Intensity-Modulated Radiation Therapy (IMRT) and gamma knife using three-dimensional planning, provide focused radiation and spare surrounding normal tissue from the toxic effects of radiation. Proton beam radiotherapy has a rapid fall-off of dose immediately distal to the target and a smaller proximal dose compared to photon therapy. This allows for potential sparing of critical structures and may decrease radiation late effects.

5.3.4 Chemotherapy

Many survivors of childhood ALL were treated with chemotherapy only. Buizer et al. performed a review of 21 studies published since 1997 and found evidence of subtle long-term neurocognitive deficits in survivors of childhood ALL after treatment with chemotherapy only. These deficits involve mainly processes of attention and of executive functioning, while global intellectual

function is relatively preserved. Young age at diagnosis and female sex emerged as risk factors [30]. The neurocognitive effect in children with ALL treated with intrathecal chemotherapy is more subtle than the effect of cranial radiation therapy [31, 32]. Methotrexate (MTX), a folate antagonist, is one of the most widely used chemotherapy agents in the treatment of ALL. It is given via different routes including oral, intramuscular, intravenous and intrathecal. Methotrexate inhibits dihydrofolate reductase, resulting in increase in homocysteine which is neurotoxic. Methotrexate also inhibits synthesis of methionine, an important metabolite necessary for CNS myelination [33, 34]. Intrathecal methotrexate can cause transient T2 hyperintensities in the white matter, which could result in cerebral edema, stroke-like symptoms and/or seizure. Diffusion Tensor Imaging (DTI) may be more sensitive in detecting white matter damage from leukemia treatment that regular MRI. Compared to normal subjects, children with ALL showed the most significant decreases in fractional anisotropy (FA), a marker of white matter integrity in association fibers involved in higher order executive functioning and memory, ventral commissural fibers, and long tracts [35].

Most commonly reported neurocognitive late effects of chemotherapy in childhood ALL survivors are deficits in attention, executive function, visual processing and visual-motor functioning, and albeit subtle, could still affect the ability to reach their academic potential [36]. High dose intravenous Cytarabine (≥1,000 mg/m^2) or high dose Methotrexate (≥1,000 mg/m^2) given in a subset of patients with high risk or recurrent leukemia, can cause clinical leukoencephalopathy, producing symptoms like spasticity, ataxia, dysarthria, dysphagia, hemiparesis and seizures. Both the intensity and extent of leukoencephalopathy can be significantly reduced after completion of therapy [37]. However, children younger than 5 years of age at the time of diagnosis are at risk of developing neuropsychological deficiencies associated with white matter changes [38]. The neurocognitive effects between high dose methotrexate (>5 gm/m^2) and intermediate dose methotrexate (100–300 mg/m^2) were studied recently by the Children's Oncology Group (COG). A subgroup of patients in this study will have Diffusion Tensor Imaging (DTI), a type of MRI method that maps molecular diffusion in tissues, which can reveal white matter fiber structure abnormalities [34]. Clearly this research will add to our understanding of the integrity of neuronal connectivity and neurocognitive outcome.

Some chemotherapeutic agents can cause long term, debilitating neurosensory deficits. For example, cisplatin can cause severe ototoxicity, especially when coupled with radiation therapy [39]. Plant alkaloids including vincristine and vinblastine can cause peripheral sensory or motor neuropathy manifested as areflexia, weakness, foot drop and paresthesias.

5.3.5 Treatment Evolution and Its Effect on the Spectrum of Late Effects

Many recent publications related to the long term effects of the CNS are from the Childhood Cancer Survivor Study (CCSS). The CCSS systematically studied a retrospective cohort of 20,720 survivors of childhood cancer diagnosed between 1970 and 1986. Patients were eligible if they were younger than 21 years at diagnosis and had survived at least 5 years from diagnosis, independent of disease status. The study recruited the nearest-age siblings of a random sample of participant patients to serve as a comparison group. There were 1,877 out of 2,888 survivors of CNS malignancies who consented and participated in the study. This time period (1970–1986) represents an era where surgery alone (26 %) or surgery followed by radiation therapy (41.6 %) were the mainstay of treatment for brain tumors. Only 27 % of patients received chemotherapy [3].

Among 4,151 childhood ALL survivors from the CCSS study, 64.5 % were treated with cranial radiation (median 23.8 Gy, range 1.5–74.4 Gy). Nearly all patients received intrathecal therapy, 12 % were treated with high-dose methotrexate (>5 gm/m^2) and 5 % underwent bone marrow transplant (BMT) [40]. Randomized clinical

trials conducted in the 1980s demonstrated that cranial radiation can be reduced or replaced safely with intrathecal chemotherapy in majority of children with ALL [41]. Currently, cranial radiation has been eliminated for most patients with ALL.

Similarly, with the addition of effective adjuvant chemotherapy, the dose of craniospinal radiation given to children with standard risk medulloblastoma has been reduced from 36 to 23.4 Gy without compromising overall survival [42]. The current COG study investigates the safety and feasibility of further reducing the dose of craniospinal radiation from 23.4 to 18 Gy in children 3 to 7 years of age. However, wider use of cisplatin in patients with medulloblastoma is likely to increase the rate of hearing impairment of patients treated after 1986 [43].

In the last two decades, infants with high risk medulloblastoma or primitive neuroectodermal tumor (PNET) were commonly treated with high dose chemotherapy with stem cell support in an attempt to avoid or minimize craniospinal radiation therapy. A few studies looked at the neuropsychological development of survivors showing encouraging quality of life and behavior at follow up [44, 45]. The long term outcome of these survivors is still not known.

Three-dimensional conformal radiation therapy which allows for lower doses to be delivered to critical structures around the tumors became widely available in the late 1990s. The switch will change the spectrum of radiation side effects associated with non-conformal radiation therapy [46].

5.4 Treatment and Potential CNS Late Effects of Common Childhood Brain Tumors and Acute Leukemia

Table 5.1 summarizes the treatment modalities and potential late effects of common pediatric brain tumors and ALL. Understanding the type of insult patients have experienced can be a helpful guide for the proper surveillance and management of late effects. The treatment of individual patients may vary based on age, tumor staging, pathological grade, time period during the treatment, local treatment standard and tumor recurrence. A treatment summary including surgical history, type and doses of chemotherapy and radiation therapy should be obtained in order to establish a plan for surveillance of late effects.

CNS-directed therapy may alter cognitive, emotional and physical performance [49]. Chronic fatigue and pain are common complaints among survivors [50, 51]. A summary of these effects are presented in Table 5.2, and are discussed below.

In the CCSS study, 82 % of the 1,877 adult survivors of childhood CNS malignancies reported at least one chronic medical condition, with 38 % reporting a serious life-threatening condition. Endocrine complications and neurologic complications are most commonly reported [52]. Among all childhood cancer survivors, survivors of CNS malignancies have the highest risk for grade 3 or 4 chronic health conditions using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) [53]. They also reported significantly higher rates of global distress, depression, and somatic distress than their siblings [3].

Among ALL survivors studied by the CCSS, one or more chronic medical conditions were reported by 50 % of survivors, compared with 37.8 % of siblings. Severe chronic health conditions were more commonly reported in survivors who received radiation therapy or experienced relapses [54].

5.4.1 Endocrinological Late Effects

Brain tumor survivors with tumor in the hypothalamic-pituitary axis (H-P axis) and those who received more than 24 Gy cranial radiation are at high risk for neuroendocrine dysfunction. The endocrinological late effects include growth failure, gonadal dysfunction, central hypothyroidism, central adrenal insufficiency, obesity and diabetes insipidus. Cranial radiation doses as low as 18 Gy can affect the growth hormone axis [55]. Panhypopituitarism,

Table 5.1 Treatment and potential CNS late effects of common childhood brain tumors and acute leukemia

Disease	Treatment	Potential CNS late effects
Craniopharyngioma	Surgical resection/biopsy, cyst fenestration, radiation therapy	Panhypopituitarism, obesity, hypogonadism, lower physical health and psychosocial difficulties
Optic Pathway Glioma	Chemotherapy (Carboplatin, Vincristine, CCNU, 6-thioguanine, procarbazine) for younger patients, local radiation (XRT) for older patients or recurrent tumors, surgical resection in selected patients	Visual impairment, growth hormone deficiency, hypothyroidism, endocrinopathies, neuropathy, neurocognitive deficit
Medulloblastoma	Surgical resection, Craniospinal XRT with boost to the posterior fossa, Chemotherapy (Cisplatin, CCNU, Cyclophosphamide, Vincristine, carboplatin)	Ataxia, cranial nerve palsy, diplopia, poor balance, hearing loss, growth failure, impaired spinal growth, neurocognitive deficit, shunt failure, second malignancy [47]
Supratentorial PNET	Surgical resection/biopsy, craniospinal XRT with boost to the tumor bed, chemotherapy (Cisplatin, Cyclophosphamide, vincristine, Carboplatin)	Seizure, motor deficit, poor hand-eye coordination, lower IQ, neurocognitive deficit, poor memory, attention deficit, emotional difficulties, growth failure, endocrinopathies, hearing loss
Ependymoma	Surgical Resection, radiation to the tumor bed for non-metastatic disease, additional multiagent chemotherapy to patients with incompletely resected tumors	Cranial nerve deficits, abnormal gait, fine motor function deficit, memory loss, dysphagia, truncal ataxia, neurocognitive deficit
Low grade astrocytoma or other glial tumor	Surgical resection. Radiation to the residual or recurrent tumor, chemotherapy for younger patients	Blindness, hearing loss, obesity, endocrinopathies (diencephalic location), lower IQ [48]
High grade astrocytoma or other glial tumor	Surgical resection. Radiation to the tumor bed, chemotherapy (Temozolomide, CCNU, Bevacizumab, irinotecan)	Neurocognitive deficit, seizure, headache, regional based late effects
Choroid Plexus Tumors (CPT)	Surgical resection, Etoposide, carboplatin and other chemo for high grade CPT	Hydrocephalus/shunt dysfunction, motor dysfunction, psychomotor retardation
CNS Germ Cell Tumors (GCT), (supraseller or pineal)	Third ventriculostomy, biopsy/ resection Radiation to the ventricular system or neuraxis± platinum based chemotherapy	Neurocognitive deficit, diabetes insipidus, hypopituitarism (supraseller GCT), neurocognitive dysfunction
Infant embryonic tumors	May receive less or no radiation therapy but more aggressive chemotherapy with autologous stem cell support	Lower visual-motor integration. Lower IQ, hearing loss, seizure, second malignancies
Acute Lymphoblastic Leukemia	Intrathecal chemo for all patients, cranial XRT for selected patients (CNS leukemia or very high risk ALL or patients treated before 1990), multiagent chemotherapy including methotrexate, vincristine, steroid, anthracycline, mercaptopurine, asparaginase	Headache, auditory-vestibular-visual sensory deficit, coordination and motor sensory disorders, seizures, brain tumor and other second neoplasms, neurocognitive deficit

Table 5.2 Clinical presentations of CNS late effects

Type of late effects	Clinical presentation	Risk factors
General	Low physical performance Lower educational achievement Not living independently	Cranial radiation, neurological deficits
Neurological	Leukoencephalopathy	Radiation, high dose methotrexate
	Coordination and motor control disorders	Radiation >50 Gy to the frontal brain
	Seizure disorder	Radiation >30 Gy to cerebral cortex regions
	Stroke	Cranial radiation >30 Gy
	Visual impairment	Optic pathway tumors
	Hearing impairment Tinnitus	Radiation >50 Gy to the posterior fossa, platinum chemotherapy
Neurocognitive	Poor attention Slow processing speed Lower visual-perceptual skills Lower executive function Poor memory Lower IQ and academic achievement	Young age at diagnosis Cortical tumors >35 Gy radiation to frontal lobe >24 Gy cranial radiation Hydrocephalus, VP shunt placement Neurosensory deficits
Endocrinological	Growth failure	>18 Gy radiation to H-P axis, age <4 years at diagnosis
	Gonadal dysfunction Central hypothyroidism Central adrenal insufficiency Diabetes insipidus	Cranial radiation ≥40 Gy
	Obesity	Female sex, young age at diagnosis, >20 Gy radiation to H-P axis
	Early menarche	<4 years old at diagnosis
	Late menarche	>50 Gy radiation to H-P axis
Second malignancies	Gliomas Meningiomas	≤5 years old received CNS radiation, ≥50 Gy CNS radiation, NF1
Psychological	Depression Anxiety Somatic distress Daytime sleepiness Social withdrawal Poor self-concept	Major medical conditions Female sex Lower socioeconomic status Lower education achievement
Social outcomes	Educational difficulties Lack of friends Unemployment Not married	Cranial radiation therapy Young age at the diagnosis Female sex

a condition in which there is inadequate or absent production of the anterior pituitary hormones, usually develops in patients who have received greater than 40 Gy of cranial radiation [56]. Gonadal dysfunction includes precocious puberty, delayed puberty and/or infertility. The CCSS reported decreased fertility among female childhood cancer survivors who received 22–27 Gy H-P axis irradiation [57]. Hyperprolactinemia can also occur in patients who received radiation to the hypothalamic/pituitary area, producing symptoms of decreased libido, galactorrhea, and amenorrhea [58].

The CCSS cohort (n = 1,607) showed that childhood brain tumor survivors had a significantly increased risk of late-onset hypothyroidism with relative risk ratio (RR) of 14.3, growth hormone deficiency (RR = 277.8), the need for medications to induce puberty (RR = 277.8) and osteoporosis (RR = 24.7) [56]. Female survivors

were more likely to have onset of menarche before age ten compared to their siblings (11.9 % vs. 1.0 %). Age ≤4 years at diagnosis was associated with an increased risk of early menarche. Additionally, survivors of CNS tumors were more likely than siblings to have onset of menarche after age 16 (10.6 % vs. 1.9 %). Doses of RT to the H-P axis >50 Gy and spinal RT conferred an increased risk of late menarche, as did older age (>10 years) at the time of diagnosis [59]. As a result, H-P axis radiation and chemotherapy with alkylating agents reduce the likelihood of pregnancy among female survivors [60].

The strongest risk factors for adult short stature were 4 years of age or younger at diagnosis and radiation treatment involving the H-P axis [61]. The risk of metabolic syndrome and/or overweight/obesity increases for those less than 4 years old at time of treatment, female sex, hypothalamic radiation dose >20 Gy and inability to exercise due to physical limitations.

5.4.2 Neurological Late Effects

Leukoencephalopathy (LE) can develop after exposures to mid-to-high dose methotrexate. This is best detected on the T-2 weighted and FLAIR images of MRIs with the prevalence ranging from 21 % to 76 %. Increasing exposure, which corresponded to more courses and higher doses of IV MTX, was a risk factor for LE. Some of the LE changes were transient, as evidenced by a significant reduction in the prevalence of LE approximately 1.5 years after the completion of IV MTX therapy [62, 63].

Coordination and motor control disorders were reported in 49 % and 26 % of survivors, respectively. Children receiving at least 50 Gy to the frontal brain region had a modestly elevated risk for motor problems [64].

Seizure disorders were reported in 25 % of survivors of brain tumor, including 6.5 % who had a late first occurrence. Radiation dose of 30 Gy or more to any cortical segment of the brain, with the exception of the posterior fossa, was associated with a two-fold elevated risk for a late seizure disorder [52, 64]. Among acute leukemia survivors in the CCSS cohort, 7 % had seizures, the majority of which was late onset [54].

Stroke has been observed in survivors of childhood leukemia and brain tumors from the CCSS cohort, particularly those with brain tumors treated with greater than 30 Gy of cranial radiation are at an increased risk of stroke [65]. The relative risk of stroke for survivors was 6.4 for leukemia and 29 for brain tumor survivors compared with the sibling comparison group. In leukemia survivors, the risk of late-occurring stroke compared to siblings was increased for survivors treated with cranial radiation (RR, 5.9) and without cranial radiation (RR, 4.0). The cumulative incidence of stroke was 0.73 % at 25 years after treatment for leukemia survivors and 5.58 % for brain tumor survivors [65]. Severe recurrent headache may be a predictor for subsequent stroke or TIA [66].

Moyamoya syndrome is a potentially serious complication of cranial irradiation in children, particularly for those patients with tumors in close proximity to the circle of Willis, such as optic pathway glioma. It is a progressive vascular occlusive disease with particular involvement of the circle of Willis, manifesting as stroke, or recurrent transient ischemic attacks (TIA). Patients with NF1 also have increased risk of developing moyamoya syndrome (HR = 3.01) [5].

Neurosensory deficit has been noted in 17 % of CCSS patients. Eye problems, including ocular nerve palsy, double vision, gaze paresis, nystagmus, papilledema, optic atrophy, visual loss and cataracts are common in childhood brain tumor survivors. The CCSS study showed brain tumor survivors were at substantial elevated risk for late-onset legal blindness in one or both eyes (RR, 14.8). Hearing impairment was reported by 12 % of patients. Radiation exposure of greater than 50 Gy to the posterior fossa was associated with a higher likelihood of developing any hearing impairment [64]. Tinnitus was common both early and late in the illness. It is likely that wider use of cisplatin and high dose carboplatin after 1986 will increase the rate of hearing impairment [67]. Auditory-vestibular-visual sensory deficits were reported in 15.1 % of ALL survivors in the CCSS study. Serious headache were most

common in ALL survivors with a cumulative incidence of 25.8 % at 20 years [54].

Chronic progressive radiation myelopathy can occur months to years following spinal radiation manifested with bilateral leg paresthesias, weakness, and painful, electric-like shock sensation elicited on neck flexion (Lhermitte's sign) [68].

5.4.3 Neurocognitive Late Effects

It is well known that survivors of childhood ALL and CNS malignancies are at greatest risk for neurocognitive impairment, particularly if they have received cranial radiation. While this manuscript will address this particular issue in separate chapters, a brief review for the reader is hereby offered. The neurocognitive sequelae are most apparent in attention, processing speed, visual perceptual skills, executive function (planning and organization) and memory. Deficits in these areas result in declines in IQ, reading comprehension, spelling, mathematics, skill acquisition and academic achievement.

Cognitive growth is also reduced in survivors, so the cognitive gap between the survivors and the general population increases with time [69]. Decreased white matter volume (WMV) was shown in the survivors of childhood ALL and malignant brain tumors which were associated directly with lower scores in intelligence, attention, and academic performance. Increased CNS treatment intensity, younger age at treatment and greater time since treatment were significantly associated with lower WMV [70]. Reported neurocognitive impairment adversely affected important adulthood outcomes, including education, independent living, employment, income and marital status [71].

Factors within the population of pediatric CNS malignancy survivors that impacted neurocognitive outcome include tumor type and site [72], age at diagnosis, and dose and volume of radiation therapy [73, 74]. Cortical tumors have been reported to result in more cognitive late effects than 3rd or 4th ventricle tumors [71, 72]. Survivors who received high-dose cranial radiation to frontal areas of their brain (i.e. >35 Gy) reported significantly more problems with attention, processing speed, memory and emotional regulation [75]. However, pediatric posterior fossa tumors have also been associated with neurocognitive sequelae including deficits in attention, planning, sequencing, executive functioning, memory, processing speed, visual-spatial organization, and modulation of affect and behavior [76–78].

Although children with pilocytic astrocytoma (PA) generally carry a better prognosis and many were treated with surgery only, the CCSS study showed that survivors of astrocytoma have high rates of impairment in attention, processing speed and memory. Impairment increases with cranial radiation exposure [3]. Aarsen et al conducted a prospective neurocognitive study of 67 children treated for PA and found that cognitive impairments are common. All children with PA had problems with sustained attention and speed. In the infratentorial group, there also were deficits in verbal intelligence, visual-spatial memory, executive functioning, and naming. The supratentorial hemispheric tumor group had additional problems with selective attention and executive functioning. More specifically, the dorsal supratentorial midline tumor group displayed problems with language and verbal memory. Predictors for lower cognitive functioning were hydrocephalus, radiotherapy, residual tumor size, and age. Predictors for better functioning were chemotherapy or treatment of hydrocephalus. Almost 60 % of children had problems with academic achievement, for which risk factors were relapse and younger age at diagnosis [79].

Survivors of medulloblastoma demonstrate a decline in IQ values because of an inability to acquire new skills and information at a rate comparable to their healthy same-age peers, as opposed to a loss of previously acquired information and skills [80]. Only 30 % of young adults who were survivors of medulloblastoma were able to drive, live independently, or find a job [81]. Over 40 % of medulloblastoma survivors had impairment in attention and processing speed regardless of RT exposure [3, 71]. Younger age at diagnosis, high-risk disease and higher baseline scores were significantly associated with poorer

outcomes in processing speed, working memory and attention over time [82]. Severe hearing impairment and posterior fossa syndrome were associated with poor neurocognitive outcomes particularly with reading ability and language skills [83].

Survivors of ALL have been found to display deficits in a variety of executive functions, including working memory. These deficits have been hypothesized to develop as a result of chemotherapeutic and/or corticosteroid agents that are administered during prophylactic treatment [84, 85]. Survivors who received cranial radiation have more impairment in memory and motor functions than non-radiated survivors [86, 87]. Female survivors diagnosed at young age performed worse in the scholastic testing [14]. Impairment in executive function skills increased with time since diagnosis, and appear to be related to functional outcomes as adults, including college graduation and full-time employment [88].

5.4.4 Psychological Late Effects

Zebrak et al. evaluated and compared psychological outcomes in long-term survivors of pediatric brain cancer and siblings of childhood cancer survivors [89]. Survivors of childhood brain cancer in the CCSS cohort appear to report significantly higher global distress and depression scores than their siblings. There is a correlation between health status and psychological functioning [89]. Those survivors with a history of a major medical condition reported more symptoms of depression, anxiety and somatic distress. As in the general population, higher levels of distress among survivors were associated with female sex, low household income, lower educational attainment, being unmarried, not being employed in the past 12 months, and poor physical health status [89]. CCSS study also showed brain tumor survivors as a particularly vulnerable group, with more psychological distress, fatigue, cognitive problems and diminished life satisfaction than other survivors. Survivors scored lower than population norms for most aspects of Health Related Quality of Life (HRQOL) measures. An increased risk of hospitalization for psychiatric disorders was observed among survivors of brain tumor [90] as well as suicide ideation [91, 92].

CNS radiation is linked to impairment in physical health, more functional impairment and more activity limitations and increase sleep disruption and fatigue. Leukemia survivors experienced increased rates of depression, anxiety and social-skills deficits compared with sibling controls during the adolescent period [75].

5.4.5 Social Outcomes

Measurement of social outcomes including education, employment, relationship and independent living closely relates to the quality of life of survivors. Diagnosis and treatment of cancer can have a great impact in social development. CNS impairment can further compromise social outcomes.

Educational Problems. Among the CCSS cohort, survivors of brain tumors and leukemia were most likely to have educational problems and no close friends [93]. Eighteen percent of young adult survivors of brain tumors had not completed high school. Seventy percent of brain tumor survivors diagnosed before the age of 6 years required special education services in school [3]. Ness et al. conducted a study of 156 adult survivors of childhood brain tumors and compared them with population-based comparison group. Physical performance (muscle strength and fitness values) was lower among survivors and was associated with not living independently and not attending college [94].

Employment and Marriage. CNS tumor survivors had the highest risk of unemployment (odds ratio = 9.9) [95]. Risk for unemployment increased with chronic medical conditions after cancer therapy, young age (<4 years) at diagnosis, cranial radiation therapy of ≥30 Gy, and female sex [93, 95]. There was a dose-dependent association between RT to the frontal and/or temporal lobes and lower rate of employment, less household income and less likely to get married

[52]. Seventy-eight percent of brain tumor survivors had never married compared to 62 % of the whole CCSS cohort [96]. Many brain tumor survivors are unable to live independently.

Children with ALL who did not receive radiation therapy and who have attained 10 or more years of event-free survival can expect a normal long-term survival. However, irradiated leukemia survivors have a slight excess in mortality, and an increased unemployment rate. Women in the irradiated group were less likely to be married [93, 97]. ALL survivors receiving cranial radiotherapy of ≥24 Gy or age less than 6 years old at diagnosis are more likely to require special education program [98].

5.4.6 Second Malignancies Affecting Central Nervous System

Within the CCSS cohort of 14,361 5-year survivors, subsequent CNS primary neoplasms were identified in 116 individuals. Radiation therapy was associated with a dose-dependent increased risk for subsequent *gliomas* (odds ratio = 6.78, 95 % CI 1.54–29.7) and *meningiomas* (odd ratio 9.94, 95 % CI 2.17–45.6). The relative risk per Gy for glioma was highest among children treated with radiation at age 5 years or younger. The risk of glioma was increased within 5–10 years after radiation, but declined to nearly background levels after 15–20 years. In contrast, the incidence of meningioma increased steadily from 5 to 10 years after radiation and showed no evidence of plateau [99]. The median age at diagnosis of glioma was 15 and 25.5 years for meningioma [100]. Among survivors of CNS malignancies, 76 subsequent malignant neoplasms were reported among 1,877 survivors. The most common second malignancies were CNS tumors (20 observed), followed by thyroid cancer (12 observed) and soft tissue sarcomas (eight observed) [3]. Survivors of CNS malignancies who received CNS-directed radiation >50 Gy had a cumulative incidence of a subsequent CNS neoplasm of 7.1 % at 25 years compared with 5.2 % for those receiving <50 Gy and, 1.0 % for those who received no CNS radiation [16, 52, 100]. Death from the second malignant neoplasms accounts for 10 % of late death of brain tumor survivors [101].

Patients with *neurofibromatosis* are at higher risk for developing secondary malignancy following radiation. The relative risk of second nervous system tumor after radiotherapy was 3.04 (95 % CI, 1.29–7.15). There is a significantly increased risk of second nervous system tumors in NF1 patients who received radiotherapy for optic pathway glioma, especially when treated during childhood [4].

In the report by Packer et al from a Phase 3 study of children with average risk *medulloblastoma* treated with craniospinal radiation therapy followed by adjuvant chemotherapy, second malignancies including myelodysplastic syndrome (MDS), pilocytic astrocytoma, T-ALL, malignant glioma (cerebellar), basal cell carcinoma, and glioblastoma were reported to develop 38–76 months from the study enrollment [47].

Radiation associated CNS neoplasms have been reported as the most common second malignancy among survivors of childhood leukemia [102]. CCSS study reported 199 second neoplasms (SN) developed in 4,151 ALL survivors. Eighty-one percent of SNs developed in survivors who received radiation therapy, with 53 % of SNs occurring in the CNS including meningioma (66), astrocytoma (22), medulloblastoma (3) and others (15) [54].

5.4.7 Late Mortality

Among childhood cancer survivors treated from 1970 through 1986 followed by CCSS, the CNS tumor survivors had the worst overall survival with a cumulative mortality rate of 17.1 % at 20 years. The major cause of death (67 %) among the 5-year survivors was recurrence or progression of the original CNS malignancy. Survivors of medulloblastoma or primitive neuroectodermal tumor have a 17-fold higher risk of death than that of the general population. Recurrence or progression was the leading cause of death until 30 years after diagnosis [52]. The risk for death

from disease recurrence was greatest in the time period of 5–9 years after initial diagnosis. This pattern of late recurrence suggests a need for continued surveillance of disease well beyond the first 5 years from diagnosis.

5.5 Surveillance of Late Effects

Improvements in treatment of brain tumor and leukemia have increased the rate of survival. Recognition of many CNS late effects in survivors of brain tumors and leukemia is important for early intervention and treatment. Survivors should receive risk-based surveillance based on prior treatment and have a plan for lifetime follow-up for potential late effects [60]. The medical team should ensure that survivors have access to multidisciplinary specialists including an oncologist, neurologist, neurosurgeon, endocrinologist, psychologist, speech and occupation and physical therapist, ophthalmologist, dentist, and audiologist as needed.

Table 5.3 summarizes the surveillance for potential CNS late effects based on risk factors. Obtaining the survivor's medical history and treatment summary can identify risk factors and direct the modality of surveillance. It is important to recognize that the pattern and incidence of late effects may change over time, with the evolution of treatment for leukemia and CNS tumors.

Advances in neuroimaging techniques are available to identify changes at an earlier stage and may influence the choice of therapy to lessen the late effects. MRI with diffusion tensor imaging (DTI) can be used to evaluate the integrity of white matter tracts. Volumetric monitoring of normal appearing white matter (NAWM) may correlate with neurocognitive test performance, which shows deficiencies when cranial irradiation is administered early in life [24]. With the prevalence of late tumor recurrence and second CNS malignancies in brain tumor and leukemia survivors, screening neuroimaging studies should be employed beyond the immediate post-diagnosis period.

Patients with primary spinal tumors or history of receiving high dose radiation dose ≥45 Gy to the lumbar/sacral spine and/or cauda equina should be evaluated for symptoms of neurogenic bladder and bowel symptoms including fecal incontinence and chronic constipation.

Growth failure, abnormal pubertal development, and other endocrinological deficits are prevalent in brain tumor survivors from radiation to the hypothalamic-pituitary axis [103]. Survivors should have their height and weight monitored every 6 months until growth is completed, then yearly. Tanner staging should be done every 6 months until sexually mature. X-ray for bone age should be obtained in poorly growing children. FSH, LH, testosterone (for male) and estradiol (for female) should be measured for precocious or delayed puberty. Thyroid function should be screened by measuring TSH and free T4 yearly.

Neurosensory deficits including visual and hearing impairment are common in children with optic pathway tumors and posterior fossa tumors. The visual screening includes yearly evaluation by an ophthalmologist for cataract, optic nerve examination, visual acuity, and visual field for patients with optic pathway tumors or treated with radiation therapy to the optic pathway. Patients who received cranial radiation to the posterior fossa or hearing apparatus and/or cisplatin should have otoscopic exam and audiological evaluation yearly after completion of therapy for 5 years, then every 5 years and yearly if hearing loss is detected. Patients with hearing loss should have otolaryngology and audiology consultation for hearing aid evaluation.

With high prevalence of neurocognitive deficits and mood disorders in brain tumor and irradiated leukemia survivors, a comprehensive neuropsychological assessment including tests of processing speed, visual motor integration, memory, comprehension of verbal instruction, verbal fluency, executive function and psychological status should be performed.

School plays an important part of life in children. Children undergoing cancer treatment may be referred to the hospital school program or home schooling. When the patient is ready to return back to school, a referral to the Cancer Center's respective school reintegration program

Table 5.3 Surveillance for potential late effects of the central nervous system

Potential late effects	Risk factors	Evaluation	Further testing and intervention
Brain Tumors (primary or secondary)	Cranial radiation particularly in patients with neurofibromatosis (NF) or younger age at treatment	Yearly neurological exam Brain MRI for symptomatic patient. MRI every other year for patients with NF	Neurosurgical and Neuro-Oncology consultation
Structural Damage of CNS			
Hydrocephalus Shunt malfunction	Primary CNS tumors	Evaluation by neurosurgeon Brain CT as indicated	Patient/family education regarding potential symptoms of shunt malfunction
Movement Disorders, Ataxia, Paralysis, peripheral neuropathy	Primary CNS tumors Brain stem and cerebellar tumors Vinca Alkaloid	Evaluation by neurologist, rehabilitation specialists as indicated	Physical and/or occupational therapy
Leukoencephalopathy (spasticity, ataxia, dysarthria, dysphagia, hemiparesis, seizures	Cranial radiation dose ≥24 Gy Young age at treatment Methotrexate (IT. IO. High-dose IV) High dose Cytarabine	Yearly review of neurological symptoms and neurological exam MRI brain with diffusion-tensor imaging to evaluate white matter MR angiography Brain CT looking for calcifications	Physical, occupational and speech therapy Neurology consultation
Cerebrovascular complications (stroke, Moyamoya, occlusive vasculopathy)	Parasellar tumor and radiation dose ≥50 Gy Sickle cell disease Neurofibromatosis	History of hemiparesis, hemiplegia, weakness, aphasia Yearly neurological exam Brain MRI with diffusion-weighted imaging and MR angiography as clinically indicated	Physical, occupational and speech therapy as clinically indicated Revascularization procedure for Moyamoya may be helpful
Seizure Disorder	Primary CNS tumors Methotrexate (IV, IT, IO)	Neurologist evaluation every 6 months for patients with seizure disorder	anticonvulsants
Neurogenic bladder/bowel	Spinal cord tumor/surgery Radiation dose ≥ 45 Gy to lumbar/sacral spine and/or cauda equina	Evaluate urinary symptoms (urgency, incontinence, retention, dysuria) Evaluate bowel symptoms (chronic constipation, fecal soiling)	Urology consultation Bowel regimen (fiber, laxatives, enema) as indicated GI consultation as indicated
Neurosensory deficits			
Visual Deficit (ocular nerve palsy, gaze paresis, nystagmus, papilledema, optic atrophy, cataract, low vision, visual field defect)	Higher radiation dose Optic pathway tumor Suprasellar tumor	Yearly eye exam (visual acuity, optic nerve disc, cataract, ocular nerve, eye irritation)	Ophthalmology evaluation and intervention
Hearing impairment	Higher radiation dose, chronic otitis, ototoxic agents (Cisplatin, Carboplatin, Aminoglycosides)	Yearly otoscopic exam Complete audiological evaluation yearly after completion of therapy for 5 years, then every 5 years. Yearly if hearing loss is detected	Otolaryngology and Audiology consultation for hearing aid Preferential classroom seating, FM amplification system, other educational assistance

(continued)

Table 5.3 (continued)

Potential late effects	Risk factors	Evaluation	Further testing and intervention
Hypopituitarism			
Central hypothyroidism	Cranial Radiation dose ≥40 Gy	Yearly height, weight, hair, skin and thyroid exam TSH, free T4 yearly	Endocrine consultation for thyroid hormone replacement
Central adrenal insufficiency	Cranial Radiation dose ≥40 Gy	History- failure to thrive, anorexia, dehydration, hypoglycemia, lethargy, hypotension Yearly 8 am serum cortisol level	Endocrine consultation Corticosteroid replacement and stress dosing
Growth failure	Cranial Radiation dose ≥18 Gy, younger age at treatment, pretransplant cranial radiation or total body irradiation (TBI)	Assessment of growth and Tanner staging every 6 months until growth and sexual maturation completed Evaluate thyroid function, growth hormone and bone age	Endocrinology evaluation for growth hormone replacement therapy
Precocious puberty	Radiation doses ≥18 Gy, younger age at treatment, female sex	Height, weight, Tanner staging yearly FSH, LH, testosterone, estradiol as clinically indicated	Endocrine consultation
Gonadotropin deficiency	Cranial radiation dose ≥40 Gy	Evaluate tanner staging, puberty, menstrual, pregnancy history, sexual function FSH, LH, testosterone, estradiol (baseline at age 13 for girls and 14 for boys)	Endocrine evaluation Infertility specialist referral
Overweight and Obesity	Cranial radiation, hypothalamic radiation dose ≥20 Gy, younger age, female sex	Height, weight, BMI, blood pressure yearly Fasting blood glucose, fasting lipid profile every 2 years	Diet and physical activity, Nutritional counseling, Endocrine consultation Cardiology consultation as clinically indicated
Neurocognitive deficits	Supratentorial tumors Cranial radiation at higher dose, larger field, young age at treatment, female sex	Yearly educational and/or vocational progress Comprehensive neuropsychological evaluation	School liaison referral to develop an individualized educational plan (IEP) Refer to vocational rehabilitation or for services for developmentally disabled CNS stimulants
Mood disorders Depression, anxiety, posttraumatic stress disorder	CNS tumor Cerebellar damage	Behavior problems, maladjustment, depression, anxiety, poor self-concept	Psychology evaluation and intervention

Reference: COG LTFU Guidelines, Version 3.0, 2008

or district school psychologist for evaluation of academic readiness and the need for educational accommodation should be obtained. This will facilitate acquisition of educational resources and social skills training.

The Children's Oncology Group's publication "*Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers*" was developed as a resource for clinicians who provide ongoing healthcare to survivors of pediatric malignancies. The purpose of these guidelines is to provide recommendations for screening and management of late effects that may potentially arise as a result of therapeutic exposures used during treatment for pediatric malignancies. The web links of the survivorship guidelines are presented in Part IV, and are presented here as well:

http://www.survivorshipguidelines.org/pdf/LTFUGuidelines_40.pdf

The screening recommendations in these guidelines are appropriate for asymptomatic survivors of childhood, adolescent, or young adult cancer presenting for routine exposure-based medical follow-up. More extensive evaluations are presumed, as clinically indicated, for survivors presenting with signs and symptoms suggesting illness or organ dysfunction. Decisions regarding screening and clinical management for any specific patient should be individually tailored, taking into consideration the patient's treatment history, risk factors, co-morbidities, and lifestyle.

5.6 Management of Late Effects

Management of many late effects discussed in this chapter including neurotoxicity, neurocognitive, and neuropsychological late effects will be reviewed in detail in later chapters of this book. A brief overview of treatment is hereby presented.

5.6.1 Hormone Replacement

Growth hormone (GH) deficiency, the most common endocrinopathy in survivors of childhood brain tumors, coupled with precocious puberty induced by cranial irradiation and impaired spinal growth from spinal irradiation can cause suboptimal adult height. It is recommended that GH therapy begin at the earliest age that is clinically feasible, at least one year tumor-free after cancer treatment due to fears of increased recurrence in the early post-treatment period [55, 104]. However, there is no increased risk of CNS tumor relapse or development of leukemia based on several large series of survivor studies.

Patients with thyroid hormone deficiency, hypopituitarism, and gonadotropin hormone deficiency and central adrenal insufficiency should also receive individual hormone replacement as discussed in Chap. 6.

5.6.2 Management of Neurological Disorders

Survivors with neurological late effects should utilize rehabilitation services to optimize physical function and support increased health related quality of life (HRQOL) [105]. Physical therapy provides exercises to improve balance and coordination while occupational therapy can provide assistance to improve hand/eye coordination and other skills needed for daily life activities. Orthotic devices can be used to support ankles and feet and help improve walking. Correction of visual and hearing deficits with glasses and hearing aids to prevent further impairment of physical function and cognitive abilities should be done. Patients with seizure disorders should be referred to neurologists for evaluation and treatment. Anticoagulation or antiplatelet agents should be considered for patients suffering from ischemic stroke. Revascularization procedures have been performed for selective patients with moyamoya [106].

5.6.3 Interventions to Improve Neurocognitive Functions

While discussed elsewhere in this manuscript, it is briefly reviewed here. The medical team should help survivors to receive the specialized cognitive, educational, and vocational services as

needed by referring to school based programs and community vocational services [75]. Children with impaired neurological and neurocognitive function should have an Individualized Educational Plan (IEP) which is provided by public schools through the Individuals with Disabilities Education Act (IDEA). IEPs include formal assessment of the student's current skill levels, special instruction and services to be provided, and the measurable and observable goals for improvement in each area of educational need. Computerized cognitive training programs are also available to target training in attention and working memory [107].

It is known that alternative circuits can be established to compensate for lost or injured areas in the brain, which is referred as *neuroplasticity* [108]. Plasticity occurs on a variety of levels, ranging from cellular changes involved in learning, to large-scale changes involved in cortical remapping in response to injury. The most widely recognized forms of plasticity are learning, memory, and recovery from brain damage. Early detection of impaired neurocognitive functions and intervention for restoration via relearning and practice is an important step to prevent further loss of function.

5.6.4 Pharmacologic Interventions

Although discussed in more detail in a later chapter, briefly, stimulant medications such as *methylphenidate* (MPH) have been used to improve neurocognitive function. Conklin et al conducted a two-day, in-clinic, double-blind, randomized, cross-over trial between MPH (0.60 mg/kg of body weight) and placebo in 122 ALL and brain tumor survivors. A significant MPH versus placebo effect on a measure of attention, cognitive flexibility, and processing speed was found. Male gender, older age at treatment, and higher intelligence were predictive of better medication response [109]. Modafinil, a psychostimulant which enhances wakefulness and vigilance, was shown to improve cognitive performance in breast cancer survivors by enhancing some memory and attention skills [110]. "A Phase II Placebo-Controlled Trial of Modafinil to Improve Neurocognitive Deficits in Children Treated for a Primary Brain Tumor" is currently being conducted through the Community Clinical Oncology Program (CCOP) and the Children's Oncology Group. Although there is some preliminary support for the efficacy and safety of stimulants for survivors of ALL and brain tumor, more research is needed concerning the long-term effects of the stimulants among cancer survivors [111].

5.6.5 Management of Mood Disorders

Psychosocial support interventions that enhance social and vocational skills via social and community services may improve a survivor's ability to enter intimate relationships or to obtain and maintain employment opportunities [89, 112]. Promotion of psychological adaptation and reduction of distress help survivors cope with anxiety and depression. Intervention with exercise programs to address fatigue is also being explored [113].

5.6.6 Prevention of CNS Late Effects

With the accumulation of knowledge on the CNS late effects of cancer chemotherapy and radiation therapy, clinicians try to optimize risk-to-benefit ratios of survival and quality of life and the potential late effect. For example, the recent clinical trials in medulloblastoma have successfully showed the feasibility to decrease the dose of radiation to the neuraxis, particularly in young children. Cranial radiation has been eliminated in majority of children with ALL. On the other hand, different profiles of CNS late effects may appear with increased chemotherapy intensity, which need to be closely monitored.

The newer advanced radiation technologies such as conformal radiation, intensity-modulated radiation therapy (IMRT) and proton beam radiation provide more targeted radiation to the tumor tissue and spare normal brain tissue. These may

also influence the rate and type of late effects [64]. There is also an increased interest in using pharmacological approaches to prevent cognitive dysfunction in patients receiving whole-brain radiotherapy. The Radiation Therapy Oncology Group (RTOG) conducted a randomized, double-blind, placebo-controlled trial with Memantine, an NMDA receptor antagonist, showed Memantine arm had better cognitive function and delayed time to cognitive decline [114]; a similar trial is being planned by the Children's Oncology Group.

5.6.7 Promoting Healthy Lifestyles

With higher incidence of tumor recurrence and secondary malignancies, survivors should be educated in healthy lifestyles including healthy behaviors and diets. Avoiding cancer-promoting behaviors such as smoking, heavy drinking, and tanning, and eating foods higher in fiber and lower in fat and salt may lower the risk of developing a second cancer (http://www.survivorshipguidelines.org/pdf/healthlinks/English/diet_and_physical_activity_Eng.pdf).

5.7 Conclusions

The survival rates of childhood cancers have greatly improved with modern cancer treatment. Survivors of childhood cancer may have many more decades of life ahead of them. However, survivors of CNS tumors and those who received CNS-directed therapy may develop multiple chronic and serious health conditions affecting their physical function and quality of life. Neurocognitive and neuropsychological sequelae may have a negative impact on education, employment, relationships and ability for independent living. Practitioners taking care of childhood cancer survivors need to review the treatment history of individual patients and perform risk-based screening and evaluation. Early detection and intervention of late effects by the multidisciplinary medical team may lessen the impact on the quality of life for survivors. Modification of treatment modalities to prevent acute and late effects of cancer therapy will continue to be the focus of clinical research in children with cancer affecting the central nervous system.

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Endocrine System

6

Wassim Chemaitilly

6.1 Introduction

Endocrine complications are frequently reported late effects in childhood cancer survivors, affecting between 20 % and 50 % of individuals [1]. High risk populations include individuals exposed to radiotherapy (cranial or total body) and high doses of alkylating agents. Hematopoietic stem cell transplant (HSCT) recipients, survivors of central nervous system (CNS) tumors and Hodgkin lymphoma are at a particularly high risk [2, 3]. Affected systems include the hypothalamus and pituitary, the thyroid, the gonads as well as various systems regulating bone health, body composition, and glucose metabolism (Tables 6.1 and 6.2).

6.2 Disorders of the Hypothalamus and Pituitary

6.2.1 Growth Hormone Deficiency

The potential for linear growth can be eroded by various endocrine and non-endocrine factors, leading to adult short stature. Growth hormone (GH) deficiency is among the main endocrine factors associated with short stature and most frequently occurs as a complication of cranial radiotherapy.

Tumors developing close to the hypothalamus and/or pituitary gland such as craniopharyngiomas, germinomas, and optic nerve gliomas can cause GH deficiency as a direct anatomical insult or because of the surgery required to remove or reduce the size of these tumors. The other hypothalamic–pituitary functions are generally affected in these situations.

Growth hormone deficiency is the most frequently observed and often the only hypothalamic–pituitary deficit in individuals treated with cranial radiotherapy [4, 5]. The deficit occurs in a time- and dose-dependent fashion. The higher the dose of radiation and the longer the time interval from treatment, the greater the risk [6]. Growth hormone deficiency can be observed within 5 years when doses exceed 30 Gy [5]. Following lower doses, such as 18 to 24 Gy, growth hormone deficiency may not become evident for 10 or more years [7]. The effects of chemotherapy alone on GH secretion are not as well established as those of radiotherapy. Growth hormone deficiency has been reported in relatively small numbers of individuals treated with chemotherapy alone [8–11].

The diagnosis of GH deficiency can be difficult to establish except in situations where direct anatomical insults to the hypothalamus and/or the pituitary are documented (e.g., sellar tumors, surgical removal). Given the kinetics of GH

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Table 6.1 Endocrine late effects and therapy related risk factors

Function	Complication	Therapy-related risks	Relationship to time, dose to gland or organ when applicable
Linear Growth	GH deficiency	Surgery	Damage to the pituitary by tumor expansion and/or surgery
		Radiotherapy to hypothalamus or pituitary	Doses > 30 Gy, effect by 5 years after exposure
			Doses 18–24 Gy, effect may appear >10 years following exposure
Puberty	Central Precocious Puberty	Radiotherapy to hypothalamus or pituitary	Doses ≥18 Gy, Girls <5 years old at exposure have a higher risk
	Hypogonadotropic Hypogonadism	Surgery	Damage to the pituitary by tumor expansion and/or surgery
		Radiotherapy to hypothalamus or pituitary	Doses >30 Gy
			Decreased fertility (partial deficit?) 22–27 Gy
Pituitary, other	ACTH deficiency	Surgery	Damage to the pituitary by tumor expansion and/or surgery
		Radiotherapy to hypothalamus or pituitary	Doses >30 Gy
		Systemic glucocorticoids	Deficiency depends on the doses used and duration of exposure
	TSH deficiency	Surgery	Damage to the pituitary by tumor expansion and/or surgery
		Radiotherapy to hypothalamus or pituitary	Doses >30 Gy
Thyroid	Primary hypothyroidism	Radiotherapy to the neck	Risk increases with dose (even <35 Gy) and time after exposure
		I131 labeled agents	Such as MIBG for neuroblastoma
	Hyperthyroidism	Radiotherapy to the neck	Doses >35 Gy
	Auto-immune diseases	HSCT	Transfer of monoclonal antibodies from donor to recipient
	Cancer	Radiotherapy to the neck	Doses 20–29 Gy; age <10 years at exposure, latency can be >20 years
Testes	Leydig cell function	Alkylating agents	Generally subclinical
		Radiotherapy to testes	Doses >24 Gy
	Germ cell function	Alkylating agents	Cyclophosphamide dose >7.5 g/m^2
		Radiotherapy to testes	Possible >0.15 Gy, high risk >2 Gy
Ovaries	Ovarian failure	Alkylating agents	Higher risk for older age at exposure
		Radiotherapy to pelvis	Acute ovarian failure at doses >20 Gy. Premature menopause/infertility at lower doses; higher risk for older age at exposure.
Bone	Osteoporosis	Chemotherapy	Methotrexate, systemic glucocorticoids
		Radiotherapy	TBI
		Associated deficits	Untreated hypogonadism, GH deficiency, nutritional causes.
Metabolism	Obesity and insulin resistance	Surgery to hypothalamus	Large resection causes “central obesity”
		Radiotherapy	Cranial radiotherapy, TBI.

GH growth hormone, *ACTH* corticotropin, *TSH* thyroid stimulating hormone, *HSCT* hematopoietic stem cell transplant, *TBI* total body irradiation

Table 6.2 Elements of clinical suspicion and screening tools for common endocrine late effects

Condition	Clinical Suspicion	Laboratory Studies	Intervention
GH Deficiency	Risk exposure (surgery, cranial radiotherapy) Decreased growth velocity, growth failure.	Bone Age IGF1, IGF-BP3 GH Stimulation Test	GH replacement
Central Precocious Puberty	Tanner stage 2 before 8 y/o in girls Menarche before the age of 10 y/o Tanner stage 2 before 9 y/o in boys	Bone Age Leuprolide Stimulation Test	GnRH agonist
Hypogonadotropic Hypogonadism	Tanner stage 1 past 12 y/o in girls Primary or secondary amenorrhea Tanner stage 1 past 13 y/o in boys Arrested Puberty	Baseline LH, FSH Estradiol (girls) Testosterone (boys)	Induction of puberty/ Sex hormone replacement
Central Adrenal Deficiency	Risk exposure (surgery, high dose cranial radiotherapy, prolonged systemic steroids) Presence of other pituitary deficits Clinical signs of adrenal insufficiency	8 AM cortisol and ACTH Low dose ACTH stimulation test if AM cortisol abnormal.	Hydrocortisone and stress dose teaching.
Hypothyroidism	Risk exposure (surgery, high dose cranial radiotherapy, radiotherapy to the neck, I131 labeled agents). Presence of other pituitary deficits Clinical signs of hypothyroidism	TSH, Free T4	Levothyroxine
Thyroid Neoplasms	Risk exposure (Radiotherapy to the neck) Nodule on careful palpation of neck.	Thyroid ultrasound (US) US guided FNAB	Per etiology
Leydig Cell Failure, males	Tanner stage 1 past 13 y/o Arrested puberty Low androgen symptoms	Baseline LH, FSH Testosterone	Induction of puberty/ Sex hormone replacement
Germ Cell Failure, males	Decreased/no progression of testicular volume	Baseline FSH, inhibin B Adults:Sperm count	Sperm banking pre-therapy
Ovarian Failure	Tanner stage 1 past 12 y/o Arrested puberty Primary or secondary amenorrhea	Baseline LH, FSH Estradiol Adults:AMH	Induction of puberty/ Sex hormone replacement
Bone Health	History of fractures Dietary restrictions Multiple hormonal deficiencies	BMD studies vitamin D 25 levels	Per etiology
Obesity, Overweight	BMI > 85th percentile in children BMI > 25 kg/m^2 in adults Evidence of abdominal obesity	Fasting glucose, lipids, insulin levels. Hemoglobin A1c Oral glucose tolerance test if fasting tests abnormal.	Diet, active lifestyle.

GH growth hormone, *IGF-1* insulin like growth factor-1, *IGF-BP3* insulin like growth factor binding protein 3, *GnRH* Gonadotropin releasing hormone, *ACTH* corticotropin, *TSH* thyroid stimulating hormone, *LH* luteinizing hormone, *FSH* follicle stimulating hormone, *FNAB* ultrasound guided fine needle aspiration biopsy, *AMH* anti-Mullerian hormone, *BMD* bone mineral density, *BMI* body mass index.

secretion, the hormone being released mostly through nocturnal pulses, deficiencies can be difficult to capture and the diagnosis has to be based on the convergence of clinical features and laboratory results. A decreased growth velocity, observed over a 6-month time interval, should raise the suspicion of GH deficiency [12]. It is important to note that other endocrine and non-endocrine factors can contribute to growth deceleration and that the elements obtained during the clinical evaluation can help in elucidating the contribution of each additional factor. For instance, high dose radiotherapy to the spine, such as following total body irradiation (TBI), can directly damage the vertebral growth plates and cause a skeletal dysplasia where the sitting height is more affected than the standing height [13–16]. It is therefore important in individuals who received such treatments to measure and plot on dedicated growth charts the sitting height of the individual and compare this to the standing height. Body weight and body mass index (BMI) are important markers of nutritional status which can influence linear growth. In addition, excessive weight gain contrasting with linear growth deceleration can reflect thyroid dysfunction. Pubertal staging is an important part of any endocrine evaluation, but is essential in this context as concurrent central precocious puberty—a fairly common endocrine complication observed in individuals treated with cranial radiotherapy—can mask the clinical signs of growth hormone deficiency with seemingly normal growth rates owing to the inappropriate secretion of sex steroids.

Given the pulsatile and circadian nature of GH secretion patterns, GH plasma measurements require dynamic testing, often referred to as GH stimulation testing. A pharmacologic agent known to increase GH secretion (or secretagogue) is injected and GH levels are measured serially over a 2-hour period. Stimulation tests are non-physiologic and can yield non-reproducible results. In children, the interpretation of the GH peak values varies with the GH assay and the standard used by the different laboratories; a normal GH peak response hence varies between 5 and 10 ng/mL depending on all these factors. In adults, different cut off values have been defined depending on the secretagogue used during the test and according to BMI [17]. The diagnosis of GH deficiency generally requires failing two stimulation tests using two different secretagogues. In patients who received irradiation to the hypothalamus and/or pituitary, however, failing one stimulation test was considered enough in the consensus guidelines published by the Growth Hormone Research Society [18]. Plasma Insulin like growth factor-1 (IGF-1) and IGF binding protein-3 (IGFBP-3) which are more stable than GH levels, are widely used as surrogate markers of GH secretion. They are used by many clinicians as screening tools before offering GH stimulation testing. This approach is problematic by several aspects. The interpretation of the IGF-1 and IGFBP-3 levels requires factoring in patient age, pubertal stage, and skeletal maturation data. Plasma IGF-1 levels are also affected by changes in liver function and by the nutritional status. Additionally, IGF-1 and IGFBP-3 levels can be inappropriately normal in children with GH deficiency following hypothalamic/pituitary irradiation or local tumoral expansion and hence cannot be used to screen for GH deficiency in this population [19, 20]. Hence, when clinical suspicion is present, GH stimulation testing should be offered even if IGF-1 and/or IGFBP-3 levels were within the normal range. A left-hand X-ray obtained to assess the degree of skeletal maturation, referred to as the "Bone Age" is an important part of the investigation of a child with growth deceleration. Differences between the bone age and the chronological age are helpful in assessing the potential for catch-up growth [21].

Replacement therapy using recombined human GH is proven to improve final height prospects in survivors with childhood onset GH deficiency [22, 23]. Initiation of replacement therapy at a younger bone age—and hence longer duration of replacement therapy—and higher doses of therapy positively correlated with a greater final height outcome [24]. Safety concerns pertaining to the use of GH in individuals with a history of malignancy are related to the known pro-mitogenic and proliferative effects of GH and IGF-1. Growth hormone replacement is generally deferred until 1 year after the successful

completion of all cancer therapies and initiated only if there are no changes in the patient's remission status. The treatment is also interrupted when a patient is diagnosed with a recurrence or a second neoplasm. In order to more systematically address these ongoing safety concerns, many large-scale studies pertaining to the long term risks associated with the use of GH in childhood cancer survivors have been published over the years. These studies did not show an increase in the risk of brain tumor recurrence, disease recurrence, or death following GH replacement therapy [25–27]. However, there was a slight increase in the risk of a secondary solid tumor, the most commonly observed being meningiomas [27, 28]. Cancer survivors treated with GH may also be at a higher risk of developing slipped epiphyses compared with children treated with GH for idiopathic GH deficiency [29]. As an entity, adult GH deficiency is increasingly being recognized given its association with increased body fat, raised plasma lipids, and decreased bone density and reduced quality of life [10, 11, 30]. Treatment with GH in adult survivors of childhood cancer seems to have a greater impact on quality of life, and to result in improvements in the metabolic parameters [11, 31–33].

6.2.2 Disorders of the Luteinizing Hormone (LH) and the Follicle Stimulating Hormone (FSH)

6.2.2.1 Central Precocious Puberty

Central precocious puberty (CPP) occurs following the premature activation of the hypothalamic–pituitary–gonadal axis [34]. Precocious puberty can lead to abnormally rapid skeletal maturation, with early fusion of the growth plates, hence contributing to the risk of adult short stature. In addition, a very early onset of puberty—of menstrual activity in girls in particular—can be a source of psychosocial stress leading to adjustment difficulties.

Cranial irradiation at both lower doses (18–35 Gy) and higher doses (>35 Gy) is associated with the development of central precocious puberty, by presumably disrupting inhibitory cortical influences [35–39]. In contrast, radiation doses >50 Gy are also associated with hypogonadotropic hypogonadism within the context of combined hormonal pituitary deficiencies [36, 39, 40]. Risk factors associated with CPP following hypothalamic irradiation include female sex, young age at treatment, and increased BMI [37, 41].

Precocious puberty is, first and foremost, a clinical diagnosis. It is defined by the onset of sustained pubertal development before the age of 8 years old in girls and before the age of 9 years old in boys [34]. The onset of pubertal development in girls is defined by the onset of breast development. In late referrals, the onset of menarche before the age of 10 years old is also considered an indicator of precocious puberty. In boys, the measurement of the testicular volume—used to assess the onset of pubertal development in the general population—may not be a reliable indicator of puberty in childhood cancer survivors, as chemotherapy and radiation can damage the seminiferous tubules, resulting in testes that are inappropriately small for a given stage of puberty. Thus, in boys, clinicians should be alerted by the early onset of other secondary sexual characters (e.g., pubic hair) prior to the age of 9 years and should not solely rely on testicular volume measurements. One of the first signs of pubertal development is an increase in the growth rate. In children who also are likely to have GH deficiency, this may result in falsely reassuring "normal" growth velocity.

Skeletal maturation can be assessed using the standard bone age (X-ray examination of the left wrist and hand) in order to estimate the individual's skeletal age [21]. Advancement of the bone age more than two standard deviations (SD) for chronological age is a consistent finding in children with precocious puberty. In girls with CPP, uterine growth on the pelvic ultrasound is a sign of estrogen stimulation, and is an earlier finding than bilaterally enlarged ovaries. Gonadotropin secretion is best assessed using the gonadotropin releasing hormone (GnRH) or GnRH agonist stimulation tests. An ample luteinizing hormone (LH) response greater than the FSH response indicates a pubertal pattern. The plasma estradiol

levels in girls and testosterone levels in boys are also important indicators of pubertal development. Various formulations are available for long acting GnRH agonists, such as the most commonly-used depot leuprolide acetate. These are used to effectively suppress LH and FSH secretion and stop the progression of puberty. This has been shown to improve the statural outcome, especially when contemporary regimens for GH replacement are used concurrently to treat GH deficiency [23].

6.2.2.2 Hypogonadotropic Hypogonadism

Hypogonadotropic hypogonadism is the clinical consequence of LH and FSH deficiencies. In individuals who have not completed pubertal development, hypogonadotropic hypogonadism results in delayed or arrested puberty. In individuals who had previously completed pubertal development it is among the causes of secondary amenorrhea in women and testosterone insufficiency in men.

Hypogonadotropic hypogonadism, as a complication of cranial radiotherapy, is less frequently observed than CPP. It tends to occur following the exposure of the hypothalamus/pituitary to high doses of radiation >30 to 40 Gy [4, 39, 42–44]. In female ALL survivors "subtle" defects of gonadotropin secretion following radiation doses in the 18–24 Gy range have been described [43, 45] while in a recent study, female survivors who received 22–27 Gy of hypothalamic/pituitary irradiation were found to have decreased fertility [46]; additional long-term follow-up data will provide a better sense of the ultimate effect of these lower doses.

In prepubertal individuals, hypogonadotropic hypogonadism can be clinically suspected through the observation of delayed puberty. This is defined by the absence of pubertal development (evidenced by breast development) past the age of 12 years old in girls. In boys, pubertal development should start prior to the age of 13 years old. As previously discussed, in boys, testicular volume may not be reliably used in the survivor population given the risk of a concomitant gonadal insult. Other markers may be useful, such as pubic hair or plasma testosterone levels. The clinical diagnosis in both sexes (and especially in males) can be difficult given the overlapping symptoms with constitutional delay of growth (simple pubertal delay). Mid-pubertal individuals would experience arrested puberty (no progression in Tanner staging and primary amenorrhea in girls). Post-pubertal women will experience secondary amenorrhea. Affected males will have symptoms of testosterone insufficiency such as reduced libido, erectile dysfunction, decreased bone mineral density (BMD), decreased muscle mass and other metabolic disturbances. The diagnosis can be further corroborated by low sex steroid levels associated with low LH and FSH levels. The treatment relies on the induction of pubertal development in prepubertal individuals and sex hormone replacement therapies in pubertal individuals.

6.2.3 Other Hypothalamic–Pituitary Deficiencies

6.2.3.1 Corticotropin Deficiency

Corticotropin (ACTH) deficiency in childhood cancer survivors is uncommon except when it occurs in the context of suppression by high dose systemic steroid medications. It can be observed along with other pituitary deficiencies as a result of local tumoral expansion or surgery or following high-dose (>30 Gy) radiation [5, 47, 48]. The symptoms evocative of central adrenal insufficiency include fatigue, nausea, vomiting, abdominal pain, hypotension, shock, unexplained clinical deterioration, vulnerability to infections and hypoglycemia. Laboratory investigations would reveal low plasma levels of cortisol and ACTH. Levels should be drawn as close to 8 AM as possible, although circadian variation is rarely present before the age of 3 months and may be impaired in severely ill patients. An 8 AM plasma cortisol <5 mcg/dL is suggestive of adrenal insufficiency while levels above 18 mcg/dL are sufficient to rule out the diagnosis [49]. Additional testing modalities include the insulin tolerance test, low dose ACTH and metyrapone stimulation tests. The treatment relies on replacement therapy with hydrocortisone and patient and family education in regards to glucocorticoid stress dosing.

6.2.3.2 Thyroid Stimulating Hormone (TSH) Deficiency

Thyroid stimulating hormone (TSH) deficiency, resulting in central hypothyroidism, occurs less often than GH deficiency and central precocious puberty following the irradiation of the hypothalamic/pituitary area. It has been reported following doses >30 to 40 Gy [4, 5, 50–52]. The clinical symptoms associated with hypothyroidism include fatigue, cold intolerance, abnormal weight gain, hair loss, low energy levels, depression, and menstrual irregularities. In children who have not completed growth, hypothyroidism is associated with a decreased growth velocity, contrasting with abnormal weight gain. Laboratory investigations are remarkable for a low Free T4 level with a TSH level that is either low or inappropriately within the normal range. The treatment is based on replacement with levothyroxine at substitutive doses. Free T4 levels are measured for dosage adjustment 6–8 weeks following the initiation of therapy and after any dosage adjustment; they can otherwise be followed every 6 months. Once the diagnosis is established and therapy is initiated, there is no need to monitor TSH levels in individuals with central hypothyroidism.

6.2.3.3 Hyperprolactinemia

Exposure of the hypothalamus to doses of radiation in the vicinity of 50 Gy and above can be associated with hyperprolactinemia [36]. Hyperprolactinemia is often mild and reported as a fortuitous laboratory finding. Hyperprolactinemia can suppress gonadotropin and cause hypogonadism in patients who otherwise have many reasons for gonadal dysfunction.

6.3 Disorders of the Thyroid

Thyroid disorders are common among childhood cancer survivors. These disorders include therapy-induced hypothyroidism and hyperthyroidism, thyroid autoimmune diseases and thyroid neoplasms.

6.3.1 Therapy Induced Primary Hypothyroidism

The thyroid gland is particularly vulnerable to radiation, and primary hypothyroidism is by far the most common thyroid disorder observed in childhood cancer survivors. Individuals treated with neck/mantle irradiation for Hodgkin lymphoma, craniospinal irradiation for brain tumors, or TBI for cytoreduction before HSCT are therefore at a significant risk of becoming hypothyroid in the years that follow the exposure [5, 7, 52–56]. Treatments with radio-labeled agents such as Iodine-131-metaiodobenzylguanidine (I131-MIBG) [57] and I131-labeled monoclonal antibody for neuroblastoma [58] have also been associated with hypothyroidism. Chemotherapy alone does not seem to cause hypothyroidism [56, 59]. The prevalence of hypothyroidism is primarily determined by the total dose of radiation to the thyroid and by the duration of follow-up. Additional risk factors for developing hypothyroidism include female gender, white race, and being older than 15 years of age at the time of diagnosis [54, 59]. As hypothyroidism can occur more than 25 years following the completion of cancer treatments, it is imperative that individuals at risk undergo lifelong surveillance.

Clinical signs suggestive of hypothyroidism include fatigue, cold intolerance, abnormal weight gain, hair loss, low energy levels, depression, and menstrual irregularities. In children who have not completed growth, hypothyroidism is associated with a decreased growth velocity contrasting with an abnormal weight gain. Given the relatively non-specific nature of many of these symptoms and knowing that many individuals would become profoundly hypothyroid before developing any of these symptoms, it is recommended to screen for abnormal thyroid functions in individuals at risk by obtaining labs at least yearly. These include plasma Free T4 and TSH levels. Elevated TSH levels contrasting with normal or low Free T4 levels are suggestive of primary hypothyroidism. The treatment consists of replacement with levothyroxine at substitutive doses.

6.3.2 Therapy Induced Hyperthyroidism

Therapy-induced hyperthyroidism is a relatively uncommon complication in childhood cancer survivors; it occurs most often following external beam radiation to the neck for Hodgkin lymphoma. The main risk factor is the exposure of the thyroid to doses >35 Gy [54, 56]. Medical treatment is determined individually depending on the severity of the presentation.

6.3.3 Autoimmune Thyroid Disease

Autoimmune thyroid disease, most likely a result of the adoptive transfer of abnormal clones of T or B cells from donor to recipient, has been reported in allogeneic HSCT recipients. Both hyperthyroidism and hypothyroidism have been described in the presence of TSH receptor auto-antibodies and thyroglobulin auto-antibody respectively [60, 61].

6.3.4 Thyroid Neoplasms

The exposure of the thyroid to either direct radiation or scatter radiation (for example after prophylactic CNS irradiation in patients treated for ALL) is a significant risk factor for thyroid neoplasms, benign and malignant. Treatment before 10 years of age and/or with doses in the range of 20–29 Gy are significant risk factors. The association between thyroid irradiation and thyroid neoplasms is linear at low doses of radiation, but shows a downward turn at doses above 20–25 Gy, with a risk that remains, nevertheless, elevated compared to the general population [62, 63]. The majority of the observed cancers were differentiated carcinoma (ie, papillary and follicular) with a median latency around 20 years [54, 62, 64]. An increased risk of thyroid cancer in association with chemotherapy (independent of radiotherapy) was recently reported but remains relatively minor compared to the effect of radiation [63].

In general, post-irradiation thyroid cancers behave in a non-aggressive fashion, similar to what is observed in de novo thyroid cancers among the young [65]. The pathogenesis of radiation-induced thyroid neoplasms is felt to be be related to rearrangements of RET-PTC induced by the exposure to radiation [66, 67]. Thyroid neoplasms following radiotherapy may not become evident for many years after exposure to radiation; therefore, all individuals at risk require lifelong clinical follow-up by an expert endocrinologist [54, 56, 65]. Periodically screening individuals at risk for the presence of clinically non-palpable thyroid neoplasms using thyroid ultrasound has been recommended by some groups [68]. This strategy remains controversial, as it may result in more frequent biopsies and has not, so far, been shown to reduce morbidity or mortality in this population [59].

6.4 Disorders of the Gonads

6.4.1 Males

The human testis harbors two functional compartments: A sex steroid-producing compartment, and a sperm-producing compartment. The former consists of testosterone-producing Leydig cells while the latter consists of the seminiferous tubules, which include germ cells as well as the Sertoli cells that support and nurture them. The two compartments are interrelated given that adequate testosterone production is necessary for normal spermatogenesis, but their functions otherwise remain relatively distinct [69]. The two functional compartments are affected in different ways by cancer treatments.

6.4.1.1 Leydig Cell Dysfunction

Leydig cell failure and testosterone insufficiency do not occur as frequently as germ dysfunction and infertility in childhood cancer survivors. Chemotherapy-induced Leydig cell failure requiring testosterone replacement therapy is rare [70, 71]. The deficit may be observed following treatment with alkylating agent regimens with

some reports indicating that from 10 to 57 % of male subjects can develop elevated serum concentrations of LH following treatment [42, 71–78]. When it does occur, chemotherapy-induced Leydig cell dysfunction is generally subclinical and does not reach levels that require substitution with testoterone [9, 79, 80].

By contrast, Leydig cells are more vulnerable to radiation-induced damage. The interpretation of the specific impact of radiation on Leydig cell function is confounded by the concurrent use of chemotherapy and by the potential effects of the malignancy itself. Leydig cell failure, nevertheless, occurs at doses of radiation higher than those associated with germ cell dysfunction. The likelihood of sustaining radiation-induced Leydig cell failure is directly related to the dose delivered and inversely related to age at treatment [81–83]. Normal amounts of testosterone are produced by the majority of males who receive <20 Gy fractionated radiation to the testes [71]. A dose of >24 Gy of fractionated irradiation as therapy for young males with testicular relapse of ALL is associated with a very high risk for Leydig cell dysfunction. The majority of boys who are prepubertal at the time they receive 24 Gy testicular irradiation will develop Leydig cell failure and require androgen replacement [81]. Testicular doses in excess of 33 Gy have been associated with Leydig cell failure in 50 % of adolescent and young adult men [84].

In pre-pubertal boys, Leydig cell failure will result in delayed/arrested puberty and lack of secondary sexual characteristics. In sexually mature men, it can result in reduced libido, erectile dysfunction, decreased BMD, decreased muscle mass and other metabolic disturbances [71]. Raised plasma concentrations of LH combined with low levels of testosterone are characteristic of Leydig cell dysfunction. Given that LH and testosterone levels are generally undetectable or very low before the onset of puberty, it can be very difficult to assess or predict Leydig cell function in the preadolescent male. Therefore, these laboratory markers cannot be used until the individual has reached mid-adolescence. The treatment relies on replacement therapy with testosterone.

6.4.1.2 Germ Cell Dysfunction

With their high turnover rates, germ cells are more vulnerable to cancer treatments than Leydig cells; sperm production is frequently impaired by radiotherapy and several types of chemotherapy. Germ cell dysfunction with resultant infertility is often associated with reduced testicular volume, increased FSH concentrations, and reduced plasma concentrations of inhibin B [85, 86]. However, for clinical purposes and counseling, assessing male fertility requires obtaining a sperm count as none of these aforementioned surrogate markers has sufficient specificity or sensitivity to predict outcome for an individual subject [77, 87].

The chemotherapeutic agents most commonly associated with impaired male fertility are alkylating agents. Impaired fertility occurs in 40–60 % of young adult survivors of childhood cancer [77]. A high probability of oligospermia, azoospermia and infertility is associated with doses of cyclophosphamide >20 g/m^2. In contrast, many individuals treated with a cumulative dose of 7.5–10 g/m^2 or less retain normal sperm production [42, 77]. Procarbazine has also been shown to induce impaired sperm production in a dose-dependent fashion. Patients with Hodgkin lymphoma who received three mechlorethamine, vincristine, procarbazine, and prednisone (MOPP) cycles alternating with three cycles of doxorubicin hydrochloride, bleomycin, vinblastine, and dacarbazine seemed to suffer less testicular damage than patients who received 6 MOPP cycles [74, 88]. Most of the young men treated with the combination of busulfan and cyclophosphamide in preparation for HSCT do appear to sustain damage to their germinal epithelium, with possible recovery for patients treated at lower doses (120 mg/kg for cyclophosphamide and 16 mg/kg for busulfan) [89, 90].

Impaired sperm production can occur at doses of radiation as low as 0.15 Gy. If the dose is under 1–2 Gy, recovery is common. At doses >2 to 3 Gy, recovery of sperm production is rare [91]. Germ cell dysfunction is present in essentially all males treated with TBI [92]. Given the high rate

of impaired sperm production in survivors, sperm banking should be offered to all adolescent males prior to the initiation of cancer therapy, whenever clinically feasible.

6.4.2 Females

In females, the estrogen producing cells and oocytes are functionally and structurally interdependent within the ovarian follicle. As a result, when ovarian failure occurs, both sex hormone production and fertility are disrupted [71]. Given the progressive decline in oocyte reserve with increasing age, older age is an important risk factor for ovarian failure following childhood cancer and its treatments [71]. Owing to a greater follicular reserve, the ovaries of prepubertal girls are more resistant to chemotherapy-induced damage when compared to the ovaries of adults [89, 93, 94]. Nevertheless, certain chemotherapeutic agents, especially alkylating agents, given at high doses can cause ovarian failure, even in younger subjects [94–97]. Older age at treatment, exposure to procarbazine at any age, and exposure to cyclophosphamide between the ages of 13–20 years old were independent risk factors for acute ovarian failure (AOF) [94]. Females who receive high-dose myeloablative therapy with alkylating agents such as busulfan, melphalan, and thiotepa in preparation for HSCT are at high risk of developing ovarian failure [98]. The majority of prepubertal girls and adolescents receiving standard chemotherapy will fortunately maintain or recover ovarian function during the immediate post-treatment period [71, 99, 100]. In women who do retain or recover function following treatment with standard doses of alkylating agents, a subset will experience premature menopause when they reach their twenties and thirties [71, 76, 95, 101, 102]. Female survivors with a history of exposure to high doses of alkylating agents, to lomustine or cyclophosphamide, were less likely to experience a pregnancy when compared to sibling controls [44]. When female childhood cancer survivors treated with chemotherapy *do* get pregnant, no adverse pregnancy outcomes were identified [103].

Females receiving abdominal, pelvic, or spinal irradiation are at increased risk of ovarian failure, especially if both ovaries were within the treatment field [38, 95, 99, 104–108]. When ovarian transposition is performed prior to radiotherapy, however, ovarian function is retained in the majority of young girls and adolescent females [71, 109]. While radiation doses of 6 Gy may be sufficient to produce irreversible ovarian damage in women >40 years of age, doses in the range of 10–20 Gy are needed to induce permanent ovarian failure in the majority of females treated during childhood [104, 109]. Radiation doses to the ovary >20 Gy were associated with the highest rate of AOF (70 %) with higher rates in older individuals (13–20 years old) when compared to those who were younger (0–12 years old) at the time of treatment [94]. Moreover, if radiation is being given while in association with alkylating agent chemotherapy, ovarian dysfunction may occur despite the use of lower doses. Childhood cancer survivors treated with radiotherapy doses >5 Gy to the ovaries/uterus were less likely to experience a pregnancy when compared to sibling controls [44]. In a recent report, uterine and ovarian doses of radiation >10 Gy significantly increased the risk of stillbirth and neonatal deaths—a risk that was increased even at doses of 1.00–2.49 Gy in girls treated before menarche [110]. The outcome of ovarian function following TBI appears to be determined to a large extent by the age of the patient at the time of irradiation. Approximately 50 % of prepubertal girls given fractionated TBI will enter puberty spontaneously and achieve menarche at a normal age [83, 111]. Ovarian failure is seen in essentially all patients who are greater than age 10 at the time they are treated with TBI [111, 112]. Recovery of ovarian function has, nevertheless, been documented in a small number of women who have received TBI [92]. These women had increased risks of miscarriage and premature delivery of low birth weight infants. This can be due to the uterine consequences of TBI [92, 112–115].

If ovarian function is lost prior to the onset of puberty, it will result in delayed puberty and primary amenorrhea. If ovarian function is lost during or after pubertal maturation, one generally

observes arrested puberty, secondary amenorrhea, and menopausal symptoms (i.e., hot flashes, vaginal dryness). Women who experience premature loss of estrogen production are also predisposed to developing osteoporosis and coronary artery disease [116]. The loss of ovarian function owing to exposure to cancer treatments can occur either early (during or immediately following the completion of treatment with so-called AOF), or many years after the completion of cancer therapy but prior to age 40 (so called premature menopause) [94, 95]. Increased plasma concentrations of gonadotropins, especially FSH, and reduced levels of estradiol are typically found in the adolescent and young adult with ovarian failure. These markers cannot be used in the younger child, as gonadotropins are often normal despite ovarian damage [93]. Anti-Mullerian Hormone (AMH) has recently emerged as a marker of follicular reserve within the ovaries with promising applications in the counseling of childhood cancer survivors in regards to their reproductive potential as they reach adulthood [117, 118]. The treatment of ovarian failure relies on sex hormone replacement therapy.

6.5 Decreased Bone Density and Risk of Osteoporosis

Childhood cancer survivors are at an increased risk for osteopenia, osteoporosis, and fractures [116, 119, 120]. There are three factors which can potentially contribute to decreased BMD in these individuals: (1) the primary disease itself [121], (2) exposure to glucocorticoids and other chemotherapeutic agents (such as methotrexate) [119, 120, 122–124], and (3) hormonal deficiencies associated with cancer and its treatments (as described earlier in the text) particularly GH deficiency, and sex-hormone deficiencies [11, 116, 119, 120, 125]. Fractures were shown to occur in <39 % of children during treatment for ALL [126]. Although BMD improves after the completion of treatment, childhood cancer survivors remain at an increased risk of osteopenia long-term [120, 127]. Genetic predisposition (such as CRHR1 polymorphisms) may increase the risk of low BMD, especially following exposure to glucocorticoids or methotrexate [128].

Subjects deemed at high risk for the development of osteoporosis should undergo periodic bone density studies [120]. While dual energy X-ray absorptiometry (DXA) remains the most widely used tool for measuring bone mineral density, its results should be interpreted according to age, pubertal stage, and height in the pediatric population using Z-scores, and not T-scores. Failure to take these elements into account may result in an over-diagnosis of osteoporosis during childhood and adolescence [125, 129]. Age adjusted Z-scores may also underestimate bone mineral density in individuals with short stature; the use of volumetric methods is then indicated [130]. Preventive measures (for example, supplementation with calcium and vitamin D, smoking cessation, weight-bearing exercise) should be encouraged in all individuals with low or borderline bone mineral density. In addition, sex hormone replacement therapy and GH replacement are useful in improving BMD in subjects with known deficiencies.

6.6 Overweight, Obesity, and Disorders of Glucose Homeostasis

Obesity and being overweight are often observed in survivors of acute leukemia and various brain tumors [131]. Risk factors for obesity include cranial irradiation, female gender and exposure to dexamethasone. Cranial radiotherapy >20 Gy, especially in females treated at a young age (<4 years) was significantly associated with obesity (i.e., BMI > 30) [132, 133]. Genetic predisposition contributes to this risk [134, 135]. Other risk factors include sedentary lifestyle [136] and GH deficiency [137]. Premature adiposity rebound, believed to be a predictor of adult obesity, was also described in childhood ALL survivors and may partly explain the increased risk for obesity in patients treated at a very young age (<5 years) [138].

Brain tumors developing near the sellar region and their treatments (e.g., surgery, radiation) can

disrupt hypothalamic and pituitary functions and induce states of morbid "central" obesity [139, 140]. Hyperphagia, resulting from a hypothalamic insult and increased parasympathetic tone leading to hyperinsulinemia (the latter promoting fat storage) have been suggested as a contributing factor to obesity in these patients. It is with regards to that latter mechanism that treatment with octreotide has been tried in a small number of patients with hypothalamic obesity [140]. Dextroamphetamine has also been used with some success in order to control weight gain in patients with obesity related to hypothalamic injury [141].

Childhood cancer survivors are at an increased risk of developing diabetes mellitus. In a report from the Childhood Cancer Survivor Study, survivors were almost twice as likely to report diabetes when compared to siblings. The main risk factors detected in this study were exposure to TBI, abdominal radiation and alkylating agents [142]. Disorders of glucose homeostasis have indeed been shown to occur in pediatric HSCT recipients, especially those treated with TBI. The primary abnormality seems to be increased resistance to insulin [143–149]. In a more recent report on survivors of childhood leukemia, central leptin resistance in individuals treated with cranial radiotherapy was described as a possible mechanism for insulin resistance, in both obese and non-obese individuals [150]. Further studies are needed in order to further understand the mechanisms related with these metabolic derangements and the best way to treat them.

6.7 Conclusion

Endocrine sequelae are among the most common late effects affecting childhood cancer survivors. These complications involve multiple endocrine systems and can have serious implications on the individual's long term health prospects. The major risk factors include radiation therapy to key endocrine organs and exposure to alkylating agents. Early detection and treatment are key elements in improving the individual's well being. It is, therefore, very important for childhood cancer survivors to pursue long term medical follow up. It is also very important for the medical providers caring for this population to recognize these complications, and to keep in mind that some of the endocrine late effects may not manifest until many years after the completion of all cancer therapies.

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Cardiovascular System

7

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7.1 Introduction

Cardiotoxicity is a late effect of pediatric cancer and its treatment that increases the risk of morbidity and mortality. Cardiotoxicity may result from a variety of antineoplastic therapies, including independent or combined effects of chemotherapy and radiation therapy. A survey of 84 pediatric cardiology centers found that 12 % of patients with cardiomyopathy (n = 5,205) followed at these centers have been treated for cancer during childhood or adolescence [1].

Childhood cancer survivors have a cumulative incidence of approximately 75 % for a chronic health condition within the first 30 years after diagnosis [2]. According to the latest 5-year estimates, the leading non-cancer-related cause of morbidity and mortality in long-term survivors of childhood cancer is cardiovascular-related disease [2–6]. Compared to the general population, survivors are eight times as likely to die from cardiovascular-related disease [7]. Compared to sibling controls, they are also 15 times as likely to experience heart failure (HF), more than ten times as likely to have coronary artery disease, and more than nine times as likely to have had a cerebrovascular accident during the first 30 years after cancer diagnosis [5]. These risks may persist and have been examined for up to 45 years beyond the end of treatment [8].

Late cardiotoxicity following anthracycline therapy is mostly subclinical, often progressive, potentially severe, and sometimes fatal [9]. More than half of survivors have subclinical cardiac abnormalities 5–10 years after chemotherapy [10–12]. The association between anthracycline exposure and the increased risk of death from cardiac causes is highlighted by a retrospective study of 4,122 5-year survivors of childhood cancer in France and the United Kingdom, which reported the relative risk of death of 7.9 (95 % confidence interval [CI], 2.3–31.3) after an average follow-up of 27 years, when compared with the general population [6]. The British Childhood Cancer Survivor Study of 17,981 5-year survivors of childhood cancer also reported an increased risk of death from cardiac causes (standardized mortality ratio: 2.3; 95 % CI, 1.3–3.9) after 45 years of follow-up when compared with the general population [8].

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The frequency and risk factors of subclinical cardiotoxicity in healthy survivors of childhood cancer after anthracycline therapy have also been studied in a systematic review of 25 studies [11]. The prevalence of subclinical cardiotoxicity, defined as abnormal left ventricular (LV) systolic function detected by echocardiography or radionuclide angiocardiography varied between 0 and 57 %. Multivariate analysis found that a higher cumulative dose of anthracycline, longer follow-up time, mediastinal radiation, female sex, higher individual dose rates, cancer diagnosis, and age at diagnosis were all independent risk factors for decreased LV systolic function and increased LV afterload [11]. Additionally, younger age of exposure (less than 5 years), African–American race, trisomy 21, combination therapy (with cyclophosphamide or amsacrine), previous cardiac disease, hypertension, and liver disease have also been associated with increased risk of anthracycline-related cardiotoxicity (Table 7.1) [11, 13, 14, 27]. Higher cumulative doses of anthracyclines can place children at risk for chronic cardiac compromise, with a cumulative dose >300 mg/m^2 increasing the risk of HF 11-fold compared to a dose <300 mg/m^2 [28].

7.2 Pathophysiology: Antineoplastic Agents Associated with Cardiotoxicity

7.2.1 Chemotherapeutics

Many pediatric patients with cancer receive chemotherapeutic agents that have potentially cardiotoxic effects. Anthracyclines are well known for their cardiotoxicity, and alkylating agents, such as cyclophosphamide, ifosfamide, cisplatin, busulfan, and mitomycin, have also been associated with cardiotoxicity. Other agents reported to have cardiac effects include vinca alkaloids, fluorouracil, cytarabine, amsacrine, and asparaginase and the newer agents—paclitaxel, trastuzumab, etoposide, and teniposide (Table 7.2) [29].

7.2.1.1 Anthracyclines

Anthracycline-induced cardiotoxicity has been recognized for over 40 years. Most long-term pediatric cancer survivors received anthracyclines, which are widely used to treat several solid tumors and hematologic malignancies [13]. Despite their wide use, the mechanism by which cardiotoxicity occurs is not well understood, though the cause is likely due to more than one variable.

Anthracyclines belong to the antineoplastic antibiotic class that interferes with cell replication by reacting with lipids, proteins, and nucleic acids—resulting in lipid peroxidation, depletion of sulfhydryl-containing peptides, and DNA damage [18]. The cytotoxic action of anthracyclines works through three major mechanisms [30]:

1. Inhibition of DNA and RNA synthesis by intercalating between base pairs of the DNA/RNA strand, thus preventing the replication of rapidly growing cancer cells.
2. Inhibition of the topoisomerase II enzyme, preventing supercoiled DNA from relaxing and thus blocking DNA transcription and replication.
3. Creation of iron-mediated, free-oxygen radicals that damage the DNA and cell membranes.

The most commonly hypothesized mechanism concerns the generation of free radicals and superoxides, known as radical oxygen species (ROS; Fig. 7.1) [31].

Cardiomyocytes have low levels of free radical scavenging systems and a highly oxidative metabolism, making them more susceptible to injury by this mechanism [21, 32]. Although the oxidative effects of anthracyclines may not be limited to cardiomyocytes, rapidly dividing intracardiac non-muscle cells may be able to replace those lost to apoptosis or necrosis leading to fibrous replacement even though anthracyclines retard cardiac fibroblast proliferation. Cardiomyocytes, which divide very slowly, if at all, may not sufficiently replace cells damaged during treatment [26].

The degree and progression of anthracycline-related toxicity varies widely among individuals, suggesting a genetic predisposition and the presence of modifiable and non-modifiable risk factors [26].

Table 7.1 Risk factors for anthracycline-related cardiotoxicity

Risk Factor	Comment	References
Cumulative anthracycline dose	Cumulative doses >500 mg/m^2 are associated with significantly elevated long-term risk	Lipshultz et al., 1991 [10]; Krischer et al., 1997 [13]; Lipshultz et al., 1995 [14]; Lipshultz et al., 2005 [12]; van der Pal et al., 2010 [15]
Time after therapy	Incidence of clinically important cardiotoxicity increases progressively after therapy	Lipshultz et al., 1991 [10]; Lipshultz et al., 1995 [14]; Lipshultz et al., 2005 [12]; Lipshultz et al., 2010 [3]
Rate of anthracycline administration	Prolonged administration to minimize circulating dose may decrease toxicity; results are mixed	Lipshultz et al., 2002 [16]; Lipshultz et al., 2010 [3]
Individual anthracycline dose	Higher individual doses are associated with increased late cardiotoxicity, even when cumulative doses are limited; no dose is risk-free	Lipshultz et al., 1995 [14]; Lipshultz et al., 2005 [12]; Lipshultz et al., 2010 [17]
Type of anthracycline	Liposomal encapsulated preparations may reduce cardiotoxicity. Data on anthracycline analogues and differences in cardiotoxicity are conflicting.	Wouters et al., 2005 [18]; Barry et al., 2007 [19]; Van Dalen et al., 2008 [20]
Radiation therapy	Cumulative radiation dose >30 Gy; as little as 5 Gy increases the risk; before or concomitant with anthracycline treatment	Giantris et al., 1998 [21]; Adams et al., 2005 [22]; Lipshultz et al., 2010 [3]; van der Pal et al., 2010 [15]
Concomitant therapy	Trastuzumab, cyclophosphamide, bleomycin, vincristine, amsacrine, and mitoxantrone, among others, may increase susceptibility or toxicity.	Giantris et al., 1998 [21]; Barry et al., 2007 [19]
Pre-existing cardiac risk factors	Hypertension; ischemic, myocardial, and valvular heart disease; prior cardiotoxic treatment	Barry et al., 2007 [19]
Personal health habits	Smoking, alcohol consumption, energy drinks, stimulants, prescription and illicit drugs	Lipshultz et al., 2010 [3]
Comorbidities	Diabetes, obesity, renal dysfunction, pulmonary disease, endocrinopathies, electrolyte and metabolic abnormalities, sepsis, infection, pregnancy, viruses, elite athletic participation, low vitamin D levels	Barry et al., 2007 [19]; Lipshultz et al., 2010 [3]; Miller et al., 2010 [23]; Lipshultz et al., 2012 [24]; Landy et al., 2012 [25]
Age	Both young and advanced age at treatment are associated with elevated risk	Lipshultz et al., 1991 [10]; Lipshultz et al., 1995 [14]; Lipshultz et al., 2010 [3]; van der Pal et al., 2010 [15]
Sex	Females are at greater risk than males	Lipshultz et al., 1995 [14], Lipshultz et al., 2010 [17]
Complementary therapies	38 % of Americans spend $34 billion on nonscientific, alternative, or complementary self-care therapies and medicines; more information needs to be collected to assess risk	Lipshultz et al., 2010 [3]
Additional factors	Trisomy 21; African American ancestry	Krischer et al., 1997 [13]

Adapted from Lipshultz SE, 2008 [26]; Reprinted with permission from BMJ Publishing Group Ltd

Three types of anthracycline-induced cardiotoxicity have been described (Table 7.3).

Acute or sub-acute cardiotoxicity is a rare form of cardiotoxicity that may occur immediately after a single dose or a course of anthracycline therapy. It may be characterized by transient electrophysiological abnormalities, a pericarditis-myocarditis syndrome, or acute LV dysfunction occurring within a week of treatment [34]. Acute changes during anthracycline infusion range from

Table 7.2 Cardiotoxic effects of chemotherapeutic agents

Drug class/agent	Adverse cardiac events
Anthracycline/anthraquinolones	
Doxorubicin, daunorubicin, epirubicin, idarubicin, mitoxantrone	Arrhythmias, pericarditis, myocarditis, HF, LV dysfunction
Alkylating Agents	
Busulfan, cisplatin, cyclophosphamide, ifosfamide, mitomycin	Endomyocardial fibrosis, pericarditis, cardiac tamponade, ischemia, MI, hypertension, myocarditis, HF, and arrhythmias
Antimetabolites	
Capecitabine, cytarabine, 5-fluorouracil, clofarabine, carmustine	Ischemia, chest pain, MI, HF, arrhythmias, pericarditis, pericardial effusions, and hemodynamic abnormalities
Antimicrotubules	
Etoposide, teniposide, paclitaxel, vinca alkaloids	Sinus bradycardia, angina, hypotension or hypertension, HF, ischemia, MI, arrhythmias, conduction abnormalities
Biological agents	
Alemtuzumab, bevacizumab, cetuximab, rituximab, trastuzumab	Hemodynamic abnormalities, LV dysfunction, HF, thromboembolism, angioedema, arrhythmias
Interleukins	
Interleukin-2, interferon-α, denileukin	Hypotension, arrhythmias, capillary leak syndrome, ischemia, LV dysfunction, coronary artery thrombosis
Tyrosine kinase inhibitors	
Imatinib mesylate, sorafenib, sunitinib, dasatinib, relotinib, gefitinib, lapatinib	HF, edema, pericardial effusion, pericarditis, hypertension, arrhythmias, ischemia, prolonged QT interval, chest pain
Miscellaneous	
Asparaginase, pentostatin, arsenic trioxide, all-*trans*-retinoic acid, thalidomide, lenalidomide	HF, hypotension, MI, electrocardiographic changes, pleural-pericardial effusion, QT prolongation, peripheral edema, bradycardia, ischemia, edema, thromboembolism and retinoic acid syndrome that includes fever, respiratory distress, weight gain, angina, Torsades de Pointes

HF heart failure, *LV* left ventricular, *MI* myocardial infarction

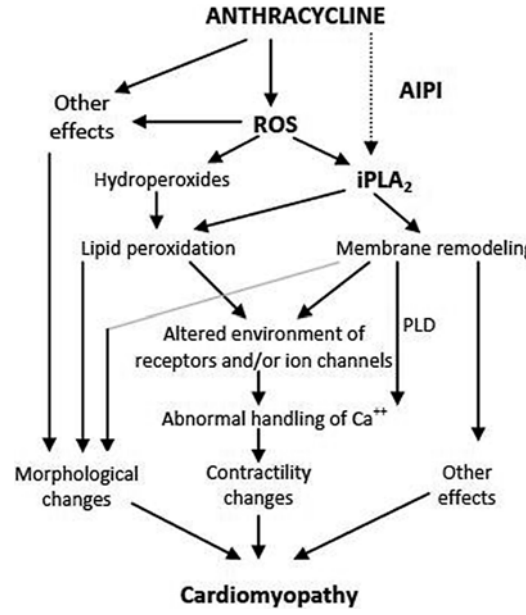

Fig. 7.1 Proposed pathways of anthracycline-induced cardiomyopathy. *ROS* reactive oxygen species, *AIPI* anthracycline-induced iPLA$_2$ inhibition, *iPLA2* independent phospholipase A$_2$, *PLD* phospholipase D. Adapted from McHowat et al. 2004 [31]. Recreated with permission from American Society for Pharmacology and Experimental Therapeutics

minor electrocardiographic abnormalities (nonspecific ST segment and T-wave changes and QTc interval prolongation) to fatal arrhythmias, including transient systolic LV dysfunction and potentially fatal congestive HF [22, 35].

Early-onset chronic progressive cardiotoxicity is characterized by depressed myocardial function after 1 week of treatment or within the first year after treatment. The depression may persist or progress even after therapy is discontinued and may evolve into a chronic dilated cardiomyopathy in adults or children, and also a restrictive cardiomyopathy in children [27]. Early-onset cardiotoxicity is likely related to cardiomyocyte damage and death.

Late-onset chronic progressive cardiotoxicity is marked by deteriorated myocardial function occurring at least 1 year after completion of

Table 7.3 Characteristics of the types of anthracycline-associated cardiotoxicity[a]

Characteristic	Acute cardiotoxicity	Early onset, chronic progressive cardiotoxicity	Late onset, chronic progressive cardiotoxicity
Onset	Within the first week of anthracycline treatment	<1 year after the completion of anthracycline treatment	>1 year after the completion of anthracycline treatment
Risk factor dependence	Unknown	Yes	Yes
Clinical features in adults	Transient depression of myocardial contractility; myocardial necrosis (cTnT elevation); arrhythmia	Dilated cardiomyopathy; arrhythmia	Dilated cardiomyopathy; arrhythmia
Clinical features in children	Transient depression of myocardial contractility; myocardial necrosis (cTnT elevation); arrhythmia	Restrictive cardiomyopathy and/or dilated cardiomyopathy; arrhythmia	Restrictive cardiomyopathy and/or dilated cardiomyopathy; arrhythmia
Course	Usually reversible anthracycline is discontinued	Can be progressive	Can be progressive

[a]Data are from Giantris et al. [21] and Grenier and Lipshultz [33]. Adapted from Adams et al. [22] Reprinted with permission from John Wiley & Sons, Inc

anthracycline therapy [10, 36, 37]. This deterioration has been attributed to impaired myocardial growth, as reflected by an inappropriately small increase in LV wall thickness in relation to somatic growth; with this, the loss of cardiomyocytes results in a progressively increased LV afterload and reduced LV contractility. The anthracycline-induced loss or damage to a critical number of cardiomyocytes might decrease the number of residual myocardial cells required to generate a normal myocardial mass, despite a marked increase in the size of the remaining cardiomyocytes [10]. Cardiomyocyte loss subsequently leads to LV wall thinning and, in some cases, to progressive LV dilation [38]. Beyond inadequate LV hypertrophy is the fact that many residual cardiomyocytes have abnormal intracellular structure and function that may persist and affect cardiac structure, function, and outcome. Cardiomyocyte mitochondrial structure and function are particularly affected by anthracycline exposure, and this may be persistent.

7.2.1.2 Alkylating Agents

Alkylating agents have also been associated with cardiotoxicity (Table 7.2). Cyclophosphamide is a non-cell-cycle-specific alkylating agent, and part of the core of many pre-transplant conditioning regimens. Its metabolite forms DNA cross-links between (during inter-strand cross linkages) and within (during intra-strand cross linkages) DNA strands to cause irreversible cell damage, or cell death. The pathogenesis of cyclophosphamide-induced cardiotoxicity is not well understood, but it is thought to involve direct endothelial damage leading to leakage of plasma proteins and erythrocytes. Abnormal LV wall thickness from interstitial edema and hemorrhage may reduce LV diastolic compliance, creating LV diastolic dysfunction and presenting as restrictive cardiomyopathy [39].

In contrast to anthracycline-induced cardiotoxicity, high-dose cyclophosphamide can cause an acute myopericarditis peaking at 2–3 weeks after therapy and cardiac dysfunction independent of cumulative dose [40]. Acute HF has been reported as early as 1–3 weeks after administration [41, 42]. The total dose of cyclophosphamide per course has been described as a risk factor [40]. The combined incidence of symptomatic cyclophosphamide-induced cardiotoxicity from two studies [41, 42] was 22 %, and the incidence of fatal cardiotoxicity was 11 % [40]. A total dose greater than about 170 mg/kg over 4–7 days was a risk factor for cardiotoxicity [40–42]. In 52 patients who had never received anthracycline therapy, the overall incidence of symptomatic cyclophosphamide-induced cardiomyopathy was

25 %, and mortality was 12 % when the dose exceeded 1.55 g/m^2 daily [40]. When the dose was <1.55 g/m^2 daily, the incidence of symptomatic cardiotoxicity was 3 % with no mortality [40]. Since younger children, have a relatively higher body surface area, dosing of cyclophosphamide based on body surface area results in a much lower relative dose, which may partially explain the lower incidence and severity of cyclophosphamide-induced cardiotoxicity in younger children than that in adolescents and adults [43].

7.2.1.3 Mediastinal Radiation

Radiation therapy has greatly improved survival for children with Hodgkin's disease and other malignancies of the chest. Successes with radiation therapy used either alone or in conjunction with other treatments have resulted in a cohort of survivors of childhood cancers who are subject to late complications from treatment, in which the therapeutic benefit is offset by potentially delayed cardiac effects.

Mediastinal radiation therapy has the potential to damage any structure of the heart. This damage may affect the heart valves, including valvular stenosis and regurgitation (primarily of the aortic and mitral valves), injury to the endothelium of the coronary arteries, fibrosis of the conduction system with subsequent arrhythmias or heart block, acute or chronic involvement of the pericardium, and interstitial fibrosis leading to inflammation of the myocardium [44]. This population is specifically vulnerable to chronic pericardial disease; premature coronary artery disease and atherosclerosis (primarily of the left anterior descending and right coronary arteries); cardiomyopathy, including LV systolic and diastolic function (restrictive cardiomyopathy) leading to HF; valvular disease; and conduction abnormalities as described above, which can appear years or even decades after treatment [45].

The means by which radiation produces atherosclerosis are not well understood, but it is likely that endothelial injury initiates the process [46]. The generation of reactive oxygen species and inflammation in response to endothelial injury that decreases the availability of nitric oxide may also promote atherosclerosis [47]. Myocardial dysfunction after radiation is caused by small-vessel ischemic disease and myocardial fibrosis leading to restrictive cardiomyopathy.

Risk factors for radiation-associated heart damage include: a mediastinal dose that includes the heart of greater than 30 Gy, a dose-per-fraction greater than 2 Gy, large amounts of irradiated heart, younger ages of exposure, cytotoxic chemotherapy, endocrine therapy, trastuzumab treatment, as well as the traditional risk factors for heart disease such as diabetes, hypertension, dyslipidemia, obesity, and smoking [48]. Radiation-associated atherosclerotic heart disease rarely occurs without other cardiovascular risk factors [49].

Most data regarding the late cardiac effects of radiation therapy are derived from experience with survivors of Hodgkin's disease and breast cancer [46, 50]. Survivors of Hodgkin's disease and breast cancer survivors treated with radiotherapy after mastectomy are among the best studied populations for radiation-associated cardiovascular disease and appear to be at high risk for radiation-associated cardiovascular disease. The relative risks range between 2.2 and 7.2 for fatal cardiovascular events post-mediastinal irradiation for Hodgkin's disease, and 1.0–2.2 after irradiation for left-sided breast cancer. This increased risk is life-long, yet the absolute risk appears to increase with time since exposure. Radiation-associated cardiovascular toxicity may, in fact, be progressive. Hull and colleagues analyzed data from 2,232 patients of all age groups with Hodgkin's disease. The relative risk for death from acute myocardial infarction was 3.2, showing that patients younger than 20 years of age who received high-dose radiation had the highest relative risk and that risk decreased with age at the time of radiation exposure, suggesting the importance for earlier surveillance in those exposed at young ages [46]. In another study of 1,474 Hodgkin's disease survivors treated mostly with radiation therapy, with or without adjunct chemotherapy, hypercholesterolemia was identified as the most important independent risk factor for the late development of coronary heart disease, suggesting that aggressive modification of

coronary risk factors is warranted in patients who have received mediastinal radiation therapy [51].

Although symptomatic heart disease occurs in only about 5 % of patients within 10 years after radiation treatment for Hodgkin's disease, the more striking data has come from asymptomatic survivors [52]. Adams et al. assessed cardiovascular status in 48 survivors of Hodgkin's disease (median time since the diagnosis of Hodgkin's disease was 14.3 years) who had received mediastinal radiation (median 40 Gy) with no symptomatic heart disease at the time of evaluation [53]. All but one patient had cardiac abnormalities, including echocardiographic evidence of restrictive cardiomyopathy (decreased LV dimension and mass without increased LV wall thickness); 20 (42 %) had marked valvular defects; 36 (75 %) had conduction defects, including persistent tachycardia and autonomic dysfunction; and 14 (30 %) had substantially reduced peak oxygen uptake during the exercise, that could be a marker of subclinical HF [53].

Heidenreich and colleagues evaluated 294 asymptomatic patients treated with at least 35 Gy to the mediastinum for Hodgkin's disease and found that valvular disease was common and that the incidence increased with time [54]. Compared to patients within 10 years of treatment, patients who had received radiation more than 20 years before evaluation were more likely to have mild, moderate, or severe aortic regurgitation (60 vs. 4 %), moderate or severe tricuspid regurgitation (4 vs. 0 %), and aortic stenosis (16 vs. 0 %). Mildly reduced LV fractional shortening (less than 30 %) was significantly more prevalent than in the Framingham Heart Study population (36 vs. 3 %). Furthermore, LV mass adjusted for age and sex was lower in the patients treated for Hodgkin's disease [54]. Similar to the gradual progressive nature of anthracycline-related cardiac toxicity, which may remain latent for up to 20 years and is usually diagnosed by screening for subclinical disease, radiation-related damage may develop slowly, and patients who have various degrees of damage may remain asymptomatic for years.

Late radiation-induced pericarditis can occur months to years after mediastinal irradiation but currently has a very low incidence [53]. Most cases of radiation-induced pericarditis and pericardial effusion resolve spontaneously, usually within 12–18 months [55]. Surgery is not typically indicated for patients with occult constrictive pericarditis, and patients who have delayed pericarditis rarely have symptomatic constriction. Overall, patients with radiation-induced pericarditis have a good prognosis.

7.3 Signs and Symptoms

Early cardiotoxic effects may include electrocardiographic abnormalities, arrhythmias, and evidence of acute HF Electrocardiographic abnormalities—which include nonspecific ST segment and T-wave changes—decreased QRS voltage, and prolongation of the QT interval, may occur in up to 30 % of patients [56]. Sinus tachycardia is the most common rhythm disturbance, but tachyarrhythmias, including supraventricular, junctional, and ventricular, have been reported. Right and left bundle branch and atrioventricular block have also been described [57]. Fortunately, these electrocardiographic changes are transient and are seldom a serious clinical problem. The corrected QT interval should be monitored carefully, and if other antimicrobial, neurologic, or gastrointestinal agents that may prolong the QT interval are used, serial electrocardiograms must be obtained. A prolonged QT interval may predispose to ventricular tachyarrhythmias, such as Torsade de Pointes, a potentially life-threatening clinical condition.

Other symptoms of acute cardiotoxicity include: hypotension, hypertension, myocarditis, pericarditis, cardiac tamponade, acute myocardial infarction, acute HF, and cardiogenic shock. Sub-acute cardiotoxicity may include acute HF, pericarditis, or a fatal pericarditis-myocarditis syndrome in very sporadic cases. This rare syndrome manifests as fever, acute pancarditis (inflammation of the pericardium, myocardium, and endocardium), and symptomatic HF, and may be quickly fatal. The risk of developing early anthracycline toxicity is also high in adults, where risk factors include age over 70 years,

prior mediastinal irradiation, abnormal ventricular function before therapy, a history of congestive HF or myocardial infarction, and chronic hypertension [58].

Children treated with anthracyclines or alkylating agents are also subject to acute congestive HF. Younger age at treatment is a particular risk factor. Heart failure is a progressive syndrome caused by cardiovascular and non-cardiovascular abnormalities and characterized by edema, respiratory distress, growth failure, and exercise intolerance and accompanied by circulatory, neurohormonal, and molecular derangements [59]. Symptoms of acute HF vary by age and may include tachypnea, respiratory distress, feeding intolerance, diaphoresis, tachycardia, hepatosplenomegaly, edema, ascites, jugular venous distension, cool extremities, fatigue, failure to thrive, exercise intolerance, dizziness, and syncope.

Heart failure symptoms have been classified in several ways to stratify patients by risk and to better delineate treatment strategies, though these classifications are not uniformly applied. The New York Heart Association (NYHA) classification [60], which is based on functional limitations, is not applicable to most children and infants. However, the Ross Heart Failure classification [61], a modified version of the New York Heart Association (NYHA) classification, and the New York University Pediatric Heart Failure Index (PHFI) [62] were designed to assess and grade the severity of HF in this younger population. When these three classifications were compared in children undergoing surgery for rheumatic valve disease, the PHFI correlated statistically significantly with electrocardiographic (the Cardiothoracic and Sokolov indexes) and most echocardiographic (end-systolic wall stress, left atrium to aorta diameter, LV mass) markers, and with the cardiomyopathy biomarker NT-proBNP [63]. There were no correlations between echocardiographic or biochemical markers and the Ross and NYHA scoring systems [63]. None of these classification indices have been validated as a surrogate clinical endpoint in large numbers of children with HF, and have not been reported in children with cancer.

Pericardial effusions stemming from cancer and its therapies are rare but are among the most common causes of cardiac tamponade in children. The pathophysiology includes altered vascular permeability, an abrupt increase in intrapericardial fluid or bleeding associated with the inflammation of the pericardium, and lymphatic obstruction by mass effect. Under normal conditions, with inspiration, negative intrathoracic pressures increase systemic venous return to the right heart, but an even greater volume of blood is accommodated by the pulmonary vascular bed, which reduces left-sided output [64]. In cardiac tamponade, as fluid accumulates, the rise in pressure is transmitted across the myocardial wall and decreases diastolic filling, resulting in a greater reduction in cardiac output, in which case emergent pericardiocentesis (draining of pericardial effusion) is indicated, with or without surgical creation of a pericardial window.

Mediastinal radiation therapy commonly affects the pericardium and may cause acute pericarditis and tamponade [65]. More acutely, electrocardiographic changes, including T-wave abnormalities and atrial arrhythmias, have been reported in patients receiving mediastinal radiation therapy [66].

As previously mentioned, early-onset cardiotoxicity may persist or progress even after therapy is discontinued and can evolve into a chronic cardiomyopathy—which is defined as chronic progressive or late-onset cardiotoxicity, appearing years to decades after chemotherapy has been completed [10, 12].

7.4 Current Pediatric Guidelines

7.4.1 Advanced Screening and Management

Table 7.4 shows many of the common modalities used for screening and monitoring cardiotoxicity in pediatric cancer patients.

We have found a poor correlation between echocardiographic measurements of LV systolic performance during treatment of childhood

Table 7.4 Most commonly used methods for evaluating and monitoring cardiotoxicity

Method	Measure(s) of interest
Echocardiography	• Structure (LV wall thickness and LV internal diameter) • LV systolic function (fractional shortening and ejection fraction) • LV diastolic function (early and atrial diastolic flow rate, E/A flow ratio, isovolumic relaxation time, strain) • LV afterload (end-systolic wall thickness) • LV load independent contractility (stress-velocity index)
Radionuclide angiography	
Radionuclide ventriculography	• LV structure (internal diameter and volume) • LV function (ejection fraction and systolic and diastolic pattern of motion)
Electrocardiograms	• Cardiac rhythm (arrhythmias) • Conduction abnormalities (QT intervals)
Stress test (in combination with above methods)	• Pharmacologic using infusion of angiotensin II or dobutamine • Physiologic using treadmills and ergometer bicycles
Standard exercise	• Integrated results of cardiac and pulmonary function and muscle work capacity
Endomyocardial biopsy	• Quantifies anatomic, histopathologic, cardiac toxicity
Doppler myocardial imaging	• Velocity, strain, and strain rate • Myocardial function and perfusion evaluation
Cardiac magnetic resonance imaging	• Myocardial function and perfusion evaluation
Blood cardiac biomarkers	
Troponins	• Cardiac injury, myocyte death
NT-proBNP	• LV wall stress associated with pressure and volume overload

high-risk acute lymphoblastic leukemia and the presence of dead and dying cardiomyocytes, as measured by blood cardiac troponin-T concentrations [67]. Five years after receiving chemotherapy, these same children had statistically significant correlations between the blood cardiac troponin-T concentrations measured during therapy and the echocardiographic measurements of LV structure and function measured 5 years later; however, there was no significant relation between the measures of LV systolic performance during therapy with the echocardiographic findings 5 years later [68]. This suggests that blood concentrations of cardiac troponin-T during therapy predict which survivors will have normal or abnormal LV structure and function as long-term survivors. This is not true for cardiac function measurements during therapy. This makes sense since many children who are acutely ill during active treatment for leukemia have high levels of circulating myocardial depressant cytokines that may lead to depressed LV systolic performance during therapy that is transient and not associated with dead and dying cardiomyocytes. If cardiomyocyte death or permanent impairment has occurred during therapy in some children, those children are more likely to have chronic abnormalities of LV structure and function. The same is true for abnormalities of heart rate, LV preload, and LV afterload which may be abnormal during active cancer and its treatments including chemotherapy. These abnormalities of heart rate and LV loading conditions lead to changes in LV load-dependent contractility, the intrinsic health of the cardiomyocyte, that may not reflect intrinsic LV contractility [10, 27, 69].

However, the primary modality for clinical cardiac surveillance has been cardiac ultrasound (echocardiography). Subclinical cardiomyopathy has been noted in up to 20 % of all children receiving anthracycline chemotherapy, which is likely to be an underestimate since we have found more than 50 % of anthracycline treated children have elevations of blood cardiac troponin-T during therapy [67], but also not truly reflective of the intrinsic health of the LV cardiomyocytes, given that most large cohort studies have used measures of LV systolic functional measures, such as LV fractional shortening and biplane volume in their primary assessment [70]. In their 2002 systematic review, Kremer et al. reported that the frequency of an abnormal LV fractional shortening, as a measure of LV systolic function, varied across studies from 0 % and 39.2 % [11]. When the studies were divided into those with mean anthracycline doses below or above 300 mg/m^2,

the percent abnormal increased: 0–15.2 % and 15.5–27.8 %, respectively. Additionally, studies evaluating decreased LV systolic function with measures of increased LV afterload in patients receiving mean anthracycline doses below or above 300 mg/m^2 also reported frequencies with smaller ranges: 0 % and 19–52 %, respectively [11]. In 2007, Ganame et al. reported that low-to-moderate doses of anthracyclines induce acute LV diastolic and systolic dysfunction [71]. Ventricular dysfunction was detected earlier using other measures of ventricular dysfunction (wall stress, strain, and myocardial performance index) earlier as compared to long-established functional criteria, such as LV ejection fraction [71]. These noninvasive ultrasound imaging techniques have detected a higher frequency of LV dysfunction, as defined by subclinical abnormalities in regional wall motion in the acute and subacute phases of therapy [71, 72]. In the late-effects population, other ultrasound modes may detect subclinical LV dysfunction in asymptomatic patients who have "normal LV systolic function," as determined by traditional ultrasound imaging [73]. However, there is a need to validate all cardiac biomarkers, whether through measurements made by cardiac imaging or blood biomarkers, with clinically signficant endpoints before stating that they have predictive value or should be used for routine screening. Currently, only the blood cardiac biomarkers, cardiac troponin-T and NT-proBNP concentrations measured during active chemotherapy have been validated as surrogate endpoints for late cardiotoxicity in long-term survivors [68]. For this reason, we questioned nearly 20 years ago the utility of using measurements of LV systolic performance to assign cardiotoxicity classifications to children receiving cancer chemotherapy and to use that as the basis for withholding potentially lifesaving chemotherapy in patients without clinical cardiac disease [69]. Our concerns remain today.

Although monitoring and reducing other coronary risk factors in patients who received mediastinal radiation should be part of the follow-up of the late-effects population [24], the value of routine noninvasive or invasive evaluation in asymptomatic patients has not been determined [69]. Further, those risk factors and interventions targeted to reducing those risk factors may be helpful but not sufficient to avert premature symptomatic cardiovascular disease. That is because the global cardiovascular risk is most relevant and at this time we understand risk factors for conventional non-cancer related cardiovascular disease but we do not fully understand the risk factors for premature cardiovascular disease that may be unique to childhood cancer and its treatments. It is the combined effect of conventional and unique risk factors that incrementally increases the risk of developing premature global symptomatic cardiovascular disease in this population.

Table 7.5 Children's oncology group guidelines for cardiac evaluation of cancer survivors, by chemotherapy and radiation exposure—presented but not endorsed by the authors since these have not been validated

Age at treatment	Chest radiation	Total anthracycline dose	Frequency of cardiac evaluation
<1 year	Yes	Any	Every year
	No	<200 mg/m^2	Every 2 years
		≥200 mg/m^2	Every year
1–4 years	Yes	Any	Every year
	No	<100 mg/m^2	Every 5 years
		≥100 to <300 mg/m^2	Every 2 years
		≥300 mg/m^2	Every year
≥5 years	Yes	<300 mg/m^2	Every 2 years
		≥300 mg/m^2	Every year
	No	<200 mg/m^2	Every 5 years
		≥200 to 300 mg/m^2	Every 2 years
		>300 mg/m^2	Every year

From the *Children's Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent and Young Adult Cancers*, Version 3.0, October 2008, used with permission [75]

Among 108 adult survivors of Hodgkin's disease evaluated at a mean of 168 months after irradiation, 12 patients (11 %) were found to have cardiac disease [74]. Of these, six patients (6 %) had constrictive pericarditis diagnosed using catheterization, four of whom had a thickened pericardium ascertained by echocardiography; five patients (5 %) had abnormal LV contractility by echocardiographic and angiographic tests. Although the Children's Oncology Group recommends the use of serial echocardiography to monitor cardiac status in this population (Table 7.5) [75],

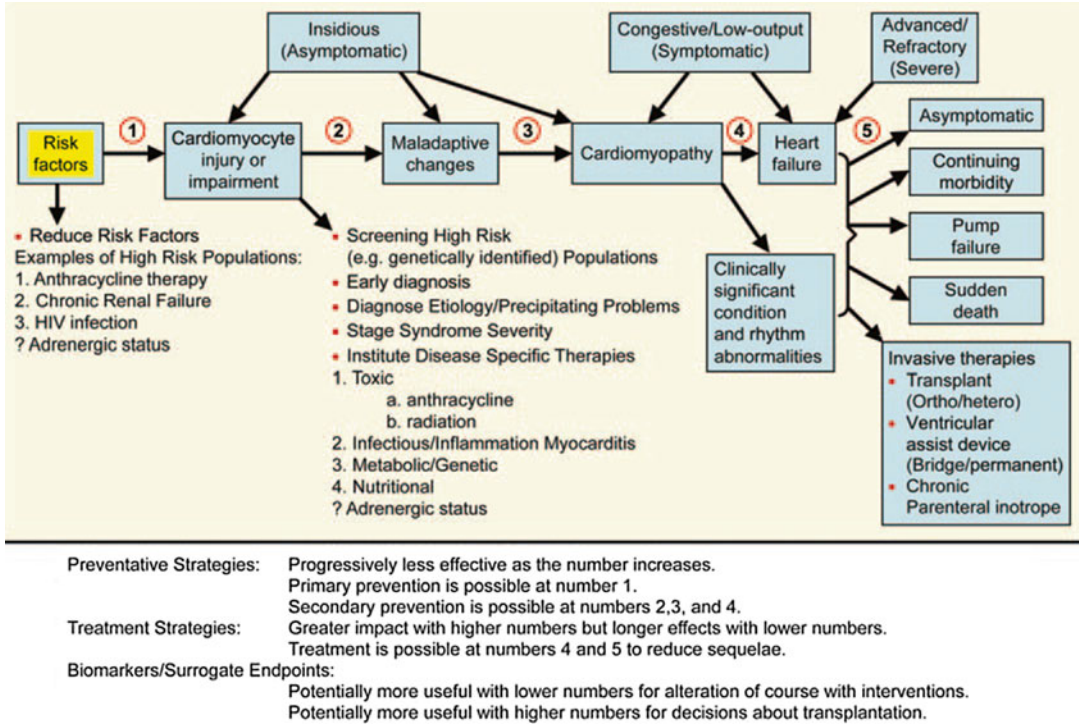

Fig. 7.2 Stages in the course of pediatric ventricular dysfunction. A review of the stages in the course of pediatric ventricular dysfunction that can be followed by echocardiographic measurements of LV structure and function in conjunction with cardiac biomarkers that have been validated as surrogates for clinically significant cardiac endpoints. The identification of risk factors and high-risk populations for ventricular dysfunction are highlighted where their use may lead to preventive or early therapeutic strategies; while the determination of etiology may lead to etiology-specific therapies. The numbers 1–5 indicate stage-related points of intervention for preventive and therapeutic strategies and where biomarkers and surrogate markers may be used. From Lipshultz and Wilkinson [76]. Reprinted with permission from Oxford University Press

their guidelines do not capture the full spectrum of potential cardiac risk factors [24, 69]. We present those recommendations for the interested reader but we do not endorse these recommendations since they have not been validated.

Biomarker screenings are sometimes done in conjunction with advanced cardiac ultrasound imaging to monitor the different stages in the course of pediatric ventricular dysfunction and identify the stages where preventative or treatment strategies may be most effective (Fig. 7.2).

Elevated serum cardiac troponin I (cTnI) levels during and immediately after infusion are associated with an increased incidence of subclinical cardiotoxicity in adults [77]. For example, the current standard for monitoring cardiac function detects cardiotoxicity only after function has become impaired [78]. Additionally, serum levels of BNP have been elevated in asymptomatic individuals treated with anthracyclines and have preceded overt HF in patients undergoing a conditioning regimen for hematopoietic stem cell transplantation [79]. Biomarker screenings are sometimes done in conjunction with advanced cardiac ultrasound imaging. Of 122 asymptomatic long-term survivors of childhood cancer, 13 % had elevated NT-proBNP levels that were significantly associated with a cumulative anthracycline dose greater than 300 mg/m^2 and with an increased indexed LV end-diastolic dimension [80]. Six other studies reviewed by the same group also suggest that BNP, NT-proBNP, and cTnI may be useful markers of early cardiotoxicity [81]. Furthermore, Lipshultz et al. found a significant association between elevated levels of cardiac troponin T

(cTnT) and NT-proBNP and late echocardiographic findings among survivors of childhood high-risk acute lymphoblastic leukemia [68]. In particular, during the first 90 days of therapy, elevated serum levels of cTnT, which indicate cardiomyocyte damage or death, were significantly associated with decreased LV mass and LV posterior wall thickness 4 years later. Similarly, abnormal NT-proBNP levels during the first 90 days of therapy were also associated with abnormal LV thickness-to-dimension ratios 4 years later, which suggests pathologic LV remodeling [68].

Exercise capacity in long-term survivors has rarely been studied. One study showed that subclinical cardiac dysfunction was associated with reduced oxygen consumption at peak exercise [82]. Another study, which compared maximal myocardial oxygen consumption ($Vo_{2\ max}$, a measure of exercise capacity, found that $Vo_{2\ max}$ was lower in survivors compared to sibling controls [83]. Furthermore, in survivors, older age, higher body fat, methotrexate exposure, and extreme measures in LV mass and function were associated with lower $Vo_{2\ max}$ [83].

7.4.2 Prevention

As discussed in a report from the Cardiovascular Disease Task Force of the Children's Oncology Group, the long-term consequences of subclinical cardiac dysfunction, including the rate of progression of asymptomatic LV dysfunction to clinical HF, are not known [49]. Several studies have reported that angiotensin-converting enzyme (ACE) inhibitors reduce the incidence of clinical HF in adults with subclinical ventricular dysfunction [84]. More specific to the anthracycline population, in 2006, Cardinale et al. found that among adult cancer patients with elevated cTnI levels immediately after anthracycline chemotherapy, those who received early treatment with an angiotensin converting-enzyme (ACE) inhibitor called enalapril experienced less late cardiotoxicity compared to the control patients who did not receive the treatment. The incidence of reduced LV ejection fraction was significantly higher in controls than in the enalapril group (43 % versus 0 %; $P<0.001$) [78]. This cohort was limited to short-term follow up and would not be adequate, along with other factors, to determine if it was applicable to reduction of late effects in childhood cancer survivors.

Studies have considered the potential value of ACE inhibitor therapy in children with cancer and acute cardiotoxicity. The data are limited for late clinically significant cardiovascular effects as these children age. Lipshultz and colleagues, in a study of the long-term effects of enalapril in 18 survivors of childhood cancer, noted that during the first 6 years of therapy, LV dimension, afterload, fractional shortening, and mass progressively improved toward normal, but deteriorated to the point of no longer having a statistically significant beneficial effect between 6 and 10 years after the initiation of enalapril [16]. Mean LV wall thickness deteriorated throughout the study, as did LV contractility and systolic blood pressures. After 6 years on ACE inhibitor therapy, all 6 patients in congestive HF at the start of therapy had either died or undergone heart transplantation, suggesting that enalapril-induced improvement in LV structure and function may only be transient [16]. Silber and colleagues compared enalapril to a placebo in a randomized double-blind controlled trial of 135 long-term survivors of childhood cancer with at least one cardiac abnormality identified any time after anthracycline exposure. Patients receiving enalapril did have reduced LV wall stress in the first year after therapy, and the reduction was maintained over the 5-year study; however, treatment did not influence exercise performance [85].

Treatment with ACE-inhibitor therapy has been shown only to potentially delay, but not to prevent, the progression of subclinical and clinical cardiotoxicity in survivors [16]. This fact emphasizes the importance of primary prevention, including using lower cumulative doses of anthracyclines, less cardiotoxic-anthracycline analogues, and cardioprotective agents [18, 20].

Dexrazoxane, an iron chelator, is a cardioprotective agent used in some adults who receive an anthracycline as part of their cancer therapy. In a randomized, double-blind study of 534 women

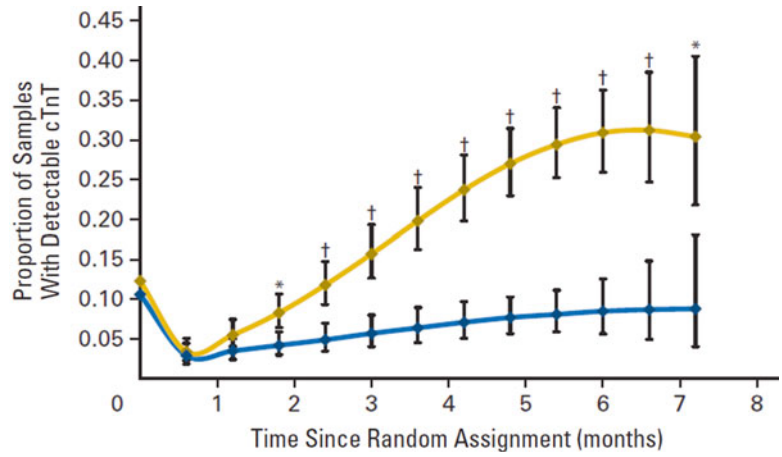

Fig. 7.3 Proportion of samples with detectable cTnT in childhood cancer survivors by time since randomization. Model-based estimated probability of having an increased cardiac troponin T (cTnT) level at each depicted time point in patients treated with doxorubicin, with or without dexrazoxane. The doxorubicin-dexrazoxane group is indicated by the *blue line*, the doxorubicin group by the *gold line*. *Vertical bars* show 95 % CIs. Increased cTnT is defined as a value greater than 0.01 ng/mL. *P value versus dexrazoxane group ≤0.05; †P value versus dexrazoxane group ≤0.001. An overall test for dexrazoxane effect during treatment was significant (P <0.001) (Color figure online). From Lipshultz et al. [68]. Reprinted with permission from American Society of Clinical Oncology

with advanced breast cancer, women who received dexrazoxane with their chemotherapy treatment were less likely to have changes in LV ejection fraction or HF compared to those who only received chemotherapy, demonstrating a significant cardioprotective effect [86]. However, only a few studies have examined this agent in children with cancer [2, 17, 67, 87, 88]. Lipshultz et al. found that children who were treated with doxorubicin alone were more likely to have elevated levels of cTnT than those who also received dexrazoxane (Fig. 7.3) [67].

Furthermore, 5 years after completion of doxorubicin treatment, the children who received doxorubicin only continued to show worse than normal LV structure and function, while those who received dexrazoxane experienced continuous cardioprotection and this was particularly true for girls (Fig. 7.4) [17]. These and other studies have found that dexrazoxane reduces the risk of long-term cardiotoxicity, without affecting anti-neoplastic efficiency [17, 67, 87, 88].

As previously discussed, doxorubicin-induced cardiotoxicity is dose-dependent, and it was therefore speculated by clinicians that continuous infusions would decrease the risk of toxicity by decreasing peak plasma levels of doxorubicin. However, a randomized study of children diagnosed with high-risk acute lymphoblastic leukemia failed to demonstrate this cardioprotective effect of continuous infusion, as opposed to bolus infusion, of the anthracycline doxorubicin. In fact, the children randomized to both continuous and bolus infusions were equally at risk of subclinical manifestations of doxorubicin-cardiotoxicity [16, 89].

Mild cardiomyocyte injury from chemotherapy may be more important in children than in adults because of the need for cardiac growth to match somatic growth and because survival is longer in children. Prevention is an important focus of research in this area, and recommendations are primarily on surveillance and clinical assessment. Thus, further investigation is essential, not only in determining the importance of subclinical cardiotoxicity but also in determining the role of HF pharmacotherapy in treating chemoradiation-induced cardiomyopathy. Secondary prevention should aim to minimize the progression of LV dysfunction to overt HF (Fig. 7.2). Approaches include altering the dose, schedule, or approach to drug delivery, using analogs or new formulations with fewer or milder

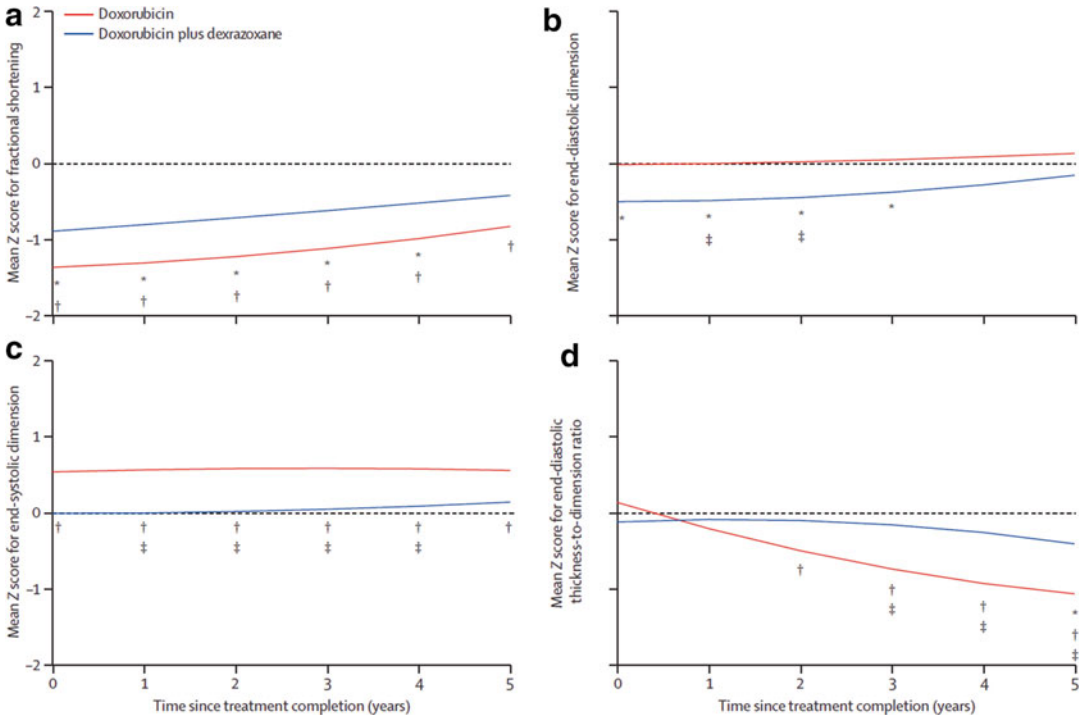

Fig. 7.4 Mean left ventricular echocardiographic Z scores (n = 134). Plots are adjusted for age and sex. *P ≤ 0.05 for comparison of the mean Z score of the doxorubicin plus dexrazoxane group with zero. †P ≤ 0.05 for comparison of the mean Z score for the doxorubicin group with zero. ‡P ≤ 0.05 for comparisons of mean Z scores between the doxorubicin and doxorubicin plus dexrazoxane groups. From Lipshultz et al. [17]. Reprinted with permission from Elsevier Ltd

cardiotoxic effects, using cardioprotectants and agents that reduce oxidative stress during chemotherapy, correcting for metabolic derangements caused by chemotherapy that can potentiate the cardiotoxic effects of the drug, and cardiac monitoring during and after cancer therapy.

7.5 Conclusion

Cardiotoxicity is one of the most important causes of acute and chronic complications of cancer therapy in children and adolescents. Three distinct forms of cancer-therapy-induced cardiotoxicity have been described: acute or sub-acute, chronic, and late-onset. Cardiac morbidity and mortality related to high-dose anthracycline chemotherapy has been reported in up to 15 % of children with cancer in the acute and subacute phase of their initial therapy. In addition, cardiopulmonary disease is the third leading late cause of death in childhood cancer survivors. Cardiac biomarkers (i.e., BNP, NT-proBNP, cTnT and cTnI), ultrasound imaging of LV systolic and diastolic structure and function, and cardiopulmonary exercise testing (evaluating maximal oxygen uptake) have each been useful in detecting cardiotoxicity in this population. No comprehensive study has analyzed the combined utility of these technologies in assessing both early and late subclinical cardiotoxicity in children with cancer. This is especially true for subpopulations with a predisposition for cardiotoxicity by the presence of either genetic or non-genetic risk factors. In addition, several reports indicate that early treatment of high-risk adults undergoing chemotherapy with ACE inhibitors has been useful in reducing short-term cardiotoxicity. Treatment with ACE inhibitors may also be useful in reducing adverse cardiac remodeling in cancer patients with evidence of cardiomyopathy but no study has demonstrated long-term cardioprotection from ACE inhibitor therapy in this

population. The value of HF pharmacotherapy in treating children with acute or sub-acute, chronic, and late-onset cardiotoxicity has not been well studied but the causes may differ and etiology-specific therapies are lacking. Many survivors with cardiotoxicity have impaired mitochondrial structure and function. For those survivors inotropic therapies may hasten their demise so careful monitoring of therapeutic effects in this population is warranted.

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Pulmonary System

8

Tara O. Henderson

8.1 Introduction

Pulmonary disease is a highly prevalent cause of premature morbidity and mortality in long-term childhood cancer survivors. In the large-scale retrospective North American cohort, the Childhood Cancer Survivor Study (CCSS), Armstrong and colleagues reported significant excess rates of death due to pulmonary disease (standard mortality ratio, 8.8), second only to death from second malignant neoplasms [1]. Pulmonary toxicity is frequently reported in survivors of Hodgkin lymphoma, germ cell tumors, acute lymphoblastic lymphoma and metastatic Wilms tumor survivors, as the chemotherapy, radiation and surgeries used to treat these pediatric cancer (among others) can result in permanent lung damage [2, 3]. This damage can manifest as acute pneumonitis, late onset fibrosis, and structurally induced dysfunction from developmental abnormalities due to impaired growth of the thorax attributable to surgery or radiation. The cumulative incidence of pulmonary problems after childhood cancer increases with time since diagnosis, as with other late-effects, suggesting that survivors are at an elevated risk of developing later-onset pulmonary morbidities as they age [4].

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8.2 Radiation-Induced Pulmonary Damage

The lungs are particularly sensitive to radiation. Pulmonary late effects occur most often in patients with malignant diseases of the chest that are treated with radiation, i.e., those involving the mediastinum, the lung parenchyma or the chest wall. These survivors typically include those treated with chest or mantle field radiation for Hodgkin lymphoma, non-Hodgkin lymphoma, or sarcoma, and those whose primary disease metastasized to the lung (i.e., Wilms tumor). In one of the largest studies of pulmonary outcomes among adult childhood cancer survivors exposed to pulmonary toxic therapy, Mulder and colleagues demonstrated that radiation was the most important risk factor for pulmonary late effects [5]. In those exposed directly or indirectly to lung radiation, abnormal radiographic findings or restrictive changes on pulmonary function testing have been reported in more than 30 % of patients. In addition to radiation dose and the volume of lung in the radiation field, fractionation and younger age at therapy are risk factors for toxicity. Radiation can inflict damage directly to the lung tissue, and at higher doses, inhibit chest wall growth. This leads to diminished lung volumes and ultimately to restrictive lung disease, particularly when patients are young children at the time of therapy. In the Childhood Cancer Survivor Study, Mertens reported that survivors

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exposed to chest radiation have a five-fold increased risk of abnormal chest wall development (RR = 5.0; 95 % CI, 2.7–9.4), an over four-fold excess risk of lung fibrosis (RR = 4.3; 95 % CI, 2.9–6.6) and an over twofold risk of chronic pneumonia (RR = 2.2; 95 % CI, 1.5–7.0) [4].

Symptomatic radiation pneumonitis is a risk factor for long-term lung dysfunction as the acute changes associated with this condition often evolve to pulmonary fibrosis. Acute pneumonitis is usually only observed in patients who receive higher radiation doses (>30 Gy) to a significant portion of their lungs and is an uncommon outcome with contemporary therapy [6]. In these high doses, radiation toxicity is characterized by acute radiation pneumonitis, occurring within 1–3 months after radiation. Cough, pink sputum, dyspnea and pleuritis are common complaints during this subacute pneumonitis phase. When pulmonary-toxic chemotherapy (i.e., busulfan or melphalan) is combined with total body irradiation (e.g., for stem cell transplantation conditioning), reactions can occur during treatment. As mentioned, the acute changes of radiation pneumonitis may result in the development of pulmonary fibrosis. This fibrotic phase of injury can start within 3–6 months of post radiation completion, stabilizes after 1–2 years but can present clinically years following treatment. When symptomatic, pulmonary fibrosis usually presents with exertional dyspnea as well as chronic, non-productive cough. These clinical changes may be progressive, static or resolve over time. However, it is important to note, *the majority of chest RT survivors are clinically asymptomatic*. And yet while asymptomatic, many of these survivors may demonstrate sub-clinical radiographic and pulmonary function testing abnormalities, including diffusion capacity or abnormal restrictive or obstructive patterns that are common even after lower radiation doses [7].

The tolerance of the whole lung to fractionated RT doses is well described, especially in Wilms tumor survivors. Early studies on the outcomes of metastatic Wilms tumor survivors have shown that whole lung irradiation mainly affects the lung parenchyma and results in reduced lung volume, impaired lung compliance and hypoplasia and deformity of both the lung and chest wall [8–10]. In a series of metastatic Wilms tumor survivors treated with whole lung irradiation (15 Gy in 10–14 daily fractions) combined with actinomycin, survivors had small lung volumes but normal gas transfer per unit lung volume when compared to predicted age and height reference ranges, suggesting that while lung RT results in chest wall underdevelopment, diffuse lung fibrosis is not significant at this dose level.

Studies in Wilms survivors have also demonstrated that exposure to partial lung radiation increase the risk for pulmonary late effects. Shaw and colleagues showed that Wilms survivors who had received partial lung radiation (20 Gy in 10 daily fractions) demonstrated significantly lower lung volumes than those who received no radiation. In addition, forced expiratory volume in 1 s (FEV1), residual volume, and total lung capacity were similar between those survivors who received whole lung radiation and those who received the partial lung radiation.

The majority of studies of pulmonary outcomes after chest radiation in lymphoma patients involve patients who were treated for Hodgkin lymphoma as adults [11–14]. The majority of these studies indicate asymptomatic restrictive lung disease in up to 30–40 % of those survivors exposed to chest radiation. Bossi and colleagues described the pulmonary outcomes of 27 pediatric Hodgkin lymphoma survivors and found that exposure to less than 20 Gy of mediastinal radiation was not associated with an increased risk of lung dysfunction. However, in patients who received over 20 Gy of mediastinal radiation and higher cumulative doses of bleomycin, pulmonary diffusion capacity was impaired [15]. In a Danish population-based study of the pulmonary function of survivors of pediatric Hodgkin lymphoma and non-Hodgkin lymphoma (N = 41), Nysom and colleagues found that at a median of 11 years after diagnosis, total lung capacity and the diffusing capacity of the lung for carbon monoxide (DLCO) were reduced in both radiated and non-radiated patients who had received chemotherapy. Survivors who were treated with radiation at a young age were particularly at risk [16]. These findings have been confirmed in studies that demonstrated that combined treatment with chest radiation and bleomycin for Hodgkin lymphoma increases the risk of a persistent decrease in diffusion capacity [17, 18].

8.3 Chemotherapy-Associated Pulmonary Damage

Several chemotherapy agents can cause pulmonary dysfunction in long-term survivors. Antineoplastic drug-associated pulmonary damage may be the result of pneumonitis or fibrosis, hypersensitivity/allergy or idiosyncratic reactions. A dose–response toxicity has been demonstrated after treatment with bleomycin, chlorambucil or nitrosoureas. Damage mediated likely through an allergic effect, though very rare, is the result of methotrexate exposure.

Bleomycin, an antibiotic chemotherapy agent frequently used in Hodgkin lymphoma and germ cell tumor protocols, is the most common chemotherapy agent associated with lung injury in childhood cancer survivors. Bleomycin can cause acute pneumonitis as well as chronic lung toxicity. Toxicity is more common in older adults than in children. Pathophysiologic studies of bleomycin attribute its pulmonary injury to free radical formation and oxidative damage. Fibrosis develops post-treatment due to immune processes that include activation of effector cells, including alveolar macrophages, and release of cytokines, with tumor necrosis factor potentially playing a role. Usually, pulmonary abnormalities occur within 3–12 months after exposure and persist or progress.

Clinically, chronic toxicity or pulmonary fibrosis after bleomycin is characterized by impairment of gas diffusion between alveoli and pulmonary capillaries, and evidenced by a reduction in DLCO on pulmonary function testing. The greatest risk of bleomycin pulmonary toxicity has been observed with doses greater than 400 units/m^2, a dose seldom used in the treatment of pediatric patients. Although less common, pulmonary toxicity has been observed in children treated with 60–100 units/m^2. Bleomycin toxicity is variably exacerbated by concurrent or previous radiation treatment.

Alkylating agents, particularly the nitrosoureas, as well as cyclophosphamide, melphalan and busulfan have been implicated in late-onset lung fibrosis and chronic pulmonary dysfunction among childhood cancer survivors. Similar to those with symptomatic pulmonary disease associated with radiation therapy, pulmonary dysfunction due to chemotherapy exposure may include chronic cough or dyspnea associated with exercise intolerance.

The nitrosoureas (BCNU [carmustine] and CCNU [lomustine]) are alkylating agents that were used historically and commonly in the treatment of pediatric brain tumors. There is a clear relationship between cumulative dose of these agents and lung injury. When survivors are exposed to cumulative BCNU doses of more than 1,500 mg/m^2, more than 50 % will develop symptoms [19]. Lung injury may occur even at lower doses in individuals exposed to chest radiation. Long-term BCNU toxicity presents as pulmonary fibrosis. In a clinicopathologic study of 31 pediatric brain tumor patients exposed to BCNU 100 mg/m^2 every 6–8 weeks for up to 2 years, restrictive lung disease was reported after up to 17 years. Of the eight survivors alive at the time of study, four had clinical symptoms of shortness of breath and cough, six had signs of upper zone pulmonary fibrosis on chest X-ray and all eight had restrictive findings on pulmonary function testing [20].

Both cyclophosphamide and melphalan, in doses used for stem cell transplantation, have been implicated in late-onset pulmonary fibrosis, although the evidence for their toxicity is not as well established as with bleomycin and the nitrosoureas. Busulfan, generally when given at doses of more than 500 mg for stem cell transplant conditioning, causes toxicity and leads to a progressive restrictive lung disease pattern (defined as a decrease in forced vital capacity [FVC] and increase in FEV1/FVC in pulmonary function testing) [21]. As with other agents, concomitant exposure to chest radiation may exacerbate busulfan toxicity.

Other agents that occasionally cause lung injury include methotrexate, cytarabine and the vinca alkaloids. Both methotrexate and cytarabine have been associated with acute respiratory distress syndrome during treatment. Methotrexate has also been associated with hypersensitivity pneumonitis, chronic pneumonitis and fibrosis. This occurs at a frequency of less than 1 % and is thought to be an idiosyncratic hypersensitivity reaction to the drug. This toxicity is typically associated with rapid reversal and complete

recovery after drug withdrawal [22]. However, in a study of 26 pediatric leukemia survivors, 65 % of them had one or more abnormalities in vital capacity, total lung capacity, reserve volume or diffusion capacity [23]. Asymptomatic changes in pulmonary function tests that do not predict clinically significant problems have been associated with low dose oral administration for over 3 years, a treatment approach obsolete in pediatric cancer treatment. Case reports have linked vinblastine exposure to diffuse interstitial pulmonary infiltrates and chronic pulmonary changes.

Lastly, it is important to note that many chemotherapeutic agents, such as actinomycin D [24], bleomycin [25], cyclophosphamide [26], and doxorubin [27], potentiate the effects of radiation toxicity on the lung. Although doxorubicin is not pulmonary-toxic in itself, it magnifies the toxicity of the radiation [28]. In addition, toxicity to the lung is seen at much lower doses when pulmonary toxic drugs are combined than would be expected when given individually. For example, bleomycin in combination with other drugs such as cyclophosphamide, vincristine and doxorubicin magnify the risk for bleomycin-induced fibrosis [29].

8.4 Lung Injury After Stem Cell Transplantation

Hematopoietic stem cell transplant (HSCT) has become increasingly successful in curing pediatric patients of both solid and hematologic malignancies. Pulmonary complications are a major cause of post-transplant morbidity and mortality [30]. Pulmonary late effects following hematopoietic stem cell transplant are characterized by complex interactions between the conditioning regimen agents (i.e., total body irradiation, Busulfan, melphalan), non-infectious etiologies (i.e., pulmonary edema, bronchiolitis obliterans, bronchiolitis obliterans organizing pneumonia, diffuse alveolar hemorrhage, graft versus host disease), and infection during the period of hematopoietic and immune reconstitution (i.e., bacterial, fungal, cytomegalovirus [CMV], varicella zoster virus [VZV], and other viruses) [2] (see Fig. 8.1).

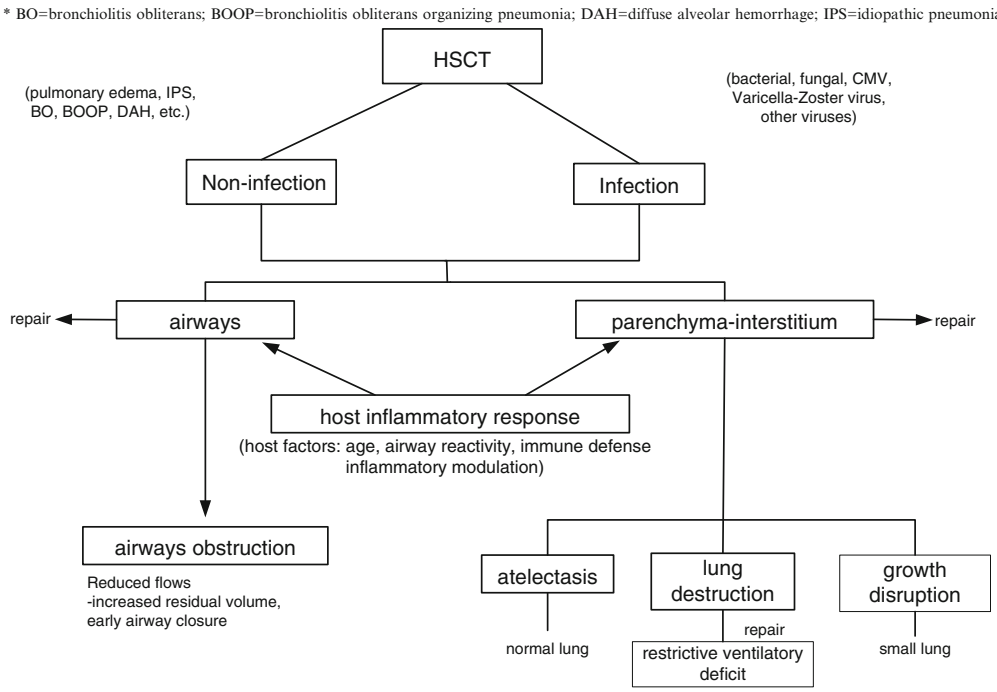

Fig. 8.1 Mechanisms of pulmonary dysfunction and/or growth by hematopoietic stem cell transplantation (HSCT). *BO* bronchiolitis obliterans, *BOOP* bronchiolitis obliterans organizing pneumonia, *DAH* diffuse alveolar hemorrhage, *IPS* idiopathic pneumonia syndroma

In other words, it is often difficult to discern which factors have the causative role in chronic lung disease. Both timing of the transplant and age at transplant are potential risk factors for late onset pulmonary morbidities. That is, those patients who received HSCT after two to three remissions (and therefore, most likely more chemotherapy incurring lung toxicity) had higher rates of these complications than those survivors transplanted in first remission [31]. Further, studies report that children transplanted at an older age had poorer pulmonary function testing values than those transplanted at a younger age [31]. Lastly, patients who have received prolonged immunosuppression for chronic graft versus host disease are at particular risk [31].

Patients undergoing total body irradiation as part of their conditioning regimen for stem cell transplantation have a high incidence of pulmonary late effects [21, 31]. As discussed, busulfan, carmustine, bleomycin and cyclophosphamide, all associated with pulmonary late sequelae, are known to cause pneumonitis and fibrosis after transplantation and this risk is increased in those who had previous radiation exposure or total-body irradiation for their preparative regimen.

Longitudinal data in survivors of HSCT during childhood demonstrate that there is a decline in lung volume and diffusing capacity from pretransplant for 3–6 months post transplant, partial recovery for 1–2 years, and then stabilization for up to 10 years post transplant. The most common finding on pulmonary function testing is restrictive lung disease, sometimes associated with a decrease in DLCO [2]. In a cohort of 89 childhood cancer survivors post allogeneic HSCT, Inaba reported progressive worsening of pulmonary function as measured by forced mid-expiratory flow (25–50 %), residual volume, total lung capacity (TLC), and DLCO. Obstructive lung disease is also observed in HSCT survivors. For example, Bruno reported that in a series of 80 children treated with allogeneic HSCT, mean FEV1/FVC values of less than 60 % of predicted were observed in patients whose chronic graft versus host disease persisted 5 years after transplant.

8.5 Thoracic Surgery and Lung Damage

A mainstay of therapy for the treatment of pulmonary metastases (particularly metastatic osteosarcoma) is surgical resection. Although children are more adaptive to lung resection than adults, a study of adult childhood cancer survivors more than 30 years post resection, demonstrated increased rates of hypertrophy or hyperinflation of the remaining lung as a compensatory effect for the long-term loss in lung volume. Radiation exposure heightens the risk of pulmonary late effects when combined with surgical resection. In a Dutch cohort of childhood cancer survivors exposed to pulmonary toxic therapy, those with a history of surgical resection combined with radiation exposure had the highest increased risk of long-term pulmonary function impairment [5].

8.6 Other Risk Factors for Pulmonary Late Effects

In addition to therapeutic exposure, children with cancer may have other risk factors that predispose them to lung disease. These include underlying asthma or chronic obstructive lung disease, infection, cigarette or marijuana use, and exposure to environmental toxins. It is not known how the aging process and associated decline in lung function will affect survivors who had lung injury during cancer therapy in combination with other co-morbid heart or lung problems. This is an area prime for future research.

8.7 Detection, Screening and Management

Care of survivors at risk for pulmonary toxicity should include an annual medical history and physical examination, and careful review of a patient's treatment summary. Chest X-ray and pulmonary function testing (including DLCO and spirometry) are recommended at entry into a long-term follow-up program and then as clinically indicated in patients with abnormal results or clinical symptoms (see Table 8.1).

Table 8.1 Pulmonary late effects and guidelines for surveillance[a]

Exposure	Potential Late Effect(s)	Risk Factors	Greatest Risk Factors	Pulmonary Health Evaluation and Counseling
Bleomycin	Interstitial pneumonitis Pulmonary fibrosis ARDS (rare)	**Host Factors** Younger age at treatment **Treatment Factors** Higher cumulative dose Combined with: – Busulfan – BCNU – CCNU **Medical Conditions** Renal dysfunction High dose oxygen support such as during general anesthesia **Health Behaviors** Smoking	**Treatment Factors** Cumulative dose ≥400 U/m^2 (injury observed in doses 60–100 U/m^2)	**Evaluation** Yearly pulmonary exam **Screening** Chest X-ray (CXR) Pulmonary function tests (PFTs; including DLCO and spirometry) *Baseline at entry into long-term follow-up. Repeat as clinically indicated in patients with abnormal results or progressive pulmonary dysfunction.* **Counseling** Tobacco avoidance/smoking cessation To SCUBA dive, patients should have medical clearance from a pulmonologist For **Bleomycin** exposed survivors, notify healthcare providers of history of exposure and risk of worsening fibrosis with high dose oxygen exposure such as during general anesthesia.

Alkylators – Busulfan – Carmustine (BCNU) – Lomustine (CCNU)	Pulmonary fibrosis	**Treatment Factors** Higher cumulative doses Combined with bleomycin **Medical Conditions** Atopic history **Health Behaviors** Smoking	**Treatment Factors** BCNU ≥600 mg/m^2 Busulfan ≥500 mg (transplant doses) Combined with: – Chest radiation – TBI	**Other considerations** In survivors with abnormal PFTs and/or CXR, consider repeat evaluation prior to general anesthesia Refer to pulmonologist in survivors with symptomatic or progressive pulmonary dysfunction.
Radiation – Chest – Whole lung – Mediastinum – Axilla – Mini-mantle – Extended mantle – Total Body Irradiation (TBI)	Pulmonary fibrosis Interstitial pneumonitis Restrictive lung disease – Growth abnormalities – Obstructive lung disease	**Host Factors** Younger age at irradiation **Treatment Factors** Radiation dose ≥10 Gy Chest radiation combined with TBI Radiation combined with: – Bleomycin – Busulfan – Carmustine (BCNU) – Lomustine (CCNU) – Radiomimetic chemotherapy (e.g., doxorubicin, dactinomycin) **Medical Conditions** Atopic history **Health Behaviors** Smoking	**Treatment Factors** Radiation dose ≥15 Gy TBI ≥6 Gy in single fraction TBI ≥12 Gy fractionated	Yearly influenza vaccines. Appropriate pneumococcal vaccination.
Stem Cell Transplant – With any history of chronic GVHD	Bronchiolitis obliterans Chronic bronchitis Bronchiectasis	**Treatment Factors** Chest radiation TBI Pulmonary toxic chemotherapy: – Bleomycin – Busulfan – BCNU – CCNU	**Medical Conditions** Prolonged immunosuppression related to chronic graft versus host disease and its treatment	
Surgery – Pulmonary lobectomy – Pulmonary metastasectomy – Pulmonary wedge resection	Pulmonary dysfunction	**Treatment Factors** Combined with pulmonary toxic chemotherapy: – Bleomycin – Busulfan – BCNU – CCNU **Medical Conditions** Atopic History **Health Behaviors** Smoking	**Treatment Factors:** Combined with: – Chest radiation – TBI	

Table adapted from Children's Oncology Group Long-Term Follow Up Guidelines (www.survivorshipguidelines.org)

Pneumococcal and influenza vaccination should be considered. Smoking exacerbates the risk for lung dysfunction, and all at-risk survivors should be counseled regarding the importance of smoking avoidance or cessation. Anecdotal reports of progressive pulmonary fibrosis after exposure to high oxygen concentration (e.g., during anesthesia) has prompted the recommendation that survivors treated with bleomycin avoid exposure to concentrated oxygen and wear a MedicAlert bracelet documenting their risk. As such, for all bleomycin-exposed survivors and for all survivors with symptomatic pulmonary toxicity or abnormal PFTs after exposure to other pulmonary toxic therapy, an anesthesia consult should be obtained prior to any surgical procedures. SCUBA diving is controversial for long-term survivors and those with risk factors for pulmonary late effects should obtain medical clearance from a pulmonologist prior to diving. Finally, any survivors that demonstrate clinical signs or symptoms of pulmonary dysfunction or abnormal imaging or pulmonary function testing, should be considered for referral to a pulmonologist.

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Renal, Genitourinary, and Reproductive Systems

9

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9.1 Pediatric Renal Tumors

This section is mostly devoted to Wilms' tumor, the most common primary malignant renal tumor affecting children. Wilms' tumors represent 92 % of all renal tumors in those 20 years old and younger; furthermore, they represent 96.2 % of renal tumors in children less than 5 years of age [1]. With multimodal therapy, the 5-year survival rates have improved to over 80 %, however, these treatments often come with long-term adverse effects or late effects that must be considered while delivering therapy [2]. The modes of therapy for pediatric renal tumors consist of surgery, radiation, and chemotherapy. Herein, we will discuss the long-term sequelae of each mode.

9.1.1 Surgery

The initial workup for Wilms' tumor is comprised of a thorough history and physical examination, laboratory tests, and detailed imaging. Surgical exploration is required unless the patient possesses bilateral tumors, a solitary kidney, an inoperable tumor based on pre-operative imaging, or extensive tumor thrombus. If the patient exhibits any of these characteristics, chemotherapy is recommended before definitive surgery (neoadjuvant chemotherapy). Surgical treatment usually comes in the form of radical nephrectomy with selective sampling of the lymph nodes under suspicion of metastatic involvement. The role of partial nephrectomy is limited, usually reserved for patients possessing bilateral tumors or solitary kidney after neoadjuvant chemotherapy.

The consequence of surgery pertains to the loss of renal parenchyma, resulting in varying degrees of renal insufficiency. Initially, the patient's renal function should be assessed every 3 months in successively increasing intervals. Given that

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almost all patients with Wilms' tumor receive chemotherapy, the impact of renal insufficiency cannot completely be attributed to surgery alone. Long-term studies utilizing the National Wilms' Tumor Study Group (NWTS) database show that the incidence of end-stage renal disease (ESRD) in unilateral disease is approximately 0.6 % in the absence of genitourinary abnormalities. For patients with bilateral disease, the incidence rises to 10–12 %. And, in those patients with congenital diseases associated with the WT-1 mutation, the incidence rate of ESRD increases to greater than 50 % [3]. As expected, in the rare cases requiring bilateral radical nephrectomy, ESRD is immediate and hemodialysis is required postoperatively.

Besides the loss of renal parenchyma from the surgery, other causes of renal insufficiency must be considered. These other causes include hyperfiltration injuries of the remaining kidney, a concern that may manifest several years after the surgery with proteinuria. Additionally, nephrectomy may result in hypertension. One analysis, specifically, of 1,171 patients showed a 7 % incidence of hypertension [4].

9.1.2 Chemotherapy

The chemotherapy regimen chosen for treatment of Wilms' tumor depends on both the tumor stage and the histology. The essential elements of the regimen are vincristine and actinomycin-D, with doxorubicin added for the patients who have Stage 3 or greater [5], and cyclophosphamide or ifosfamide added with the presence of diffuse anaplasia in Stages 2–4 [6].

Doxorubicin has been demonstrated to cause cardiomyopathy with a long-term risk of congestive heart failure of between 4 and 17 % [7]. It is unclear, however, whether doxorubicin individually causes this clinically significant cardiomyopathy, as opposed to the additive effects of both the chemo and radiation therapies. In a long-term, multi-institutional retrospective cohort study of the Childhood Cancer Survivor Study (CCSS) database with a 25-year follow-up, there was no clear association of congestive heart failure (CHF) in the absence of radiation therapy (RT) to the cardiac musculature [8]. However, the hazard ratio for CHF was increased in patients who received chemotherapy and RT, rather than RT alone, without doxorubicin (13.0 vs. 6.6, respectively).

Alkylating agents, including cyclophosphamide and ifosfamide, may result in various long-term side effects. Ifosfamide is nephrotoxic, with a dose-dependent risk of renal insufficiency. Cyclophosphamide, as well, may result in decreased sperm count, hemorrhagic cystitis, as well as secondary malignancy within the bladder. Vincristine, a plant alkaloid, may result in neurotoxicity [3, 8].

9.1.3 Radiation

External beam radiotherapy is given to patients at a high risk for relapse, including those possessing advanced stages and unfavorable histologies. Radiation carries a unique set of side effects in the still-growing pediatric population. Both muscle and bone growth may be affected within the radiation field, resulting in patients' decreased stature and scoliosis due to spinal irradiation.

Furthermore, because radiation is delivered to the abdomen, the reproductive organs may be involved. In males, this may result in hypogonadism with a potential delay in sexual maturation, as well as temporary azoospermia. In females, this may cause ovarian failure with resultant premature menopause. The uterus may also be affected, and previously-irradiated patients will hold future risks for low birth weight, prematurity, and congenital malformations of offspring [9, 10].

Lastly, radiation increases the risk of secondary malignancies estimated to be much higher than those in the adult population [11]. This risk may be amplified when combined with chemotherapy. Potential malignancies include hepatocellular carcinoma, acute myeloid leukemia, and tumors of the digestive tract and sarcomas.

9.2 Pediatric Testis Tumors

Prepubertal testicular and paratesticular tumors account for approximately 1–2 % of all pediatric solid tumors [12]. The types of tumors exhibited by this population are distinct when compared to the post-pubertal population, with benign tumors pre-

senting themselves more commonly [13]. In a retrospective review of 124 prepubertal patients over a 27-year period from the Surveillance, Epidemiology and End Results (SEER) database, inclusive incidence of testis cancer was 1.6 %, with yolk sac accounting for approximately 1.2 %, teratoma accounting for 0.4 %, and choriocarcinoma and seminoma each accounting for 0.02 % of cases [14].

Initial diagnosis of testis tumor is done through physical examination, usually presenting as a painless, testicular mass. The finding is confirmed by ultrasonography (US), although imaging cannot reliably distinguish between the benign and malignant lesions. An anechoic cystic lesion, however, may suggest the presence of a benign lesion. Initial blood work entails testicular tumor markers, which include alpha-fetoprotein (AFP), beta human chorionic gonadotropin (B-hCG), and lactate dehydrogenase (LDH). AFP elevation is indicative of tumor containing yolk sac elements, although using the normal adult reference value of <10 ng/mL is accurate only after approximately 8 months of age, as the infant can synthesize significant amounts of AFP from the liver/gastrointestinal tract. B-hCG is rarely elevated in prepubertal testis cancer. LDH serves as a marker for the overall tumor burden [14].

9.2.1 Initial Surgical Intervention

The initial surgical intervention is dependent on the type of testis tumor suspected, as the majority of these tumors are benign and may be managed with a testis-sparing approach.

Yolk sac, mentioned previously, is the most customary malignant prepubertal testis tumor [14]. If the serum AFP is elevated, yolk sac elements must be assumed; radical inguinal orchiectomy must be performed with high ligation of the spermatic cord. The inguinal approach is preferred due to avoidance of scrotal violation as well as the ability to perform the high ligation of the cord. The spermatic cord should be ligated with dark non-absorbable suture to facilitate identification at the time of retroperitoneal lymph node dissection, if necessary.

In the setting of negative tumor markers, a benign etiology for the mass is more likely. As such, partial orchiectomy may be attempted. These testis tumors are often well encapsulated, which facilitates the performance of a partial orchiectomy. In such cases, a pathology evaluation by frozen section must always be obtained intraoperatively to confirm absence of malignant elements. If the tumor is confirmed to be mature teratoma in the prepubertal male, partial orchiectomy may possibly be completed. However post-puberty, these tumors should be managed with radical orchiectomy, as a possibility exists for malignant change and metastasis. Seminoma and choriocarcinoma must be managed similarly with radical inguinal orchiectomy.

A number of long-term implications must be considered prior to the performance of the orchiectomy. During the operation, the ilioinguinal nerve should be identified and spared, as the inadvertent ligation of this nerve will result in ipsilateral numbness of the anterior thigh and scrotum. Although theoretically, the child remains with a contralateral testis, it has been demonstrated that this remaining testis can be subfertile [15]. Fertility is often a paramount concern along with cancer control for parents of these children. Certainly when possible, testis-sparing surgical techniques should be performed. Also, a thorough discussion regarding sperm cryopreservation must occur with the parents as well as with the post-pubertal child. Sperm preservation from the excised testis may still be possible from histologically-normal sites through extraction of seminiferous tubules. And, lastly, one must consider the effects of cosmesis for the patient. In the post-pubertal patient, concurrent or delayed placement of a testicular prosthesis may be considered. In the prepubertal patient, testicular prosthesis placement should be delayed until the contralateral testis is fully grown, to allow symmetric placement.

9.2.2 Chemotherapy

Treatment of testis tumors after surgical confirmation of pathology is dependent on staging. Prepubertal testis tumors are staged using the Children's Oncology Group (COG) germ cell

tumor-specific staging system, illustrated as follows [16]:

- Stage I—Limited to testis, tumor markers normal after appropriate half-life decline
- Stage II—Transscrotal orchiectomy, microscopic disease in scrotum or high in spermatic cord (<5 cm from proximal end), retroperitoneal lymph node involvement (<2 cm), increased tumor marker levels after appropriate half-life decline
- Stage III—Retroperitoneal lymph node involvement (>2 cm), no visceral or extra-abdominal involvement
- Stage IV—Distant metastases, liver metastases

The advent of platinum-based chemotherapy has improved the cure rates dramatically, to above 95 % [17]. Chemotherapy, however, results in numerous long-term sequelae [17]. Cisplatin has been implicated in long-term renal toxicity, with reduction in glomerular filtration rate (GFR) up to 20 %, as well as tubular dysfunction [17]. Peripheral neurotoxicity has also been attributed to cisplatin-based regimens, resulting in a number of late effects, including decrease in sensation, paresthesias, postural hypotension, and ototoxicity (hearing loss and tinnitus) [17].

Cisplatin-based chemotherapy has been implicated in a number of cardiovascular toxicities. Symptoms of Raynaud's phenomenon secondary to vascular toxicity have also been linked to bleomycin and cisplatin, likely in a synergistic fashion. The incidence of secondary cardiovascular disease is as high as 18 % [17]. The patients receiving chemotherapy for germ cell tumor (GCT) are at a twofold relative risk of cardiovascular disease, and, as well, are at an increased risk for cardiovascular-related mortality. Causation theories include direct endothelial cell damage as well as indirect damage via increase in the incidence of hypertension, hyperlipidemia, and metabolic syndrome.

Bleomycin results in dose-related toxicity to the lungs with mortality related to pulmonary sequelae between 1 and 3 %. This dose-related toxicity has resulted in consideration of regimens without bleomycin, such as etoposide/cisPlatin (EP) alone for 4 cycles, rather than Bleomycin/etoposide/cisPlatin (BEP) given for three cycles [17].

Cisplatin may result in azoospermia in the short-term, but at least 50 % of patients achieve recovery of sperm production [18].

Lastly, GCT survivors treated with cisplatin-based chemotherapy were at a greater risk for developing secondary malignancies [19]. The incidence of non-GCT in this specific population is 60–100 % higher with chemotherapy [19]. These malignancies include tumors of the GI tract, bladder, connective tissue and hematopoietic malignancies (leukemia/lymphoma). The risk for secondary malignancy is amplified when chemotherapy is delivered in conjunction with radiotherapy.

9.2.3 Radiation

The long-term adverse effects of radiation must be considered for radiotherapy, as well as the significant radiation doses young patients receive with repeated computed tomography.

Radiation may cause decreased renal function, though these effects may not be apparent until up to 5 years post-treatment. Etiology of this impairment has been postulated to be secondary to small vessel sclerosis, and direct parenchymal injury.

As mentioned previously, radiation may cause a significantly increased risk for second malignancy. This risk is highest in patients receiving both chemotherapy and radiotherapy (relative risk 2.9) [19].

9.2.4 Retroperitoneal Lymph Node Dissection (RPLND)

Retroperitoneal lymph node dissection is the process of lymphadenectomy targeted to the expected landing sites of malignant testis cancer. It may be performed primarily, as in seminoma, or post-chemotherapy, after tumor markers have normalized.

As RPLND is within the retroperitoneum, there is always risk of damage to the structures therein with their resultant sequelae. Rarely, injury occurs to the kidney, particularly in cases with bulky lymphadenopathy. Additionally, those

cases necessitating an extensive hilar dissection may be complicated by damage to the renovascular system, which might result in renal insufficiency and hypertension in the long-term [19].

Neurologic sequelae include injury secondary to intraoperative positioning or inadvertent ligation of nerves. Stretch injury may occur to the femoral nerve and the brachial nerve; this type of injury may cause long-term deficits in the extremities. In addition, in the rare cases with extensive mobilization of the aorta and ligation of lumbar arteries, paraplegia may come as a result of ischemia of the spinal cord [19].

Finally, for males the effects of seminal emission must be considered, as the lymph node dissection occurs within the area of the postganglionic sympathetic nerve plexus responsible for this function. The hypogastric nerve plexus innervates the bladder neck and the vas deferens, prostate, and external urinary sphincter. If the bladder neck does not contract during seminal emission, retrograde ejaculation occurs. Newer techniques involve careful sparing of this plexus along the aorta. If retrograde ejaculation does persist, however, sperm harvest from the urine may be necessary to aid in fertility.

Screening for infertility should be performed if the patient has been actively attempting to conceive children for more than 1 year without success. Upon referral to urology, an initial semen analysis will be performed to assess the quantity and quality of sperm present.

9.3 Pediatric Rhabdomysarcoma

Rhabdomyosarcoma (RMS) is the most widespread pediatric sarcoma, with 20 % of all RMS arising from the genitourinary system (bladder, prostate, vagina/uterus, and paratesticular) [20]. Initial clinical presentation is dependent on specific organ involvement. RMS involving the prostate and bladder often presents as urinary obstruction and hematuria. Vaginal/uterine RMS may present with vaginal mass or bleeding. Paratesticular RMS usually presents similarly to testis cancer, with a painless scrotal mass. This section will focus on bladder and prostate RMS, as these occur most frequently.

9.3.1 Surgery

Although radical extirpation was historically the definitive treatment for RMS, advances in multimodal therapy and an emphasis on bladder sparing have resulted in an evolution in treatment. Definitive surgery is now reserved for after an initial course of chemotherapy and/or radiotherapy. As a result, it is difficult to distinguish the cause of long-term sequelae of bladder dysfunction.

However, the treatment of bladder/prostate RMS may require the need for bowel segments in the use for either bladder augmentation, or urinary diversion. The use of bowel in the context of urine management results in a number of long-term problems due to its inherent characteristics. Mucus production, infection, and stone formation are chronic issues associated with the use of bowel in the urinary tract. Vitamin B12 deficiency may be an issue, particularly when the ileocecal junction is required in the reconstruction. Bowel obstruction has been observed as both an early and late complication, particularly when ileum is used versus colon [21].

There are a number of potential metabolic issues related to the absorptive nature of bowel. Ileum is usually the segment of choice in both augmentation and diversion. This may result in hyperchloremic, hypokalemic, metabolic acidosis, requiring electrolyte surveillance. Also, these metabolic dysfunctions have been shown to negatively impact growth and development, particularly when intervention is performed at a young age.

The development of alternatives to standard bowel may decrease the incidence of these long-term sequelae. Current studies include the use of stem cells to aid in bladder regeneration, as well as the use of demucosalized bowel with autologous urothelial cell implant [21].

9.3.2 Chemotherapy

Chemotherapy has become the mainstay in the treatment of rhabdomyosarcoma. In RMS involving the bladder and prostate, current regimens involve the use of vincristine, actinomycin D, and cyclophosphamide [22]. Vincristine holds the potential to cause neurotoxicity and alopecia.

Long-term side effects of actinomycin D typically are related to radiation therapy, causing an additive effect on organ damage. Lastly, cyclophosphamide has been implicated in cardiomyopathy, hemorrhagic cystitis, and bladder cancer (~10-year latency period) [23]. Mesna, which binds the toxic metabolite of cyclophosphamide, may be administered concurrently to decrease the risk of hemorrhagic cystitis.

9.3.3 Radiation Therapy

Radiation therapy has been implicated in the most drastic long-term sequelae in the treatment of RMS. It can have a profound negative impact on bladder function, and may make both extirpative and reconstructive surgery complex. As a result, it should be reserved only for cases of residual disease after surgery and chemotherapy.

In a series of 11 patients followed over an average of 6.6 years, 7 of the 11 children received radiotherapy [24]. The remaining four children who were not treated with radiotherapy maintained normal bladder capacities and voiding patterns. The seven children, who were irradiated developed nocturnal enuresis, continuous dribbling, abnormal bladder capacity, and/or abnormal voiding patterns. Four of these children developed upper tract dilation. In another series of 109 patients treated for RMS, 52 retained their bladders and were followed long-term, and 57 had their bladders removed. Of the 52, 43 patients received radiation, and of these, 13 (30 %) developed bladder dysfunction. This is in stark contrast to the one out of nine who were not irradiated [25].

In a series of 26 females treated with radiation, late effects were observed in multiple organ systems [26]. The most common systems affected included endocrine, gynecologic, renal, musculoskeletal, and gastrointestinal. Endocrine side effects included ovarian failure and pubertal delay. Gynecologic sequelae included vaginal stenosis and fistulae. Renal effects included pyelonephritis and urinary tract obstruction.

The effects of radiation on the developing musculoskeletal system of the young child are dramatic. Hypoplasia of the bones can develop within the radiation field, resulting in severe retardation of the growth of the pelvic bones, and limb length discrepancy (see Chap. 11 for additional discussion on the musculoskeletal system).

Finally, radiation may result in secondary malignancies of up to six times the expected rate. These patients may develop hematopoietic malignancies (e.g., leukemia), cutaneous melanomas, bone and soft tissue sarcomas, and breast cancer [27].

Survivors of childhood rhabdomyosarcoma must be followed closely for late effects due to chemotherapy, surgery and radiation. They require lifelong surveillance, and depending on the therapy received, may necessitate the assistance of a multidisciplinary team. Education in survivorship, as well as the support of their families, will equip them to become better advocates for their healthcare. The screening guidelines can be accessed in detail at www.survivorshipguidelines.org, under COG Long-Term Follow-up guidelines [Children's Oncology Group Long-Term Follow-up Guidelines, (2008) version 3.0] [28].

9.4 Adnexal Masses in Young Girls and Adolescents

The pediatric population has an overall 1 % ovarian malignancy rate, however, ovarian masses when discovered in childhood have a very concerning 10 % malignancy rate [29, 30]. National protocols to maintain fertility and preserve the ovary have not been implemented, resulting in high oophorectomy rates in many centers for benign large ovarian masses. There are no well-defined guidelines for managing ovarian tumors in childhood, and it is unclear how best to preoperatively evaluate these ovarian lesions. In order to implement ovarian preservation and salvage techniques for ovarian malignancies in children, they should be approached with preoperative risk assessment useful to the patient.

Operative management should differ based on the size and characteristics of the lesion, as well as age of the child. Fertility preservation should be discussed at diagnosis, because the options available after treatment are very limited. This section will describe the common malignancies of the reproductive system seen in children, with emphasis on fertility preservation.

9.4.1 Neonates

Neonatal masses are largely cystic and resolve, for the most part, spontaneously within 10–12 months due to maternal withdrawal of hormonal stimulation. Simple cysts less than 5 cm resolve spontaneously within 10 months of age. If an ovarian mass or cystic mass is noted on imaging, then it is recommended that surveillance with imaging be done, either with computerized tomography (CT) or ultrasound (US) or both, and that it continues at 6- to 12-week intervals until resolution [29, 30]. If a cyst does not completely resolve by 12 months of age but is decreasing in size, continued surveillance is still appropriate [30]. Cystic masses of the ovaries in newborns require surgery if they are symptomatic, persist after 12 months of age, or have a large size greater than 6 cm, with evidence of calcifications, excrescences, or mural nodules which are concerning for malignancy [29, 30].

9.4.2 Pediatric/Adolescents

For children and adolescents, preoperative risk assessments have been studied to guide therapy and provide indications which may be more concerning for malignancy. Oltmann et al. in 2010 performed a single institution, 15.5-year retrospective review to provide pre-operative risk assessment for pediatric patients presenting with ovarian masses on imaging [30]. The age-adjusted incidence for girls under 9 years of age was 0.102/100,000 (0.00102 %), in those aged 10–19, an incidence of 1.072/100,000 (0.001072 %), and 11.446/100,000 (0.011446 %), in the adult female population older than 19 [29, 30].

9.4.3 Clinical Presentation

The chief complaint most associated with malignancy is the presentation of a pelvic mass or precocious puberty.

9.4.4 Findings on Imaging

Preoperative imaging can reveal a pelvic mass on either ultrasound, CT scan, or MRI. Pelvic masses that are 8 cm or larger on preoperative imaging are more likely to be malignant [30–32]. Solid ovarian masses must always be considered malignant, until proven otherwise by histological evaluation. Ultrasound or CT findings of a solid mass are more commonly associated with malignancy (33–60 %), as compared to heterogeneous (15–21 %) or cystic (4–5 %) lesions [30, 31]. The suspicion of malignancy goes even higher when the following findings are presented: thick-walled cyst, adnexal masses with peritoneal metastasis, extraovarian spread, and intracystic vegetations. The differential diagnosis of pediatric solid ovarian tumors includes dysgerminoma, neuroblastoma, Wilms' tumor, rhabdomyosarcoma, lymphoma, leukemia, and other nongenital tumors located in the pelvis. Pre-operative chest CT is also helpful to evaluate for metastatic disease [30, 31].

9.4.5 Tumor Markers

In one study, tumor markers were obtained in 71 % of patients, with approximately 54 % of the results being elevated [30, 33]. Elevated Cancer Antigen-125 (CA-125), Alpha feto-protein (AFP), and Beta-hCG (B-hCG) were significantly associated with malignancy, while an elevated Carcinoembryonic antigen (CEA) was not. It is recommended that if precocious puberty is present, serum hormone levels including Follicle Stimulating Hormone (FSH), Luteinizing Hormone (LH), Estradiol, Lactate Dehydrogenase (LDH), and Testosterone should also be added to pre-operative labs. Even if tumor markers are not entirely conclusive, they may be useful for

post-operative surveillance, serving as important markers for disease recurrence. Baseline tumor markers are recommended preoperatively [29, 32].

9.4.6 Pre-operative Risk Stratification

When evaluating for percentage of malignancy in relation to ovarian mass, 1- to 8-year-olds have the highest rate of malignancy [30, 31]. Patients who are prepubescent are at a 25 % chance of presenting with malignancy when a pelvic mass is also present [30, 31]. Complaints of pelvic mass or precocious puberty are more likely to be associated with malignant neoplasm. The usage of tumor markers can be helpful; when these markers are not elevated, however, this does not necessarily exclude a malignancy.

9.5 Germ Cell Tumors of the Ovary

Ovarian cancer is the most common gynecologic malignancy in women ≤25 years-of-age, with 35–45 % of ovarian cancers in children approximating malignant germ cell tumors [29, 34, 35]. Germ cell tumors comprise one-half to two-thirds of ovarian neoplasms in girls less than 18 years of age, compared with 20 % of ovarian tumors in adult women [36–38]. Approximately 80 % of ovarian neoplasms in girls less than 9 years of age are malignant. Epithelial neoplasms occur rarely in the prepubertal age group. Malignant ovarian germ cell neoplasms (OGCNs) occur more frequently among Asian/Pacific Islander and Hispanic women than among Caucasians (www.uptodate.com) [37, 38].

Pediatric germ cell tumors have several distinguishing features that vary from adult germ cell tumors. In children, the extragonadal site accounts for 50 % of tumors compared with only 10 % extragonadal in adults [35, 36]. The introduction of bleomycin, etoposide and cisplatin significantly improved the survival in children, allowing preservation of vital organs with extensive metastatic tumor involvement.

9.5.1 Cell Types

The tumors are divided into five subgroups based on degree of differentiation and cellular components involved. Each type of tumor arises from a primordial germ cell, causing expression of different tumor markers with varying malignant potential. The incidence by histology is the following: pure dysgerminomas (39 %), teratomas, immature plus mature with malignant transformation (39 %), and nondysgerminoma or mixed cell types (29 %) [39, 40]. Ovarian germ cell neoplasms present with rapid growth, unlike the more common epithelial ovarian neoplasms. Most patients, however, present with stage IA disease. Benign cystic teratoma, dysgerminoma, or a tumor with components of dysgerminoma (mixed germ cell tumor) is present with bilateral adnexal masses in 10–12 % of cases [39, 40].

9.5.2 Clinical Manifestation

Abdominal pain and abdominal mass comprise 85 % of presenting symptoms. Fever or vaginal bleeding occurs in 10 % [34]. Ovarian germ cell neoplasms tend to be large, with an average diameter of 16 cm [34]. Additional findings are ascites, which occur in 20 %, rupture which occurs in 20 %, and torsion that is reported in 5 % of the population [34].

9.5.3 Tumor Markers

Clinical biomarkers are beneficial pre-operatively by identifying which histological type of ovarian tumor is present. Alpha-fetoprotein (AFP) is produced by endodermal sinus tumors, mixed germ cell tumors, and immature teratomas. Lactate dehydrogenase (LDH) is elevated in dysgerminomas. CA-125 is an epithelial ovarian cancer marker, which is not very specific even though it is highly sensitive and can be elevated in a variety of other processes such as endometriosis, pelvic inflammatory disease, pregnancy, or Crohn's disease. Human chorionic gonadotropin (hCG) will be elevated in pregnancy, hydatidiform moles,

placental site tumors, nongestational choriocarcinoma, and embryonal ovarian carcinomas. Thrombocytosis can arise in ovarian torsion cases and has been associated with ovarian malignancies in young girls and adolescents [34, 37].

9.5.4 Staging

Ovarian germ cell tumor staging, used frequently by gynecologic oncologists, is the (FIGO) staging system, which is based on an adequate staging operation at the time of diagnosis. Stage 1 is defined by tumor limited to the ovaries. Such occurs when the tumor is confined to one ovary and no ascites are present, with an intact capsule. Stage 1B includes the disease present in both ovaries, also without any evidence of ascites, and an intact capsule. Stage 1C includes a ruptured capsule or capsular involvement, with positive peritoneal washings, or malignant ascites. Stage 2 is defined to be an ovarian tumor with pelvic extension. Stage 2A describes pelvic extension to uterus or tubes; Stage 2B includes pelvic extension to other pelvic organs (bladder, rectum, or vagina). Stage 2C occurs when there is evidence of pelvic extension, and the findings indicated for Stage 1C. Stage 3 is defined by tumor outside the pelvis, or positive nodes. Stage 3A is defined by microscopic seeding outside the true pelvis. Stage 3B is defined by gross deposits 2 cm or smaller, and Stage 3C is defined by gross deposits larger than 2 cm or the presence of positive nodes. Stage 4 is the presence of any distant organ involvement, including liver parenchyma or pleural space [34, 37].

9.5.5 Fertility-Preserving Surgery

Fertility-preserving surgical intervention is directed toward the preservation and protection of reproductive and sexual function. When frozen section is utilized at the time of the surgery, unilateral salpingo-oophorectomy with preservation of an otherwise normal-appearing uterus and contralateral ovary is an appropriate procedure. If malignancy is suspected, unilateral salpingo-oophorectomy and appropriate staging is performed, with a second procedure done after the final pathology specimens are reviewed. This would be preferred to an unnecessary permanent procedure prior to final pathology. If malignancy is suspected or confirmed, adequate staging includes abdominal and pelvic exploration, peritoneal washings, biopsies of suspicious areas, and periaortic and pelvic lymph node sampling. Laparoscopy is safe and effective in the hands of an experienced surgeon. It is recommended to use a laparoscopic retrieval bag to prevent spillage and upstaging the patient. The ipsilateral fallopian tube is also to be removed because of rich lymphovascular connections between the tube and ovary. Gynecologic oncologic outcomes are not compromised by conservative surgery, even with metastatic disease elsewhere. Occult contralateral ovarian involvement approaches 10 % and is most common with dysgerminomas [35–37, 41]. Some surgeons routinely perform a wedge biopsy of a normal-appearing contralateral ovary for patients with dysgerminomas [36, 41]. However, this practice is not universally accepted because these tumors are typically chemosensitive. Unnecessary surgery on normal ovaries should be avoided because postoperative adhesions are common and may impair fertility.

9.5.6 Survival

The Intergroup Germ Cell studies, created by the Pediatric Oncology Group (POG) and the Children's Cancer Group (CCG), were conducted from 1990 to 1996 and evaluated the overall survival of children with germ cell tumors. A 95.7 %, 6-year survival rate was observed for Stage 1 and 2 in ovarian and testicular tumors and 88.9 % for Stage 2 and 4 gonadal and Stages 1–4 extragonadal tumors (Table 9.1) [36–38]. Immature teratomas have a 3-year survival rate of 93 with 80 % of recurrences salvaged with chemotherapy [36]. Management of Stage 1 tumors with surgery alone

Table 9.1 Treatment/postoperative chemotherapy

Stage	N	Treatment	6-Year EFS%	6-Year survival
1	41	S + BEP	95	95.1
2	16	S + BEP	87.5	93.8
3	58	S + HDP/EB vs. BEP	96.6	97.3
4	16	S + HDP/EB vs. BEP	86.7	93.3

Table adapted with permission from Bilmire et al. (2004) [36]
HDP high dose cisplatin, *E* etoposide, *B* bleomycin, *S* surgery

was based on excellent survival in girls with microscopic yolk sac tumors treated with surgery alone.

Tumor volume is one of the most important determining factors for prognosis [34, 37]. Malignant germ cell neoplasms are highly sensitive to platinum-based chemotherapy and can spread via the lymphatics, bloodstream, or by intraperitoneal dissemination; however, nodal involvement is less common, as these neoplasms are known to spread hematogenously to the liver and lungs. Females with metastatic or incompletely resected disease favor a poor prognosis. Even without randomized trials, there has been indirect evidence that patients with malignant ovarian germ cell tumors who have optimally debulked disease (defined as all areas of residual disease less than 1 cm) have a higher remission rate from chemotherapy and have better long-term outcomes than those with bulky unresectable disease [29, 32, 34, 37]. The majority of adolescents with ovarian germ cell tumors should undergo maximal surgical cytoreduction before starting chemotherapy. With modern cisplatin-based adjuvant chemotherapy, approximately 80 % of patients who present with advanced disease will be long-term survivors, even if they have residual disease remaining after cytoreductive surgery [34, 37, 42, 43]. This treatment regimen is tolerated well by the pediatric population, however, well-known side effects can still be observed. Etoposide can lead to a secondary malignancy such as an acute leukemia, while bleomycin has a 1 % risk of pulmonary fibrosis.

9.5.7 Menstruation/ Fertility

After chemotherapy, it is reported that at least 80 % of these patients will resume normal menstrual function [39, 42, 43]. In those who become pregnant, there is no apparent increase in pregnancy complications. Utilization of oocyte donors has enabled patients with a uterus and no ovaries to become pregnant and carry a child. Cryopreservation of fertilized eggs, ovarian tissue, and oocytes has allowed patients of a young age to plan for future fertility (see Sect. 9.10 below).

9.6 Ovarian Sex Cord Stromal Tumors

Ovarian malignancy comprises 1 % of childhood cancer, with sex cord stromal tumors comprising 7 % overall, and approximately 5–12 % of pediatric ovarian neoplasms [44]. The most common presenting types are juvenile granulosa cell tumors which present in 7–8 % of girls under 20 years old, followed by Sertoli-Leydig cell tumors presenting in 1–2 %. Classic clinical presentations include abdominal pain or distension, an abdominal mass or gastrointestinal symptoms. Sex cord stromal tumors are unique, in that, many patients may present with clinical evidence of sex hormone production with isosexual precocious puberty such as breast enlargement, galactorrhea, vaginal bleeding, virilization, or primary/secondary amenorrhea.

9.6.1 Diagnosis

Any patient with suspected ovarian malignancy should be screened for serum tumor markers. These include alpha fetoprotein (AFP), beta-human chorionic gonadotropin (β-hCG), carcinoembryonic antigen (CEA), cancer antigen 125 (CA-125), inhibin A and B, lactate dehydrogenase (LDH) and serum calcium. Measurement of inhibin B may be more specific, however, it may

not be elevated in pre-pubertal children. These tumors may also secrete mullerian inhibitory substance (MIS). It is also recommended to obtain androstenedione and testosterone, even in the absence of clinical signs or symptoms.

9.6.2 Fertility Preserving Surgery

Stage 1 disease requires unilateral salpingo-oophorectomy with examination of contralateral ovary. Visible tumors should be removed when reasonable and considered safe. Schneider et al. [45, 46] reported preservation of uterus and the contralateral ovary for children with Stage 2 and 3 disease. Rare lymph node metastasis discourages the need for a routine staging lymphadenectomy, but those which seem to be enlarged at surgery or on imaging should, however, be removed.

Experienced surgical and anesthetic teams are performing minimally invasive surgeries with minimal complications. Care must be taken to avoid intraoperative spillage or rupture, which will upstage the patient. Laparoscopy has the advantage of exploring the abdominopelvic cavity through a small incision, evaluating both ovaries and allowing for fertility-sparing surgery to be performed. The ovary can be removed through one of the port sites after being ligated and transected from its vascular pedicle and its attachment to the uterus. There are also emerging techniques with single port laparoscopy, requiring a single umbilical incision that may improve cosmetic outcomes. Traditional exploratory laparotomy with unilateral salpingo-oophorectomy can also be performed using a vertical incision, which is recommended in the setting of large adnexal masses.

9.6.3 Postoperative Chemotherapy

FIGO Stage 1A with complete resection does not necessitate further treatment or adjuvant chemotherapy. Currently only surveillance with clinical and radiographic monitoring along with tumor markers every 3 months for 2 years is recommended.

FIGO stage 1C with juvenile granulosa cell tumors is treated based on intraoperative rupture and the presence of a low number of mitosis. In such cases, some may argue for observation with frequent imaging, clinical follow-up and serial tumor markers. Standard treatment consists of adjuvant platinum-based chemotherapy after resection, followed by 4 or 6 cycles of BEP for Stage 1C tumors—those with pre-operative rupture and/or malignant ascites (positive washings) or Stages 2/3/4. This regimen is also considered for Stage 1C due to intraoperative rupture with >20 mitosis/10hpf. FIGO Stage 1C or greater with Sertoli-Leydig tumors must be treated with adjuvant platinum-based chemotherapy. Detailed chemotherapy regimens have traditionally been platinum-based: cisplatin/etoposide/ifosfamide (PEI), Bleomycin/Etoposide/Cisplatin (BEP), etoposide/bleomycin, paclitaxel/carboplatin, vincristine/adriamycin/cytoxan, vincristine/cisplatin/bleomycin [44–47].

Regarding those with poorly differentiated tumors, high number of mitosis, and particularly those with Sertoli-Leydig cell tumors, higher intensity chemotherapy regimens are recommended. Sertoli-Leydig tumors are aggressive tumors that carry a high risk of relapse and tumor-related death, versus granulosa cell tumors present in other patients. Stage 4 is rare and carries a poor prognosis, with little evidence to guide therapy [44–47].

9.6.4 Surveillance

Patients should be followed with routine imaging: CT, ultrasound, and MRI during and after therapy. Imaging at 3-month intervals is recommended for the first 3 years after diagnosis, with lessening intervals thereafter. Most recurrences happen within the first 3 years following diagnosis. Juvenile granulosa cell tumors recur within the same time period, however, adult granulosa cell tumors may recur after more than 10 years [44, 46]. Tumors markers such an inhibin B and other such hormonal markers, if elevated at diagnosis, should be measured serially every 3 months during follow-up, after completion of therapy [44, 46, 48].

9.6.5 Survival

Patients with Stage 1 disease have Event-Free Survival (EFS) of 95.1 % and Overall Survival (OS) of 95.1 % [44, 46]. Those with Stage 2 disease have EFS of 87.5 % and OS of 93.8 % after treatment with standard 6 cycles of cisplatin, bleomycin, and etoposide (BEP). Patients with Stage 3 or Stage 4 disease are usually given higher dose chemotherapy, and may experience greater toxicity without exhibiting any significant difference in survival [44, 46]. Stromal tumors are often confined to one ovary and frequently present with Stage 1 disease, and surgery is the effective management of these tumors, with a favorable prognosis. Patient outcomes are associated with tumor stage and mitotic activity. Tumors with >20 mitosis/10 hpf have an EFS of 0.48, versus those with tumors <20 mitosis per 10 high power field with an EFS of 1.0. Recurrence of Stage 1 ovarian sex cord-stromal tumors is uncommon. Recurrence is most common during the first 2.8 years, usually in the abdominopelvic area or regional lymph nodes. Rare case reports of hematogeneous spread to the chest, liver and bone have been described more commonly with adult granulosa cell tumors [44, 46]. However, the majority of patients will present with a low tumor stage, and therefore will have an excellent prognosis.

9.6.6 Menstrual and Subsequent Pregnancy

Fertility-preserving surgery and adjuvant chemotherapy appear to have little negative effect on future fertility, and most patients will regain their menstrual cycle with a good overall survival [48, 49].

9.7 Borderline Tumors

Borderline epithelial tumors are characterized as epithelial tumors with varying degrees of nuclear atypia that lack stromal invasion of the ovary. These tumors are more common than invasive epithelial carcinomas in children, accounting for roughly 31 % of epithelial malignancies. These tumors are very rare with high cure rates. The majority of borderline tumors occur in postmenarchal patients with a median age of 19.7 years old at the time of diagnosis. Borderline tumors, also known as tumors of low malignant potential (LMP), have comprised as much as 20 % of epithelial tumors in children under the age of 18 [50, 51].

9.7.1 Fertility Preserving Surgery

Recommendations include resection of all visible tumor, omental biopsy, and appendectomy if a mucinous tumor is present. This is indicated for the possible presence of a synchronous appendiceal lesion. Cystectomy for Stage 1 borderline tumors is considered appropriate management. Guidelines suggest that there is no benefit to lymph node dissection in clinically normal lymph nodes or random peritoneal biopsies or removing clinically uninvolved areas [50, 51]. Intraoperative frozen section sensitivity has ranged from 62 to 75 %, and therefore necessitates final and thorough pathology review for a correct diagnosis [52, 53]. FIGO recommends unilateral salpingo-oophorectomy or ovarian cystectomy for borderline tumors in patients desiring future fertility. Published data have not suggested that laparotomy is superior to laparoscopy in the hands of a skilled surgeon [50, 51].

9.7.2 Recurrence/Survival

Rate of recurrence after fertility-sparing surgery is as high as 37 %, with the rate increasing after an ovarian cystectomy (12–37.5 %) [50, 51]. Inadequate tumor-free margins after a cystectomy were a risk factor for recurrence [50, 51]. Long-term prognosis is favorable with 5- and 20-year survival of 90 and 80 %, respectively [50–53]. Those patients who underwent cystectomy had a shorter time to recurrence, however, the exact type of surgery does not appear to

impact long-term survival, with studies suggesting close follow-up [50, 51, 54]. Long-term recurrences have occurred greater than 10 years from initial surgery in the adult population [50, 51, 54]. Rare case reports have demonstrated invasive recurrence after Stage 1 borderline tumors, and is estimated to be less than 1 % [50, 51, 54]. Patients who under fertility-sparing surgery have excellent reproductive outcomes with fertility rates ranging from 40 to 70 %. The use of infertility treatments is safe for these patients [50–53].

The National Comprehensive Cancer Network guidelines recommend follow-up every 3–6 months for up to 5 years, followed by annual evaluations. Patients should undergo a physical exam which includes a pelvic examination and continued serum markers if elevated prior to surgery (CA-125) [55].

9.8 Epithelial Ovarian Cancer in Adolescents

Epithelial ovarian neoplasia in adolescent girls and young women is very rare, but remains part of the differential diagnosis of any ovarian mass. Studies have shown that epithelial tumors affect roughly 10–28 % of the pediatric and adolescent population, with approximately 65 % of the epithelial tumors occurring in patients over the age of 17 [56]. These are much lower than the 60–80 % reported in the adult population. Tumors most commonly are unilateral and vary in size from 2.5 to 21 cm with mean diameter of 11.7 cm. Epithelial tumors comprise less than 20 % of ovarian tumors in pediatric patients, and rarely occur before menarche [54, 56]. Many authors have suggested that hormonal stimulation is necessary to trigger the development of epithelial ovarian tumors. Specifically in one report, all epithelial tumors in patients under 14 years of age were benign, whereas the 8 malignant epithelial tumors in this series occurred in patients over 15 years old [54]. The histological subtypes that commonly present in childhood are the serous and mucinous tumors. These tumors are further classified into benign, malignant, or borderline (of low malignant potential).

Benign cystadenomas are the most frequent type of epithelial tumor in this population, with serous cystadenomas more prevalent than mucinous ones [54]. Adenocarcinoma in children is a rare phenomenon, with only case reports in the literature. Mortality rates are clearly higher when these carcinomas arise in premenarchal girls. Imaging studies are useful for preoperative assessment to evaluate the presence of ascites and to anticipate the extent of disease. The most commonly used modalities are abdominal and pelvic computerized tomography (CT) or magnetic resonance imaging (MRI). Chest CT may also be performed to evaluate for pleural effusion, pulmonary metastases, and mediastinal lymphadenopathy.

Unlike germ cell tumors, epithelial ovarian tumors frequently cause an elevation in CA-125. Careful follow-up of these patients is required by routine surveillance with imaging and CA-125 levels.

9.8.1 Fertility-Sparing Surgery

Intraoperative adult staging protocols are recommended if there is concern for epithelial ovarian cancer present, with optimal responses to chemotherapy achieved in the setting of minimal disease. Roughly 25 % of adult patients present with tumors confined to the ovary (Stage 1) or tumors beyond the ovary but confined to the pelvis (Stage 2). These patients must be managed with maximal cytoreductive surgery. Systemic chemotherapy may or may not be recommended. When the tumor has metastasized throughout the peritoneal cavity or involves paraaortic or inguinal lymph nodes (Stage 3), or the tumor has spread to more distant sites (Stage 4), the standard of care is surgery followed by systemic chemotherapy. Improved survival rates are noted with the combination of optimal cytoreductive surgery (defined as less than 1 cm in maximum diameter of residual tumor) and platinum-based chemotherapy. Studies have shown that the volume of

residual disease after cytoreductive surgery inversely correlates with survival [29, 57]. Many studies have demonstrated an improved response to therapy, less platinum resistance, and improved survival with cytoreduction to <1 mm or no visible disease.

A vertical midline incision is the best approach for staging and primary cytoreductive surgery, and generally pfannensteil incisions should be avoided, as they can potentially limit exposure of the pelvis and abdomen, and prevent access to the peritoneal cavity and upper abdomen. Obtaining any free fluid or washings for cytologic evaluation is recommended. Exploration of all intraabdominal organs and surfaces including the bowel, liver, gallbladder, diaphragms, mesentery, omentum, and the entire peritoneum should be visualized and palpated, with suspicious areas biopsied. If there are no such suspicious areas, multiple biopsies should be obtained from the peritoneum of the cul-de-sac, paracolic gutters, bladder, intestinal mesentery, as well as the diaphragm. Omentectomy should be performed, along with an evaluation of pelvic and periaortic nodes with suspicious nodes sent for frozen section and additional node sampling sent for evaluation to exclude the possibility of Stage 3 disease. A total abdominal hysterectomy and bilateral salpingo-ophorectomy is recommended only after pathology has been confirmed and finalized. Fertility-conserving surgery with unilateral salpingo-oophorectomy is an option, especially for Stage 1A epithelial ovarian cancer. Most surgeons do not routinely biopsy the contralateral ovary if it appears normal. Clinically occult bilateral ovarian involvement has been noted in only 2.5 % of women undergoing staging for ovarian malignancy. Ovarian surgery may impair future fertility, which is the purpose of conservative surgery [57].

Pseudomyxoma peritonei may be present, commonly erupting free mucin deposits into the peritoneal cavity with implants of mucinous epithelium. Pseudomyxoma peritonei has been diagnosed in combination with benign, malignant, and borderline tumors of the ovary. Prognosis relies upon successful removal of all visible mucin, and mucin-producing epithelium [57]. Surgical management consists of removal of the appendix, bilateral ovaries, omentum, and residual mucin. Resection of bowel, diaphragm, peritoneum and mesentery may be required, followed by irrigation, and subsequent chemotherapy.

9.8.2 Adjuvant Chemotherapy

Treatment of early-stage epithelial cancer includes intravenous adjuvant chemotherapy. Standard protocols consist of six cycles of a platinum-based doublet, such as paclitaxel and carboplatin, as this has demonstrated efficacy in the adjuvant therapy of women with advanced-stage epithelial ovarian cancer. Maximal benefit of six cycles has typically been limited to women with serous cancers or stage II disease [57]. It is advisable to individualize the number of treatment cycles based upon patient risk factors and chemotherapy tolerance, with a minimum of three cycles.

9.8.3 Surveillance

Follow-up should include office visits with physical and pelvic exams every 3–6 months for up to 5 years post-treatment, and then annually. Careful follow-up with post-operative imaging and CA-125 levels is critical to detect recurrence or progression of disease. CA-125 levels should continue for every visit if initially elevated, with computed tomography scan, or transvaginal ultrasound in those who underwent fertility-sparing surgery, as clinically-indicated.

9.8.4 Survival

The 10-year survival rate of patients under 20 years of age with malignant epithelial ovarian carcinoma was 73 % [58]. Patients with Stage 1 disease have an overall survival (OS) of 100 %, while those with Stage 3 disease have an OS of 50 % [57].

9.9 Small Cell Carcinoma

Small cell carcinomas of the ovary are extremely rare, with an incidence of one child or adolescent in a population of 80 million. These tumors are known to be very aggressive with unfavorable prognosis, and may demonstrate paraneoplastic hypercalcemia in 66 % of patients [59]. The tumors are predominately unilateral with a mean diameter of 14.5 cm. Less than 30 % of small cell carcinomas of the ovary develop in patients under 20 years old, and less than 1 % develop in children, with the youngest patient diagnosed at 14 months of age [59]. Patients commonly present with FIGO Stage 2 to Stage 4 disease. The most common presenting symptoms are abdominal pain, constipation, and weight-loss. These are commonly misdiagnosed and require an accurate immunohistochemical work-up for inhibin, which will be positive for sex cord-stromal tumors and negative in small cell carcinomas of the ovary. The staining may demonstrate positivity for parathyroid hormone-related peptide, which explains the etiology of hypercalcemia in these patients. Key management for hypercalcemia includes hydration and diuretic therapy. Favorable prognostic factors include age over 30 years, normal pre-operative calcium, tumor size less than 1 cm, and absence of large cells on pathology [60].

9.9.1 Fertility-Sparing Surgery

Studies have suggested that preservation of the uninvolved ovary and uterus in conjunction with intensive multi-adjuvant chemotherapy does not compromise patients' overall survival. Due to the highly aggressive nature of the disease, attempts at maintaining reproductive function are only reserved for Stage 1A disease. Aggressive surgical resection is advised with unilateral salpingoophorectomy, lysis of adhesions, omentectomy, appendectomy, bilateral pelvic and periaortic lymphadenectomy, followed by chemotherapy [59]. There is no definitive consensus within the literature, and therefore should be left to the operating surgeon's discretion.

9.9.2 Treatment

Optimal management includes adjuvant chemotherapy combinations of platinum-based regimen with etoposide, alkylating agents and anthracyclines, with no role for expectant management, even in those with Stage 1A disease. MAKEI protocol recommends adjuvant chemotherapy with 6 cycles of cisplatin, ifosphamide, and doxorubicin, with consolidating high-dose chemotherapy consisting of carboplatin and etoposide in order to reduce the high doses of etoposide leading to secondary leukemia. Some studies have suggested that radiotherapy has a significant therapeutic impact in patients with Stage 1 disease. In patients with macroscopic residual tumor, local deep hyperthermia may be considered [59].

9.9.3 Survival

Patients diagnosed with Stage 1A disease have an event-free survival (EFS) of 33 %; those with 1C have 10 %, and those with Stages 2–4 have an EFS of 6.5 % [59].

9.10 Oncofertility

9.10.1 Ovarian Tissue Cryopreservation

Preservation of fertility is critical to young adult cancer survivors. Numerous survivors will maintain their reproductive potential after the successful completion of treatment, but many still may face problems with infertility several years after the completion of therapy. Infertility is defined as the inability to conceive after 1 year of intercourse without contraception. Rates of permanent infertility and compromised fertility after cancer

treatment vary and depend on many factors. Whole pelvic radiation, and numerous chemotherapy regimens containing high dose alkylators put adolescents at risk for acute ovarian failure or premature menopause. The ultimate impact of treatment on reproductive potential depends on the age of the patient at the time of treatment, the type of treatment, the duration, and the total cumulative dose of the treatment administered [61, 62].

9.10.2 Effect of Cancer Regimens on Female Infertility

Females are born with a finite number of primordial follicles, which are depleted through each menstrual cycle leading to maturation of oocytes and subsequent atresia. The chemical toxicity of chemotherapy treatments involves prevention of cell division and adversely affects DNA function within ovarian cells. Each treatment carries a different risk for premature ovarian failure. Higher rates of fertility preservation are seen in women under 30-years-old undergoing treatment with standard protocols. Alkylating agents are as a whole more toxic than the platinum-based therapies. Pelvic irradiaton can have significant effects on the ovary, many of them permanent, even in young girls. Total body irradiation in hematologic malignancies has been shown to affect uterine volume, which is only minimally improved with hormonal therapy [61]. Cranial radiation greater than 35–40 Gy can impair the hypothalamic-pituitary function, and cause hypogonadism through gonadotropin-releasing hormone (GnRH) deficiency [54, 62, 63].

Historically, the assessment of fertility has relied on subjective reports of menstrual history instead of objective parameters of FSH (Follicle-Stimulating Hormone) levels, ovarian volume, antral follicle counts, and AMH (Anti-Mullerian Hormone) levels [48, 64, 65]. Despite resumption of normal menses, there exists a persistent vulnerability for diminished ovarian reserve. Lee et al. found that when objective parameters such as ultrasound and laboratory data were used, reduced follicle counts and alterations were demonstrated in the following hormone levels: FSH, AMH, inhibin B and LH [66]. It should be emphasized that female fertility may be compromised despite the continuation or resumption of seemingly normal cyclic menses and that regular menstruation does not guarantee normal fertility. Any diminished ovarian reserve may result in a lower chance of conception and higher risk of early menopause. Even if women are initially fertile after cancer treatment, the duration of their fertility may ultimately be shortened (see Table 9.2 below) [67].

9.10.3 Fertility Preservation Options in Females

9.10.3.1 Embryo Cryopreservation

The most established and effective fertility preservation technique is embryo cryopreservation, which is commonly performed by reproductive endocrinologists and infertility specialists. The process begins with a 10–14 day course of ovarian stimulation from the beginning of the menstrual cycle to produce a large number of mature eggs, or oocytes. The patient then undergoes a minor outpatient surgical procedure to harvest the oocytes through transvaginal aspiration. In vitro fertilization is utilized once the oocytes have been harvested, along with sperm that is fresh or frozen, requiring either the partner or donor's sperm to create an embryo. These embryos can then be frozen with the use of vitrification, a rapid-freezing method that minimizes crystallization of the embryo to allow for storage, and later, implantation. The cost hovers around $8,000 per cycle and $350 per year for storage fees [67].

9.10.3.2 Oocyte Cryopreservation

Oocyte cryopreservation is still a relatively new technique that requires harvesting and freezing of oocytes or unfertilized eggs after a patient has undergone 10–14 days of ovarian stimulation from the beginning of menstrual cycle. The partner or donor's sperm is not needed for this process. The oocytes are harvested during an outpatient surgical procedure through transvaginal aspiration, and are then frozen with the use of vitrification. This is an excellent option for

Table 9.2 Effect of cancer treatment and development of amenorrhea [67]

High risk	>80 % Women develop amenorrhea
	Whole abdominal/ pelvic radiation ≥15 Gy in prepubertal girls and ≥10 Gy in postpubertal girls.
	External beam radiation that exposes the ovaries
	Cyclophosphamide 7.5 g/m^2 in females under 20 years of age
	Any alkylating agent (cyclophosphamide, ifosphamide, busulfan, BNU, CCNU) + TBI or whole pelvic irradiation
	Cranial/ brain radiation ≥40 Gy
Intermediate risk	30–70 % women develop amenorrhea after treatment
	Whole abdominal/pelvic radiation 10 to <15 Gy in prepubertal girls
	Whole abdominal/pelvic radiation 5–10 Gy in postpubertal girls
	Spinal radiation ≥25 Gy
Low risk	<20 % develop amenorrhea after treatment
	*CMF, CEF, CAF x 6 cycles for women <30 years-of-age
	Nonalkylating chemotherapy: ABVD, CHOP, COP
	Anthracycline + cytaribine
Low risk	Negligible affects on menses
	Methotrexate + fluorouracil
	Vincristine
	Bleomycin/Dactinomycin

Table adapted with permission from Levine et al. (ASCO 2010) [67]
**CMF* cyclophosphamide, methotrexate, fluorouracil, *CAF* cyclophosphamide, doxorubicin, fluorouracil, *CEF* cyclophosphamide, epirubicin, flurouracil, *ABVD* dactinomycin, bleomycin, vinblastine, doxorubicin, *CHOP* cyclophosphamide, doxorubicin, vincristine, prednisone, *COP* cyclophosphamide, vincristine, prednisone

patients who may not have a partner, or who are in the pediatric age group. As of 2010, there were over 900 reported deliveries with approximately 60 % of mature oocytes surviving the thaw. The cost is approximately $8,000 per cycle and $350 per year for storage fees [67].

9.10.3.3 Ovarian Cryopreservation and Transplantation

Ovarian cryopreservation and transplantation entails the freezing of ovarian tissue and reimplantation of the tissue after completion of cancer treatment. For most ovarian cancers where preservation of ovarian tissue poses a risk of recurrence, this procedure is not recommended. It holds many advantages, such as possessing no requirement of a sperm donor or ovarian stimulation, and it is an immediate procedure, minimizing delay prior to chemotherapy. It is a same-day outpatient surgical procedure, often performed laparoscopically to harvest the ovarian tissue. This is not a common procedure for suspected ovarian malignancies, but may be utilized for other pelvic tumors requiring chemotherapy [67].

9.10.3.4 Gonadal Shielding During Radiation Therapy

Some clinicians have proposed shielding the ovaries to reduce the dose of radiation delivered to the reproductive organs. This is only possible with selected radiation fields and is dependent on the anatomy, usually not recommended for ovarian malignancies [54, 67, 68].

9.10.3.5 Ovarian Transposition (Oophoropexy)

Oophoropexy, or ovarian transposition, is the use of surgical repositioning of the ovaries away from the radiation field in patients undergoing pelvic radiation. It is an outpatient surgical procedure, where transposition is performed just prior to radiation therapy. Large cohort studies and case series suggest only a 50 % chance of success due to altered ovarian blood flow and scattered radiation. Many patients need repositioning or in vitro fertilization (IVF) in order to conceive [54, 67, 68].

9.10.4 Ovarian Suppression with Gonadotropin Releasing Hormone (GnRH) Analogs or Antagonists

The use of hormonal therapies to protect ovarian tissue during chemotherapy or radiation therapy has been entertained, however, large studies have failed to show any benefit. Studies have looked at administration of certain medications prior to and during treatment with chemotherapy without

compelling evidence of success. The cost is approximately $500 per month [48, 54, 67, 68].

ASCO guidelines for Fertility Preservation Methods in Cancer Patients [66]

9.10.5 Points of Discussion Between the Patient and Physician

When discussing fertility preservation with a patient, individual factors such as disease, age, treatment type, dosages, and pretreatment fertility should be considered when counseling patients about the likelihood of infertility. This discussion should take place at the time or soon after diagnosis for patients who are interested in fertility preservation to maximize successful outcomes. The effects of cancer and its treatment on fertility may vary. Female fertility treatments are dependent on the menstrual cycle phase and can only be initiated at monthly intervals. Review of available resources and information should be incorporated into the treatment planning and decision-making, as well as referral to a reproductive endocrinologist in order to avoid the delay of fertility treatment. Patient advocacy resources include Fertile Hope, the Lance Armstrong Foundation Livestrong, and the Susan G. Komen Breast Cancer Foundation (see Table 9.3) [42]. The two methods of fertility preservation with the highest likelihoods of success are sperm cryopreservation for males, and embryo freezing for females. Conservative surgical approaches and transposition of ovaries or gonadal shielding prior to radiation therapy may also preserve fertility in selected cancers. Currently, there is no substantial evidence suggesting an increased risk of disease recurrence associated with most fertility preservation methods and pregnancy, even in hormonally-sensitive tumors. Aside from hereditary genetic syndromes and in utero exposure to chemotherapy, there is no evidence that a history of cancer, cancer therapy, or fertility interventions increase the risk of cancer or congenital abnormalities in the offspring. Chemotherapy and treatment-related infertility may be associated with psychosocial distress, and early referral for counseling has been shown to be beneficial in patients [40, 54, 67, 68].

9.10.6 Fertility Preservation Options in Males

Pretreatment counseling is essential for those undergoing potential gonadotoxic therapy. Early referral to a reproductive endocrinologist is extremely helpful and encouraged. Fertility preservation requires individualization, including the type of treatment, time available, patient's age, and disease and partner status.

9.10.7 Sperm Cryopreservtion

Sperm cryopreservation is an effective and the most well-established technique for fertility preservation in males treated for cancer. It is an outpatient procedure, where sperm is retrieved after masturbation, and subsequently frozen. The cost is approximately $1,500 for three samples stored for 3 years, with an additional storage fee for additional years [67]. Available interventions are unlikely to delay initiation of cancer treatment. For pre- and post-treatment, patients should undergo semen analysis to assess their reproductive status, and patients who remain azoospermic may consider techniques such as testicular sperm extraction (TESE). For patients who are unable to ejaculate, techniques for stimulation or electroejaculation may be useful. Spermatogonial stem cell transplantation, cryopreservation of testicular tissue for autotransplantation, xenotransplantation, and in vitro maturation of sperm are still under investigation. Alternative options such as donor sperm and adoption may also be presented as a means of fatherhood. Aside from hereditary genetic syndromes, there is no evidence that a history of cancer or cancer treatment increases the risk of cancer or congenital abnormalities in the offspring of survivors [67].

In vitro fertilization technology and sperm banking procedures have revolutionized new

Table 9.3 Summary of fertility preservation options in females

Characteristic	Embryo freezing	Egg freezing	Ovarian tissue freezing	Radiation shielding of gonads		Ovarian transplantation
Definition	Harvesting eggs, IVF, and freezing of embryos for later implantation	Harvesting and freezing of unfertilized eggs	Freezing of ovarian tissue and reimplantation after cancer treatment	Use of shielding to reduce scatter radiation to reproductive organs		Surgical repositioning of ovaries away from radiation field
Pubertal status	After puberty	After puberty	Before or after puberty	Before or after puberty		Before or after puberty
Time requirement	10–14 days from menses; outpatient surgery	10–14 days from menses; outpatient surgery	Outpatient surgery	During radiation treatment		Outpatient surgery
Success rates	40 % per transfer; varies per age and transfer; thousands of births	21.6 % per embryo transfer; 900 live births	Case reports of seven live births (as of 2010)	Only possible with selected radiation fields and anatomy		Approximately 50 % as a result of altered blood flow and scattered radiation
Cost	$12,000/cycle, pregnancy and storage fees; additional cost	$12,000/cycle, pregnancy and storage fees; additional cost	$12,000 for procedure, storage fees and reimplantation; additional cost	Generally included in cost of radiation		Unknown, may be covered by insurance
Timing	Before or after treatment	Before or after treatment	Before or after treatment	During treatment		Before treatment
Special Considerations	Need partner/donor sperm	Attractive for single women or those opposed to embryo creation	Not suitable if high risk metastasis; only cryopreservation option for prepubescent girls	Expertise required/does not protect against chemo effects		Expertise required
Characteristic	**Radical trachelectomy**	**Ovarian suppression**	**Donor embryos**	**Donor eggs**	**Gestational surrogacy**	**Adoption**
Definition	Surgical Removal of he cervix with preservation of uterus	GnRH analogues used to suppress ovaries	Embryos donated by a couple	Eggs donated by a woman	Woman carries a pregnancy for another woman or couple	Process that creates a legal parent–child relationship
Pubertal status	After puberty	After puberty	After puberty	After puberty	After puberty	After puberty
Time requirement	Inpatient surgical procedure	In conjunction with chemotherapy	Varies; is done in conjunction with IVF	Varies; is done in conjunction with IVF	Varies; time is required to find surrogate and implant embryos	Varies depending on type of adoption
Success rates	No evidence of higher cancer recurrence rates in appropriate candidates	Unknown; conflicting results; larger randomized studies in process	Unknown	40–50 %	Similar to IVF (30 %)	N/A
Cost	Generally included in cost of cancer treatment	$500 per month	$5,000 to $7,000 (in addition to IVF costs)	$5,000 to $15,000 (in addition to IVF)	$10,000 to $100,000	$2,500 to $35,000
Timing	During treatment	During treatment	After treatment	After treatment	After treatment	After treatment
Special consideration	Limited to early stage cervical cancer; offered at a limited number of centers	Does not protect from radiation	Donor embryos available through IVF clinics or private agencies.			Medical history often a factor

techniques available for men with extremely reduced sperm count and motility. Spermarche, the production of sperm, occurs at approximately 13–14 years of age, but once sperm are present, the patient's age does not seem to affect the quality of sperm produced. DNA damage caused by exposure to chemotherapy or radiation leads to compromised sperm production, quality, and motility. The American Society of Clinical Oncology (ASCO) recommends that sperm be collected before initiation of cancer therapy, and prior to any toxic altering effects on the sperm's DNA integrity [66, 67]. Sperm DNA may be compromised even after a single treatment. Cancer itself can be associated with low sperm counts, and has been demonstrated in men with Hodgkin's lymphoma and testicular cancer. Intracytoplasmic sperm injection (ICSI) ushered in the opportunity for patients with low sperm count or sperm quality to create an embryo by allowing a single sperm to be used to fertilize the egg. It is reasonable and recommended to make every effort to bank sperm, since recent progress in Andrology laboratories and in the use of assisted reproductive techniques, allows the successful freezing and future use of a very limited amount of sperm.

In noncancer populations, there is no evidence of an increased risk of adverse outcomes if cryopreserved rather than fresh sperm are used for assisted reproductive techniques. Studies have shown, however, that with the use of assisted reproductive techniques, there may be a higher associated rate of major birth defects than with unassisted conception, but further long-term data is still needed for any conclusive evidence.

9.10.8 Testicular Suppression with Gonadotropin Releasing Hormone (GnRH) Analogs or Antagonists

The efficacy of gonadoprotection through hormonal manipulations has only been evaluated in very small studies in cancer patients and has not been demonstrated to be of any value. Hormonal therapy in men is not successful in preserving fertility when highly sterilizing chemotherapy had been administered nor has it been shown to speed recovery of spermatogenesis [64, 67].

9.10.9 Testicular Sperm Extraction (TESE)

This is a well-established procedure where a small portion of tissue from the testicle under local anesthesia is removed and a few viable sperm cells are extracted for the purpose of intracytoplasmic sperm injection (ICSI). This procedure allows the use of minimal available sperm, sometimes even only one sperm, to be used for fertilization with a mature oocyte. TESE is performed as an outpatient surgical procedure. Sperm can also be obtained via freezing sperm obtained through testicular aspiration, electroejaculation under sedation, or from a postmasturbation urine sample [67].

9.10.9.1 Gonadal Shielding During Radiation Therapy

Gonadal shielding is used to reduce the dose of radiation delivered to the testicles. It has only been done in a few case series, and is often only possible with selected radiation fields and anatomy [67].

9.10.9.2 Testicular Tissue Cryopreservation

Testicular tissue cryopreservation is still experimental, along with testis xenografting. This procedure requires spermatogonial isolation by freezing testicular tissue or germ cells and reimplantation after cancer treatment or maturation. This technique has only been shown in animals and has not been yet tested in humans. It has been performed as an outpatient surgical procedure (Table 9.4) [67].

Table 9.4 Summary of fertility preservation options in males

Procedure	Sperm banking	Sperm banking (alternative methods)	Radiation shielding of gonads	Testicular tissue freezing	Testicular sperm extraction	Donor sperm	Adoption
Definition	Sperm is obtained through masturbation, then frozen for future use	Sperm obtained through testicular extraction or electro-ejaculation under sedation	Use of shielding to reduce the dose of radiation delivered to the testes	Tissue obtained through biopsy and frozen for future use	Use of biopsy to obtain individual sperm from testicular tissue	Sperm donated by a man for artificial insemination or IVF	Process that creates a legal parent–child relationship
Pubertal status	After puberty	After puberty	Before and after puberty	Before and after puberty	After puberty	After puberty	After puberty
Time requirement	Outpatient procedure	Outpatient procedures	In conjunction with radiation treatments	Outpatient procedure	Outpatient procedure	Readily available for purchase	Varies depending on the type of adoption
Success rates	Generally high. The most established technique for men	If sperm is obtained, similar to standard sperm banking	Possible with select radiation fields and anatomy	No available human success rates	30–70 % in post-pubescent patients	50–80 %	N/A
Cost	Approx. $1,500 for three samples; storage fees average $500 per year	Varies greatly based on collection method	Generally included in the cost of radiation treatments	$500 to $2,500 for surgery; $300 to $1,000 for freezing; $500 per year for storage	$4,000 to $16,000 (in addition to costs for IVF)	$200 to $500 per vial (in addition to costs for IUI or IVF)	$2,500 to $35,000
Timing	Before treatment	Before treatment	After treatment	Before treatment	Before or After treatment	After treatment	After treatment
Special consideration	Deposits can be made every 24 h	Can be considered if male cannot ejaculate	Expertise required; does not protect against effects of chemotherapy	May be only option for pre-pubescent boys	Center should be able to freeze sperm found at time of biopsy	Can choose donor based on wide range of characteristics	Medical history often a factor

Table adapted with permission from Levine et al. (ASCO 2010 and Livestrong.com) [67]

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Gastrointestinal and Hepatic Systems

10

Jacqueline Casillas and Amy Jacobson

10.1 Introduction

Abdominal complaints are one of the most common reasons for outpatient medicine office visits [1]. For the pediatric cancer survivor, it may be more than just a common psychosomatic complaint or attempt to avoid school and warrants careful consideration. Disruptions to the gastrointestinal system from cancer treatment can affect nutritional intake and lead to failure to thrive, chronic pain and hospitalization. The liver, one of the body's most vital organs, is also susceptible to the long-term and late effects of cancer treatment. In this chapter, we will provide an overview of potential gastrointestinal and hepatic late effects from pediatric cancer treatment with guidelines for screening examinations and specialist referral.

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10.2 Gastrointestinal

10.2.1 Risk Factors

A history of radiation therapy is highly associated with late effects to the gastrointestinal (GI) tract, which may manifest several decades following treatment [2, 3]. Although chemotherapy alone is more frequently associated with acute gastrointestinal complications such as diarrhea, Vincristine may have the long-term effect of slowing intestinal transit [4]. Chemotherapy and radiation administered concurrently may have a synergistic effect that increases GI toxicities [4]. Modern radiation therapy has advanced with the development of 3-D simulation and dose tracking techniques, but normal gastrointestinal mucosa that falls within the radiation field is vulnerable to damage [3]. Ionizing radiation alters DNA of tumor cells, leading to apoptosis [3]. Normal intestinal crypt epithelial stem cells are susceptible to this same process, leading to acute GI injury [3]. Chronic enteropathy, such as stricture formation, functional abnormalities, ischemia and fibrosis, occurs through complex changes as the tissue rebuilds [3, 4]. Additionally, children who underwent hematopoietic stem cell transplantation (HSCT) and experienced acute or chronic graft-versus-host disease may experience complications beyond the end of treatment [3, 5]. (See Chap. 13 for a more thorough discussion of the impact of HSCT.) The combined factors of com-

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promised pre-transplant health status, intensive treatment regimens, and immune system dysregulation contribute to widespread cellular injury and inflammation, resulting in late effects to the gastrointestinal system [6]. Exploratory surgery for tumors located in the abdominal region, such as Wilms' tumors or an abdominal neuroblastoma, is a risk factor for adhesions and bowel obstructions throughout the lifetime [7].

10.2.2 Late Effects

10.2.2.1 Esophageal Damage

The esophagus is the entry point of the gastrointestinal system, extending from the throat to the stomach. Acute damage to the esophagus during treatment may come from esophagitis or strictures induced by radiation, chemotherapy or candidal infections due to compromised immunity [8]. Late effects such as fibrosis and ulcerations have been reported up to 10 years after the end of treatment [8]. The esophagus is also a common site of complications from chronic graft-vs-host disease, resulting in desquamation, strictures and dysphagia [9, 10].

10.2.2.2 Chronic Graft-vs.-Host Disease

Chronic graft-vs-host disease of the gastrointestinal tract may affect both the upper and lower tracts of hematopoietic stem cell transplant survivors [4]. Survivors may present with xerostomia or ulcerations of the oral cavity [4] (Additional information on oral late effects is covered in Chap. 20). New onset diarrhea more than 100 days after transplant may represent lower intestinal involvement [4].

10.2.2.3 Cholelithiasis

Gallstones are a common gastrointestinal finding for adults, with estimates of 10–15 % of the U.S. population having gallbladder disease [11]. Certain risk factors have been well established as the cause for gallstone formation, such as age (over 40), female gender, and obesity [11]. However, gallstones may develop in pediatric cancer survivors not fitting the common profile due to a history of abdominal surgery which affects the biliary tree and/or abdominal radiation of at least 3,000 cGy [12].

10.2.2.4 Bowel Obstruction

Peristalsis is responsible for the movement of nutrients, gas and waste through the small bowel. This process may be slowed or stopped due to bowel obstructions and result in pain, vomiting, dehydration and in very rare cases, death [13]. Pediatric cancer survivors who received abdominal radiation may have scarring of the intestines, which contributes to small bowel obstruction [14]. Adhesions develop in the majority of abdominal surgeries, both open and laparoscopic [7]. Formed from the infiltration of fibroblasts at the site of surgical trauma, adhesions connect two intestinal surfaces that normally move fluidly and unrestricted, resulting in pain and obstruction [7].

10.2.2.5 Colorectal Cancer

Radiation therapy to the abdomen and pelvis at doses of greater than 3000 cGy for pediatric cancer treatment is a strong risk factor for the development of secondary gastrointestinal cancer, especially colorectal [15, 16]. This risk is further elevated in survivors who have a family history of colorectal cancer, most notably in families with confirmed genetic syndromes such as Lynch Syndrome, also known as Hereditary Nonpolyposis Colorectal Cancer (HNPCC) or Familial Adenomatous Polyposis (FAP) [17].

10.2.2.6 Neurogenic Bowel

Pediatric cancer survivors who had spinal cord involvement of their tumors may have resulting neurogenic bowel dysfunction [18]. Injury to the nerves innervating the intestines can result in decreased bowel motility, fecal incontinence, chronic constipation and have devastating psychological implications [18, 19].

10.2.2.7 Impaired Glucose Metabolism/Diabetes Mellitus

A recent finding among childhood cancer survivors who received abdominal radiation is an increased risk for the development of impaired glucose metabolism and Diabetes Mellitus [20]. Abdominal radiation is typically administered in

the treatment of abdominal neuroblastomas and Wilms Tumors [20]. It should also be noted that patients treated with Total Body Irradiation (e.g. for Acute Lymphoblastic Leukemia) incur this same risk [20]. It has been theorized that the Pancreas may be inadvertently injured from radiation exposure, degrading its ability to produce insulin, but the exact cause is unknown [20].

10.2.3 Assessment

Assessment of any pediatric cancer survivor should begin with a history of the patient's cancer diagnosis, surgical history, chemotherapy and radiation exposures, and transplant history [21]. There are multiple differential diagnoses for abdominal pain, but taking the pediatric cancer survivors' past treatment history into account will allow for the ruling in or out of etiologies related to late effects. A family cancer history pedigree that includes, at minimum, all first and second degree relatives is necessary to identify patients who may be at high risk for a secondary colorectal cancer, regardless of past treatment exposures.

Targeted gastrointestinal assessment includes determining if symptoms are acute or chronic, with chronic abdominal symptoms defined as those lasting more than 1 or 2 months [22]. Included in the history should be questions about difficulties with swallowing or food avoidance, which may indicate esophageal dysfunction or gastrointestinal obstruction [8]. Symptoms of odynophagia, or painful swallowing, may be elicited with a simple question to the patient if it hurts to swallow or if the parent reports the child adamantly refuses food at mealtime [23]. A child with dysphagia may not be able to verbalize their symptoms, so parents should be asked about certain hallmark signs including coughing or choking during meals, excessive drooling, increased sinus congestion with intake of food or drinks and/or "wet" voice quality after swallowing, indicating retained saliva in the mouth [24]. Inquiries should be made to the use of over the counter remedies for stomach pain or indigestion, which may mask more serious symptoms. If protracted vomiting is reported, determining if the emesis is bilious is critical, as it is a strong indicator of a bowel obstruction that requires emergent attention [25]. Asking the patient and caregivers about the most recent bowel movement will allow for determining if constipation, defined as delay or difficulty in defecation for more than 2 weeks, is at the root of abdominal symptoms [26]. It is also important to assess for symptoms of reflux or heartburn, which can contribute to long term esophageal damage if untreated [8]. Unless the patient reports an appendectomy, appendicitis should be considered among the differential diagnoses if the patient reports lower right quadrant pain [25].

Lab values that may be considered in long term survivors at risk for gastrointestinal late effects include a complete blood count, serum ferritin and iron levels to evaluate for anemia. A Vitamin B12 level may be helpful in suspected malabsorption syndromes such as radiation enteropathy [27]. Guaiac fecal occult blood testing may also be performed if there is a suspicion of underlying blood loss from the gastrointestinal tract [28]. Biennial fasting blood glucose or Hemoglobin A1C is recommended screening for Impaired Fasting Glucose/Diabetes Mellitus [28].

A physical exam that is positive for signs of guarding, tenderness, or Murphy's sign ("catch" during inspiration when costal margin is palpated) are strongly indicative of gallbladder involvement [25]. Visual assessment of the abdomen should note any distention, and hypoactive or absent bowel sounds are a concerning finding that needs further investigation with imaging [28]. Biennial fasting blood glucose or Hemoglobin A1C is recommended screening for Impaired Fasting Glucose/Diabetes Mellitus [28].

10.2.4 Referrals

Survivors requiring emergent referral are those with a history of abdominal surgery that report acute onset and progressive abdominal pain that may also be accompanied by fever and/or bilious vomiting. Survivors with chronic symptoms should be evaluated by a gastroenterology specialist, due to the risk for complications from their past treatments [28]. An Esophagogastroduodenoscopy (EGD) is indicated for upper gastrointestinal tract

symptoms, and allows for examination and tissue sampling of the esophagus, stomach and upper duodenum [29]. A colonoscopy provides evaluation of the colon and rectum [29]. Patients experiencing fecal incontinence due to neurogenic bowel or as a late effect from radiation therapy (radiation proctopathy) may benefit from rehabilitation strategies and/or medical interventions and should be referred to a specialist in this area [27, 30]. If lab values return as abnormal for fasting blood glucose or Hemoglobin A1C, referral to an Endocrinologist is recommended [28].

Referral for screening colonoscopy for asymptomatic survivors at risk for colorectal cancer due to radiation exposure begins 10 years after the exposure or age 35, whichever occurs last [28]. Further screening is recommended every 5 years, but frequency is determined by the pathological findings of the first exam. Any survivor with a significant family history of colorectal cancer or colon polyps should be referred to a genetic counselor specializing in cancer genetics for consideration of testing for familial colorectal cancer syndromes [17]. Genetic Counselors are best qualified to take a detailed family history, recommend appropriate testing for all family members and provide information on appropriate screening for high-risk individuals [17]. If lab values return as abnormal for fasting blood glucose or Hemoglobin A1C, referral to an Endocrinologist is recommended [28].

10.2.5 Patient Education

Patient teaching includes the importance of a well-balanced, healthy diet. Dietary fiber intake should be emphasized, as adequate fiber intake promotes a healthy gastrointestinal system and is currently lacking in the diets of many children and adolescents [31]. Well-done red meats and processed meat intake should be kept to a minimum, as clinical studies have demonstrated an increased risk for the development of colorectal cancer [32]. Patients should also be counseled on the importance of avoiding cigarette smoking throughout their lifetime, which contributes to the risk for esophageal and colorectal cancers [33, 34].

10.3 Hepatic

10.3.1 Risk Factors

When assessing for the risk of late effects to the liver of the pediatric cancer survivor, relying on clinical criteria may cause some patients to be overlooked, as not every hepatic late effect presents with obvious signs or symptoms. The history should take several factors into consideration: (1) did the patient receive blood transfusions, if so, how many and when; (2) does the patient report any acute liver toxicities during treatment from chemotherapy, (3) did the patient receive radiation to a field that may involve the liver and (4) was a hematopoietic stem cell transplant necessary and what were the characteristics of that transplant (e.g. matched sibling donor, matched unrelated donor, mismatched related, etc.). These quick screening questions can allow a practitioner to quickly detect patients who may be at higher risk for liver dysfunction and in need of additional screening.

10.3.2 Late Effects

10.3.2.1 Blood Transfusions: Hepatitis C

Prior to the screening of the blood supply, transfusions of blood and blood products presented a major risk for transmission of the Hepatitis C virus to a recipient [35]. The implementation of multiantigen testing in 1992 significantly reduced the risk of transmission from an infected donor to 0.001 % of unit transfused [36]. Although a small number of patients clear the virus with no symptoms, the majority is at risk for the development of chronic hepatitis, which leads to cirrhosis and hepatocellular carcinoma [37].

10.3.2.2 Blood Transfusions: Hepatitis B

The risk for Hepatitis B from blood transfusions should be a concern for patients who report blood transfusions before 1972, when Hepatitis B surface antigen testing of the blood supply began

[37]. Additionally, the risk for Hepatitis B from a transfusion is greatly reduced among childhood cancer survivors who were immunized against the virus at birth, as recommended by the Centers for Disease Control in 1991 [38].

10.3.2.3 Blood Transfusions: Iron Overload

Children treated for cancer are susceptible to anemia, both from their illness or from the treatments received. For those who have complications, extensive surgery, multiple chemotherapy regimens or bone marrow transplants, numerous packed red blood cell transfusions may be needed throughout treatment [39, 40]. As the number of transfusions increase, the risk for iron overload of the liver also increases [39]. This condition can carry over into survivorship, as iron deposits into hepatic tissue are not readily cleared once transfusions end, leading to cirrhosis and liver failure [39].

10.3.2.4 Chemotherapy: Hepatic Fibrosis

Certain chemotherapies are associated with acute liver injury at the time of administration. These include antimetabolites such as 6-Thioguanine, 6-Mercaptopurine and Methotrexate, therapies commonly used in the treatment of childhood leukemia [41]. The majority of patients who sustain acute hepatic effects from these medications recover with no sequelae, but a small number may develop hepatic fibrosis [41].

10.3.2.5 Radiation: Cirrhosis

Although modern radiation techniques shield the liver and other major organs from exposure, the liver may receive radiation scatter from other treatment fields such as the lung, abdominal or renal bed [42]. The pediatric liver shows evidence of irreversible damage at dosages of greater than 3,000 cGy [41, 42]. This is due to scarring of the vessels supplying blood to the liver (including the portal veins and hepatic arterioles), resulting in cirrhosis [42]. This disruption of the hepatic circulation and subsequent congestion results in portal hypertension, causing splenomegaly [42]. Patients with prolonged portal hypertension are at risk for the development of esophageal and gastric varices, which may hemorrhage and lead to severe blood loss or death [42].

10.3.2.6 Hematopoietic Cell Transplant: Chronic Graft Versus Host Disease (GVHD) of the Liver

Although advances have been made in reducing hepatic complications from hematopoietic cell transplant, chronic graft versus host disease (GVHD) of the liver may still occur in some patients, with highest risk for those patients who undergo unmatched allogeneic transplants [10, 43]. Venoocclusive disease, and Chronic GVHD of the liver, if untreated or treatment-resistant, can lead to liver injury, including progressive damage to the epithelium of small bile ducts [44].

10.3.2.7 Non-Alcoholic Fatty Liver Disease (NAFLD)

Survivors of pediatric leukemia are at risk for the development of non-alcoholic fatty liver disease due to the prevalence of obesity and overweight in this population [41, 45, 46]. Fatty liver is associated with metabolic syndrome (insulin resistance, elevated fasting serum glucose, abdominal obesity, high blood pressure and dyslipidemia) which has also been reported as a late effect in these survivors [47]. Fatty liver is characterized by accumulation of fat in hepatocytes, and results in hepatomegaly, inflammation and eventual fibrosis if not treated [45].

10.3.2.8 Focal Nodular Hyperplasia

Focal Nodular Hyperplasia (FNH) of the liver has been reported in long term survivors of solid tumor malignancies, but hematopoietic cell transplant is a strong predictor for the development of these growths [48–50]. FNH is an ultimately benign finding of hepatocyte hyperplasia [50]. The exact pathogenesis behind FNH is not well established, but there may be a correlation with its development and previous liver injury during treatment with therapies such as Busulfan, Melphalan or abdominal radiation, venoocclusive disease or graft-vs-host

Table 10.1 Cancer therapy associations linked to potential hepato-biliary late effects in survivors of childhood and adolescent cancers

Cancer treatment risk factor	Potential late effect	Additional risk factors	Recommended evaluation	Evidence score[a]
Mercaptopurine Thioguanine	Veno-occlusive disease (VOD)	Viral hepatitis	Screening	2A
		Prior VOD		
		Siderosis		
Mercaptopurine Thioguanine Methotrexate	Hepatic dysfunction	Viral hepatitis	ALT	
		Treatment before 1970	AST	
		Abdominal	Bilirubin	
		Radiation		
		Prior VOD		
Abdominal radiation ≥ 30 Gy	Hepatic fibrosis Cirrhosis	Chronic hepatitis	Considerations for additional testing/ intervention	
Hematopoietic stem cell transplant (HSCT)	Hepatic dysfunction	Prior history of VOD	Prothrombin time	
	Chronic hepatitis	Higher radiation dose (≥40 Gy to atleast 1/3 of liver;	Screen for viral hepatitis	
	Cirrhosis	20–30 Gy to entire liver)	Ferritin/measure of liver iron burdenb	
	Iron overload	Alcohol use	Hepatitis A and B immunizations	
Abdominal radiation	Cholelithiasis	Chronic GVHD	COG health links	1
		Chronic hepatitis	http://www.survivorshipguidelines.org/pdf/LiverHealth.pdf	1
		Siderosis		2B
		Steatosis		
		Multiple transfusions		
		Radiation to liver		
		Prior antimetabolite therapy		
		Alcohol use		
		Obesity		
		Pregnancy		
		Family history of cholelithiasis		
		Ileal conduit		
		Abdominal radiation		
		Total parenteral nutrition (TPN)		

[a]Screening recommendations and literature evidence for therapy associations can be found at (http://www.survivorship-guidelines.org); GVHD Graft versus host disease
bSpecific to HSCT survivors

disease of the liver [48, 50, 51]. Additionally, FNH is generally found incidentally many months after the end of treatment, as there are few symptoms associated with its development, but its discovery raises high concern for recurrence as the liver is a site for metastases [50].

10.3.3 Assessment

Table 10.1 summarizes the potential hepatobiliary late effects in relation to cancer therapy received. Baseline AST, ALT and bilirubin are recommended at the time of entry into long term

follow-up. If these have not been completed at initial assessment, they should be done, as they are key indicators of liver health [28]. Additionally, they should be completed in long-term survivors who present with new onset symptoms as liver dysfunction may lay dormant and resurface many years after treatment ends [52]. Abnormal results will need further assessment with a prothrombin time, INR and albumin to evaluate hepatic synthetic function [28]. At a minimum, all bone marrow transplant survivors should have a serum ferritin level measured at 1-year post-transplant [5]. Physical exam findings of liver dysfunction include hepatomegaly, jaundice, and icteric sclera [28]. Patients may also report dark urine and skin changes such as spider angiomas [28]. Liver ultrasound may be considered as the initial imaging modality, given its low cost and non-invasive nature. Abnormalities found on ultrasound will require additional imaging with MRI or CT before proceeding to biopsy, as advances in imaging techniques have allowed for most benign hepatic lesions (e.g. Focal Nodular Hyperplasia, hemangiomas) to be diagnosed and monitored without subjecting patients to invasive procedures [53].

If a patient is a long term survivor at risk for transfusion related hepatitis, a screening Hepatitis B surface antigen (HBsAg), Hepatitis B core antibody (HBcAb) and/or Hepatitis C antibody are recommended [28]. If a patient is uncertain of their transfusion history, at a minimum Hepatitis C screening should be initiated, as the majority of long term survivors are lacking this basic screening and the outcome of the disease can be altered with medical and lifestyle interventions [54]. If a Hepatitis C antibody test returns as positive, further testing with Hepatitis C PCR is advised to confirm the initial findings [28].

10.3.4 Referral

Referral to a Gastroenterologist/Hepatologist is indicated for patients with persistent abnormal liver function tests or evidence of hepatomegaly either by physical exam or by imaging [28]. Survivors with confirmed Hepatitis C need close medical monitoring and should also have psychological assistance available, as patients with Hepatitis C report feelings of depression, stigma and anger associated with their disease [55]. This may be confounded by a history of childhood cancer, which is also associated with psychosocial distress [56].

10.3.5 Patient Education

All survivors, regardless of past exposures, should be educated on the potential for liver damage from medications, both over-the-counter and prescription, as well as from supplements [57, 58]. Acetaminophen is a well-established hepatotoxin, and patients should be educated that acetaminophen comes in various forms in combination over-the-counter pain and cold remedies [59]. Alcohol intake should be limited or eliminated completely as it is a major contributor to accelerating liver damage. Survivors should also be educated that emerging research is showing tattooing to be a risk factor for Hepatitis C, even among those with no other risk factors and having tattoos done in licensed parlors [60].

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Musculoskeletal System

11

Tao Ji, James B. Hayden, and Bang H. Hoang

11.1 Introduction: Osseous and Soft Tissue Tumors in Children

Primary malignant tumors of bone are rare, with an estimated incidence of 8.7 per million in children and young adults under the age of 20 [1]. Osteosarcoma (OS) and Ewing's sarcoma (ES) together form the majority of bone cancers in people younger than 20 years of age. There are roughly 450–600 new cases of osteosarcoma (Fig. 11.1) and 200–250 cases of the Ewing sarcoma family of tumors diagnosed in the United States each year [2]. These tumors tend to occur at the extremity long bone metaphysis. The distal femur and proximal tibia account for 45–78 % [3], followed in frequency by the proximal humerus and middle and proximal femur.

Soft tissue sarcomas (STS) comprise a diverse group of malignancies. About 850–900 STS are diagnosed each year in the United States, in children 0–19 years of age [4]. Rhabdomyosarcoma (RMS) is the largest diagnostic group in children. Non-RMS diagnoses include fibrosarcoma, malignant fibrous histiocytoma, leiomyosarcoma, liposarcoma, synovial sarcoma (Fig. 11.2), along with other rare types of sarcomas.

Patients most commonly present with pain at the site of the primary tumor, often accompanied by a palpable mass on physical examination and a lesion on radiographic imaging. Both CT and MRI scans have been employed and provide differentiating information regarding soft-tissue spread and bone and/or joint involvement. Detailed examination of the lungs by CT scan and the bones by bone scan is required to evaluate clinically detectable metastatic lesions. Laboratory blood tests may show elevations in alkaline phosphatase (ALK), lactate dehydrogenase (LDH), or erythrocyte sedimentation (ESR). The definitive diagnosis relies on the biopsy, even when physical findings and radiographs appear pathognomonic for OS and ES. The surgeon should plan a biopsy very carefully, with consideration for subsequent definitive surgery or radio-

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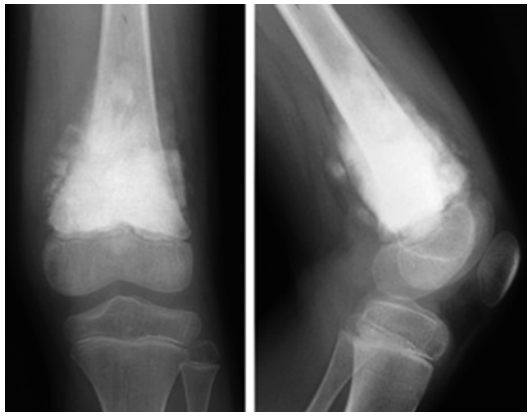

Fig. 11.1 Typical osteosarcoma of *left distal femur* in an 8-year-old boy. An osteoblastic process permeates the medullary cavity. The periosteum is elevated, producing a Codman triangle

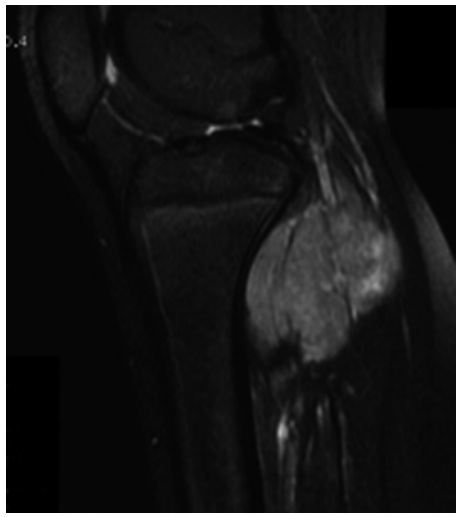

Fig. 11.2 Nine-year-old girl presented with a rapidly enlarging mass in her calf. T2-weighted MRI shows the tumor located in posterior compartment of the leg. The biopsy revealed a synovial sarcoma

therapy. A poorly-conceived or poorly-placed biopsy may jeopardize the subsequent treatment, especially during a limb-salvage procedure [5]. An improper biopsy can lead to tumor spread and problems removing the tumor later on. An incisional biopsy done in the wrong place can make the subsequent removal of the malignant tumor much more complicated.

Primary bone and soft tissue tumors are most commonly staged with the Musculoskeletal Tumor Society (MSTS) system devised by Enneking et al. [6] in 1980. The American Joint Committee on Cancer (AJCC) has proposed an alternative staging system based on the primary tumor, lymph node metastases, and systemic metastases [7, 8]. The specific therapeutic approaches for patients vary with the tumor pathology and the presence or absence of metastatic disease. Treatment of malignant bone and soft tissue tumors involves neoadjuvant chemotherapy for systemic control and surgery and/or radiation for local control. The major surgical procedures are amputation and limb salvage. With the advances in multimodality treatment, better understanding of tumor biology, new diagnostic imaging techniques and supportive care, the survival rate has increased dramatically since the 1970s and 1980s. Based on a recently published meta-analysis on worldwide data [9], the survival rate measured in 47,227 patients with osteosarcomas remained stable at approximately 20 % from the 1910s to the 1960s, with a sudden surge to approximately 60 % during the 1980s. Since that time, despite new innovative therapies, the survival rate has continued to remain unchanged. During this time, however, there was a shift in the surgical approach. Whereas limb amputation was the procedure of choice in the 1970s, limb salvage surgery is often a viable option today [10]. The use of chemotherapy is critical to a successful surgery and should be considered an integral part of the surgical plan.

11.2 Brief Overview of Surgical Treatment

The goal of surgery in pediatric bone and soft tissue sarcomas is curative resection and, when possible, preservation of bone growth. The ideal procedure should maximize the patient's cosmetic and functional outcome but should not jeopardize the patient's long-term survival. In most cases, limb salvage has obvious cosmetic advantages, provides psychological benefit as well as improved functional outcome, and avoids the needs and complications of external prosthetic devices. However, limb sal-

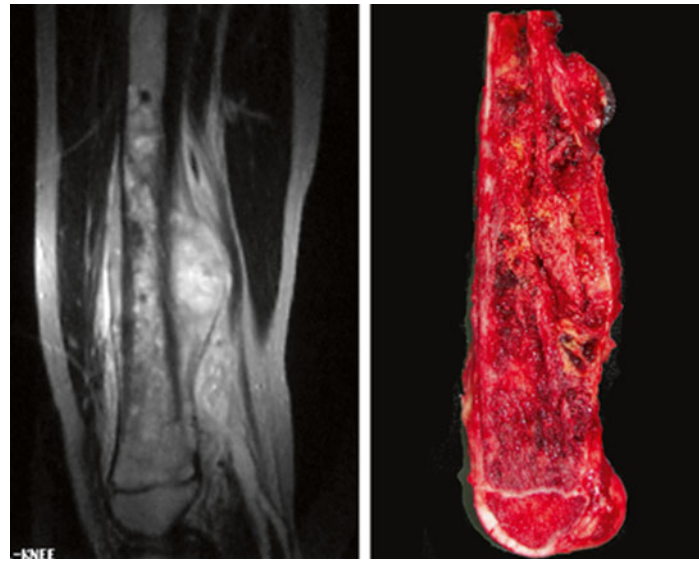

Fig. 11.3 Osteosarcoma in the distal metaphysis of the femur of an 11-year-old boy. (*Left*) Sagittal MRI shows the tumor is in contact with the growth plate. (*Right*) The specimen shows the growth plate is resected

vage surgery is more technical and has a higher rate of complications, including infection, nonunion, fracture, poor joint movement, leg-length discrepancy, prosthetic loosening, mechanical failures and local recurrence than amputation does [11]. These late complications can be problematic, and the perceived advantage of limb salvage can be negated by the need for additional revision surgeries, or ultimately an amputation. Amputation may be the treatment of choice in some situations, including biopsy incisions that contaminate the soft-tissue envelope, tumor involvement of the nerves and/or major blood vessels, and pathologic fracture. However, a pathologic fracture is not always a contraindication for limb salvage, and vessels can be resected and bypassed if encased by tumor. In these circumstances, the decision for limb salvage has to be made on a case-by-case basis [12].

Most of the tumors will occur in patients who are skeletally immature. The location of these tumors in the growing areas of bone commonly necessitates the removal of the involved growth plate (Fig. 11.3) [13].

In the growing child, limb salvage procedures present unique challenges. These include the small size of the pediatric skeleton, the growth potential of the patient, the proposed final length of the unaffected limb, and the need for correction of the ensuing limb salvage discrepancy [14]. Amputation can also produce problems in growing patients. Stump overgrowth (bone growing after an amputation in skeletally immature patients) can lead to painful pressure on the soft tissue stump after amputation, requiring revision surgery [2].

Young sarcoma survivors not only have to deal with limb function-related problems, but they also have an increased mortality because of therapy-related late effects. This chapter presents late complications commonly observed after surgical treatment for pediatric patients with musculoskeletal malignancy.

11.3 Late Local and Distant Relapse

As more pediatric cancer patients enter long-term follow-up as survivors of their cancer, it is important for both patients and physicians to appreciate the risk of late local and distant relapse. Some young adult survivors of childhood cancer eventually outgrow their pediatric care and have uncertain medical follow-up in their adulthood [15].

Most patients with musculoskeletal malignancy who develop recurrent disease do so within

2–3 years after completion of treatment. Relapse after being disease-free for 5 or more years is uncommon. Late relapse has, however, been documented in long-term follow-up of large series of patients with osteosarcoma. Vigilance must therefore be encouraged for both the patients and the multidisciplinary medical professionals who treat them. The Cooperative Osteosarcoma Study Group (COSS) published a detailed analysis of the long-term outcome of 1,702 patients with extremity and trunk osteosarcoma. With a median follow-up of 5.5 years, 23 (1.4 %) patients were found to have relapsed after 5 years, with the latest care being 14.3 years after treatment [16]. The Rizzoli data showed an incidence of late relapse of 5.5 % [17]. The latest recurrence of osteosarcoma reported was recurrence as late as 17 years from initial diagnosis and treatment [18]. Besides osteosarcoma, very late (>10 years) local recurrence of Ewing's sarcoma has also been reported [19].

The lungs are the most common sites for the development of metastases in pediatric patients with bone and soft tissue tumors. Skeletal metastases are less common but have also been reported in the literature [20]. Patients with metastatic osteosarcoma limited to the lung, who have received a complete resection of the pulmonary disease, have reported survival rates of up to 30 % [21, 22]. There is no uniform surgical guideline on how to manage osteosarcoma pulmonary metastases. However, complete resection should be attempted, regardless of approach or operation performed, as long as the primary tumor is controlled [23]. Pulmonary metastasectomy in most cases means resecting single pulmonary nodules located near the pleura. All thoracic interventions have their place in pulmonary metastasectomy from wedge resections to laser resection and extended chest wall replacement [24]. Currently, the most common approach to the OS patient with unilateral pulmonary metastases is unilateral thoracotomy with resection, followed by close surveillance [21]. A retrospective study suggested that osteosarcoma patients with early unilateral pulmonary metastases might not benefit from exploration of the contralateral hemithorax [25].

The prognosis of patients who relapse with bone metastases is worse than the prognosis of patients who first relapse with lung metastases. The experience from Rizzoli indicated that, even if treated with aggressive surgery and chemotherapy, only 10 % of patients with OS who relapse with bone metastases actually survive [26].

These findings highlight the need for lifelong follow-up of bone and soft tissue sarcoma patients. Meticulous follow-up is required to permit early detection and successful therapeutic intervention.

11.4 Late Complications of Limb Salvage Procedure

The major surgical procedures for bone and soft tissue tumors are limb salvage and amputation. In children for whom limb salvage surgery is an option, the choice between amputation and limb salvage is not always clear. Quality of life in terms of function, psychological outcome and endpoint life span achievements such as marriage and employment apparently do not differ significantly between amputee and nonamputee osteosarcoma survivors [27, 28]. In most cases, limb salvage has an obvious cosmetic advantage, and is more acceptable to patients. However, limb salvage procedure has a higher rate of complications. It is always challenging for the musculoskeletal oncologist to make the appropriate decision in choosing between limb salvage and amputation.

Within limb salvage, there are also multiple procedures to choose from. Multiple options for limb salvage surgery have been developed over the past 30 years (Table 11.1). The choice of limb salvage procedure depends on the location and extent of tumor, psychosocial considerations, and the age of the patient. Endoprosthetic and biological reconstruction are two major types of limb salvage surgeries. There is additional challenge in the bony reconstruction of children, due to their continuing growth. The potential for further limb growth is affected when tumor removal necessitates resection of one or more growth plates. The related late complications will be discussed below.

Table 11.1 Surgical options after tumor resection in pediatric limb salvage procedure

Endoprosthetic replacement
Allograft
Allograft prosthetic composite (APC)
Vascularized graft (or combined with allograft)
Devitalized and re-implantation of tumor bone
Bone transportation using an external fixator
Rotationplasty

11.4.1 Biological Reconstruction

11.4.1.1 Autograft

Both free and vascularized fibular grafts are used frequently in the reconstruction of bone defects, which occur after tumor resection in children. Fibular graft has been used most successfully in the reconstruction of upper limb bones (Fig. 11.4) [29]. Attempts have been made to maintain epiphyseal growth by harvesting the fibula in young children while maintaining the blood supply to the fibular epiphysis [30]. The fibula provides well-perfused bone and the capability of osteogenesis, but it often lacks the structural strength of allografts for lower limb reconstruction [31]. Fibular grafting is particularly attractive when considering bony reconstruction in the adolescent and pediatric population, in which long-term viability and mechanical stability are required. Long-term radiographic studies showed fibular incorporation into the allograft (Fig. 11.5) [32, 33]. Stress fracture and nonunion are two major complications after fibular reconstruction. The stress fracture of the transferred fibula was reported ranging from 12.5 % to 28.5 % [34, 31]. The nonunion or delayed union rate was reported to be 8–14 % [29, 35].

Another autograft option is to use the diseased bone after devitalization. The patients' own tumor-bearing bone is sterilized by irradiation, microwave, pasteurization or autoclave, however, this technique will be useful only for diaphysis or flat bones in children [36]. There are very little reports on large numbers of cases with recycled tumor bone reconstruction, and the complication rates varied widely among different studies. Infection and fracture of the reimplant, though, are the main complications [37, 38].

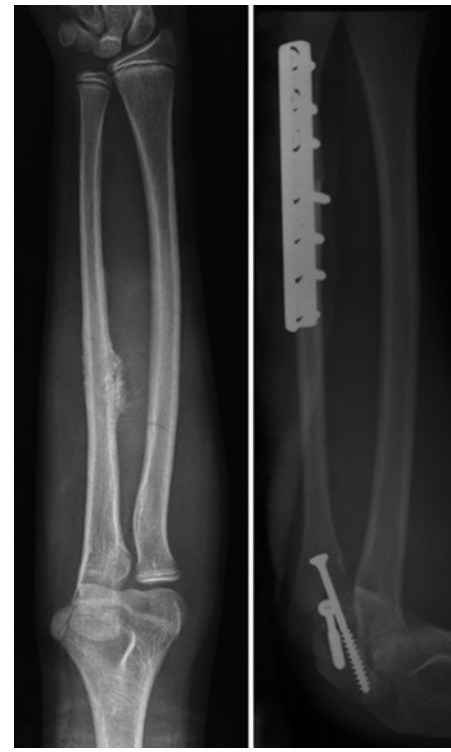

Fig. 11.4 Radiograph showing osteosarcoma of the left ulna in a 13-year-old boy. The tumor was resected and the bone defect was bridged with free fibular graft

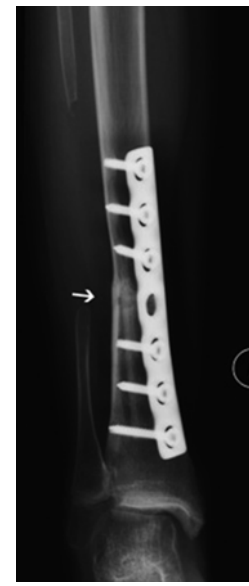

Fig. 11.5 Osteosarcoma in the distal metaphysis of the tibia of a 9-year-old boy. Reconstruction with an osteoarticular allograft and intra-medullary vascularized fibular graft stabilized with plate after tumor resection. The incorporation of the allograft at the proximal osteotomy (*arrow*) was observed at 1 year after surgery

Table 11.2 Complication rates of allograft reconstruction in children

Study	Year	Number of cases	Complication		
			Infection (%)	Nonunion (%)	Fracture (%)
Muscolo et al. [41]	2008	22	4.5	4.5	13.6
Ramseier et al. [45]	2006	21	9.5	–	28.6
Brigman et al. [42]	2004	116	16	34	27
Alman et al. [39]	1995	26	11.5	11.5	53.8

11.4.1.2 Allograft and Allograft-Prosthesis Composite (APC)

Allograft can be used alone or in combination with prosthesis as an APC or in combination with a vascularized fibula graft. However, allografts do not have osteo-inductive function, which can induce new bone formation. Allograft can include the epiphysis (osteoarticular), replace a midsection of bone (intercalary), or be used as part of a resection arthrodesis [39–41]. Bone allograft can restore articular congruity, preserve bone stock, and provide musculotendinous attachment sites for host soft-tissue structure, theoretically improving function [41–43].

Allograft reconstruction procedures have higher rates of complication in children than adults [10]. Osteoarticular allograft has higher failure rates in the lower extremity. Intercalary allograft does better. Complications of allograft reconstruction have been well described in literature. However, there are only a few references in literature, which exclusively describe pediatric sarcoma population. Fracture, nonunion, and infection are common complications after allograft reconstruction in children (Table 11.2). The overall 5-year and 10-year allograft survival rates were 69–78 % and 63 % respectively [40, 44].

Infection is a potentially devastating complication of allograft reconstruction. Surgical extent, soft tissue loss, multiple operations, and chemotherapy cause the allograft to be more susceptible to infection [44]. Union at the graft-host interface is dependent on the proliferation of host bone cell, quality of contact, and stability of the junction. Hornicek et al. analyzed the factors affecting nonunion and found that chemotherapy negatively affected union at the allograft-host junction [46]. The fracture rate in children has been reported to be significantly higher than the studies that included patients in all age groups [10, 39]. Spanning the entire length of the allograft with internal fixation theoretically splints the graft and offers protection from bending and torsional forces, which can cause fractures [47]. The mechanical failure of internal fixation can be observed in mid-to-long-term follow-up (Fig. 11.6). Leg length discrepancy is commonly seen in most patients who received allograft reconstructions secondary to loss of the growth plate. The degree of leg discrepancy depends on the age of the patients at the time of their first treatment.

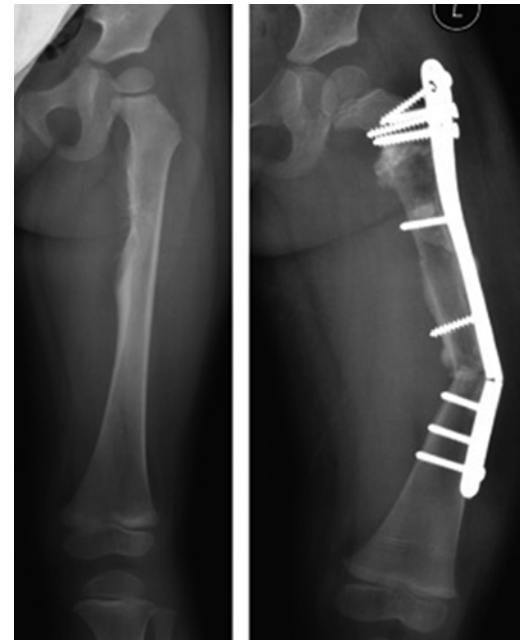

Fig. 11.6 The radiograph showing an Ewing's sarcoma in the diaphysis of femur of a 5-year-old girl. Reconstruction was carried out with an intercalary allograft. Mechanical failure of the plate occurred 18 months postoperatively

11.4.2 Endoprosthetic Reconstruction

In adults, modular tumor endoprostheses, an implantable artificial metal device to replace a missing segment of bone and adjacent joint, are becoming a standard option for reconstructing the limb after resection of malignant bone tumors. However, reconstruction with the standard static prosthesis is neither a practical nor a functional option in the skeletally immature patient due to the length discrepancy [14]. In order to solve the problem in children, the concept of the expandable endoprosthesis was introduced by Scales in 1976 [48]. An expandable endoprosthesis can be lengthened as the child grows, similar to the standard endoprosthetic reconstruction. It allows immediate weight bearing with early rehabilitation and return to function. The design of expandable endoprosthesis has significantly evolved over the past 30 years (Fig. 11.7).

By then, all the lengthening mechanisms required a formal surgical procedure, which resulted in a high incidence of infection [49]. The younger the child, the more operations were needed not only for lengthening, but also for management of complications such as stiffness, infection, wear, and loosening. The latest design has a noninvasive lengthening mechanism, which relies on an electromagnet outside the body to transfer energy to the sealed implant inside the body. Today, there are several noninvasive products that have the ability to lengthen a child's limb without having to undergo an operation [13, 36, 50, 51]. This provides a substantial advantage for both the child and the parents. Not all children are candidates for an expandable prosthesis. The size, age, and potential growth of the patients need to be evaluated carefully. Endoprosthetic reconstruction is not recommended for patients younger than 6–8 years old or for small children who have tall parents, since their potential of growth is too much to be corrected even with the use of expandable prosthesis [14, 52]. Beebe et al. [53] analyzed the functional outcome and gait of children after reconstruction with noninvasive expandable prosthesis at a mean follow-up of 31.5 months. Increased time spent in double-limb support and decreased gait velocity was observed, indicating weakness of hip abductors. However, the reconstruction produces satisfactory functional outcome and the patients maintain high levels of emotional acceptance.

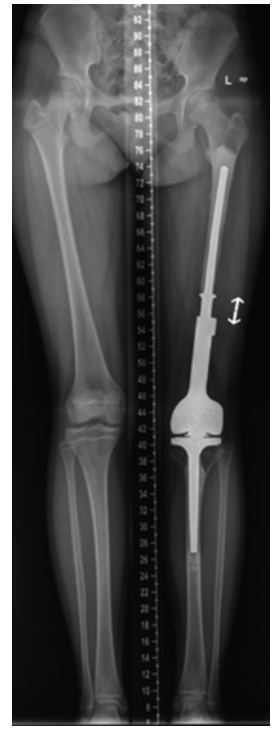

Fig. 11.7 Radiograph at a follow-up of 4 years showing 38 mm lengthening (*extension arrowed*) of a female patient aged 12 years at implantation of a minimal invasive expandable endoprosthesis

Complications of expandable endoprosthesis include infection, loosening of implants, stiffness, unplanned shortening or lengthening, outgrowing the available extension, and implant and periprosthetic fracture [49]. Infection poses the largest iatrogenic risk to limb salvage. The deep infection rate is reported to be 10.9–17.6 % [54–56], most prevalent in the proximal tibia. Infection of an implant is difficult to eradicate because of the adherent colonies of bacteria in a polysaccharide matrix, collectively called a biofilm [57]. Infecting bacteria can remain on the surface of an implant for a variable length of time. Clinical symptoms can be caused by the local proliferation of bacteria shed by the biofilm, and may present themselves from several months to years after index surgery. Chronic infection usually requires a two-stage revision with a 70 %

Table 11.3 Studies describing outcomes of expandable endoprostheses in literature

Author	Year	No. of cases	Endoprosthesis	Average length of expansion (mm)	Overall complication rate (%)	Function score (MSTS) (%)
Henderson et al. [56]	1996–2009	38	Stryker[a] 18	30	42	87
			Biomet[b] 12	31		
			Stanmore 8	81		
Saghieh et al. [60]	2002–2009	17	Wright	25.8	70.6	90
Picardo et al. [54]	2002–2009	55	Stanmore	38.6	29.1	80.7
Hwang et al. [55]	2002–2009	34	Stanmore	32	23.5	85.6
Baumgart [61]	NA	5	Implantcast	78	60	NA
Wozniak [61]	2000–2010	118	Stanmore[b] 47	NA	31.9	85
			Wright 4		50	
			Implantcast 67		26.8	

[a]Minimal invasive expandable endoprosthesis

[b]Invasive expandable endoprosthesis

success rate, but some patients still require amputation [49]. Aseptic loosening of endoprosthesis is the most frequent complication in pediatric limb salvage, which has been reported to be 7.1–26.3 % [58, 50]. This is largely due to the long lever arm created at the bone-implant interface, and also, difficult anchoring conditions. Mechanical failure is another frequently reported complication in the literature, most frequently involving failure of the expansion mechanism. There are also reports regarding the fatigue fracture of the prosthesis [59]. The primary biological limiting factor to using an endoprosthesis in children is the diameter of the host residual shaft diameter. Under long-term cyclical loading, even strong material will fail if the stem diameter is less than 8 mm [51]. Picardo et al. reported that revision procedure was performed in 16.4 % of the cohort after the endoprosthesis was maximally extended. The revision rate due to mechanical complications was 18.2 % [54]. Despite these complications, the literature suggests the existence of a role for expandable prostheses in pediatric limb reconstruction after resection of a primary malignant bone tumor (Table 11.3).

11.4.3 Leg Length Discrepancy

Limb length discrepancy remains a critical late effect after limb salvage procedure in children (Fig. 11.8) [14].

Differences in length between upper extremities are not often a problem, but leg length discrepancies can cause significant functional deficits. The distal femur and proximal tibia are the most common sites for primary malignant bone tumors, and the epiphyses of the distal femur and proximal tibia contribute approximately 35 % and 30 %, respectively, to growth of the lower extremity [36]. Also, many other factors contribute to the overall limb length discrepancy, including systemic chemotherapy, slowing of the preserved growth plate in the affected joint, muscle atrophy, muscle loss and overgrowth of the contralateral limb. Several options, including conservative method and surgical intervention, such as expandable prosthesis, epiphyseal preservation, contralateral epiphysiodesis or distraction osteogenesis, have been developed to solve the problem. In order to choose the proper elongation method, it is important to estimate the expected limb length inequality resulting from both segmental resection and loss of subsequent normal growth. Several methods have been developed to estimate final height at skeletal maturity, including Paley's "multiplier" method [62, 63], Moseley graph [64] and Green-Anderson growth remaining charts [65].

Leg length discrepancies less than 2 cm in the lower extremities is well tolerated and normally has little-to-no functional or clinical significance. These discrepancies can be easily corrected by shoe lift. Discrepancies of 2–5 cm are associated with gait abnormalities [66] and can be corrected

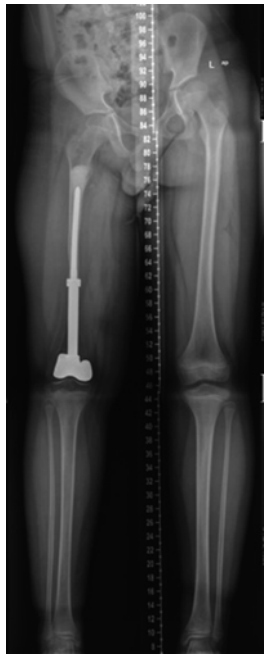

Fig. 11.8 Eight-year-old boy with a distal femur osteosarcoma that has been resected and the defect was constructed with a semi-articular knee endoprosthesis. A leg-length discrepancy of 5 cm developed at 4 years after reconstruction

Table 11.4 Treatment option for categories of expected leg-length discrepancies [67]

Leg length discrepancy (cm)	Treatment
0–2	No treatment required
2–5	Shoe lift and/or epiphysiodesis
5–15	Lengthening, expandable prosthesis, distraction osteogenesis
>15	Multiple procedures, rotationplasty, amputation

with a shoe lift or a contralateral epiphysiodesis. Inequality larger than 5 cm often requires surgical management (Table 11.4).

Distraction osteogenesis is a surgical process used to lengthen the long bones. After corticotomy, the two bone ends are gradually moved apart during the distraction phase, allowing novo bone to form in the gap (Fig. 11.9). It is based on accelerating the functional remodeling and integration seen with fracture healing [68, 69]. Distraction is usually started 7–14 days after the osteotomy, with a rate of 1 mm/day [70],

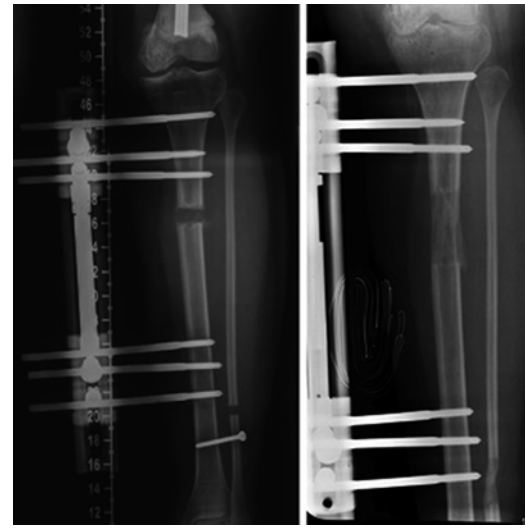

Fig. 11.9 Limb-length discrepancy occurred at 10 years after removal of an osteosarcoma in the distal femur of an 18-year-old patient. A unilateral lengthener was utilized to correct the 6 cm discrepancy. Radiograph showing excellent novo bone formed over 8-months

however the consolidation phase is usually twice as long as the distraction phase. Duration is estimated on the basis of 1 month/cm of increased length [71, 72]. The most common complications using this method are pin tract infection, pin break, fracture of regenerate, dislocation/subluxation of nearby joint, skin invagination, bone resorption and loss of alignment. Tsuchiya et al. [73] reported a complication rate of 52.6 %. Physeal distraction procedures have the advantages of more rapid ossification, earlier weight bearing, and fewer complications than do other lengthening techniques but should be used only in children under 12. Cãnadell et al. used distraction osteogenesis to expand the tumor-free margin and to preserve the epiphysis by physeal distraction.

11.5 Rotationplasty

Rotationplasty can be described as an intercalary amputation of the knee joint with rotation of the distal limb by 180° so that the former ankle joint functions as a knee joint (Fig. 11.10) [74–76].

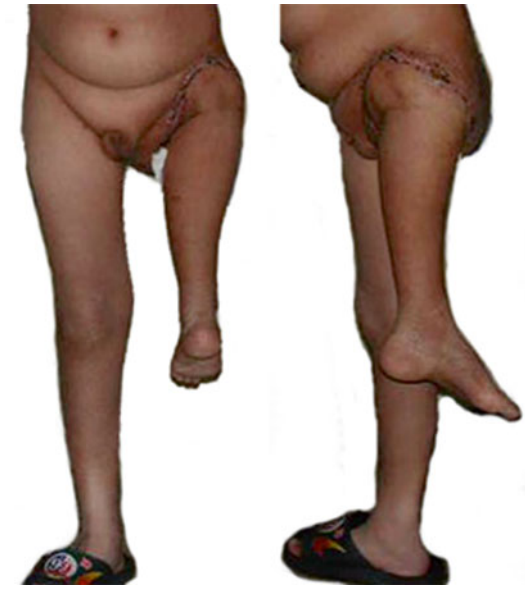

Fig. 11.10 An 11-year-old boy received rotationplasty after resection of a large osteosarcoma involving total femur. The ankle became a functional knee joint

Kristen et al. were the first to introduce rotationplasty as a limb salvage procedure in the treatment of malignant tumors around the knee [77]. It is considered as the halfway mark between amputation and limb salvage surgery, and it is particularly useful in the skeletally immature patient, younger than 8–10 years, with significant potential growth inequality between the two extremities. The advantages of rotationplasty include a functional knee joint, a longer lever arm for the prosthesis, and better tolerance for the socket load by foot than allowed with an above-the-knee amputation [14]. Rotationplasty has been shown to be functionally superior, with the lowest rate of postoperative complications of all limb salvage procedures, compared to above-the-knee amputation. Compared to endoprosthetic reconstruction, rotationplasty has not been associated with any disadvantages with regard to function or quality of life [78].

Winkelmann reported his experience with 134 patients with rotationplasty. The complications included seven vascular complications, two deep infections, four pseudoarthroses, two permanent nerve palsies and five late fractures [79]. Gottsauner-Wolf et al. [80] reviewed their experience in 70 patients who received this procedure with a mean follow-up of 4 years. Occlusion of the reanastomosed vessels was found to be the most severe postoperative complication with an incidence of 10 %, leading to amputation. Late complications included eight fractures, two infections, two delayed unions, and one lymphatic fistula. Despite good functional and quality-of-life results, the cosmetic appearance may be the most serious disadvantage of rotationplasty. Rotationplasty is rarely the first-choice procedure given the availability of extendable endoprostheses. However, there is still a role for this procedure in specific circumstances and the decision to perform it must be made on a case-by-case basis.

11.6 Amputation

For many patients and their families, amputation is seen as a failure of treatment. However, children with amputations adjust to their situation rapidly and often have superb functional results, especially with more distal amputations [36]. In one excellent review on comparison between amputation and limb salvage in terms of long-term effect, Nagarajan et al. [81] showed that survival was equivalent between the two groups and complications occurred more frequently in limb salvage (Table 11.5). In several studies, the quality of life after limb salvage was found not to be superior to that after amputation [27, 28, 82, 83].

Although prosthetic technology is rapidly advancing and the artificial limbs are much more sophisticated than before, amputees may return to their doctors for infection, ulceration, pain, or functional impairment. Most of these problems can be resolved with the help of an experienced prosthetist. Phantom limb pain sensations remain a substantial and unpredictable problem. Residual pain can be caused by poor socket fit over a bony prominence or by growth of stump bone. When bony prominence cannot be accommodated by prosthetic modification, bone excision combined with soft tissue reconstruction should be considered. Some ulcers may occur from a change in the residual limb volume or shape, which can be solved by prosthetic socket modification.

Table 11.5 Complications of limb salvage and amputation [81]

	Early complication	Late complication
Limb Salvage	Soft tissue necrosis	Nonunion
	Deep infection	Pathologic fracture
	Artery/vein/nerve damage	Aseptic loosening
	Venous thrombosis	Leg-length discrepancy
	Delay in chemotherapy	Implant breakage
	Poor joint movement	Poor joint movement
Amputation	Inadequate wound coverage and healing	Stump-prosthesis problems
	Infection	Stump pain
	Delay in chemotherapy	Phantom limb pain
	Phantom limb pain	Stump bony overgrowth

11.7 Osteoporosis and Osteonecrosis

All forms of cancer therapy, including surgery, chemotherapy, and radiation, can affect the musculoskeletal system of a growing child or adolescent [84].

Intensive chemotherapy may affect bone mass. Patients who have been diagnosed with acute lymphoblastic leukemia (ALL) may have decrement in bone mineral density (BMD). The etiology of BMD decrement can be attributed to multiple factors including genetic endowment, lifestyle behaviors, disease process, and treatment exposures, especially corticosteroids and radiotherapy [85, 86]. Chemotherapy for pediatric malignancy utilizes corticosteroids and methotrexate (MTX), which are both known to affect bone metabolism. Corticosteroids may cause a decrease in osteoblastic activity and directly affect the bone matrix, resulting in decreased formation. MTX, an antimetabolite agent, can impact long-term bone health by reducing BMD and attainment of peak bone mass. A large cohort study revealed that patients who received corticosteroid doses greater than 9,080 mg/m^2 (prednisone) over 3 years or greater than 3,000 mg/m^2/year for an indefinite amount of time held the risk of reduced BMD [87]. And a study, determining the BMD in long-term survivors (>10 years) of highly malignant, chemotherapy-treated osteosarcoma, showed a significant lower BMD compared with the healthy and age-matched reference population [85].

Osteonecrosis is a rare complication observed predominantly in survivors of pediatric bone and soft tissue malignancies treated with corticosteroids [88]. The reported prevalence of osteonecrosis affecting childhood cancer patients has varied from 1 % to 15 % based on the study population, treatment protocol, method of evaluation, and time from treatment [87–89]. Osteonecrosis is often multiarticular and bilateral, affecting weight-bearing joints predominantly. In a prospective survey of a cohort of 116 patients with hematological malignancies, 15 % had evidence of osteonecrosis on MRI [90]. The knee was the site involved most frequently. Surgical management options are of concern in young, growing subjects. Novel approaches include the use of anti-resorptive drugs and strategies for prevention, such as the use of lipid-lowering agents, and are currently being explored [88].

Radiotherapy plays an important role in the management of pediatric malignancy. A study focusing on the late effects of radiotherapy for pediatric extremity sarcomas analyzed 15 patients with a median follow-up of 20 years and found radiation-induced fracture rates of 33 % [91]. The incidence of radiation-induced fracture was reported to range from 15 % to 44 % in Ewing's sarcoma patients [92, 93]. Ewing sarcoma family of tumors often extensively involves cortical bone; and fractures frequently occur through the cortex with even minor injuries.

11.8 Conclusion

Due to the advancement of treatments, the survival and quality of life of pediatric patients with bone sarcomas has improved within the last few decades. Despite these important improvements, these patients are still subject to further health risks; therefore, it is imperative for them to be closely monitored as an adult. Health problems can persist once treatment ends, along with comorbidities associated with previous cancer therapy, including surgery, radiation and chemotherapy. The long-term health problems have become a major issue because of our improved success in treating the primary disease. Adequate screening, surveillance and prevention are needed to minimize the impact of late effects of cancer treatment. Long-term follow-up for childhood sarcoma survivors typically begins when they are in remission and fully recovered from the immediate effects of treatment. It is important for all survivors to continue to have regular medical care for life. Most survivors need long-term follow-up visits once a year with their family doctor, pediatrician, oncologist and orthopedic surgeons, although the schedule may vary considerably depending on individual circumstances. The survivor or their parents should keep a treatment summary of their primary treatment, and give them to the healthcare providers for follow-up.

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Eye, Ear and Oral Health

12

Jacqueline Casillas and Amy Jacobson

12.1 Introduction

Primary Care Providers are commonly the first to detect issues with vision, hearing and oral health during routine patient care visits. For the pediatric cancer survivor, surveillance of these vital systems is particularly important as they are susceptible to late effects from multiple cancer treatment modalities, including chemotherapy, radiation and supportive medications (e.g. antibiotics). For childhood cancer survivors, vision and hearing late effects may significantly impact academic performance if not addressed promptly. In this chapter, we will provide an overview of late effects to the vision, hearing and oral health of pediatric cancer survivors and provide evidence-based recommendations for screening and referral.

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12.2 Eyes

12.2.1 Risk Factors

As with all late effects, having documentation of what treatment the patient received is critical to understanding the late effects they are at risk for. Exposure to orbital/eye radiation, cranial radiation, total body irradiation, glucocorticoids and/or hematopoietic cell transplant may cause potential for visual disturbances [1, 2].

12.2.2 Late Effects

12.2.2.1 Cataracts

Cataracts are the most common reported late effect to the eye of childhood cancer survivors [1]. Although painless, cataracts impair vision, which in turn negatively affect a child's ability to read, view classroom displays, and participate in sports.

The therapies responsible for early-onset cataract development are radiation, Busulfan and corticosteroids (Prednisone and Dexamethasone). Although the eye is shielded during radiation administration, the lens is still highly susceptible to its effects [1]. Radiation can accelerate cell injury, and as the eye does not shed its dead cells, these cells then accumulate and lead to clouding. The exact pathophysiology responsible for the early onset of steroid induced cataracts and

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Busulfan is uncertain, but the cataract itself is distinct for being located in the posterior subcapsular region [3, 4].

12.2.2.2 Dry Eye

Dry Eye, also known as keratoconjunctivitis sicca or xerophthalmia, is a late effect of radiation treatment, with more severe symptoms reported at higher doses [1]. It may also be a lasting result of chronic graft-versus-host disease (GVHD). Graft-versus-host disease is an immunologic response of the donor cells against the host cells, and is considered chronic if it occurs more than 100 days following the transplant [5]. The lacrimal gland is responsible for tear production and its functioning is affected due to fibrosis from both radiation and GVHD [1, 6]. Patients will typically report symptoms of eye dryness, burning, itching, fatigue and the presence of a foreign body [7]. Dry eye may lead to corneal abrasion, and children who excessively rub their eyes are at risk for the introduction of infectious pathogens that can lead to conjunctivitis.

12.2.2.3 Other Eye Toxicities

Other eye toxicities of concern in the pediatric cancer survivor include legal blindness, double vision, glaucoma, retinal damage, and ptosis [1, 8]. Of note, these conditions are more prevalent among survivors treated with higher doses of cranial radiation or ocular/eye radiation [1].

12.2.3 Assessment

At a minimum, screening for visual abnormalities from cancer treatment should continue annually throughout the survivor's lifespan [9]. Assessment for visual abnormalities for a younger child begins with taking a history from the parent or guardian, which includes their interpretation of the child's visual behavior [10]. Subjective visual assessment for adolescents and adults is best obtained by asking questions about changes to activities of daily living, such as impaired driving at night, reading small print, and/or watching television [11]. In the case of the pediatric cancer survivor, the history should also document any radiation therapy, including the field and dosage, hematopoietic cell transplant, as well as exposure to glucocorticoids and/or Busulfan [12].

The American Academy of Pediatrics has published a policy statement on Eye Examination in Infants, Children and Young Adults by Pediatricians, which can also be applied to the pediatric cancer survivor [10]. Their recommendations for patients from birth to 3 years of age include:

1. Ocular history—including the parent's observations of their child's visual behavior
2. Vision assessment—ability to fixate and follow an object
3. External inspection of the eyes and lids
4. Ocular motility assessment
5. Pupil examination—pupils should be equal round and react to light

For patients older than three, it is recommended to add:

6. Age-appropriate visual acuity measurement—Snellen Acuity Chart, Tumbling E, Allen Cards
7. Ophthalmoscopy—to evaluate optic nerve and retinal vasculature

12.2.4 Referral

A referral to an ophthalmologist is indicated for pediatric cancer survivors reporting vision problems, or if an abnormality is noted on exam [10]. Supportive care for dry eye may be initiated in the form of artificial tears, but patients need education on its proper use and the signs and symptoms of a more serious pathology.

12.2.5 Emergent Referral

In rare cases, a more serious late effect to the eye may occur, and following are red flag symptoms that require emergent referral:

- Acute vision loss
- Amaurosis fugax (transient, painless vision loss in one eye)
- Dilated pupils
- Sluggish pupillary reaction to light
- Acute eye pain

- Unilateral photopsia (flashing light)
- Sudden, increasing floaters in one eye
- Metamorphopsia (wavy distortion of objects) [13]

12.2.6 Patient Education

Eye protection and prevention of injuries is critical education for all patients, particularly cancer survivors to prevent acceleration of any damage that occurred during their treatment. Key teaching points for survivors and their families include:

- Keeping household chemicals locked and out of the reach of children
- Proper eye protection use during sports or around hazardous equipment (e.g. polycarbonate goggles)
- Choosing toys with no sharp or protruding edges
- Adult supervision at all times with darts, fireworks and BB guns
- Sunglasses that provide 98–100 % UV-A and UV-B protection [14, 15]

12.3 Ears

Hearing, like vision, is a complex process, and can be damaged by cancer treatments at a young age. Ototoxicity may result not only from chemotherapy and radiation, but also from medications used to treat the complications of cancer and its treatment.

12.3.1 Risk Factors

There should be a high suspicion for hearing loss in survivors who received platinum chemotherapies (e.g. Cisplatin and high dose Carboplatin, generally used in the treatments of sarcomas, hepatoblastoma, neuroblastoma, germ cell tumors and central nervous system tumors) [16]. The Cochlea is a key element in the ability to hear sounds as it houses the Organ of Corti, whose tiny hair cells vibrate to stimulate signals sent along the auditory nerve. Platinum chemotherapies irreversibly damage these hair cells, which results in both high and low frequency hearing loss [16]. Although there are clinical trials underway to find methods of otoprotection from platinum chemotherapies, there is still much research to be done in this area and most patients exposed to these agents are still at risk for hearing loss [17].

Cranial radiation alone may also affect the Cochlea, starting at doses of 3,200 cGy [18]. Patients with a history of radiation may have issues with cerumen impaction, as radiation may affect the ear canal through stenosis, and also through the disruption of the normal ear epithelium [19]. It is also important to note that patients who received both radiation and platinum chemotherapies are at higher risk for hearing loss than those who received only one treatment modality [18].

Survivors who experienced prolonged illnesses with complications during treatment are also at risk for hearing loss. Pediatric cancer patients experience severe immunosuppression, placing them at increased risk for infections and sepsis [20]. Aminoglycoside antibiotics (e.g. Gentamycin) are used commonly as part of broad-spectrum coverage in serious gram-negative infections [21]. Like platinum chemotherapies, aminoglycosides cause irreversible damage to the Organ of Corti [21]. There may also be risk of hearing loss due to loop diuretics (e.g. Furosemide) commonly used in cases of fluid overload or heart failure [18].

12.3.2 Late Effects

Hearing loss may occur at both high and low frequencies, and is irreversible. Even mild hearing loss in children can result in deficits in classroom attention, speech articulation and self-esteem [22]. Prevention of any additional insults to the auditory system is critical for these patients throughout their lifetime [18, 23].

12.3.3 Assessment

The Children's Oncology Group Long Term Follow Up Guidelines recommend a baseline complete audiologic evaluation for every pediatric

cancer survivor at the end of active treatment with Cisplatin and myeloablative Carboplatin [9]. Additionally, those who received greater than 3,000 cGy of radiation to the cranium, ear, nasopharynx, Waldeyer's Ring (tonsillar) with or without Total Body Irradiation are advised to have yearly audiograms for the first 5 years following treatment, then every 5 years thereafter [9]. Initial assessment of the pediatric cancer survivor exposed to these agents should include an inquiry as to whether or not this testing has been completed, as well as its results. If the patient has not had an audiogram, or if hearing loss was detected and no follow-up has been completed, referral for a complete audiological evaluation (which includes pure tone air and bone conduction, speech audiometry and tympanometry for both ears) should be made, even if the patient does not complain of hearing difficulties [9]. If hearing loss is detected, regardless of the severity, testing should continue each year to monitor for any changes [9].

To assist the provider in a busy practice, a screening questionnaire has been developed specifically for childhood cancer survivors to assess for hearing loss (Table 12.1). Of note, this questionnaire is particularly helpful in determining which survivors may need screening, as it includes parental concern of their children's hearing loss, which is considered to be more accurate than physician examinations [24].

Physical examination should include both the external and internal ear, with pneumatic otoscopy as the standard for assessment of the internal ear and tympanic membrane [25]. If physical examination reveals excessive cerumen, it is not advised for Primary Care Physicians to attempt removal through irrigation or manual methods, but rather, a referral to a Head and Neck specialist should be made to avoid complications in compromised ear canals [26].

Table 12.1 Hearing loss screening questionnaire

Question	Response
Did the patient have any of the following tumor types: neuroblastoma, brain tumor, germ cell tumor, osteosarcoma, hepatoblastoma?	☐ Yes ☐ No
Did the patient receive cisplatin chemotherapy?	☐ Yes ☐ No
Did the patient receive cranial radiation or ear radiation?	☐ Yes ☐ No
Did the patient have a bone marrow transplant?	☐ Yes ☐ No
Has the patient had any type of surgery involving the brain or ear?	☐ Yes ☐ No
Does the patient have a VP shunt?	☐ Yes ☐ No
Has the patient received aminoglycoside antibiotics?	☐ Yes ☐ No
Has the patient received loop diuretics?	☐ Yes ☐ No
Was the patient less than 4 years old at diagnosis?	☐ Yes ☐ No
Was the patient's birth weight <2,500 g (5 pounds, 8 ounces)?	☐ Yes ☐ No
Does the patient experience ringing or noise in his/her ears?	☐ Yes ☐ No
Does the patient receive any speech therapy or accommodation in school?	☐ Yes ☐ No
Does the patient appear to have difficulty hearing in noisy situations?	☐ Yes ☐ No
Does the parent have any concerns about the child's speech or hearing?	☐ Yes ☐ No
Has the survivor had any kind of hearing assessment in the past?	☐ Yes ☐ No

Instructions: This questionnaire is to be used in primary care settings to facilitate identification of children at risk for hearing loss following therapy when treatment records are unavailable or incomplete. If the answer to any question is "yes" the patient should be referred to an audiologist.
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12.3.4 Patient Education

Patient education for those exposed to ototoxic agents should include avoidance of loud noises, which can worsen existing hearing loss [18]. This is of particular concern to adolescent patients, who place themselves at risk with the use of personal music players played at loud volumes for long periods of time, as well as through exposure to loud music in clubs and concert venues [27]. Patients and their families should also be educated to promptly report any new onset ear pain, cerumen impaction and/or tinnitus for evaluation and treatment to prevent progression to more severe conditions that may contribute to additional hearing loss.

Patients, families and the other members of their healthcare team require education on choosing, as appropriate given the clinical diagnosis, alternative

medications to those that are known to be ototoxic, such as loop diuretics (Furosemide), aminoglycosides (Gentamycin), and salicylates, to prevent further damage [28].

Patients and their families should be educated on the avoidance of ear candling, an alternative method of earwax removal, which is also claimed to have "purification" properties and curatives for cancer [29]. The U.S. Food and Drug Administration have deemed ear candles not only to be ineffective in the removal of ear wax but also dangerous to children who are at an increased risk for injury from their use [29].

12.4 Oral Health

Oral Health in America: A Report of the Surgeon General (2000) [30] found that oral diseases and disorders affect a person's health and well-being throughout life, the mouth reflects general health and well-being, and all care providers can and should contribute to enhancing oral health. This is particularly true in the case of the childhood cancer survivor, as therapies received during their treatment may affect their oral health for many years after treatment ends. Research has shown that survivors do not utilize routine dental care, despite their high risk for dental late effects [31].

12.4.1 Risk Factors

Survivors who were treated with chemotherapy before the age of 5 are at the highest risk for dental abnormalities, particularly those exposed to alkylating agents such as Cyclophosphamide [32]. Additionally, survivors who received cranial radiation or fields involving the oral cavity at any age are at risk at for late effects, with more complications reported with higher doses [32]. Children and young adults who underwent hematopoietic cell transplantation are also at risk, both from the intensive treatment regimens that include both radiation and chemotherapy, but also from the toxicity of chronic graft versus-host-disease [2].

12.4.2 Late Effects

12.4.2.1 Xerostomia

Dry mouth is a side effect of radiation, not due to destruction of the gland, but rather due to the effect on the saliva-producing cells [33]. The resulting saliva is sparse, viscous and more acidic [33]. This can lead to additional complications including pain, difficulties with eating and swallowing and increased dental caries [33]. Xerostomia may continue to worsen for months after the end of treatment, and is generally considered irreversible [33].

12.4.2.2 Oral Squamous Cell Carcinoma

A secondary cancer in the form of squamous cell carcinomas of the oral cavity is an unfortunate reality for survivors who experienced chronic oral graft vs. host disease following hematopoietic cell transplantation [34, 2]. This secondary malignant neoplasm is likely due to mucosal injury brought on by chronic inflammation [34].

12.4.2.3 Structural Abnormalities

Hypodontia (developmentally missing teeth) and microdontia (small teeth) are documented late effects for survivors who were treated at younger than 4 years of age, when tooth development is particularly sensitive to the effects of therapy [35]. These effects are also a documented side effect of cranial radiotherapy, with a synergistic relationship noted for patients who also received alkylating chemotherapy [32].

12.4.2.4 Osteoradionecrosis

A rare but serious late effect of radiation is osteoradionecrosis of the jaw, in which the bone, once exposed through trauma or dental procedures, is unable to heal [36]. Osteoradionecrosis occurs with higher doses (at least 4,000 cGy) of radiation to areas involving the mandible, including cranium, neck, upper chest, nasopharyngeal and/or oropharyngeal sites [37]. Although the exact pathophysiology behind the development of osteoradionecrosis is debated, survivors are at risk for complications from this for many years following therapy [37].

12.4.3 Assessment

Patient assessment should include frequency of brushing and flossing, and date of last dental visit. Survivors should also undergo an annual cancer oral examination, and those at highest risk should have an exam completed every 6 months [2]. The components of a complete physical exam include inspection of the hard palate, and inspection and palpation of the lymph nodes and salivary glands, inner and outer lips, cheeks and floor of mouth. One of the most critical areas to inspect is the tongue, as it is a common site for squamous cell carcinomas to develop [38]. The patient should be asked to stick their tongue out and up, which allows for visualization of both surfaces [38]. Then, the examiner should grasp the tip of the tongue with a 2×2 gauze pad, and gently pull the tongue out and up to the right and left, inspecting both sides from the tip to the tonsillar region [38].

12.4.4 Patient Education

The American Academy of Pediatric Dentistry published guidelines on the care of pediatric cancer patients before, during, and after therapy [39]. After cancer therapy is completed, preventive strategies to promote good dental health throughout the lifespan include:

- Good oral hygiene consisting of brushing with a soft nylon brush at least twice per day, with a toothpaste containing fluoride
- Daily flossing
- Education on limiting cariogenic foods and drinks, such as fruit juices, sugared drinks and candy
- Protecting lips with lanolin-based creams and ointments, avoidance of petroleum-based products
- Emphasis on routine follow-up with a dental professional at a minimum of every 6 months, or more frequently as recommended by the plan of care [39, 40].

Patients who experience xerostomia should be educated on the increased risk for dental caries. For patients who have undergone hematopoietic cell transplant, assess for any history of salivary dysfunction and educate on the use of sugar-free gum and candies, alcohol-free rinses and oral moisturizers. Saliva-stimulating drugs, such as Pilocarpine, have not been tested for safety in patients under the age of 18 and should be avoided [39].

Special consideration should be given to the oral health of hematopoietic cell transplant recipients. If the patient reports a history of chronic oral GVHD, they are at an increased risk for the development of oral squamous cell carcinomas [2]. As most oral cancers are detected at a late stage, these patients should be taught self-exam and to report the early signs of an abnormal oral lesion, including white (leukoplakia) and/or red (erythroplakia) patchy lesions on the mucosa and bleeding [2, 38].

Lip and tongue piercings are popular trends among adolescents and young adults [41]. However, in transplant survivors this is contraindicated [2]. The practice of oral piercing should be prevented in all patients; and those considering piercings should be educated on the high risk for bacterial infections, tooth and gum damage and risk for bleeding [42].

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Hematopoietic Stem Cell Transplant

13

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13.1 Introduction

Each year, over 3,750 pediatric allogeneic hematopoietic stem cell transplants (HSCT) are performed worldwide [1], and many more children and adolescents undergo autologous HSCT for treatment of a malignant disease. With an increasing number of malignant and non-malignant diseases being treated with HSCT, the availability of new sources of hematopoietic stem cells (such as umbilical cord blood), and improvements in supportive care, the population of long-term survivors of HSCT during childhood or adolescence is growing. Survivors of HSCT are at considerable risk for serious morbidity and premature mortality due to the risk for recurrence of their primary disease, the sequelae of pre-HSCT therapy, and the consequences of the transplant itself. Some late effects arise from the combined effect of the initial therapy and the HSCT, while others (such as chronic graft versus host disease [cGVHD] and delayed immune recovery) are a direct consequence of the transplant.

Data on long-term outcomes after pediatric HSCT are limited; much of the current knowledge about HSCT survivors has been derived from studies that have included a combination of children and adults, or adults alone. Further, since children who undergo HSCT for a malignant disease received combinations of chemotherapy, radiation and surgery prior to their transplant, it is often difficult to determine the independent impact of the transplant on long-term outcomes. The Bone Marrow Transplant Survivor Study (BMTSS) compared long-term outcomes in survivors of hematologic malignancies treated with HSCT with childhood cancer survivors treated without HSCT, and a sibling control group [2]. Almost 80 % of the 145 HSCT survivors included in the study reported one or more chronic health conditions, and over a quarter had developed a severe or life threatening condition. HSCT survivors were more likely than cancer survivors treated without HSCT to report a chronic health condition, a severe chronic health condition or multiple health conditions (Fig. 13.1).

Further, survivors of HSCT were more likely to report adverse general health, functional impairment and activity limitations.

Survivors of HSCT are also at risk for early mortality, even if they survive beyond the peri-transplant period. The BMTSS reported that

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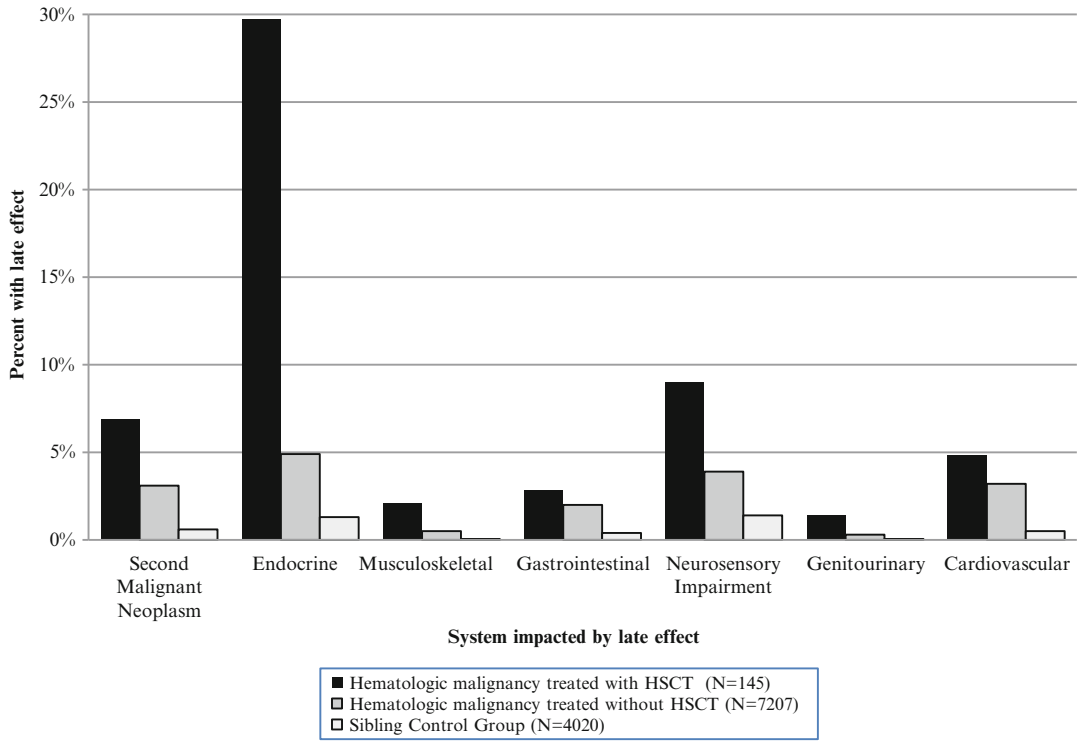

Fig. 13.1 Frequency of specific late effects in survivors of childhood cancer treated with or without HSCT and their siblings (adapted from Armenian et al. [2])

patients transplanted prior to age 18 years who survive for 2 years after their transplant are almost 17 times more likely to die than the similarly aged general population [3]. Although recurrence of the primary disease is the leading cause of death in HSCT survivors, cGVHD, infection, subsequent malignant neoplasms and specific organ toxicities (e.g. cardiac, pulmonary) can also cause premature death.

In this chapter, we will discuss the long-term outcomes observed after HSCT during childhood or adolescence, and will examine the impact of the type of transplantation, the conditioning regimen and the presence or absence of cGVHD on the risk for these outcomes. Given their risks, all survivors of childhood HSCT require lifelong follow-up care from a clinician with expertise in the late effects observed in these survivors and the surveillance and health promotion strategies needed to minimize long-term morbidity. We will present the health care requirements of childhood HSCT survivors and will summarize the existing surveillance recommendations for this growing population.

13.2 Types of HSCT

13.2.1 Autologous HSCT

Prior to the introduction of high-dose chemotherapy with autologous stem cell rescue (autologous HSCT), delayed or absent bone marrow recovery after high-dose chemotherapy limited the intensity of chemotherapy that could be given to children with some cancers. The development of technolo-

gies to harvest a patient's stem cells, store them and subsequently re-infuse them has allowed for the safe delivery of doses of chemotherapy above bone marrow tolerance [4]. The potential for improved disease-free survival after autologous HSCT must be balanced with the increased risk of treatment-related morbidity associated with such intense regimens. Although there is a small increase in the risk for transplant-related mortality during the acute phase of autologous HSCT, the risk of late effects and the long-term follow-up required after this procedure are similar to those in children who have been treated with intensive chemotherapy regimens without autologous HSCT. After transplant, these children are usually followed by their primary oncology team rather than a stem cell transplant specialist.

13.2.2 Allogeneic HSCT

Over the last four decades, allogeneic HSCT has been established as a curative option for many children with malignant and non-malignant diseases. Advances in supportive care, donor and patient selection, and better design and delivery of conditioning regimens have led to improved patient outcomes. However, as more children survive after allogeneic HSCT, special attention must be paid to the development of late effects. The increasing availability of unrelated donors along with a worldwide unrelated cord progenitor stem cell banks allowing HSCT with one or more human leukocyte antigen (HLA) mismatches has led to better survival because of graft-versus-leukemia (GVL) effect, but at the expense of a significant increase in HSCT late effects due to cGVHD and its life-long complications. Compared to childhood cancer survivors in general, survivors of allogeneic HSCT have a higher incidence of late effects, with 93 % of children reporting at least one late effect at a median follow-up of 7 years after HSCT. In 25 % of these children, the late effects are severe, disabling or even life threatening [5]. This chapter will focus on the late effects that can arise from allogeneic HSCT conditioning regimens and from the subsequent development of GVHD, particularly the chronic form.

13.3 Graft-Versus-Host Disease (GVHD)

13.3.1 Acute GVHD

The availability of new stem cell sources and the development of non-myeloablative conditioning regimens that are associated with later onset GVHD have negated the historical definition of GVHD. Previously, acute GVHD (aGVHD) was diagnosed when the disease occurred before day 100 after HSCT, in contrast to chronic GVHD (cGVHD) which was defined as occurring beyond day 100 [6]. Although cGVHD is the main contributor to late effects in long-term survivors, there are occasions where aGVHD remains active years after HSCT. This may manifest as inflammatory dermatitis, enteritis or hepatitis with persistence of cytotoxic lymphocytes and inflammatory cytokines that can cause ongoing tissue and organ damage [7, 8]. Prolonged aGVHD and its treatment can lead to further immunosuppression and delayed immune recovery with a risk for repeated infections in long-term survivors. A salient example of an acute transplant-related process that can contribute to a chronic late effect is the "allo lung syndrome". In this syndrome, a respiratory infection that occurs shortly after HSCT contributes significantly to the later development of permanent lung damage manifested as bronchiolitis obliterans (BO) in the context of cGVHD [9]. aGVHD has also been established as a major risk factor for the development of cGVHD with consequent late effects in HSCT survivors [10–14].

13.3.2 Chronic GVHD

Chronic GVHD (cGVHD) is the most important cause of non-relapse morbidity and mortality following allogeneic HSCT [15, 16]. Although the incidence of cGVHD is lower in children (30–50 %) than adults (70–80 %) [17], its prevalence has increased dramatically in recent years due to the use of stem cell sources other than bone marrow, particularly peripheral blood stem cells (PBSC) [18, 19]. In general, umbilical cord blood

(UCB) transplantation is associated with a lower risk of cGVHD [20]; however, since greater HLA disparity is tolerated when choosing a UCB donor, more children may develop cGVHD after UCB transplantation.

The presence of cGVHD is directly related to decreases in quality of life, impaired mental health, activity limitations and impaired physical function, and inferior long-term survival after HSCT [21–23]. cGVHD grading systems have important prognostic significance. Historically, severity was characterized as either "limited" or "extensive" [24]. These definitions have been expanded to include other measurements that correlate with prognosis, namely thrombocytopenia, progression of GVHD despite therapy, extensive skin involvement, gastrointestinal involvement, and low performance status at diagnosis of cGVHD [25, 26]. Recently, the National Institutes of Health (NIH) published consensus criteria which classify cGVHD as mild, moderate or severe [6].

Figure 13.2 displays many of the manifestations of cGVHD.

Treatment of cGVHD in children varies between transplant centers and is generally derived from the adult experience. Despite there being no proven standard therapy for cGVHD, cyclosporine and prednisone are commonly used as frontline treatment. Therapy may be needed for a long period of time (5 years or longer) [27]. Initial response to therapy is vital, as there is strong evidence that 90 % of patients who will ultimately respond to therapy will have shown signs of improvement by 3 months after initiating treatment. Patients should be observed carefully for response to frontline therapy, GVHD-related complications and morbidities stemming from glucocorticoid and immunosuppressant therapy. These include recurrent infections which can be bacterial, viral or fungal. Such infections may be life threatening and vigilance is required to prevent or promptly treat infections even years after the HSCT. Other side effects such as hypertension, diabetes and new malignancies can occur after prolonged immunosuppressant therapy. If frontline treatment is unsuccessful, salvage regimens include sirolimus, mycophenolate mofetil (MMF), pentostatin, rituximab, extracorporeal photopheresis (ECP) and targeted agents such as daclizumab and etanercept. These agents are potent immunosuppressants. ECP may increase the risk for infections because of a prolonged need for a large central venous access. These catheters may also increase the risk of thromboses and can hinder daily activities and life style. Furthermore, therapy for cGVHD is usually needed for a prolonged period, and clinicians must consider the impact of therapy on growth (especially with prolonged use of glucocorticoids), nutrition, organ function (in particular, the impact of the calcineurin inhibitors such as cyclosporine, tacrolimus and sirolimus on kidney function), immune reconstitution and psychosocial functioning.

13.4 Pulmonary Late Effects

Pulmonary toxicity is a major cause of both acute and long-term morbidity and mortality after HSCT [28]. Bronchiolitis obliterans (BO) is a well recognized cause of severe lung damage with a high rate of mortality [29–31]. The median time to BO onset after HSCT is 328 days (range 48–927 days) [32]. Risk factors for BO development include patient factors (such as reduced baseline respiratory status prior to HSCT), donor factors (such as related or unrelated donor, the degree of HLA matching and the stem cell source), and transplant factors (such as the intensity of the conditioning regimen and the type of GVHD prophylaxis). cGVHD is the most important risk factor [33–38]. Although establishing a diagnosis of BO requires the exclusion of intercurrent infection, there is increasing evidence that respiratory tract infections early after HSCT increase the risk of developing BO at a later date (the "allo lung syndrome", discussed above) [9]. Pathologically, BO results from obstruction and/or obliteration of the small airways due to luminal occlusion of the terminal and respiratory bronchioles caused by inflammation and fibrosis. In severe cases, the airway develops circumferential scarring with complete obliteration of the lumen leading to the clinical presentation of obstructive lung disease (OLD) characterized by cough, shortness of breath and/or wheezing [39, 40].

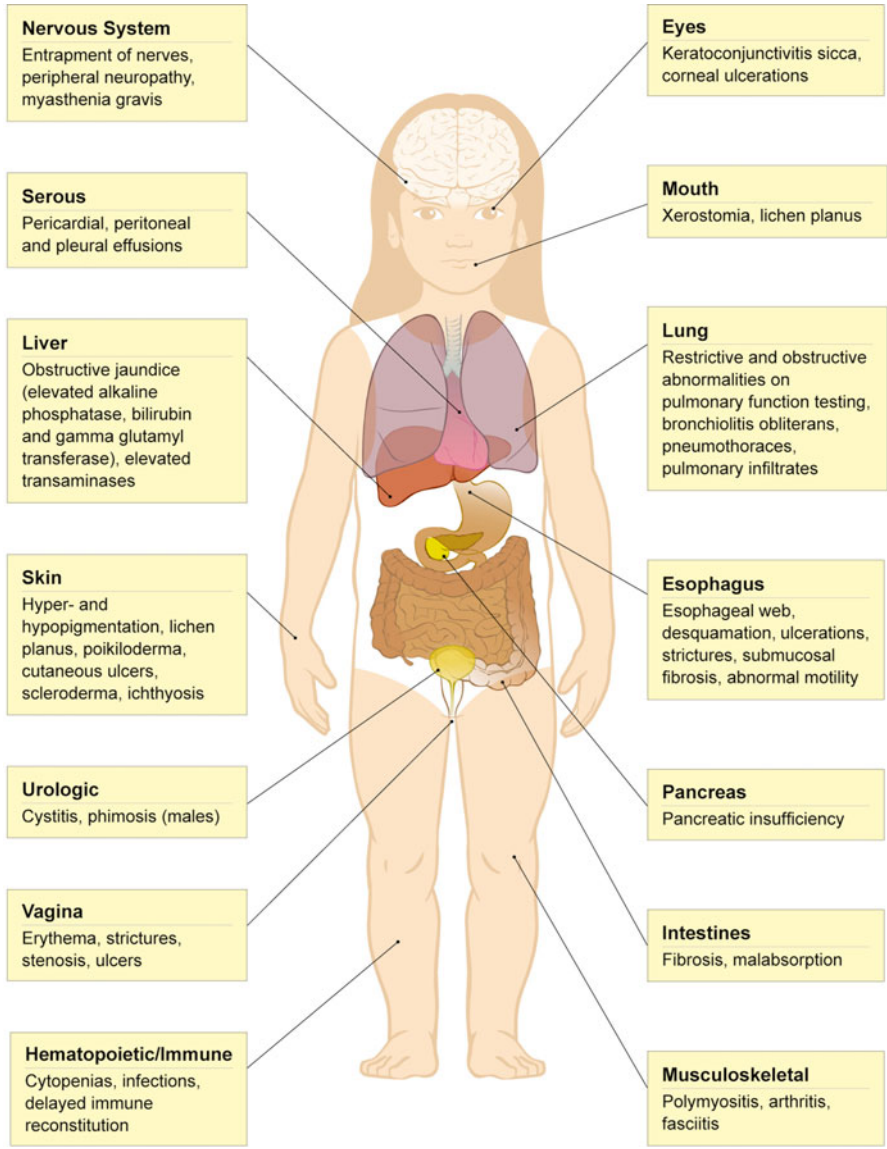

Fig. 13.2 Manifestations of chronic graft-versus-host disease in survivors of allogeneic HSCT

Restrictive lung disease (RLD) and impaired diffusion capacity are more common than OLD. They may represent persistence of lung injury sustained prior to HSCT, usually as a result of previous treatment with chemotherapy or radiation [41, 42]. The risk for RLD is modified by the transplant conditioning regimen, the primary cancer diagnosis, the development of scleroderma or contractures, and donor relation. Patients treated with Busulfan or total body irradiation (TBI) have the highest risk of RLD. In the largest pediatric study published to date, pulmonary function tests were performed at a median of 10 years (range 5.0–27.5) after HSCT [43]. Forty percent of survivors had either RLD or OLD, and at least 15 % had an isolated low diffusion capacity of lung for carbon monoxide (DLCO). Moderate-to-severe pulmonary function impairment was present in 45 % of patients with RLD or OLD. In addition to RLD and OLD, other lung morbidities after

transplant include recurrent lower respiratory infections and chest wall fibrosis.

Prior to the development of irreversible lung damage, children may have a prolonged asymptomatic period or symptoms that are attributed to infections. Survivors may present with subtle chest symptoms such as a dry cough. Progressive shortness of breath and wheezing might develop over time. In severe cases, tachypnea and weight loss due to increased work of breathing may ensue. If there is a suggestion of pulmonary disease on a survivor's routine history or physical examination then a chest X-ray or high resolution CT scan may reveal an infectious process or air trapping. Pneumothorax, pneumomediastinum, and subcutaneous emphysema are usually signs of advanced disease. Serial pulmonary function testing should be performed in any survivor at risk for pulmonary disease since the NIH guidelines advise that a diagnosis of BO may be suggested based on these tests alone [6]. All survivors of allogeneic HSCT who are able to perform PFTs should have regular testing every 6 months in the first 2 years after HSCT and less frequently thereafter if they are asymptomatic and their PFTs are stable. Consideration for more frequent PFT screening in recipients of mismatched unrelated donor grafts, or patients with active cGVHD is advised. Invasive procedures such as bronchoalveolar and lung biopsy are reserved for survivors with significant pulmonary disease or when the diagnosis is unclear. Early diagnosis is crucial to preserving pulmonary function with the use of effective immunosuppressant agents such as high-dose systemic pulse glucocorticoids which may stabilize OLD and prevent further progression [44]. Other treatment modalities are mainly supportive, and include inhaled glucocorticoids, bronchodilators, oxygen support, and pulmonary rehabilitation. Lung transplantation has been performed on rare occasions when there is an appropriate candidate with severe BO. Given the complexity of lung complications after HSCT, treatment of BO and other pulmonary morbidities is usually a co-ordinated effort between the transplant team and a respiratory physician with expertise in lung injury after HSCT.

13.5 Gastrointestinal Tract and Hepatic Late Effects

Late effects involving the gastrointestinal (GI) tract occur mainly as a result of cGVHD. These late effects may also represent persistence of GI pathology that arises during the acute transplant period. Symptoms include nausea, loss of appetite, non-specific abdominal pain, weight loss, cramping or diarrhea [45]. In severe cases of cGVHD, intestinal malabsorption and pancreatic insufficiency may lead to weight loss, and trace element and vitamin deficiencies [46]. Rarely, esophageal stricture resembling achalasia occurs with resulting dysphagia. Unexplained peritoneal effusion has also been reported [47].

The most common long-term hepatic presentation after HSCT is a non-specific elevation of liver enzymes with normal synthetic and metabolic function and no signs or symptoms of liver disease [48, 49]. In most cases, no particular cause is found. However, causes of abnormal liver enzymes after HSCT include cGVHD, iron overload, chronic viral hepatitis B or C, autoimmune hepatitis and prolonged total parenteral nutrition (TPN) [50–55]. cGVHD involving the liver usually manifests with cholestasis and obstructive jaundice as a result of fibrosis—patients present with increased alkaline phosphatase (ALP), gamma glutamyl transferase (GGT) and serum bilirubin levels [56]. Recently, hepatic cGVHD has been recognized more frequently in children with isolated increases in serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) [57]. The development of focal nodular hyperplasia (FNH) is also reported after HSCT. This benign liver tumor may mimic metastases or subsequent malignant neoplasms [58].

Physicians caring for HSCT survivors must obtain a detailed diet history, chart height and weight, and inquire as to symptoms of abdominal pain, diarrhea, nausea and vomiting. If there is concern about GI or liver dysfunction then the work-up should include assessment of hepatic function as well as testing for malabsorption or pancreatic insufficiency (serum trypsinogen, fecal fat assessment, and vitamin and trace element levels). In

cases of dysphagia, a chest X-ray or a barium study may be needed to establish the diagnosis. Referral to a gastroenterologist may prompt upper or lower GI endoscopy or liver biopsy in certain cases.

13.5.1 Iron Overload Post HSCT

Iron overload is a common contributor to liver dysfunction after HSCT in children with thalassemia as well as in those transplanted for hematological malignancies [59, 60]. Abnormal liver function tests are common signs of iron overload after HSCT. However, liver function abnormalities can also be caused by GVHD, drug toxicity and infections [60]. In children with pre-existing iron overload, red cell transfusions during transplantation can further damage the liver and other organs. Children without pre-existing iron overload are at risk for the development of iron overload due to the multiple transfusions in the peri-transplant period. In a study of 13 children with normal abdominal MRI scans prior to HSCT, 10 (77 %) were noted to have post-transplant iron overload in the liver. Six showed iron overload in the spleen (46 %) and four in the bone marrow (38.5 %) [61]. Although the majority of liver biopsies carried out in the late post transplant period are performed to assess for GVHD, these biopsies commonly demonstrate significant iron overload [62]. MRI can be used to measure liver iron concentration non-invasively, and to delineate specific areas suitable to perform these measurements [63]. In contrast, estimates obtained by needle biopsy show considerable variability depending on site of biopsy [64]. Serum ferritin, although less specific, has been shown to be an important marker for iron overload and may be a valuable tool for monitoring response to phlebotomy or iron chelation [54].

13.6 Hematopoietic and Immune Dysfunction

Prolonged hematopoietic or immune system dysfunction occurs mainly in the context of GVHD. Damage to the bone marrow stroma or autoimmune phenomena can lead to cytopenias [59–61, 65–67]. Thrombocytopenia is the most common hematopoietic manifestation of cGVHD and usually confers an inferior outcome [25].

Immune reconstitution after HSCT is complex—both recipient and donor factors play a role. Important recipient factors include the patient's age (with older children at a greater risk for delayed immune recovery, particularly after a UCB HSCT), the primary disease and its therapy, the patient's general condition at time of HSCT, the conditioning regimen and GVHD prophylaxis [68]. The type and source of the graft substantially affect the recovery of the recipient's immune function. For example, T-cell depleted and UCB grafts require more time for immune recovery. Natural killer (NK) cells are the first immune cells to reconstitute and may be present as early as 100 days after transplant. The B and T lymphocytes are reduced in numbers and function for many months after the HSCT. However, in the absence of significant GVHD, they gradually normalize after 1 year [69]. This process is much slower when UCB is used and may take up to 2 years for reasonable immune function [70, 71]. While engraftment and restoration of immune function is normally quicker after PBSC than after BM or UCB grafts, the higher incidence of GVHD in children treated with PBSC may compromise immune recovery. Generally, for all the three stem cell sources, the presence or absence of GVHD (particularly cGVHD) is the most important factor influencing immune reconstitution [72].

Children require repeated administration of vaccinations following recovery from allogeneic HSCT. The United States Centers for Disease Control (CDC) and the European Blood and Marrow Transplantation group (EBMT) have published recommendations about the timing of initiation of revaccination after HSCT [73]. Factors such as immunosuppressive therapy and the presence of GVHD may affect these timelines in individual patients. A recommended vaccine schedule is shown in Table 13.1.

Surveillance for hematopoietic system recovery involves periodic complete blood counts and occasionally bone marrow testing if there are

Table 13.1 Suggested immunization schedule for children after allogeneic HSCT

Timing post HSCT	Diphtheria, tetanus and pertussis[a]	HiB	IPV	Pneumo-coccus	Men-C	MMR	Var	HB	HPV	Influenza
12 months	■	■	■	■[b]	■	–	–	■	–	–
14 months	■	■	■	■	–	–	–	■	–	–
16 months	–	–	–	(■)[c]	–	–	–	–	–	–
24 months	■	■	■	–	–	–	–	–	–	–
24 months	–	–	–	■	–	■	■[d]	■	–	–
30–36 months	–	–	–	–	–	■	–	–	–	–
4–6 years old	(■)[e]	–	–	–	–	–	–	–	–	–
Grade 8 females	–	–	–	–	–	–	–	–	■	–
14–16 years old	(■)[f]	–	–	–	–	–	–	–	–	–
Every Autumn	–	–	–	–	–	–	–	–	–	■[g]

[a]For children <7 years old use DTaP; if ≥7 use Tdap for the first dose and Td for the next two doses
[b]For children >5 years old use Pneu-P-23; for ≤5 use Pneu-C-13
[c]For children <5 years old who have received Pneu-C-13 for first two doses, should receive booster with Pneu-P-23
[d]Provided is off of immune suppressive therapy and does not have significant chronic GVHD
[e]DTaP if <7 years old, Tdap if >7; if last dose of initial series given after this age then this booster is omitted
[f]Tdap—If last dose of initial series given after this age then this booster is omitted
[g]Annually every autumn provided at least 6 months from transplantation
The use of IVIG is not a contraindication for immunization with most vaccines, but there should be an interval of at least 6 months between IVIG and live viral vaccines such as MMR and Varicella vaccine (AAP Red Book 2009). This schedule is constructed from guidelines available from the Province of Ontario's Ministry of Health and Long-term Care (http://www.health.gov.on.ca/english/providers/program/immun/pdf/schedule.pdf) and Health Canada's immunization guidelines (http://www.phac-aspc.gc.ca/publicat/cig-gci/p03-07-eng.php). Timing to start immunizations varies between transplant centers. Twelve months is the standard timing; however, 6 months is acceptable in some centers
Black boxes meas that specific vaccine is required at that time point

prolonged cytopenias. As many infections lead to myelosuppression, testing for infectious agents such as viruses is warranted. Immune reconstitution studies are the mainstay of immunologic surveillance after HSCT. While some transplant centers routinely perform lymphocyte subset analysis, lymphocyte proliferation studies and assess for antibody response to common vaccines, other centers will perform these tests in only selected patients such as those patients with cGVHD, or when a decision regarding immunization or antiviral therapy is dependent on these tests.

13.7 Cutaneous, Ocular, Dental, and Oral Late Effects

Cutaneous late effects usually occur in the context of cGVHD. Manifestations include hypo- or hyperpigmentation, lichen planus, poikiloderma, telangiectasias, cutaneous ulcers, sclerodermatous skin changes that may lead to decreased joint movements and contractures, ichthyosis, onychodystrophy, alopecia and loss of sweat glands. While superficial cGVHD involving the skin can lead to dry skin, pruritus, erythema and rash, deep sclerotic changes resulting from inflammation and fibrosis of the dermis, subcutaneous tissue, or fascia can lead to significant long-term functional disability [74]. Skin care should include attention to topical moisturizers, sun protection, and surveillance for skin cancers.

Cataracts are the most reported ocular late effects in children after HSCT. Incidence has been reported to be between 30 % and 75 % in different studies [75, 76]. The use of TBI is strongly associated with later development of cataracts [77, 78]. Prolonged use of glucocorticoids and the presence of cGVHD may also play a role in cataract development. Other ocular late effects, mainly related to cGVHD, include

cicatricial conjunctivitis, keratoconjunctivitis sicca, punctate keratopathy and blepharitis. Symptoms include dry, gritty or painful eyes and photophobia leading to reduction in vision and in severe cases, blindness. Surveillance for cataracts is recommended for all survivors after HSCT, particularly those at highest risk (TBI recipients, prolonged corticosteroid use and cGVHD). Specialized ophthalmology care is recommended for long-term follow-up of ocular cGVHD to prevent irreversible damage.

Dental late effects after HSCT include abnormal development of teeth (tooth agenesis, hypodontia, microdontia and abnormal roots), delayed eruption, over-retention and increased risk for dental caries [79, 80]. Children younger than 5 years of age at the time of HSCT have the highest risk of dental late effects [79, 80]. Radiation involving the head and neck is a recognized risk factor for dental abnormalities [81, 82].

Oral late effects such as xerostomia, gingivitis, fibrosis and decreased salivary flow are more common in the context of cGVHD and can lead to significant reduction in quality of life [83]. These changes may increase the risk for secondary viral (especially herpes simplex) and yeast infections [84]. Furthermore, oral cGVHD and the topical immunosuppressant therapy used to control it may increase risk of subsequent malignant neoplasms such as oral squamous cell carcinoma [85]. Regular dental care by a dentist who is familiar with HSCT-related oral and dental complications and strict oral hygiene are vital in preventing or reducing these late effects.

13.8 Subsequent Malignant Neoplasms

Survivors of HSCT are at increased risk for the development of a subsequent malignant neoplasm (SMN). Their risk is increased if their pre-HSCT treatment includes radiation therapy or exposure to certain classes of chemotherapy agents, particularly oxazaphosphorines (e.g. cyclophosphamide) and epipodophyllotoxins (e.g. etoposide), or if their HSCT conditioning includes total body irradiation (TBI), or agents such as cyclophosphamide or etoposide. The risk is compounded by the development of cGVHD or the need for prolonged immunosuppression. HSCT survivors are at risk for solid neoplasms, hematological malignancies, and post transplant lymphoproliferative disorders (PTLD). The BMTSS reported that survivors of pediatric HSCT were almost 9 times as likely as survivors treated without HSCT to develop a SMN, even when controlling for exposure to brain or chest radiation and treatment with oxazaphosphorines or epipodophyllotoxins [86].

Solid neoplasms have been reported with increased frequency, particularly in survivors of allogeneic HSCT. The incidence of these malignancies increases with time, and does not appear to plateau [87]. Radiation therapy is likely the most important risk factor for their development, and several studies (but not all) have demonstrated that TBI conditioning increases the risk [88, 89]. Tumors of the thyroid as well as oral cancers are among the more common SMN observed [90, 91]. Non-melanoma skin cancers (basal cell carcinoma, squamous cell carcinoma) have also been observed with increased frequency in these patients [92].

Secondary leukemias and myelodysplastic syndrome (MDS) occur with increased frequency in survivors of autologous HSCT [93], but are uncommon after allogenic HSCT [87]. Pre-transplant therapy with oxazaphosphorines or epipodophyllotoxins and conditioning with TBI have been associated with increased risk. These malignancies are more common in adults treated with autologous HSCT than in similarly treated children [93].

Finally, post transplant lymphoproliferative disease (PTLD) is an uncommon occurrence after allogeneic HSCT. Risk factors include HLA disparity, T-cell depletion of donor marrow, use of anti-thymocyte globulin and both acute and chronic GVHD [93, 94]. Most cases are associated with Epstein-Barr Virus (EBV) infection [93]. PTLD usually develops in the first year after transplant, so it is infrequently a problem in long-term survivors. Survival is poor [91].

The Children's Oncology Group's (COG) *Long-Term Follow-Up Guidelines for Survivors*

of Childhood, Adolescent, and Young Adult Cancers (available at www.survivorshipguidelines.org) present recommendations for surveillance of SMN in survivors deemed to be at increased risk. Survivors must also be encouraged to comply with cancer screening advocated for the general population (e.g. PAP smears, routine mammography, colorectal cancer screening) and to adopt lifestyle practices (such as sun protection and avoiding cigarette smoking) that will reduce their long-term cancer risks.

13.9 Endocrine Late Effects

Among the many late effects of childhood cancer therapy and HSCT, endocrine manifestations are particularly common. Complications derive from damage to endocrine tissues as a result of radiation or chemotherapy during pre-transplant conditioning, or from effects of the primary disease or its treatment, including surgery or direct tumor extension. Endocrinopathies are frequently insidious in onset and may not manifest in overt clinical symptoms until reasonably advanced. Failure to recognize (and treat) signs and symptoms of endocrine dysfunction may contribute to impaired quality of life among HSCT survivors; thus, awareness of these potential outcomes is of vital importance for the treating clinician.

Recent estimates suggest that 30 % of patients who have undergone HSCT experience at least one grade 3–5 (classified as "severe, life-threatening or fatal") endocrine complication, compared to 4.9 % of childhood cancer survivors [2]. In addition, nearly one in every two female survivors of HSCT report ovarian failure (48 %), compared to 4 % of female survivors of childhood cancer treated with conventional chemotherapy. While these data are derived from retrospective cohort studies, reflecting transplant regimens in place between 1974 and 1998, the magnitude of the effect remains sobering.

As with other late effects of HSCT, surveillance and treatment of endocrine complications is adapted to the specific exposures (both pathologic and therapeutic) experienced by the patient. Overall, endocrine manifestations are more common among patients who received TBI as a component of their conditioning regimen, although gonadal toxicity and infertility remain highly prevalent following conditioning using alkylating agents alone (busulfan, cyclophosphamide, melphalan) [5, 95, 96]. Typical doses of TBI (12 Gy for neoplastic disease and 3–8 Gy for non-neoplastic conditions) are unlikely to result in substantial or permanent hypothalamic-pituitary dysfunction. Nevertheless, endocrine late-effects also reflect the combined sequelae of primary disease therapy in combination with treatments administered during the transplant process. Thus, anticipation of these sequelae must take both exposures into consideration.

13.9.1 Abnormalities of Linear Growth

Normal growth results from combined effects of hormonal influences [growth hormone (GH), thyroid hormones and sex steroids], genetic potential and adequate nutrition. Several studies have demonstrated reduced final height among survivors of childhood HSCT [96–98]. Radiation exposure is the primary treatment factor associated with compromise of final adult height. While cranial irradiation in excess of 30 Gy (generally in the context of primary treatment of a CNS malignancy) places patients at increased risk for GH deficiency, TBI also confers an independent risk for growth restriction [99–101]. In contrast to patients who undergo TBI and/or cranial radiation, those exposed exclusively to conditioning with cyclophosphamide or busulfan experience normal growth rates [98, 102–104]. Multiple elements of radiation treatment regimens may compromise final adult height, including the impact of radiation on the hypothalamic-pituitary axis which can result in impairment of GH secretion and pubertal precocity, while peripheral effects include direct radiation toxicity to the vertebral epiphyses [105, 106]. The greatest detrimental effects on growth are experienced by those with prior cranial irradiation and single-dose TBI, while fractionation of TBI helps mitigate the

effect [98, 101]. Similarly, age at TBI appears to be a major determinant of height-loss with the most pronounced effect among those receiving radiation prior to age 8 years [107]. Prolonged systemic glucocorticoids may also adversely affect growth.

Due to the complex interplay of factors that guide linear growth, prediction of the likelihood of growth failure is challenging. Nonetheless, the most sensitive diagnostic procedure for assessing early growth failure is serial, precise anthropometry and pubertal staging. Ancillary measures such as bone age measurement and hormonal assessment may be indicated but do not form the basis of screening.

Estimates of GH deficiency in HSCT survivors vary widely from 25 % to 85 % [76, 99, 106, 108]. This wide range reflects differences in conditioning regimens, prior history of cranial irradiation and different methods of GH testing. A substantial interval may exist between timing of HSCT and clinical signs of GH deficiency. For those treated with >30 Gy cranial irradiation [109] (as may be administered for primary CNS malignancy), evidence may be present within 5 years of treatment, while smaller cumulative doses (i.e. 18–24 Gy, given during treatment of CNS relapse for ALL) may result in an interval of ≥10 years [103]. Despite these discrepancies, significant improvement in final height has been observed in children who received GH treatment, irrespective of biochemical evidence of GH deficiency [99, 105, 110]. Children treated with GH prior to 10 years of age have the best response to GH therapy, while male patients are reported to reap less benefit in terms of final height [98, 99]. Additionally, patients with combined GH-deficiency and pubertal precocity (see below) may benefit from pubertal suppression with GnRH agonists to arrest premature epiphyseal closure [111]. Notwithstanding negative effects on growth, several series have demonstrated that a majority of HSCT survivors achieve final heights within 2 standard deviations of the general population, albeit diminished relative to their potential [98, 112, 113].

Given its role in promoting cellular proliferation and mitogenesis, concern has been raised about the risk of tumor recurrence and SMN in cancer survivors treated with GH. Prolonged large-scale follow-up of childhood cancer survivors treated with GH reveals no increased risk of primary tumor recurrence [114–116], although there may be a small but significant increased rate of SMN, primarily meningiomas [117, 118]. While specific data from survivors of HSCT are lacking, given an overall increased incidence of SMN among survivors of HSCT, care should be taken in selecting patients most likely to benefit from GH therapy.

GH deficiency in adults is associated with osteopenia, decreased lean body mass, dyslipidemia, diminished cardiac function as well as decreased quality of life [119]. Thus, replacement therapy may be indicated in adult survivors with a history of GH deficiency, although specific guidelines remain to be established [120–125].

13.9.2 Gonadal Dysfunction and Reproductive Failure

Perhaps no endocrine late-effect of HSCT therapy has as great an impact on quality of life as does gonadal dysfunction and infertility. These effects can manifest at varying stages of patients' lives including puberty and reproductive years, and stem from damage to both the central (hypothalamic/pituitary) controls and the gonads. Apart from direct physiologic effects on puberty and reproductive health, alterations in gonadal function and fertility may influence body image, interpersonal relationships, sexuality and sense of overall well-being [126, 127]. Moreover, sex steroid deficiency may lead to compromise of other systems such as bone health and linear growth. Although there is clear interplay between effects on fertility and testosterone/estrogen production, consideration of late-effects is facilitated by reviewing these separately.

13.9.3 Puberty and Gonadal Sex Steroid Production

Normal pubertal initiation and progression requires the function of an intact hypothalamic-

pituitary-gonadal axis. Resultant stimulation of gonadal sex steroids has effects on osseous maturation, redistribution of body fat, increases in muscle mass, development of secondary sexual characteristics and uterine maturation in girls. While pre-transplant cranial irradiation may result in central (hypogonadotrophic) hypogonadism, far more common among HSCT survivors is primary gonadal failure, resulting from direct gonadal toxicity from radiation and alkylating agent chemotherapy.

Hypogonadism has been reported in approximately a third of long-term survivors of HSCT and is much more common in females (69–95 %) than in males (9–47 %) [128, 129]. In the adolescent, this generally manifests as delayed or dysfunctional puberty, while in adults, hypogonadism may manifest with any of menopausal symptoms in women (menstrual irregularity, hot flashes, vaginal dryness, etc.), diminished libido, altered sexual function, or more vaguely with mood changes or decreased vitality [130].

Normal puberty is considered to be age-appropriate when signs (either breast or testicular enlargement) are first noted between ages 8 and 13 years in girls and between ages 9 and 14 years in boys. Outside of these ranges, pubertal timing may be abnormal and deserving of further evaluation by a pediatric endocrinologist. Absence of menarche by age 16 (or 3 years after first breast development) is also considered abnormal.

Central hypogonadism, due to deficits of LH and FSH secretion, is far less common than GH deficiency among HSCT survivors, but may present following radiation to the sella exceeding 30–40 Gy [131–133]. These doses are most often encountered following primary treatment for a CNS malignancy. Similarly, central pubertal precocity (CPP) is rarely associated with radiation exposures from HSCT alone, but may manifest following cumulative CNS radiation exceeding 18 Gy, presumably by relieving pubertal inhibitory signals within the hypothalamus.

Far more common than *central* hypogonadism is that resulting from direct gonadal toxicity due to radiation and/or chemotherapy. Treatment regimens incorporating alkylating agents (e.g. busulfan, cyclophosphamide) may compromise testosterone or estrogen production. Males treated with cumulative doses of cyclophosphamide >7.5 g/m^2 are at highest risk for testicular toxicity [103]. Testicular radiation doses exceeding 24 Gy are associated with Leydig cell dysfunction and testosterone deficiency [134, 135]. Nevertheless, sex hormone production in boys is more resistant to cytotoxic drugs and radiation than are germ cells and the majority of boys will initiate and complete sexual maturation without hormone replacement. Much smaller exposures are required to compromise male fertility, as will be discussed below.

In contrast, girls are at high risk for ovarian failure following HSCT. There is a 9.3-fold increased risk of ovarian failure as compared to all survivors of childhood cancer and 39.3-fold increased risk compared to the general population [2]. The degree of ovarian compromise is related to age at exposure (with less compromise at younger age at treatment), dose of abdomino-pelvic radiation and chemotherapeutic exposure (specifically, alkylating agents such as procarbazine) [129]. Permanent ovarian failure can result from radiation doses of >6 Gy in adult women, and >10 Gy in girls treated during childhood and adolescence [136]. These exposures are commonly encountered in the course of TBI for neoplastic disease, but may be avoided when transplanting for non-neoplastic conditions. Conventional doses of TBI during conditioning therapy for HSCT result in ovarian dysfunction in almost all girls older than 10 years and half of those younger than 10 years [137].

Female survivors of HSCT who maintain normal ovarian function after treatment are still at risk for premature ovarian failure (early menopause), with dose-dependent risk factors including increasing exposure to pelvic radiation and alkylating agents, as well as older attained age and a diagnosis of Hodgkin lymphoma. Among those exposed to alkylating agents *and* pelvic radiation, the risk for premature menopause approaches 30 % [136]. Implications of these findings pertaining to family planning should be

shared with female survivors, who may then elect to initiate efforts to attain pregnancy (whether naturally, or with assisted reproductive technologies) at a younger age.

There are compelling reasons to support sex hormone replacement for all individuals with testicular or ovarian failure, given their role not only in pubertal induction, progression and sexual health, but also in maintaining adequate growth, cardiovascular fitness, bone health and sense of well-being. Generally, replacement continues until the age of menopause in women and indefinitely in men. Nonetheless, there are limited data on the risks of hormone replacement among cancer-survivors for the extremely long time periods that are indicated in these patients, and there is at least a theoretical possibility that hormone replacement could exacerbate the inherent long-term morbidities associated with childhood cancer treatment including SMN (particularly in hormone-responsive tissues) and coagulopathy. Thus, a careful assessment of risk factors (including family history of BRCA1/2 mutation and Factor V Leiden) is warranted at the outset of therapy. Arguments for and against routine sex hormone replacement in childhood cancer survivors have been reviewed recently [138, 139].

In some instances, gonadal function has been noted to recover after months to years of insufficiency [140]; thus, for individuals receiving hormone replacement, intermittent withdrawal may be indicated to assess for this recovery under the guidance of an endocrinologist or fertility specialist.

13.9.4 Infertility (Germ Cell Failure)

In both sexes, infertility may result from hormone deficiencies as well as direct germ cell damage. The latter can be the consequence of gonadal irradiation (whether TBI, abdominal, pelvic or lumbosacral) and/or alkylating agents used during treatment of the primary disease or in the course of myeloablation prior to transplant. Germ cell compromise is present in the majority of patients treated with cytoreductive chemotherapy or radiation, and infertility is common.

In males, increasing doses of radiation lead progressively to reversible oligo-azoospermia (gonadal doses of 1–3 Gy), azoospermia that is less likely to be reversible (3–6 Gy) or permanent azoospermia (doses >6 Gy) [134, 141]. In a recent study, pre-pubertal therapy was identified as a risk-factor for male infertility, although the magnitude of the effect of age and pubertal status was small [142].

Women who have undergone allogeneic HSCT are unlikely to achieve pregnancy due to the ovarian toxicity of conditioning regimens prior to transplant. Abdomino-pelvic radiation doses as low as 4 Gy are able to destroy up to 50 % of oocytes [143, 144]. Prior cranial irradiation >22 Gy (as may be the case in patients with CNS tumors) also places women at risk for reduced fertility [145]. While there are several reports of pregnancy following HSCT with or without TBI [146–149], those who do become pregnant are at increased risk of miscarriage, premature delivery, and delivery of low- or very low birth weight infants [95, 136, 150]. These complications have not been observed among offspring of male HSCT survivors. There is no increase in rates of malformations or genetic syndromes in offspring of survivors of either gender. The increased miscarriage rate likely results from germ cell compromise as the result of ovarian radiation, while radiation to the uterus has been reported to result in diminished uterine size, muscular elasticity and uterine vascular damage, and this may account for the observed risk of prematurity and low birth weight [151]. In contrast to males, females are at increasing risk for infertility with treatment at advancing age (presumably due to progressive depletion of ovarian reserve) [142].

Measures aimed at fertility preservation in women, including ovarian autotransplant and ovarian wedge resection with cryopreservation and in vitro maturation, are currently being explored, but remain at the investigational stage [152]. Pubertal males maintain the option of sperm banking; however, no such option exists for pre-pubertal boys undergoing treatment. For those boys that are pubertal at the time of an initial oncologic diagnosis, consideration should be given to sperm banking prior to primary therapy if

there is a possibility that HSCT *may* be an eventual treatment modality, even if not first-line.

13.9.5 Thyroid Dysfunction

Thyroid dysfunction following HSCT is common, affecting up to 50 % of survivors [153], compared to 0.6–1.6 % of childhood cancer survivors [154]. Either overt primary hypothyroidism (increased TSH with low free T4) or compensated hypothyroidism (increased TSH with normal free T4) are the most common manifestations. Exposure to single-dose radiation as low as 10 Gy is associated with development of thyroid dysfunction [155, 156]. Cytoreductive chemotherapy without TBI may also be associated with risk of hypothyroidism [157]. Additionally, patients with a history of cGVHD are at 3.2-fold increased risk for development of post-transplant hypothyroidism [158]. In contrast, central hypothyroidism (TSH or TRH deficiency) is rare, unless high doses of cranial irradiation (>40 Gy) are administered [159, 160]. Autoimmune thyroid disease has also been described among HSCT recipients when the donor was affected by thyroid autoimmunity and typically manifests as autoimmune thyroiditis or Graves' disease [161–163]. Symptoms may appear several months to years after transplant with no obvious plateau in risk, even 25 years after treatment [154]. Furthermore there is a significant increase in the appearance of thyroid nodules and primary thyroid malignancy among survivors treated with radiation doses up to 30 Gy [164]. Survivors treated with radiation to a field that involves the thyroid (including TBI) require annual assessment of their thyroid function as well as examination of the thyroid.

13.9.6 Bone Health and Complications Among HSCT Survivors

Multiple components of primary disease therapy, as well as that involved in HSCT place patients at risk for compromised bone health. These include radiation therapy, prolonged systemic glucocorticoids and other chemotherapeutics (e.g. methotrexate) and, when superimposed, deficiencies in growth hormone and sex steroids. As a result, survivors of childhood cancer therapy and of HSCT are at increased risk for decreased bone density and osteonecrosis.

13.9.7 Diminished Bone Mineral Density (BMD)

Multiple studies have demonstrated a reduction in overall bone mineral density (BMD) among survivors of HSCT, particularly that population treated for cGVHD [165–167], although this finding is not replicated in all cohorts [168, 169]. Predictors of low BMD include dose and duration of glucocorticoid treatment, duration of treatment with Cyclosporine A or tacrolimus, older age at transplant and female gender [166, 170]. Race, primary diagnosis and time from transplant do not appear to be associated with risk. Although there is some recovery of BMD following treatment, survivors remain at increased risk for low BMD through adulthood [171, 172]. There is some suggestion that treatment with bisphosphonates prior to [173] or following [174–176] conditioning may preserve bone density, although studies are small and have not been performed among children undergoing HSCT. Accepted preventative therapeutic modalities include optimization of Calcium and Vitamin D intake, encouragement of weight-bearing exercise and identification (and treatment) of underlying growth hormone and sex steroid deficiencies. BMD assessment by DEXA or quantitative CT is recommended for all patients at entry to long-term follow-up and periodically thereafter [171]. Results of DEXA analysis in children must be interpreted according to age, pubertal status and height, using Z-scores rather than T-scores (which are the standard among adults). Failure to use appropriate comparators may result in overdiagnosis of low BMD [169, 177]. Moreover, in contrast to the adult literature, there is little pediatric evidence to support extrapolation of BMD to future fracture risk.

13.9.8 Osteonecrosis

Prolonged glucocorticoid therapy, most notably in the setting of cGVHD, places patients at increased risk for osteonecrosis (avascular necrosis). Osteonecrosis (ON) results from diminished blood supply and bone marrow ischemia. Symptoms include pain, swelling, immobility and decreased range of motion. In one study, osteonecrosis was noted on MRI in 44 % of children who had undergone HSCT [170]. Other factors associated with increased risk of osteonecrosis include TBI and age >10 years at the time of transplant [178–181]. In one study, children who underwent HSCT who did not develop cGVHD were no more likely than their siblings to develop osteonecrosis, while those with a history of GVHD developed ON at significantly higher rates [158]. Children carrying a polymorphism of the PAI-1 gene have been found to be at increased risk for ON following HSCT [182]. While the hip is the most commonly affected joint, other commonly affected joints include the humerus and other weight bearing long-bones. Annual screening via musculoskeletal examination is indicated, and suspicion of ON should prompt evaluation with MRI. MRI, however, has not yet been demonstrated to be an appropriate modality for routine screening. Apart from limiting glucocorticoid exposure, wherever possible, there is little to help prevent development of ON. Treatment requires consultation with an orthopaedic surgeon and may include physical therapy, analgesia and/or surgical intervention. There is recent evidence from limited non-controlled studies supporting the use of bisphosphonate therapy for symptomatic treatment of ON [183, 184].

13.9.9 Metabolic Consequences of HSCT

13.9.9.1 Overweight and Obesity

Survivors of acute lymphoblastic leukemia (ALL) are at increased risk for becoming overweight or obese [185, 186], though there is little data to suggest any additional risk accrued during the course of HSCT. Although one study demonstrated increased fat mass in survivors of HSCT when compared to controls (34.9 % fat mass vs. 24.3 %) [187], all patients in this study carried primary diagnoses of ALL or lymphoblastic lymphoma. Moreover, another study demonstrated a propensity towards underweight in HSCT survivors [188]. Mechanisms of altered body composition in these populations may include GH deficiency and disruption of hypothalamic satiety and energy-regulating centers. Additionally, restrictions of physical activity due to hospitalization and illness during the periods of primary disease treatment and HSCT may contribute to altered BMI.

13.9.9.2 Metabolic Syndrome

Survivors of HSCT are at increased risk for developing the metabolic syndrome (MS), defined by the National Cholesterol Education Program as any three of central obesity, hypertriglyceridemia, low HDL-cholesterol, elevated blood pressure, or increased fasting glucose. A recent study estimated the relative risk for MS among HSCT survivors at 2.2-fold over the general population [189–191]. Among survivors of childhood leukemia, HSCT with TBI (and not HSCT without TBI) was the only factor demonstrated to have a significant association with development of the MS [192]. Dyslipidemia may develop in up to 28 % of survivors [193]. Further biochemical comparison of this population with those in the general population with MS highlights significantly higher levels of leptin, CRP and TNF-α [194], suggesting possible underlying hypothalamic (e.g. hyperleptinemia) and/or systemic inflammatory mechanisms. Other proposed mechanisms for development of MS include endothelial dysfunction and nutritional insults during vulnerable developmental stages, both of which are plausible mechanisms in the face of treatment and disease-related stresses of HSCT [185]. While increased risk for the MS may partially explain the increased cardiovascular complications reported among survivors of cancer [195, 196] and HSCT [2], improvement in the parameters of MS has not yet been demonstrated to decrease CV risks in this population.

13.9.9.3 Diabetes

Although perturbations in glycemic control are common in the immediate post-transplant period, long-term effects on glycemia are less-well characterized [197–199]. Survivors of allogeneic HSCT were 3.7 times more likely to report diabetes than siblings [200], while childhood cancer survivors treated with conventional therapy were 1.8 times more likely to report diabetes than siblings [201]. In a recent pilot study, 5 out of 10 young adult survivors of HSCT had biochemical evidence of diabetes despite the absence of clinical symptoms, suggesting a high rate of occult disease [202]. Similarly, hyperinsulinemia without hyperglycemia (i.e. a state of insulin resistance) was noted following an intravenous glucose tolerance testing in a cohort of 24 survivors of childhood HSCT who underwent TBI, but not those who had isolated thoraco-abdominal radiation or who were not radiated, suggesting that the effect was generalized and not solely a result of pancreatic damage [203].

Diabetes among HSCT survivors appears to be distinct from both Type I and Type II diabetes. It is predominantly characterized by insulin resistance, rather than diminished beta-cell function, although patient characteristics are distinct from those classically associated with Type II diabetes [197, 198, 200, 202–204]. Specifically, among HSCT survivors that develop diabetes, BMI is not necessarily elevated, there is rarely a positive family history of diabetes and patients do not necessarily derive from "high-risk" ethnic groups. Diabetes in HSCT survivors is invariably insidious in onset and rarely associated with diabetic ketoacidosis [205]. Development of post-transplant diabetes was reported in a recent cohort in 28/369 (7.6 %) patients, although this estimate was based on retrospective analysis and may represent an under-diagnosis, given the nature of the disease [128]. As with the metabolic syndrome, post-transplant diabetes has not been specifically demonstrated to accrue the same risk of micro- and macrovascular disease as "conventional" Type I or Type II diabetes.

13.10 Cardiac Late Effects

Therapy with anthracyclines and treatment with radiation to a field that involves the heart can lead to cardiac disease in childhood cancer survivors. Many children who undergo HSCT will be exposed to these cardiotoxic therapies prior to transplant. Their risk for cardiac disease can be compounded by their transplant conditioning (e.g. TBI) [206]. Although high-dose cyclophosphamide has been proposed as a possible risk factor for cardiac toxicity, the evidence for this is limited [207]. Anthracycline agents are most commonly linked to myocardial damage with an increased risk for reduced cardiac function that, in severe cases, can manifest as congestive heart failure. Radiation therapy can also damage the myocardium, and it is also associated with coronary artery disease, pericarditis, valvular disease, and conduction abnormalities. As discussed above, HSCT survivors are also at risk for metabolic sequelae of their transplant such as diabetes mellitus, hypertension [207] and lipid abnormalities [192] that can impact negatively on their cardiac health. One study demonstrated that the presence of two or more of obesity, dyslipidemia, hypertension or diabetes in survivors of adult HSCT was associated with a five-fold increased risk of cardiovascular disease [208].

Survivors who have been treated with an anthracycline or chest radiation (including TBI) require cardiac imaging (by echocardiogram or MUGA) every 1–5 years, depending on their age at treatment, cumulative anthracycline dose, and radiation exposure [209]. Care providers should be aware of their risks for metabolic sequelae and should assess weight and blood pressure at all visits, and screen for glucose intolerance or dyslipidemia periodically.

13.11 Renal Late Effects

Many of the medications used for transplant conditioning or supportive care are nephrotoxic. In particular, aminoglycoside antibiotics, antifungal agents, calcineurin inhibitors (such as

cyclosporin and tacrolimus), nephrotoxic chemotherapy (such as ifosfamide or platinum agents), radiation used prior to transplant and for transplant conditioning, and acute illness during the transplant period (such as veno-occlusive disease of the liver [210] or sepsis) can lead to renal dysfunction during transplant or within the first year after the procedure. Acute renal dysfunction is an important risk factor for chronic renal disease [210]. This risk may be compounded by the use of TBI [211, 212] and cGVHD [212]. Some studies have suggested that increasing age (particularly transplantation during adulthood) is associated with a greater risk of chronic renal disease [212, 213]. Given the small number of children included in studies of long-term renal outcomes after HSCT, the true prevalence of chronic renal disease in survivors of pediatric HSCT is unknown. Any survivor whose cancer history places them at increased risk for renal dysfunction should have an annual assessment of their blood pressure and a urinalysis. Electrolytes and renal function should be assessed on entry into long-term follow-up care, and then as clinically indicated.

13.12 Neurocognitive Sequelae

As with other late effects, assessment of the risk for long-term neurocognitive decline after HSCT must consider the therapy received prior to the transplant. For example, survivors who require cranial radiation for high-risk leukemia or surgery and radiation for medulloblastoma are more likely to present with neurocognitive difficulties than those who have not received therapies that impact the central nervous system. Studies of neurocognitive function after HSCT have been hampered by a lack of baseline testing prior to diagnosis (making it difficult to determine the independent impact of the pre-transplant therapy and the transplant itself), combination of inhomogeneous groups of patients, and an absence of appropriate control groups. In general, most survivors of HSCT develop minimal or no neurocognitive or academic sequelae after their transplant [214]. Even conditioning with TBI (which delivers 12 Gy radiation to the brain) has not been show to have a major impact on outcome. However, lower socioeconomic status [214], younger age at transplant (<3 years old) [215] and poorer neurocognitive functioning prior to transplant [216] have been shown to increase the risk for poorer outcomes. Since there is a wide range of neurocognitive outcomes observed in survivors, it is important that clinicians be aware of the risks and be prepared to provide formal neuropsychological assessment and intervention if needed. During their school years, survivors' academic performance should be monitored, and appropriate referrals for assessment should be considered if a survivor reports school difficulties or a change in academic performance.

13.13 Health-Related Quality of Life (HRQL), Psychosocial and Psychological Outcomes

The long-term impact of HSCT extends beyond the physical sequelae of the procedure. Survivors are at risk for decreased HRQL, inferior vocational and social outcomes, and psychological morbidities. Clarke and colleagues [217] reviewed the literature regarding HRQL outcomes after pediatric HSCT published between 1966 and 2008. HRQL was often decreased in the periods preceding, during and immediately following transplant, but tended to improve in the months following the completion of therapy. Long-term survivors generally reported their HRQL to be comparable with (or better) than population norms, although their parents and teachers often reported decreased HRQL in survivors. Despite the generally positive assessment of their HRQL, individual survivors reported pain, poor self esteem, and impaired functioning at school or work. Interestingly, survivors' perceptions of their HRQL do not appear to depend on the number of physical late effects that they have developed [207].

Multiple studies have reported that children and adolescents are at risk for anxiety and depression prior to and during their HSCT, and that some survivors develop symptoms of post-traumatic stress disorder in the period following transplant [218]. However, it has not been established how frequently these psychological challenges persist once these patients become long-term survivors. In fact, studies in adults have suggested that some survivors of HSCT may experience positive psychological changes following their cancer therapy, a phenomenon labelled "post-traumatic" growth [219].

Although many survivors of childhood HSCT report living "normal" lives, even in the presence of physical morbidities stemming from their therapy, some fail to attain their social and vocational goals. Studies have reported that HSCT survivors may be less likely to marry [220], and may report concerns with sexuality as well as worries about their fertility [221]. Survivors may also be at increased risk for unemployment [222]. The wide variation in outcomes between survivors, and an absence of robust predictors for poor outcome, suggests that clinicians who care for this population should screen for psychosocial difficulties and decreased HRQL in *all* HSCT survivors that they see in follow-up.

13.14 Long-Term Care of the HSCT Survivor

All survivors of childhood cancer require a lifelong plan for periodic health care and surveillance targeted at the specific risks arising from their prior therapy. Several organizations have published such guidelines for survivors of HSCT. The European Group for Blood and Marrow Transplantation (EBMT), the Center for International Blood and Marrow Transplant Research (CIBMTR) and the American Society of Blood and Marrow Transplantation (ASBMT) have all published consensus guidelines for screening and preventive practices in HSCT survivors [94]. However, these guidelines are directed at survivors of adult HSCT. The Children's Oncology Group (COG) has published *Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers* (available at www.survivorshipguidelines.org). These document the recommended surveillance for all pediatric cancer survivors, including those who have undergone an HSCT. Similarly, the United Kingdom's Children's Cancer and Leukemia Group addresses the needs of HSCT survivors in their *Therapy Based Long Term Follow Up Practice Statement*. Specific guidelines for survivors of HSCT are focused on the incremental risks over and above those that occur as a result of their cancer therapy preceding transplantation. Table 13.2 summarizes some of the major risks and the recommended surveillance strategies from the COG guidelines.

13.15 Conclusion

Given their high risk for morbidity, it is essential that HSCT survivors receive their follow-up care from a health care practitioner knowledgeable in the physical and psychological sequelae of their cancer therapy and transplant. Once they enter adulthood, the majority of cancer survivors will receive such care from a primary care clinician in their community, rather than at a cancer center. It is critical that these clinicians have access to detailed information on the survivor's prior therapy, complications of that therapy, and the recommendations for their long-term surveillance. To that end, every survivor should be provided with a treatment summary and survivor care plan prior to their discharge from the transplant center. In addition, the transplant center should be available to provide support to clinicians caring for survivors, and to expedite appropriate referral if problems arise. Survivors with significant morbidity (such as active cGVHD) likely require care from a specialist, and should continue to be seen at a cancer-center based transplant clinic or long-term follow-up program.

Table 13.2 Recommended surveillance for selected late effects arising after HSCT as recommended in the Children's Oncology Group's *Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers* (available at www.survivorshipguidelines.org)

	Potential late effect	Highest risk factors	Specific questions on annual history	Specific maneuvers on annual physical examination	Laboratory tests and imaging
Any patient treated with HSCT	Psychosocial disorders		Psychosocial assessment with attention to education/vocation, depression, anxiety, post-traumatic stress, social withdrawal		
	Gonadal dysfunction (males)	TBI, alkylating agent conditioning		Tanner staging, testicular volume until sexually mature	LH, FSH, testosterone if indicated. Semen analysis if requested by survivor.
	Gonadal dysfunction (females)	TBI, alkylating agent conditioning	Menstrual/pregnancy history	Tanner staging yearly until sexually mature	LH, FSH, estradiol if clinically indicated
	Acute myeloid leukemia/ myelodysplasia	Older age, autologous HSCT for lymphoma	Fatigue, bleeding, easy bruising	Dermatologic exam for pallor, petechiae, purpura	Annual CBC up to 10 years after transplantation
	Solid tumors	TBI		Complete examination including thyroid, skin etc.	
	Hepatic toxicity (chronic hepatitis, cirrhosis, iron overload)	Chronic hepatitis C		Stigmata of liver disease	AST, ALT, bilirubin, ferritin at entry into long-term follow-up and repeated as clinically indicated
	Osteonecrosis	Prolonged corticosteroid therapy (e.g. for chronic GVHD)	Joint pain, swelling, immobility, limited range of motion	Musculoskeletal system	MRI only if signs/ symptoms suggesting osteonecrosis
	Reduced bone mineral density	Older age at treatment, prolonged corticosteroid therapy			Bone density evaluation (DEXA or quantitative CT) at entry into long-term follow-up. Repeat as clinically indicated.

(continued)

Table 13.2 (continued)

	Potential late effect	Highest risk factors	Specific questions on annual history	Specific maneuvers on annual physical examination	Laboratory tests and imaging
HSCT with any history of chronic GVHD	Dermatologic toxicity (permanent alopecia, nail dysplasia, vitiligo, scleroderma, squamous cell carcinoma of the skin)			Hair, nails and skin	
	Xerophthalmia (keratoconjunctivitis sicca)	Radiation to the eye ≥30 Gy or radiation fraction ≥2 Gy	Dry eyes (burning, itching, foreign body sensation, inflammation)	Eye exam	
	Oral toxicity (xerostomia, salivary gland dysfunction, dental caries, periodontal disease, oral cancer)	Radiation to the salivary glands ≥30 Gy or use of azathioprine for cGVHD management	Dry mouth	Annual oral exam. Dental exam and cleaning every 6 months	
	Pulmonary toxicity (bronchiolitis obliterans, chronic bronchitis, bronchiectasis)	Prolonged immunosuppression related to GVHD and its treatment	Cough, dyspnea, wheezing	Pulmonary exam	Chest x-ray and PFTs (including DLCO and spirometry) at entry into long-term follow-up and repeated as clinically indicated
	Immunologic complications (secretory IgA deficiency, hypogammaglobulinemia, decreased B cells, T cell dysfunction, chronic infections)	Active cGVHD or prolonged immunosuppression related to GVHD and its treatment	Chronic conjunctivitis, sinusitis or bronchitis, or sepsis or recurrent unusual infections	Eye, nasal and pulmonary exam	
	Esophageal stricture	Radiation dose ≥40 Gy, gut GVHD	Dysphagia, heart burn		
	Vaginal fibrosis/stenosis	Pelvic radiation	Dyspareunia, vulvar pain, post-coital bleeding, difficulty with tampon insertion		
	Joint contractures			Musculoskeletal exam	

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Second Malignant Neoplasms 14

Smita Bhatia

14.1 Introduction: Epidemiology of Subsequent Malignant Neoplasms

Second or subsequent malignant neoplasms (SMNs) are defined as histologically distinct cancers developing after the occurrence of a first cancer. Previous studies utilizing large cohorts of children with cancer report a three- to six-fold increased risk of SMNs compared with the background incidence of cancer in the general population. This risk continues to increase with the ageing of childhood cancer cohorts. Follow-up of 47,697 Nordic children diagnosed with a primary cancer between 1943 and 2005 demonstrated a 3.3-fold increased risk of developing an SMN when compared with an age- and gender-matched healthy population [1]. A British population-based cohort of 17,981 5-year survivors of childhood cancer diagnosed with a primary cancer between 1940 and 1991, demonstrated a four-fold increased risk of developing a new cancer, when compared with the general population [2]. Another retrospective cohort of 14,359 children diagnosed between 1970 and 1986 in the US, and surviving at least 5 years, was followed by the Childhood Cancer Survivor Study (CCSS) [3]. The estimated 30-year cumulative incidence was 7.9 % for SMNs (excluding non-melanoma skin cancers). Overall, the cohort was at a six-fold increased risk of developing a second cancer. Childhood cancer survivors are at risk for the development of multiple primaries. The cumulative incidence of a third primary approaches 47 % at 20 years after the second primary [4]. Radiation-exposed survivors, who developed a non-melanoma skin cancer as an SMN, carry a higher risk of a subsequent invasive SMN when compared with those without a history of a non-melanoma skin cancer.

SMNs are classified into two distinct groups, based primarily on the unique associations with specific therapeutic exposures: chemotherapy-related myelodysplasia and acute myeloid leukemia (t-MDS/AML), and radiation-related solid SMNs. Characteristics of t-MDS/AML include a short latency and association with alkylating agents and/or topoisomerase II inhibitors. The risk of t-MDS/AML usually does not extend beyond the first 10 to 15 years after therapeutic exposure. Solid SMNs have a well-defined association with radiation, and are characterized by a latency that typically exceeds 10 years [3, 5–7]. Eighty percent of the entire burden of SMNs is accounted for by radiation-related solid SMNs, such as breast, skin and thyroid cancer, central nervous system (CNS) tumors, and bone and soft tissue sarcomas [8–10].

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t-MDS/AML has been reported after successful treatment of Hodgkin lymphoma (HL), non-Hodgkin lymphoma (NHL), acute lymphoblastic leukemia (ALL), and bone and soft tissue sarcomas [5, 8, 11–15]. The risk of t-MDS/AML is typically low, approaching 2 % at 15 years after conventional therapy [5], except among children with ALL treated with epipodophyllotoxin therapy where a cumulative risk of 3.8 % at 6 years was reported [16], or among children with metastatic Ewing sarcoma treated with high doses of alkylating agents and topoisomerase II inhibitors, where the incidence of t-MDS/AML exceeded 10 % [11]. Using the WHO classification, two types of t-MDS/AML are recognized, related closely to the therapeutic exposure: alkylating agents/radiation and topoisomerase II inhibitors [17]. The alkylating agent-related t-MDS/AML typically develops 4–7 years after exposure. Cytopenias are common. Two thirds of the patients present with myelodysplasia; the remaining present with AML but carry myelodysplastic features. Abnormalities involving chromosomes 5 (−5/del[5q]) and 7 (−7/del[7q]) are frequently seen. AML secondary to topoisomerase II inhibitors presents as overt leukemia, without a preceding myelodysplastic phase. The latency is brief, ranging from 6 months to 5 years, and is associated with balanced translocations involving chromosome bands 11q23 or 21q22. The schedule of epipodophyllotoxin (rather than cumulative dose) increases the risk of topoisomerase II inhibitor-associated t-AML [18].

Solid SMNs are related to radiation therapy used to treat the primary cancer; radiation-related solid SMNs develop within the radiation field [5, 6, 8, 19, 20]. The latency for radiation-related solid SMNs usually exceeds 10 years [5, 6, 8, 20]. The risk is highest when radiation exposure occurs at a younger age [5, 7, 20–27], and increases with increasing doses of radiation and with increasing time since radiation [6, 8]. Some of the well-established radiation-related solid SMNs include breast cancer, thyroid cancer, CNS tumors, sarcomas and basal cell carcinomas (BCCs) [3, 5–8, 25, 28].

Breast Cancer: Breast cancer is the most commonly reported SMN among female survivors of childhood HL treated with mantle field irradiation (Standardized Incidence Ratio [SIR] = 24.7, 95 % Confidence Interval [CI], 19.3–31.0), and the risk remains markedly elevated for many decades after exposure [5, 20, 28–31]. The survivors are at a tremendously increased risk (have up to a 55-fold) of breast cancer compared with the general population, and the cumulative incidence of developing a secondary breast cancer approaches 20 % for survivors that are 45 years of age [8]. Moreover, 40 % of the patients with radiation-related breast cancer develop contralateral disease. The incidence is also increased among those exposed to total body irradiation (TBI) as the only source of radiation to the chest when compared with those who did not receive TBI (17 % vs. 3 %) [32]. The risk of breast cancer increases in a linear fashion with radiation dose, reaching 11-fold for local breast doses of ~40 Gy relative to no radiation [33]. The risk of radiation-related breast cancer declines with age at radiation, such that the relative risks compared with the general population are comparable to those of the general population after age 40 [34]. There appears to be a protective effect of early menopause induced either by alkylating agents or radiation dose >5 Gy to the ovaries, suggesting that ovarian hormones play an important role in promoting tumorigenesis once an initiating event has been produced by radiation [28, 33, 35, 36].

Thyroid Cancer: Secondary thyroid malignancies, typically papillary carcinoma, are generally associated with radiation to the thyroid gland as part of CNS irradiation, either prophylactic or for treatment of CNS leukemia, as part of therapeutic irradiation of cervical lymph nodes in HL patients, or as part of conditioning with TBI for hematopoietic cell transplantation (HCT) [5, 7, 8, 12, 20]. Thyroid malignancy typically develops 10 or more years from treatment. Thyroid cancer risk increases linearly with radiation dose up to 20 Gy, where the relative risk peaked at 14.6-fold; at thyroid radiation doses >20 Gy, a downturn in the dose–response relationship is observed. Sex

(higher risk among females), age at exposure (higher risk at a younger age at exposure) and time since exposure (higher risk with longer time), are significant modifiers of the radiation-related risk of thyroid cancer [37]. HCT recipients are at a 3.3-fold increased risk of thyroid cancer, when compared with age- and sex-matched general population [38]. Younger age at HCT (<10 years), neck radiation, female sex, and chronic graft versus host disease (GvHD) are associated with an increased risk of thyroid cancer. The long-term outcome for survivors diagnosed with a secondary thyroid malignancy is excellent.

Central Nervous System (CNS) Tumors: Brain tumors develop after cranial radiation for treatment of histologically distinct brain tumors [6], or management of CNS leukemia [7, 12, 20]. The risk is 16.9-fold higher than that of the general population for ALL survivors and is 14.2-fold increased for brain tumor survivors. Histologically, radiation-related late-occurring CNS tumors include high-grade gliomas, (glioblastomas and malignant astrocytomas), peripheral neuroectodermal tumors, ependymomas and meningiomas [7, 13, 39, 40]. Gliomas are diagnosed a median of 9 years from radiation; for meningiomas, the latency is longer (17 years) [6]. Radiation exposure is associated with increased risk of both subsequent glioma (OR = 6.8) and meningiomas (OR = 9.9). The dose–response for the excess relative risk is linear. For gliomas, the excess relative risk per Gy is highest among children exposed at less than 5 years of age.

***Sarcomas*:** The risk of sarcoma after an initial diagnosis of childhood cancer is reported to be nine-fold that in the general population; the risk is particularly elevated after a primary soft tissue sarcoma (24.7-fold), bone tumor (10.6-fold), HL (11.7-fold), or renal tumors (14.6-fold) [41]. Sarcomas develop within the radiation field after a latency of ~10 years.

Carcinomas: With extended follow-up of cohorts of young survivors, increased risks of common adult carcinomas, including colorectal, lung and stomach have emerged, and these cancers are being diagnosed at younger ages than observed in the general population [8, 28, 42–44]. In a large population-based study, breast, lung and gastrointestinal cancers accounted for almost two-thirds of the estimated excess number of cases [45]. In another population-based cohort of 5-year survivors, the greatest excess risk associated with SMNs among survivors older than 40 years of age, was for digestive and genitourinary neoplasms [2]. The risk of carcinomas (other than breast, thyroid, skin) is four-fold higher than that expected [46]. The most common sites are head and neck (mostly parotid gland), gastrointestinal tract, female genitourinary tract, and kidney. The risk is highest among survivors of neuroblastoma and soft tissue sarcoma; the risk is also elevated for patients who have received radiation therapy.

Skin Cancer: Ionizing radiation is a well-established cause of non-melanoma skin cancers (primarily basal cell and squamous cell carcinoma); radiation is associated with a 6.3-fold increased risk [24, 47]. Over 90 % of non-melanoma skin cancers develop within the radiation field [5–7, 12, 13, 20].

14.2 Pathogenesis of Subsequent Malignant Neoplasms

Understanding the underlying etio-pathogenetic pathways that lead to SMNs is critical to developing targeted prevention and intervention strategies, optimizing risk-based health care of cancer survivors, and improving quality of life. The observed inter-individual variability in risk of developing an SMN for any given exposure to radiation and chemotherapy suggests a role for genetic variation in individual susceptibility. Genetic predisposition and its interaction with therapeutic exposures can potentially exacerbate the toxic effect of treatment on normal tissues. The risk of chemotherapy- or radiation-related SMNs could potentially be modified by mutations in high-penetrance genes that lead to serious genetic diseases e.g., Li-Fraumeni syndrome [48], and Fanconi anemia [49–52]. However, the attributable risk is expected to be

very small because of the extremely low prevalence of the high-prevalence genes such as those implicated in Li-Fraumeni syndrome. The inter-individual variability in the risk of SMNs is more likely related to common polymorphisms in low-penetrance genes that regulate the availability of active drug metabolite, or those responsible for DNA repair. Genetic variation contributes 20 % to 95 % of the variability in cytotoxic drug disposition [53]. Polymorphisms in genes involved in drug metabolism and transport are relevant in determining disease-free survival and drug toxicity [54]. Variation in DNA repair plays a role in susceptibility to de novo cancer [55–59], and likely modifies SMN risk after exposure to DNA-damaging agents, such as radiation and chemotherapy.

Drug Metabolism: Metabolism of genotoxic agents involves activation of substrates into highly reactive electrophilic intermediates that can damage DNA (phase I enzymes)—a reaction principally performed by the cytochrome p450 (CYP) family of enzymes; and inactivation of genotoxic substrates (conjugation—phase II enzymes). Inactivating proteins comprise the glutathione S-transferase (GST), NAD(P)H:quinone oxidoreductase-1 (NQO1), and others. The balance between the two sets of enzymes is critical to the cellular response to xenobiotics; e.g., high activity of phase I enzyme and low activity of a phase II enzyme can result in DNA damage from the excess of genotoxic exposure. The expression of these enzymes is highly variable among individuals because of several functionally relevant genetic polymorphisms [60]. Using a candidate gene approach, investigators have examined the association between polymorphisms in the glutathione S-transferase genes (*GSTM1*, *GSTT1* and *GSTP1*) and t-MDS/AML [61]. Individuals with at least one *GSTP1* codon 105 Val allele were significantly over-represented in t-AML cases compared with de novo AML cases (OR = 1.8, 95 % CI, 1.1–2.9). Also, relative to de novo AML, the *GSTP1* codon 105 allele occurred more often among t-AML patients with prior exposure to chemotherapy (OR = 2.7, 95 % CI, 1.4–5.1), particularly among those with prior exposure to known *GSTP1* substrates (OR = 4.3, 95 % CI, 1.4–13.2).

DNA Repair: An individual's DNA repair capacity appears to be genetically determined [62]. A number of DNA repair genes contain polymorphic variants, resulting in large inter-individual variations in DNA repair capacity [62]. Individuals with altered DNA repair mechanisms are likely susceptible to the development of genetic instability that drives the process of carcinogenesis as it relates to both chemotherapy-related t-MDS/AML as well as radiation-related solid SMNs.

Mismatch repair (*MMR*) functions to correct mismatched DNA base pairs that arise as a result of misincorporation errors that have avoided polymerase proofreading during DNA replication [63]. Defects in the MMR pathway result in genetic instability or a mutator phenotype, manifested by an elevated rate of spontaneous mutations characterized as multiple replication errors in simple repetitive DNA sequences (microsatellites)—functionally identified as microsatellite instability (MSI). Approximately 50 % of t-MDS/AML patients have MSI, associated with methylation of the MMR family member MLH1 [64, 65], low expression of MSH2 [66], or polymorphisms in MSH2 [67–70]. The appearance of MMR-deficient, drug-resistant clones during genotoxic treatment for a primary cancer could be a vital factor in SMN susceptibility, particularly because the mutator phenotype (inherent of MMR-deficient cells) would be expected to accelerate the accumulation of further mutations and eventually SMN initiation. In addition, loss of MMR may result in deregulation of homologous recombination repair and consequent chromosomal instability [71].

Double-Strand Breaks (*DSBs*) in DNA may lead to loss of genetic material, resulting in chromosomal aberrations. High levels of DSBs arise following ionizing radiation and chemotherapy exposures. Cellular pathways available to repair DSBs include homologous recombination (HR), non-homologous end-joining (NHEJ), and single-strand annealing [72]. HR uses the second, intact copy of the chromosome as a template to copy the information lost at the DSB site on the damaged chromosome—a high-fidelity process. RAD51 is one of the central proteins in the HR pathway, functioning to bind to DNA and promote ATP-dependent homologous pairing and

strand transfer reactions [73, 74]. *RAD51-G-135C* polymorphism is significantly over-represented in patients with t-MDS/AML compared with controls (C allele: OR = 2.7) [75]. *XRCC3* also functions in the HR DSB repair pathway by directly interacting with, and stabilizing *RAD51* [76, 77]. *XRCC3* is a paralog of *RAD51*, also essential for genetic stability [78, 79]. A polymorphism at codon 241 in *XRCC3* gene results in a Thr→Met amino acid substitution [80]. The variant *XRCC3-241Met* allele has been associated with a higher level of DNA adducts compared with cells with the wild type allele, implying aberrant repair [81], and has also been associated with increased levels of chromosome deletions in lymphocytes after exposure to radiation [82]. Although *XRCC3-Thr241Met* was not associated with t-MDS/AML (OR = 1.4, 95 % CI, 0.7–2.9), a synergistic effect resulting in an eight-fold increased risk of t-MDS/AML (OR = 8.1, 95 % CI, 2.2–29.7) was observed in the presence of *XRCC3-241Met* and *RAD51-135C* allele in patients with t-MDS/AML compared with controls [75]. NHEJ pathway joins broken DNA ends containing very little homology. This process is not always precise and can result in small regions of non-template nucleotides around the site of the DNA break, potentially relevant in MLL-translocation associated with t-MDS/AML. Many of the translocation junctions have been sequenced and found to contain regions of microhomology consistent with the operation of the NHEJ pathway and an impairment of this pathway may modulate t-MDS/AML risk [83].

Base Excision Repair (*BER*) pathway corrects individually damaged bases occurring as a result of ionizing radiation and exogenous xenobiotic exposure. The *XRCC1* protein plays a central role in the BER pathway and also in the repair of single strand breaks, by acting as a scaffold and recruiting other DNA repair proteins [84, 85]. The protein also has a *BRCA1* C-terminus (BRCT) domain—a characteristic of proteins involved in DNA damage recognition and response. The presence of variant *XRCC1-399Gln* has been shown to be protective for t-MDS/AML [86] and BCC [87].

Nucleotide Excision Repair (*NER*) removes structurally unrelated bulky damage induced by radiation and chemotherapy. The NER pathway is linked to transcription, and components of the pathway comprise the basal transcription factor IIH complex (TFIIH), which is required for transcription initiation by RNA polymerase II. One of the genes involved in the NER pathway (*ERCC2*) is a member of the TFIIH complex. The polymorphic Gln variant (*ERCC2 Lys751Gln*) is associated with t-MDS/AML [88].

Results from studies examining genetic susceptibility in the development of SMNs are summarized in Table 14.1; some of these studies were highlighted above within the context of defective pathways; others are highlighted below.

Using a case–control study design, Ellis et al. examined the association between t-MDS/AML and 2 common functional p53-pathway variants—the *MDM2* SNP309 and the *TP53* codon 72 polymorphism [89]. While neither polymorphism demonstrated a significant association individually, an interactive effect was detected such that individuals carrying both a *MDM2* G allele and a *TP53* Pro allele were at increased risk of chemotherapy-related t-MDS/AML.

Knight et al. used a case–control study design, to conduct a Genome-Wide Association Study (GWAS) in patients with t-MDS/AML [90]. The discovery set included 80 cases and 150 healthy controls; relevant findings were replicated in an independent set of 70 cases and 95 healthy controls. The investigators identified three SNPs (rs1394384 [OR = 0.3, 95 % CI, 0.2–0.6], rs1381392 [OR = 2.1, 95 % CI, 1.3–3.4], and rs1199098 [OR = 0.5, 95 % CI, 0.3–0.8]) to be associated with t-MDS/AML with chromosome 5/7 abnormalities. rs1394384 is intronic to *ACCN1*, a gene encoding an amiloride-sensitive cation channel that is a member of the degenerin/epithelial sodium channel; rs1199098 is in LD with *IPMK*, which encodes a multikinase that positively regulates the prosurvival AKT kinase and may modulate Wnt/beta-catenin signaling; rs1381392 is not near any known genes, miRNAs, or regulatory elements, although it lies in a region recurrently deleted in lung cancer. Although the investigators were able to confirm findings in an independent replication cohort, utilization of a non-cancer healthy control group raises concerns about the case–control differ-

Table 14.1 Role of genetic susceptibility in the development of treatment-related adverse events

Study	GWAS vs. candidate gene	Study design	Replication	Sample size	Results
Therapy-related leukemia-associated with exposure to alkylating agents and topoisomerase II inhibitors					
Genome-wide association studies					
Knight et al. 2009 [90]	GWAS	Case–control (healthy controls)	Yes	Discovery set: 80 cases; 150 controls Replication set: 70 cases; 95 controls	Among patients with acquired abnormalities of chromosomes 5 or 7; 3 SNPs (rs1394384 [OR = 0.3, 95 % CI, 0.2–0.6], rs1381392 [OR = 2.1, 95 % CI, 1.3–3.4], and rs1199098 [OR = 0.5, 95 % CI, 0.3–0.8]) were associated with t-MDS/AML
Candidate gene approach					
Ellis et al. 2008 [89]	Candidate gene (2 common functional p53-pathway variants, the *MDM2* SNP309 and the *TP53* codon 72	Case–control (healthy controls)	Yes	Discovery set: 80 cases Replication set: 91 cases	Neither polymorphism alone influenced the risk of t-MDS/AML; however an interactive effect was detected such that *MDM2* TT *TP53* Arg/Arg double homozygotes, and individuals carrying both a *MDM2* G allele and a *TP53* Pro allele, were at increased risk of t-MDS/AML (OR = 2.0, 95 % CI, 1.2–3.5, $P_{interaction} = 0.009$)
Allan et al. 2001 [61]	Candidate gene approach Polymorphisms in *GSTM1*, *GSTT1*, *GSTP1*	Case–control	No	89 cases; 420 patients with de novo AML; 1,022 healthy controls	Individuals with at least one *GSTP1* codon 105 Val allele were over-represented in t-AML cases compared with de novo AML cases (OR = 1.8, 95 % CI, 1.1–2.9). Compared with de novo AML, the *GSTP1* codon 105 allele occurred more often among t-AML patients with prior exposure to chemotherapy (OR = 2.7, 95 % CI, 1.4–5.1), particularly among those with prior exposure to known *GSTP1* substrates (OR = 4.3, 95 % CI, 1.4–13.2)
Worrillow et al. 2003 [67]	Candidate gene hMSH2 –6exon 13 polymorphism Evaluation of MSI	Case–control	No Verification performed by direct sequencing	91 cases; 420 patients with de novo AML, 837 healthy controls	The variant (C) hMSH2 allele was significantly overrepresented in t-AML cases that had previously been treated with O6-guanine alkylating agents, including cyclophosphamide and procarbazine, compared with controls (OR = 4.0, 95 % CI 1.4–11.4); 38 % of the patients were MSI positive
Worrillow et al. 2008 [98]	Candidate gene Polymorphism of *MLH1* (position –93, rs1800734)	Case–control	No	133 cases 420 patients with de novo AML, 242 patients with primary HL, 1,177 healthy controls	Carrier frequency of MLH1-93 variant was higher in patients who developed t-AML after alkylating agents exposure for HL, compared to patients without alkylating agent exposure. The MLH1 -93 variant allele was also over-represented in t-AML cases when compared to de novo AML cases and was associated with increased risk of t-AML (OR = 5.31, 95 % CI, 1.40–20.15) among patients exposed to alkylating agents

Seedhouse et al. 2002 [86]	Candidate gene Polymorphisms in *XRCC1*, *XRCC3*, *XPD*, *NQO1*	Case–control	No	34 cases; 134 patients with de novo AML; 178 healthy controls	Presence of at least one *XRCC1* 399Gln allele indicated a protective effect for the allele in controls compared with patients with t-AML (OR = 0.4, 95 % CI, 0.2–0.9)
Jawad et al. 2006 [74]	Candidate gene C/T-3′ untranslated region (UTR) polymorphism in HLX; Polymorphism in *RAD51* (135G/C-5′ UTR)	Case–control	No	42 cases; 166 patients with de novo AML; 189 healthy controls	Presence of the variant *HLX1* allele significantly increased the risk of t-AML (OR = 3.4, 95 % CI, 1.7–6.8). Polymorphism in *RAD51* (135G/C-5′ UTR) also increased the risk of t-AML. Combined analysis revealed, a synergistic 9.5-fold increase (95 % CI, 2.2–40.6) in risk for t-AML
Subsequent solid malignancies-associated with exposure to radiation therapy					
Genome-wide association studies					
Best et al. 2011 [91]	GWAS	Case–control (controls: cancer survivors with no SMNs)	Yes	Discovery set: 100 cases; 89 controls Replication set: 62 cases; 71 controls	Two variants at chromosome 6q21 (rs4946728 [OR = 11.4, 95 % CI, 3.2–40.3]; rs1040411 [OR = 6.6, 95 % CI, 3.2–13.5]) were associated with SMNs in childhood Hodgkin lymphoma (HL) survivors, but not in adult-onset HL survivors
Candidate gene approach					
Mertens et al. 2004 [99]	Candidate gene Polymorphisms in *GSTM1*, *GSTT1*, *XRCC1*	Cohort study	No	650 patients with HL (178 with subsequent malignancy)	Individuals lacking *GSTM1* were at increased risk of any subsequent malignancy (OR = 1.5, 95 % CI, 1.0–2.3). A non-significant increased risk for thyroid cancer was observed in individuals lacking either *GSTM1* (OR, 2.9, 95 % CI, 0.8–10.9) or *GSTT1* (OR, 3.7, 95 % CI, 0.6–23.5). Individuals with the genotype of the Arginine/glutamine polymorphism at codon 399 in the *XRCC1* gene (R399)r showed a nonsignificant increased risk of breast cancer (OR, 1.4, 95 % CI, 0.7–2.7)

ences being generated by genetic susceptibility to the primary cancer vs. t-MDS/AML.

Best et al. performed a GWAS to identify variants associated with radiation-related solid malignancies in HL survivors [91]. They identified two variants at chromosome 6q21 associated with SMNs. The variants comprise a risk locus associated with decreased basal expression of *PRDM1* and impaired induction of the *PRDM1* protein after radiation exposure. These data suggest new gene-exposure interaction that may implicate *PRDM1* in the etiology of radiation therapy-induced second malignancies.

Studies such as those described above are being increasingly described. Large populations, with well-validated cases, appropriate controls, and good quality biospecimens are needed to understand the pathogenesis of SMNs. Furthermore, it is critical to replicate the findings in clinically independent cohorts, and also examine the functional relevance of the genes implicated in the development of SMNs. Nonetheless, understanding the pathogenesis of SMN will facilitate focused medical follow-up care and surveillance of the ever-growing population of childhood cancer survivors.

14.3 Screening

Several groups have developed recommendations for cancer surveillance on the basis of therapeutic exposures, recognizing that these cancers are a leading cause of non-relapse late mortality [92] and serious morbidity [93]. The underlying premise for these surveillance recommendations is that almost half of the SMNs can be detected at an early stage by periodic surveillance [1, 3, 94, 95]. In general, because survival rates are strongly associated with the stage of disease at diagnosis, early initiation of SMN surveillance is recommended. This early surveillance is even more necessary because options become limited for the treatment of SMNs because of prior therapeutic exposures. The COG LTFU Guidelines [96] recommend monitoring for t-MDS/AML with annual complete blood count for 10 years after exposure to alkylating agents or topoisomerase II inhibitors. Most other SMNs are associated with radiation exposure, present as solid tumors and are site-specific. Screening recommendations include careful annual physical examination of the skin and underlying tissues in the radiation field. For example, young women treated for a childhood cancer with a moderate-to-high dose of chest radiation have a greatly increased risk of breast cancer, similar in magnitude to that of carriers of the *BRCA* mutation [97]. Mammography, the most widely accepted screening tool for breast cancer in the general population, may not be the ideal screening tool by itself, for radiation-related breast cancers occurring in relatively young women with dense breasts, hence the American Cancer Society recommends adjunct screening with MRI. Thus, the COG LTFU recommendations for females who received radiation with potential impact to the breast (i.e., radiation doses of 20 Gy or higher to the mantle, mediastinal, whole lung, and axillary fields) include monthly breast self-examination beginning at puberty; annual clinical breast examinations beginning at puberty until age 25 years; and a clinical breast examination every 6 months, with annual mammograms and MRIs beginning 8 years after radiation or at age 25 (whichever occurs later). Screening of those at risk for early-onset colorectal cancer (i.e., radiation doses of 30 Gy or higher to the abdomen, pelvis, or spine) should include colonoscopy every 5 years beginning at age 35 years or 10 years following radiation (whichever occurs last).

14.4 Conclusion

Our knowledge is constrained by the follow-up of childhood cancer survivors that does not extend beyond three decades. It is only with the accrual of adequate numbers of survivors in their 4th and 5th decade after diagnosis of primary cancer will we learn how the normal ageing processes and the natural increase of cancer in the general population influences the development of SMNs in the ageing cohort of childhood cancer survivors.

More research is needed to understand the pathogenesis of treatment-related cancers, and to characterize those individuals at highest risk. This information needs to be used to develop cancer-risk prediction models to estimate individual risk, and help discussions between the healthcare pro-

vider and the survivor about surveillance for SMNs. There is a critical need to promote and optimize screening for SMNs, and develop behavioral and pharmacologic intervention trials to stop or reverse the process of progression of premalignant lesions into overt malignant diseases. Finally, there is an equally critical need to use this information to modify upfront therapy, while balancing cure with long-term morbidity.

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Part III

Neuropsychological Late Effects

Neuropsychological Outcomes in Children with Acute Lymphoblastic Leukemia

15

Peter A. Dodzik and Randy Fulton

15.1 Introduction

Childhood cancers are among the leading causes of death in children, second only to accidents [1]. However, with advances in medical interventions, mortality rates have declined steadily over the past 50 years [2]. Acute lymphoblastic leukemia (ALL) is the most common malignancy diagnosed in children, representing nearly one third of all pediatric cancers and 75 % of all leukemias [3]. The annual incidence of ALL is approximately 9–10 cases per 100,000 in childhood. Children from infancy to age five are at highest risk for being diagnosed with ALL, though survival rates for this age group are currently over 90 % [4]. The peak incidence of ALL occurs in children aged 2–5 years. In the United States, the incidence of ALL is higher in Caucasians than in African Americans by a ratio of 1.8:1. In addition, ALL is slightly more common in boys than in girls [5].

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Survival rates for ALL have changed dramatically over the past 50 years. In the late 1960s, less than 5 % of children with ALL survived longer than 5 years [2]. By the 1970s, these rates increased to 60 % and by 2000, and the survival rates had increased to over 80–85 % [6–8]. More recent studies have shown 4-year survival rates above 90 % with some protocols [9]. Much of the improvements in survival rates can be attributed to advances in treatment options for children. While data regarding survival rates for ALL has been encouraging, there is a wealth of emerging data suggesting iatrogenic deficits resulting from these improved cancer treatments. This data has resulted in increased attention towards standardization of treatment protocols to maximize the response to intervention of the cancer, while minimizing the impact on long-term CNS functioning. Future research into molecular therapeutics also may eventually replace standard combination chemotherapy and hematopoietic stem-cell transplantation in the management of patients with ALL and alter the course of negative cognitive outcomes in this group [10].

15.2 Pathophysiology of All

ALL is characterized by the malignant clonal proliferation of lymphoid cells that are blocked at an early stage of differentiation [11]. The ultimate cause of ALL remains unknown, though the etiology is likely multi-factorial, including

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environmental risk factors such as radiation and other toxins as well as genetic variables [12, 13]. What is known is that the process leading to ALL begins in the bone marrow, where irregularities occur in the development of lymphoid stem cells (lymphoblasts), which are then circulated through multiple systems, most commonly lymph nodes and the CNS, where leukemic cells readily cross the blood–brain barrier. When leukemic lymphoblasts accumulate, the result is loss of red and white blood cells, leading to low oxygen and anemia, as well as reduced immune system functioning. Reduced platelet production also occurs, causing bleeding and bruising (thrombocytopenia). The diagnosis of ALL is made through the use of blood and bone marrow tests and management of the disease is usually through a hematologist–oncologist.

Genetic involvement in the ALL process has focused on increased susceptibility in patients with germ line (sequence of inherited cells from egg and sperm DNA) abnormalities. Commonly linked conditions such as Down's syndrome carry up to 20-fold increase in incidence of leukemia [14] though specific genetic conditions represent a limited number (5 %) of ALL cases overall [12, 13]. Recent Genome-Wide Association Studies (GWAS) in the US and UK have identified multiple susceptible loci though these studies tended to combine subtypes of ALL [15, 16]. In a GWAS conducted in Germany, a specific genetic translocation subtype was analyzed and results indicated that the TP63 gene (involved with migration and homing of chronic lymphocytic leukemia cells to the bone marrow; [17]) and PTPRJ gene (involved with the regulation of cellular processes including cell growth, differentiation, mitotic cycle and oncogenic transformation; [18]) may play a role in tumorigenesis and may modulate susceptibility to certain types of leukemia [11].

Environmental factors, such as exposure to pesticides and herbicides, maternal use of alcohol, cigarettes, recreational drugs and contraceptives, and chemical contamination of groundwater have all been studied, although no definitive link to the development of childhood ALL has been established [19, 20].

15.3 Treatment Protocols for All

Several studies of ALL provide increasing evidence that current therapies are far less neurotoxic than those that were available 20 years ago [21–25]. Until the mid-1980s, many children, particularly preschoolers, who were successfully treated for ALL could be expected to exhibit developmental impairment that would significantly diminish their functional status later in life [26, 27]. However, children diagnosed more recently and treated on the major investigational protocols have shown reduced long-term deficits, though many will still experience some cognitive problems, albeit of a more mild severity than in years past [24, 25, 28]. Children treated at younger ages have been shown to have higher probabilities for long-term cognitive dysfunction, particularly those with onset prior to age 1 year, which is a biologically distinct disease [29].

The goal of present day treatment protocols is to ensure initial response to treatment and reduce likelihood of relapse while limiting CNS toxicity, leading to use of less toxic therapies. Antimetabolite chemotherapy with methotrexate, cytarabine, and mercaptopurine is currently used in low, standard, and high risk ALL, with cranial radiation therapy (CRT) reserved for those with high risk ALL. Use of corticosteroids, such as prednisone and dexamethasone are also used in current treatments, and are used typically in the induction phase of therapy [10].

Risk-based treatment assignment is the primary strategy utilized for treatment of children with ALL, and protocols are designed for specific patient populations that have varying degrees of risk for treatment failure. Factors associated with risk of treatment failure include patient characteristics at diagnosis, leukemia cell characteristics at diagnosis and response to initial treatment. Common predictive patient characteristics include age at diagnosis. In general, young children (ages 1–9) have more favorable cytogenetic profiles than infants or adolescents and thus present with better treatment outcomes [30]. Infants with ALL have a particularly high risk of treatment failure.

Failure rates are highest in infants under 6 months and in those with extremely high presenting leukocyte counts and/or a poor response to a prednisone prophase [31–33]. Specific genetic translocations are also associated with poor outcomes in infants [32]. Other salient risk factors related to patient characteristic include: white blood cell count at diagnosis [34], CNS involvement, race, gender and testicular involvement [35].

Leukemia characteristics are also related to treatment failure. The World Health Organization (WHO) classifies ALL as either *B lymphoblastic leukemia* or *T lymphoblastic leukemia*. B lymphoblastic leukemia is subdivided by: the presence or absence of specific recurrent genetic abnormalities, t(9;22); MLL rearrangement, t(12;21); hyperdiploidy/hypodiploidy, t(5;14) and t(1;19) [36]. Precursor B accounts for 80–85 % of all childhood ALL cases. Approximately 75 % of patients with precursor B ALL have the B-cell immunophenotype and best response outcome. Two other less common subtypes of precursor B ALL patients exist with less favorable outcomes [37]. T-cell ALL is defined by expression of the T cell-associated antigens (cytoplasmic CD3, with CD7 plus CD2 or CD5) on leukemic blasts and is often associated with several common clinical features, including male gender, older age, leukocytosis, and mediastinal mass. With appropriately intensive therapy, children with T-cell ALL have an outcome similar to that of children with B-lineage ALL [38–40].

A number of recurrent chromosomal abnormalities have been shown to have prognostic significance, especially in B-precursor ALL. In addition, other cytogenetic factors are related to risk assessment including hyperdiploidy, which is defined as 51–65 chromosomes per cell or a DNA index greater than 1.16. This abnormality occurs in 20–25 % of cases of precursor B-cell ALL but very rarely in cases of T-cell ALL [41]. Chromosomal translocations, particularly ETV6-RUNX1 (t[12;21]) in which fusion of the ETV6 gene on chromosome 12 to the RUNX1 gene on chromosome 21 occurs. This can be detected in 20–25 % of cases of B-precursor ALL but is rarely observed in T-cell ALL [42]. The Philadelphia chromosome (t[9;22] translocation) is present in approximately 3 % of children with ALL, and leads to production of a BCR-ABL1 fusion protein with tyrosine kinase activity. This subtype of ALL is more common in older patients with precursor B-cell ALL and high WBC count [43]. Translocations involving the MLL (11q23) gene occur in up to 5 % of childhood ALL cases and are generally associated with an increased risk of treatment failure [6].

Response to initial treatment is another prognostic indicator of treatment failure. Long-term outcome is associated with the rate of response to induction chemotherapy. Children who show reduction in leukemia cells to less than 5 % in their bone marrow within 7 or 14 days following initiation of chemotherapy have a more favorable prognosis than those with slower clearance rates [44]. Good response to initial induction of prednisone (as defined by reduction in peripheral blast count to less than 1,000 μL after a 7-days) is associated with better outcomes and in general, the fewer the number of blasts in the blood on day 7, the better the expected outcome [35, 45, 46]. Similar findings have been shown in initial response to multiagent chemotherapy in days 7 through 10 [47]. These rates are similar in T-cell and B-cell types of leukemia [47]. Conversely, patients with induction failure (defined by >5 % lymphoblasts at the end of the induction phase) have poor outcomes. In the French FRALLE 93 study, the 5-year overall survival rate was 30 % [48]. Patients with T-cell phenotype (particularly those without a mediastinal mass) and patients with B-precursor ALL with very high presenting leukocyte counts and/or the Philadelphia chromosome are at high risk for induction failure [40]. Currently, these previous important milestones are being re-evaluated and replaced by molecular testing in an effort to further stratify those at highest risk for treatment failure and relapse. Finally, measurements of minimal residual disease (MRD) at day 8 and at the end of induction have been used as an independent marker of outcome risk. Those patients with higher levels of MRD are associated with worse outcomes [49]. MRD frequently is used as a factor in determining the intensity of post induction treatment and patients with higher MRD levels are allocated to more intensive therapies [49].

15.3.1 Risk Models

Risk models are essential to assigning patients to the most effective treatments with the lowest probability for iatrogenic damage. The National Cancer Institute (NCI) also has developed a three-tiered risk assignment for children with ALL. In the recent clinical trial titled: Risk-Adapted Chemotherapy in Younger Patients With Newly Diagnosed Standard-Risk ALL, patients were stratified as low risk, standard risk, or very high risk for end-induction treatment based on cytogenetics, day 8 peripheral blood MRD, and day 28 bone marrow MRD [50].

Retrospective analyses were conducted through the Children's Cancer Group (CCG) and the Pediatric Oncology Group (POG), which has led to a tiered risk model for initial treatment assignment [51]. According to the data collected from the CCG and POG, patients with precursor B-cell ALL are considered standard risk or high risk based on age at time of diagnosis and WBC. Patients aged 1–9.99 years with less than 50,000 WBC/μL are considered standard risk. All children with T-cell phenotype are considered high risk regardless of age and initial WBC count. These patients were treated on a T-cell specific clinical trial. The Children's Oncology Group (COG) has recently developed a new classification system for precursor-B ALL. Cytogenetic findings are used to classify risk. Patients with certain translocations (e.g., t[9; 22]) or hypodiploidy (fewer than 44 chromosomes) are always considered high risk) [51]. Several other institutions have conducted similar analyses to determine treatment risk assessment and most include some analyses of ALL subtype, age at diagnosis, MRD following induction and cytogenetics.

15.3.2 Treatment Process

Initial goals of treatment in children with ALL were to deliver the highest amount of cranial radiation therapy tolerable (usually 18–24 Gy), as the relapse usually occurs in the CNS. However, children treated with 18–24 Gy cranial radiation therapy (RT) were consistently found to have adverse neurocognitive outcomes and globally reduced IQ levels [52, 53]. Today, the treatment consists of multi-agent drug combination, and is stratified by risk level and disease characteristics. As more aggressive treatment schedules with multiple anti-metabolites are associated with higher rates of iatrogenic and late effects, chemotherapeutic drugs are given at a dose, which is commensurate to their level of risk and response to treatment [54]. The selection of a specific treatment regimen for ALL is dependent on several factors, including white cell count, presence of leukemic cells in the CNS, and ALL subtype [55].

Treatment of pediatric ALL typically consists of a remission-induction phase, intensification (consolidation) phase, and continuation (maintenance) therapy targeted at eliminating residual disease [10]. In the induction phase, the antineoplastic agent vincristine is typically administered through IV once per week over a 3–4 week period. Glucocorticoids are included in the induction phase due to their lymphocytotoxic effects. Commonly used glucocorticoids include prednisone, prednisolone, and dexamethasone. Asparaginase is the third drug included during induction therapy. For high-risk patients, an anthracycline antibiotic such as doxorubicin is typically added to this regimen [56]. The addition of cyclophosphamide and intensive treatment with asparaginase is also beneficial in the treatment of T-cell acute lymphoblastic leukemia [40, 57]. Mature B-cell ALL needs to be treated like disseminated Burkitt lymphoma, with short-term intensive chemotherapy, including high-dose methotrexate (MTX), cytarabine, and cyclophosphamide over a 6-month period [58]. In the consolidation phase of therapy, it is common for patients to receive a combination of drugs which are different from those used in the induction phase, both in mechanism and site of action, to reduce the occurrence of drug resistance [10]. The CNS is targeted during this phase with intrathecally-administered antimetabolites, such as cytarabine (Ara-c) and methotrexate (MTX), which are the only drugs in this class of medication that can be safely administered intrathecally. Antimetabolites are typically administered in

weekly intervals either orally, intrathecally, or intravenously when given at high doses. Side effects are common during this phase and include headache, backache, abnormal liver function tests, hair loss, immunosuppression, fatigue, sensitivity to light (eyes and skin), and diarrhea [10, 59, 60].

Other commonly used agents in this phase include anthracyclines, and alkylating agents such as cyclophosphamide. However, these drugs are used sparingly due to their known contribution to cardiovascular damage. An epipodophyllotoxin, such as etoposide or teniposide is also used as a topoisomerase inhibitor [59, 60].

In the maintenance phase of therapy, patients at lesser risk typically receive weekly MTX and 6-mercaptopurine (6-MP), both given orally typically at bedtime. 6-MP induces mild immune suppression, which helps to reduce platelet destruction. Side effects include abnormal liver function, rash, nausea, and low blood counts [54]. During maintenance, patients at standard-risk may also receive vincristine and corticosteroids in addition to 6-MP and MTX. Patients with high-risk ALL continue to receive a more frequent interval of treatment with a combination of agents [54]. Children undergoing treatment for ALL are at risk for infections throughout treatment. To prevent Pneumocystis jirovecii (carinii) pneumonia, patients are often given trimethoprim-sulfamethoxazole, dapsone, pentamidine, or atovaquone [54].

Cranial radiation therapy (CRT) is typically reserved for high-risk patients as a preventative measure after a failure to induce remission [10]. 24 Gy was formerly used as a common dose for all patients with ALL. The current dose of <18 Gy showed therapeutic efficacy with no increase in CNS relapse rate [54, 61].

Despite overall improvement in long-term neurocognitive outcomes in pediatric ALL, late neurocognitive effects are still common with present day therapy protocols. The degree of deficits and relative presence of late effects has varied across studies, likely due to heterogeneity in sample sizes, ages at diagnosis, gender, dosage of CRT, and time since exposure to chemotherapy. More recent studies with homogenous samples have allowed for insight into how the natural history of late effects varies among each protocol and have established a consistent relationship between therapy protocols and neurocognitive outcomes [61, 62].

15.3.3 Palliative Drugs

The World Health Organization has developed a three-level "analgesic ladder" to guide palliative care in cancer patients. The WHO ladder begins with non-opioids such as aspirin, followed by mild opioids such as codeine, and finally strong opioids such as morphine. Psychotropic drugs to manage fear and anxiety through the course of treatment are recommended at each level on an as-needed basis. Geeta et al. [63] found that the WHO analgesic ladder was effective in managing pain in children with leukemia, with the majority of cases treated successfully with non-opioids, weak opioids, and adjuvants. Please see Chapter 20 for a more thorough discussion of palliative care.

15.3.4 Supplements

As methotrexate is a folic acid antagonist, supplements should be given without added folic acid. Folic acid interferes with the action of methotrexate. Sunscreen is and sunglasses are recommended when being treated with methotrexate. Glutamic acid supplements may be given to protect against the neurotoxic effects of antineoplastic agents.

15.3.5 Summary

Children with ALL have consistently benefitted from a more deliberate course of treatment that takes into account the multiple predictive factors related to specific disease type and best practices for treatment protocols. The changes to dosing, duration and therapy combinations have steadily evolved over the past several decades. Figure 15.1 shows the timeline for treatment discoveries over time and can aid in establishing and understanding of patient cohorts and likely treatments from previous decades.

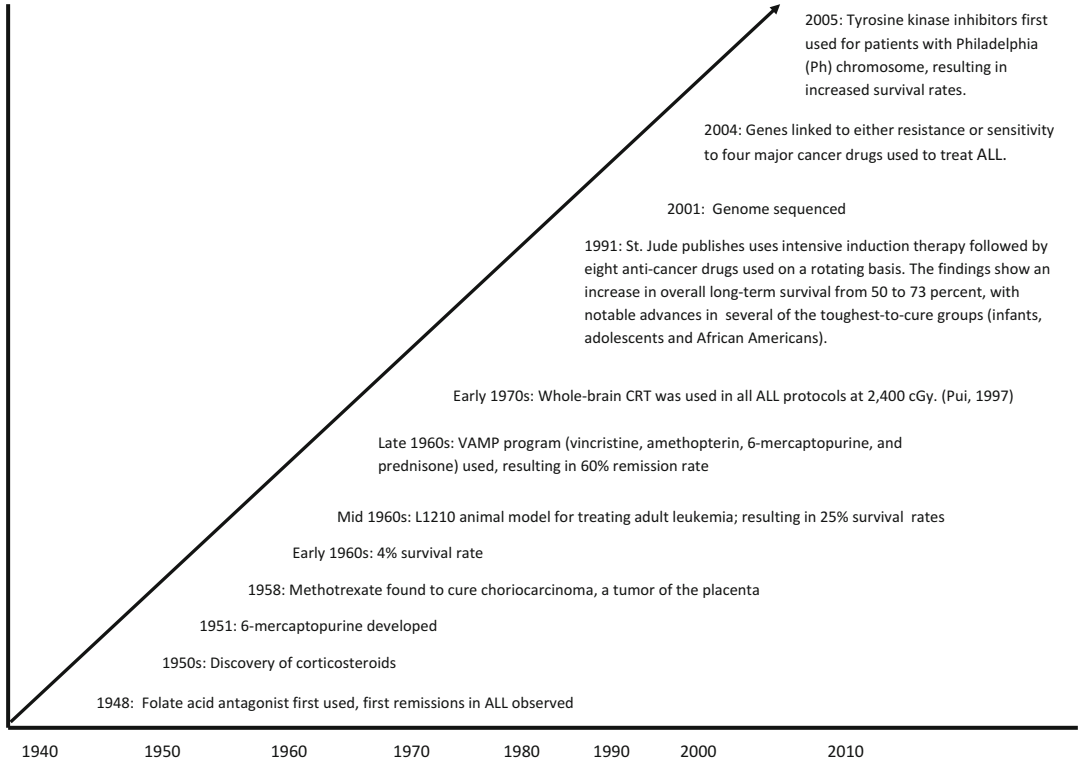


Fig. 15.1 Timeline for treatment progress for patients with ALL

15.4 Neuropsychological Sequelae of All Treatment

15.4.1 Cranial Radiation

By 1980, 24 Gy CRT for children with ALL resulted in 5-year survival rates of over 50 % [26]. As survival rates increased, so did reports of cognitive difficulty among survivors. In a meta-analysis conducted during the late 1970s to 1987, Cousens et al. [26] reported 16 of 31 studies showed significant deficits in IQ among irradiated patients. Further, in their review of 21 studies meeting criteria for having a healthy control group with both baseline and repeated full-scale IQ measurement, they found a 10-point average reduction in IQ from baseline. Presently only those children who are considered high risk ALL are treated with CRT, and modern dose levels have been reduced from 24 to 18 Gy. Despite reduced levels of CRT, reductions in global IQ are reported, with one study reporting a loss of 3.65 IQ points per year treated with 18 Gy CRT [64]. Declines have been reported on measures of visuomotor integration, processing speed, attention, and immediate memory [65]. In some studies, verbal and language abilities appear to less likely decline [66].

Effect of CRT Dose Reduction. Moore et al. [67] compared two groups of children aged 9–14 years who were treated with a similar protocol of corticosteroids and two doses of intrathecal methotrexate (IT MTX); however, one group was administered 24 Gy of CRT, the other with 18 Gy CRT. Both groups were in the average range on measures of full-scale, performance, and verbal IQ (utilizing the Wechsler Intelligence Scale for Children—WISC). The mean full-scale IQ of the 24 Gy group was ten points below the average of the 18 Gy group, largely due to a reduction on verbal subtests. Scores on the Beery-Buktenica

Visual-Motor Integration Test (VMI) were similar in both groups, each ranking within the lower third of the normative sample. On a measure of academic performance, the Wide Range Achievement Test (WRAT), those who received 24 Gy scored ten points lower than the 18 Gy group on measures of spelling, arithmetic, and reading. All standard scores (SS) on the WRAT were in the average range with the exception of the arithmetic subtest, which was below average (SS = 85.83). However, time-since-treatment appeared to have the largest effect size in this study. When the authors used time-since-treatment (within 2-months or greater than 2-months) as a covariate, the dose of CRT did not have a significant effect on IQ, academic functioning, or visual-motor integration.

When compared directly to chemotherapy-only regimens, a recent meta-analysis of 28 empirical studies between 1980 and 2004 demonstrated uniformly lower IQ, academic and neurocognitive (including fine motor, memory, processing and visuospatial) scores in all treated children regardless of treatment. Effect sizes in nine neurocognitive domains ranged from −0.34 to −0.71. All groups receiving CRT performed more poorly than those that did not. Reductions in memory ability as well as academic achievement were also more pronounced relative to chemotherapy only. However, inconsistent impairment across studies and other moderating variables limited the conclusions of the differential impact of CRT [68].

15.4.2 CRT Plus Chemotherapy

Administration of CRT in conjunction with IT-MTX resulted in 70 % survival rates by the mid-1990s [21]. In a study of demographically matched children aged 7–16 years at least 2 years post-treatment, Anderson et al. [21] compared a group receiving CRT + MTX and a group receiving methotrexate alone. Results showed group differences across intellectual and academic domains. Mean IQ scores in both groups were in the average range. Differences between the groups were mild but significant, with the most significant reductions in the CRT + MTX group on verbal subtests and those tapping attentional skills, such as Digit-Span. Compared to the chemotherapy alone group, the CRT + chemotherapy group were generally 10 points lower on reading, spelling, and mathematical tests, with all scores in the below average range.

In a 7 year follow-up of 201 children receiving a standardized chemotherapy regimen which included corticosteroids and MTX, plus 18 Gy of CRT, an 82 % overall survival rate was reported after 5 years. Among the survivors, performance on measures of intellectual ability and memory were in the average range. However, 51 % of these children had low performance on the Rey Complex Figure Copy task, suggesting difficulties with executive function, particularly organization and management of complex novel information [69].

15.4.3 Chemotherapy Only

When chemotherapy is used without CRT, there is some degree of variability in the literature in terms of cognitive outcome. This is to be expected due to the use of different treatment protocols, which also combined glucocorticoids and multiple anti-metabolites [62]. It is more common now than in the past to use one chemotherapy agent, typically MTX. In terms of cognitive effects during the acute phase of treatment, motor speed and working memory are the most commonly affected cognitive domains [62, 70]. Long-term changes among children 2–5 years post remission have shown no lasting deficits in IQ, but negative trends do occur consistently in domains of visuomotor integration and math ability. IQ typically remains average relative to controls [71]. Among the anti-metabolites, MTX is thought to be the most damaging to the CNS, and to white matter tracts in particular [72]. MTX has been shown to reduce cerebral glucose metabolism, resulting in cellular damage and demyelination [72, 73]. As the peak age of ALL onset occurs during a sensitive period of brain myelination within the prefrontal cortex, the timing of MTX administration and brain

maturation are one explanation for reductions in frontal white matter and associations with executive deficits [71]. The relationship between cognitive deficits and methotrexate appears to be dose-dependent. Both the number of doses and cumulative dose has been associated with deficits in visuomotor and global IQ reductions [62]. The proposed effect of MTX to vascular structures will be reviewed briefly in the section on radiological findings.

15.4.4 Glucocorticoids

Glucocorticoids inhibit glucose metabolism/utilization by neurons and glia resulting in an increase of glutamate, causing neural excitotoxicity and cell death. Neural toxicity occurs regularly in the hippocampus (a high-concentration corticosteroid binding site) [74]. Thus, it is not surprising that memory deficits result as a late effect of treatment with glucocorticoids [75]. There are differences in CNS affinity among glucocorticoids. Dexamethasone more readily penetrates the CNS and has a longer half life than prednisone and prednisolone [76]. Waber et al. report poorer memory and visuospatial organization in children treated with dexamethasone instead of prednisone [75].

15.4.5 Summary

Overall, neurocognitive deficits are common, but vary from mild to severe, and are moderated by a number of variables related to the patient (i.e., age and gender) and the treatment protocol (i.e., level of methotrexate and/or use and dose of CRT).

15.5 Neurophysiological Changes in All

Despite the elimination of cranial radiation from most treatment protocols for ALL, intrathecal and systemic chemotherapy have been shown to cause acute and long-term damage to the brain [71]. Common morphological changes found on neuroimaging include white matter changes [52, 71, 77], widening of the ventricles and/or sulci [52, 71], and cerebral calcifications [78]. Reduced prefrontal cortex, cerebellum, and cortical white matter volumes have also been reported [77].

Damage of oligodendroglia cells and vascular structures are thought to contribute to reductions in white-matter volume [77]. Methotrexate reduces folate levels, which in turn elevates homocysteine levels, which is toxic to vascular structures. White matter abnormalities have been found to be transient during early phases of treatment [79], though have been found in long-term survivors of ALL.

Hertzberg et al. [52] investigated a sample of 118 patients, 39 receiving IV and IT MTX only, 41 who received CRT before IV and IT MTX, and 38 patients who received CRT during and after IV and IT MTX. Over half (51.7 %) of the total sample was found to have abnormal MRI or CT abnormalities. Within each sample, 38.5 % of the MTX only group had abnormal findings, and 56.1 % of those who received CRT before MTX, and 60.5 % of those in the CRT during and after MTX had abnormalities. An overall significant difference in abnormalities was found between the MTX only and CRT plus MTX groups ($P=0.043$), with no apparent mediating effect of age. Four patients were found with calcifications, all of whom received CRT.

Iuvone et al. [78] evaluated an Italian sample of 21 patients, all at least 4 years post-remission. Children were treated with 18 Gy (n=15) and 24 Gy (n=6) plus intrathecal CNS prophylaxis. A multi-agent regimen including prednisone, vincristine, daunorubicin, L-asparaginase, cyclophosphamide, cytosine arabinoside, and 6-mercaptopurine was used to induce remission. For high-risk patients, a reintensification protocol was used, including dexamethasone, vincristine, doxorubicin, L-asparaginase, cyclophosphamide, cytosine arabinoside, 6-thioguanine, and IT MTX. Standard-risk patients were treated with 18 Gy RT, and high-risk patients were treated with 24 Gy. Ages ranged from 6.9 to 19.4 years, and time since treatment ranged from 4.3 to 12.1 years. Intracerebral calcifications and white matter volumes were measured through CT and MRI,

respectively. Time since diagnosis did not correlate with neuroimaging abnormalities. Age at diagnosis was found to be significantly related to calcifications. Brain calcifications were detected in five of the eight patients who were younger than 3 years of age at the time of diagnosis. Age at diagnosis did not correlate with leukoencephalopathy or cerebral atrophy. The number of IT MTX injections, which ranged from 4 to 10 in this study, was reported to slightly correlate with the presence of calcifications at a significance level of 0.06, but did not correlate with white-matter abnormalities.

Reddick et al. [77] compared a group of ALL survivors who received chemotherapy alone (n=84) with a group of survivors treated with chemotherapy plus irradiation at 18 Gy (n=28), and a control group comprised of healthy siblings (n=33). All ALL patients received high dose MTX, multiple doses of IT MTX, hydrocortisone, and cytarabine. Exclusionary criteria included a prior diagnosis of ADHD, seizures, tics, use of psychotropic medications, and recurrent tumor. Patients who received chemotherapy alone showed significantly greater white matter volumes than patients who received chemotherapy plus CRT. The authors of this study note that the younger age of the chemotherapy only group, relative to that of the chemotherapy plus CRT group, is important, as older children should display more white matter volumes than younger children. The effect of gender and overall grey matter volumes could not account for the differences in white matter volume, according to the authors. When compared to the healthy sibling control group, the chemotherapy only group displayed significantly smaller white-matter volume, with no differences in overall grey-matter volume. On neurocognitive testing, both clinical groups performed significantly worse (>1 standard deviation) than the normative sample on the Conners' Continuous Performance Test (CPT) on both omissions and **β** (Bias/response style, or the strategy used in making decisions on whether to respond or not). Only the chemotherapy plus CRT group performed >1 standard deviation from the normative sample on measures of academic achievement as measured by the abbreviated Wechsler Individual Achievement Test (WIAT). A regression analysis suggested that performance on the CPT was best predicted by overall white matter volume, regardless of treatment agents. Larger white-matter volumes were positively correlated with greater performance on IQ and on all academic achievement measures of the abbreviated WIAT, except for spelling.

Earlier studies of volumetric white matter changes in ALL have not been able to examine the effect on regional white matter volumes. Carey et al. [71] investigated regional white matter differences in a group of childhood survivors of ALL, treated with IT chemotherapy without RT. Mean age at diagnosis was 5 years. Treatment protocols were heterogeneous, as the survivors in the study were diagnosed between 1987 and 2000. All survivors were diagnosed before 18 years of age. The study compared 14 survivors of ALL and 18 healthy controls on MRI and a neuropsychological evaluation using the Wechsler Intelligence Scale for Children, 3rd Edition (WISC-III) or Wechsler Adult Intelligence Scale, 3rd Edition (WAIS-III), Woodcock-Johnson-III (WJ-III) Letter Word Identification, Calculation, and Story Recall, and Delis-Kaplan Executive Function System (D-KEFS) Trail Making Test 4, Letter Fluency, Category Fluency, Category Switching, and Tower Test. Using Voxel-Based Morphometry, Cary et al. [71] found two areas of regional difference between the clinical and control groups in the areas of the right middle and right superior frontal gyri. After controlling for FSIQ, the clinical group had significantly lower scores on the Wechsler Block Design, Vocabulary, and Digit Span tasks, and also had lower scores on the D-KEFS Trail Making Test, Verbal Fluency and Category Switching. A nonsignificant lower mean score was found on the WJ-III Calculation test in the clinical group. Pearson correlations displayed a significant relationship between regional white matter volume in the area of the right medial frontal gyrus and the WJ-III Calculation scores ($r=0.65$, $P<0.001$). A significant relationship was also found between reduced white matter volume in the area of the right superior frontal gyrus and lower scores on the Wechsler Vocabulary test ($r=0.50$, $P<0.007$).

15.6 Neuropsychological Outcomes in All Past and Present

The changes in treatment protocol for ALL over the past 30 years, the young age of onset, and the evolution of instruments available for the assessment of neuropsychological functions have led to difficulties in the establishment of a consistent pattern of cognitive deficits in children with ALL. Children exposed to cranial radiation, chemotherapy or both must be separated when considering the literature on late-stage cognitive deficits. In addition, the lack of comparison groups, pre and post treatment test data and paired radiological/neurobehavioral measures limits the understanding of the impact of ALL and its treatment. Still, a number of studies have been conducted over the years, which present findings from known treatment groups.

15.6.1 Intelligence

Moleski [80] conducted the most extensive review of studies conducted in the 1980s and 1990s of ALL patients treated with IT MTX and/or CRT. Two thirds of the 33 studies found declines in one or more areas of intellectual functioning in ALL patients treated with CNS prophylaxis chemotherapy and/or CRT [80]. Roughly half of the studies employed some healthy control group including siblings or non-CNS cancer patients. Several studies reported no differences between ALL patients receiving MTX with or without CRT though all studies using siblings as controls reported significant lower scores in ALL patients. These studies highlight the need to employ matched controls as opposed to reliance on normative data from the test manual [80]. In the best well-controlled studies [81], ALL patients demonstrated an average of 12 points lower than siblings and non-CNS cancer groups. The latter finding is also significant as non-CNS control groups often still endure the disruptions of day-to-day life and education seen in ALL children and these types of controls aid in our understanding of the impact these disruptions may have on IQ and cognitive development, if any.

Langer, Martus, Ottensmeier, Hertzberg, Beck, & Meier [82] investigated the long term outcomes of ALL children treated with either the German BFM-ALL (ALL-relapse-Berlin/Frankfurt/Münster-Study-Group) or COALL (Cooperative study with modified BFM protocols) protocols. The subjects were medium and standard risk patients and were divided into MTX only and MTX with CRT. Patients with encephalitis, secondary malignancies and preexisting neurological or mental health conditions were excluded. Participants included 121 patients (63 females) who were off-therapy for at least 4.5 years (mean = 7.2 years, maximum = 10.6 years). The average age at initial diagnosis was 5.8 years (range = 0.3–16.1 years), the age at investigation was 14.8 years (range = 8.0–27.8 years). No pretreatment data were available for comparison. Subjects were administered the Hamburg-Wechsler Intelligence Scale for Children-Revised in addition to several other neurocognitive measures. Results indicated that patients in the MTX + CRT group scored 8.7 points lower on the Full Scale IQ (FSIQ) than patients receiving MTX alone (109.9 vs. 101.2). Significant differences also were found with the Verbal IQ (VIQ) (7.4 points), Freedom from Distractibility (8.6 points) and non-significant (but similar magnitude) in the Performance IQ (PIQ) (8 points). All results indicated higher performance in the MTX only group. CRT had a differentially negative impact on males in this study. Males with MTX only scored 17 points higher on FSIQ than males with MTX + CRT (115.6 and 98.6, respectively). No gender differences were seen in corresponding female samples. No relationship was found between the amount of CRT (range 12–18 Gy) nor the amount of MTX (range 26 and 156 mg). Results support the conclusion that preventive CRT usage is associated with lower (though still average) IQ scores compared to MTX alone.

The presence of comparison groups is critical as declines in overall IQ scores are modest and often continue to fall in the average range. Waber et al. [69] evaluated children treated for high-risk

ALL on the Dana-Farber Cancer Institute Protocol 87–01, which included 18-Gy CRT as a component of CNS treatment. Their results indicated excellent 5-year overall survival (82 %) and disease recurrence (<1 %) rates in the CNS. WISC-III scores 7 years after diagnosis were generally average (FSIQ = 98–102) and did not vary based on age at diagnosis, gender, or MTX dosing. However, no pre-treatment data, sibling control or chemotherapy only groups were utilized.

In a recent study conducted in Norway, Lofstad, Reinfjell, Hestad & Diseth [83] examined the long-term impact of 35 ALL children treated with chemotherapy (NOPHO-ALL 1992 Protocol) only. Inclusion criteria allowed for examination of a small group of high-risk children and apart from severity and age, most other factors were controlled yielding a homogenous sample of ALL children. Normal controls (N = 35) were recruited for comparison and matched for age, gender and SES. However, no pre/post treatment data were collected on the ALL children. Results indicated significantly lower scores for the ALL group on six of the seven WISC-III scales including Full Scale IQ (FSIQ), Verbal IQ (VIQ), Performance IQ (PIQ), Vverbal Comprehension Index (VCI), Perceptual Organization Index (POI) and Freedom from Distractibilty Index (FDI) and Processing Speed Index (PSI). The POI also trended lower. ALL children were 9–16 IQ points or more below healthy controls, though all mean scores fell within the average range except the PSI (SS = 88.8). The authors note the high correlations between global measures within the entire sample, which suggests lower overall cerebral functions. Thus, the majority of the lower scores on subtests are the result of deficits in higher mental or frontal lobe functions, which the authors contend may represent a shared factor. However, processing speed was also significantly lower in the ALL group and was not significantly correlated with global measures in the ALL group and could represent a focal deficit related to chemotherapy in this study. No comparison of risk groups with ALL on WISC-III scores was made [83].

Kingma, et al. [84] conducted one of the few studies utilizing MRI, serial neuropsychological evaluations at 3 months following treatment and then 5 years later. In addition, MRIs were conducted at the 5-year follow-up. Parents of these children also were asked to completed questionnaires of school performance for their ALL child and their siblings at the 10-year post treatment mark. Forty-five (45 %) of the children completed both evaluations. Seventeen (17) received chemotherapy only and 28 received chemotherapy and CRT. The healthy controls consisted of 225 community-recruited children matched for age, SES and geographic region. The CRT group had lower scores than the MXT group on all measures. However, neither the CRT nor MTX-only group had significant changes in IQ scores from time one to time two. In addition, 63 % of the CRT children showed MRI abnormalities as opposed to 38 % of MTX-only treatment. Finally, school performance rating scales indicated no difference between MTX-only group and their siblings; but significant differences between CRT and siblings were noted with the CRT group scoring lower. When compared to themselves, no differences in FSIQ were noted (MTX-only 103.6 and healthy controls 107.0) in the MTX-only group at follow up [84]. These findings suggest that baseline data and serial follow-up studies may be more useful in quantifying actual loss in IQ from late-stage effects of cancer-related treatments.

In one of the largest study to date on neuropsychological outcomes of ALL, Halsey et al. [85] assessed 866 children (555 patients and 311 controls). No significant differences were seen between patients and healthy controls at baseline. However, significant differences were seen between groups at 3 years (ALL = 97.7 and Controls = 104.8) and at 5 years (ALL = 100.0 and Controls at 105.3). It is worth noting, however, that ALL patients showed no appreciable drop in IQ scores from baseline (5 months) to the 5-year mark. The investigators were also able to compare low risk ALL randomized to IT MTX or high dose systemic MTX at 3-year and 5-year intervals and no significant differences were noted. High risk ALL patients were treated with IT MTX and

then randomized into additional treatment using high dose systemic MTX or CRT. No differences were seen between groups in the high-risk sample though larger differences (favoring high dose MTX) were seen. All IQ scores at all points in time were in the average range. There were no gender differences seen in either the high or low risk groups in this study and the impact of age at the time of onset treatment (above or below 5 years) was associated with higher probability of IQ score under 80 (17 vs. 7 %). The authors predicted that improvements in neuropsychological outcomes for children with ALL would depend more on the individualized therapy for children at high risk of CNS morbidity than on avoidance of specific CNS-directed therapy regimens in unselected patient cohorts [85].

15.6.2 Academics

Several studies have looked at subjective and objective measures of academic functioning in children with ALL treated with chemotherapy with and without CRT. Many of these studies also included IQ measures. Early studies found specific deficits in areas of arithmetic [86]. However, unlike innate abilities, academic skills also can be affected by the multiple life stressors associated with cancer treatment such as frequent hospitalizations, protracted medical treatment, fatigue, etc. Many of the complications surrounding treatment of ALL co-occur with the child's initial foray into the school setting with average diagnoses coming at or near kindergarten.

Anderson et al. [21] attempted to control for the impact of life stress from cancer treatment in general through the inclusion of a non-CNS cancer group in their study of 100 children with ALL treated with MTX and CRT (18–24 Gy). Fifty [53] children with acute myeloid or lymphoblastic leukemia, or non-CNS tumor treated with chemotherapy alone and 100 healthy controls stratified to control for demographic factors including SES were assessed. All subjects were administered the WISC-R, Wide Range Achievement Test (WRAT) and Child Behavior Checklist (CBCL). Significantly lower FSIQ were found in the IT MTX + CRT group (SS = 94.9, SD = 13.1) from the MTX only cancer group (SS = 102.3, SD = 13.5) or healthy controls (SS = 101.7, SD = 12.3). As with other studies, FSIQ was still within the average range for all groups. However, WRAT scores for the IT MTX + CRT were significantly lower in all areas (Reading, Spelling and Math) than either the non-CNS cancer or healthy control groups. In addition, all three domains fell into the low average range (Reading SS = 88.0, Spelling SS = 87.8, Math SS = 88.3). The other groups averaged nearly 10 points higher in all areas. The authors concluded that children treated with chemotherapy alone (with or without CNS involvement) showed no declines in IQ or academics [21]. Finally, CBCL data comparing the two cancer groups revealed significantly higher scores on measures of anxiety, social functioning and attention problems and significantly lower scores on school functioning compared to healthy controls. Overall, these findings did suggest lower academic functioning and increased psychosocial stress in children treated with MTX and CRT compared to cancer and healthy controls. The inclusion of the chemotherapy-only cancer group also suggests these differences could not be explained by life stressors alone. Findings indicate children treated with non-CNS chemotherapy did not differ from normal controls.

While Anderson et al. [21] collapsed children receiving 18 and 24 Gy CRT, other authors [87] evaluated the impact of higher dose CRT on WISC-R and WRAT scores in ALL compared to a cancer control group (Wilms' tumor). Children receiving the 18 Gy dose scored significantly higher than the 24 Gy group and at the same level as cancer control groups. In fact, the 18 Gy group and cancer control group average 10–15 points higher an all IQ and academic measures. The 24 Gy group fell into the low 90s on all scores except Math, which was a mean standard score of 86 [87]. Sample sizes were small but results suggested significant differences based on level of whole brain CRT on all IQ and academic measures. Other authors using larger samples [88] did not find declines in overall IQ comparing 18 and 24 Gy children; however, academic performance was not considered.

Brown et al. [89] conducted a prospective analysis of 38 ALL/AML children treated with IT MTX (Australia–New Zealand Children's Cancer Study Group Protocols) to 25 matched non-CNS cancer children treated with a variety of protocols not involving IT MTX. Subjects were between 2–15 years old at time of treatment and follow up was conducted over 3 years. This study is unique in that no differences were found between age, gender, father's occupational rating, or survival rates. In addition, attendance was tracked throughout the study to provide an estimate of the impact or CNS and non-CNS prophylactic cancer treatment. Subjects receiving IT MTX missed more days of school in the 3-year period, with significant differences in year 2 accounting for most of the days missed. The increased absentee rate is due to the longer duration of IT MTX treatment protocols and suggests a longer active state of potential neurotoxic impact. Full Scale IQ estimates based on (McCarthy Scales of Children's Abilities and WISC-R) increased slightly from baseline to year 3 in the non-CNS group (SS = 106.7 to 116.2) but not for the CNS group (SS = 106.6–105.1). This trend was true for the Verbal and Performance scales as well. Academic achievement was assessed using the WRAT-R. Non-CNS subjects showed similar level and patterns of improvement over time from baseline (Reading SS = 102.6, Spelling SS = 99.7; Arithmetic SS = 99.5) to year 3 (Reading SS = 112.7; Spelling SS = 107.6; Arithmetic SS = 101.4). The reverse trend was seen in the CNS group from baseline (Reading SS = 114.3, Spelling SS = 110.0; Arithmetic SS = 107.1) to year 3 (Reading SS = 94.0; Spelling SS = 92.4; Arithmetic SS = 87.0). Thus, while no declines was seen in any IQ scales over time, the CNS group showed significant declines in the rate of academic achievement and by year 3 and were approximately one standard deviation below their non-CNS peers. The authors concluded that the prolonged nature of IT chemotherapy treatment and insidious neurotoxicity of the treatment were possible factors in the declining performance in academics over time. This study highlights the need for aggressive tutoring in early and late stages of cancer treatment [89]. These authors provided year 4 data in a 1998 study on these same children [90]; however, samples sizes were much smaller for both groups. Results continued to suggest a near one standard deviation drop in academics in the CNS group.

15.6.3 Attention

Problems with attention have been consistently reported among the late cognitive effects of pediatric ALL. However, the precise nature of attentional dysfunction has been difficult to characterize, likely due to different assessment techniques across studies. Some studies have attempted to categorize the attention deficits in ALL survivors according to DSM-IV criteria for ADHD, while other studies have utilized a more in-depth cognitive battery to assess sub-domains of attention, such as working memory and processing speed.

Kahalley et al. [91] assessed a group of 100 survivors of childhood cancer (50 ALL, 50 Brain Tumor), ranging from ages 12–17. The authors sought to determine the percentage of the sample, which would be classified as having a DSM-IV diagnosis of ADHD or Secondary ADHD. Participants were given a structured clinical interview, the Conners' Continuous Performance Test (CPT), and behavior rating scales. Nine out of 100 survivors met criteria for ADHD or Secondary ADHD. Of these, eight out of nine were characterized solely by inattentive symptoms. On the Conners' CPT, slow response time (Hit RT) was significantly slower among survivors meeting criteria for ADHD. However, the authors note that elevated ratings on behavior scales were common throughout the entire group of ALL survivors, including those not meeting a formal ADHD diagnosis. The authors conclude that a DSM diagnosis of ADHD is not useful for characterizing the deficits found in those childhood cancer survivors. Anderson & Mullens [92], in their review of the aforementioned study, agree with the conclusion that it is inaccurate to liken the late effects seen in survivors of ALL to the diagnosis of ADHD. They note that key differences in etiology between late effects and ADHD

appear to lead to different expectations in terms of symptom severity, prognosis, and treatment.

Schatz et al. [93] used a measure of broad cognitive functioning (Kaufman Brief Intelligence Test [K-BIT]) and stand-alone measures of processing speed (PS) and working memory (WM) in children following CRT + chemotherapy and chemotherapy alone. Twenty-seven participants age 9 or older in at least 30 months of continuous remission were matched by age and gender to 27 healthy controls. Fifteen received 18 Gy of CRT in addition to a chemotherapy regimen, three received 24 Gy, and nine received chemotherapy only. Working memory deficits were most profound in the CRT group when compared to age matched healthy controls. The chemotherapy only group was found to have lower WM, PS, and over all IQ compared to controls, though not to the degree of the CRT group. The difference between the CRT and chemotherapy group in overall IQ was accounted for primarily by reduced working memory scores. Processing speed did not fully account for the differences, suggesting a moderating effect of CRT directly on working memory ability. Working memory difficulties were found primarily on tasks requiring verbal span and spatial span while including interference, with intact performance on verbal span without interference. Thus, all spatial tasks and verbal tasks with interference appeared to characterize the working memory deficit. Studies, which utilize neuroimaging, have recently found a relationship between white matter changes in the right hemisphere and reductions in attention and spatial abilities [71].

In terms of treatment for the attention-related late effects of pediatric ALL, there is some evidence to support the use of methylphenidate (MPH). Mulhern et al. [65] studied the short-term effect of methylphenidate at 3 weeks in a randomized, double blind, placebo controlled trial among survivors of childhood cancer. Results indicated significant improvements across teacher and parent reports of attention and cognition. The low dose of MPH on the Conners' Parent and Teacher Rating Scales inattention and cognitive problems index resulted in effect sizes of 0.42 and 0.62, respectively. The moderate dose yielded effect sizes of on symptoms of inattention (0.52) and cognitive problems (0.53) on the Conners' Parent and Teacher Rating Scales. On the social skills rating scales, no change was found on the parent report. However, on the teacher report, effect sizes were reported on indices of social skills (LD = 0.49, MD = 0.68), problem behaviors (LD = NS, MD = 0.37), and academic competence (LD = .55, MD = .73). Side effects were tolerated among most of the sample, with symptoms including irritability, crying, and hyper vigilance. Five percent of the sample had dose-limiting side effects, and tended to be those in the brain tumor group.

Conklin et al. [94] studied the long-term effectiveness of MPH over a 12-month period. Though effect sizes were not reported, significant differences were reported in a MPH group on CPT indices, parent teacher and self-report ratings of attention, and parent ratings of social and behavioral problems. On the Conners' CPT, significant differences within the MPH group were found on omissions, Hit reaction time, Reaction time variability, and d′ (difference between the signal and noise distributions, a measure of the ability to distinguish and detect targets from non-targets). When compared to the clinical control group, significant improvement from baseline was found on the overall CPT index, reaction time variability, d′, and commissions.

Mulhern and Butler [95] suggest that metacognitive strategies, which teach children to monitor their own thinking approach may be useful in improving attentional processes in survivors of ALL, based upon promising studies, which have utilized this approach in children with brain injuries. Contingency management, problem solving skills training, social skills training, relaxation training, anger management and working with parents are components of metacognitive strategies. Please see Chap. 27 for a more detailed review of cognitive remediation strategies for survivors of cancer.

15.6.4 Sensorimotor, Visual-Motor, and Visual-Spatial Skills

There have been few studies that have investigated the impact of fine and gross motor skills in children with ALL. Many of these studies are

limited in terms of sample sizes [96–98]. However, deficits in fine motor abilities, tactile-perceptual skills, and perceptual-motor skills are consistent findings across outcome literature [99–103]. However, many of these studies are limited by the length of longitudinal follow up data points.

Hockenberry et al. [104] conducted a longitudinal study with ALL children with low, standard and high-risk protocols. A total of 82 children participated in repeated neuropsychological testing including IQ, the Developmental Test of Visual-Motor Integration (VMI) and Purdue Pegboard Test. Testing was conducted at baseline and years 1 and 2 of treatment. Mean age at baseline was 7.2 years. Results indicated significant reductions in fine motor speed at baseline in chemotherapy treated patients regardless of risk protocol and these deficits persisted through the 2 years of the study. In addition, visual-motor integration deficits were not evident at baseline but emerged by year 1 and continued to decline at year 2. These deficits were not related to overall declines in IQ; but VMI scores were correlated with baseline deficits on the Purdue Pegboard Test, suggesting fine motor speed deficits related to vincristine and methotrexate toxicity. Acute changes in white matter were proposed as the causal factor in fine motor and VMI deficits in ALL and may suggest specific points of intervention for children during and after treatment [104].

To evaluate the long-term impact, Copeland et al. [97] conducted a study of 99 children (51 received IT chemotherapy, 48 treated systemically with chemotherapy) with various types of cancers who did not receive CRT. These children were evaluated on 4 occasions during and after treatment with long-term follow up as late as 5–11 years post diagnosis. Gender, age, ethnicity and SES were included in the analyses. A full battery of neuropsychological tests was administered at each assessment period. Fine motor control and speed (Finger Tapping and Grooved Pegboard) were assessed along with visuomotor integration (VMI). Results indicated that IT chemotherapy group showed significant declines in VMI scores relative to the non-CNS chemotherapy group at early (<3 years) and late (5–11 years) stages. These results were present even when SES was controlled. In addition, younger age of diagnosis was associated with increased impairment in VMI scores. However, while these differences in VMI scores were robust when other demographical and medical variables were controlled, the overall scores were still within the average range.

15.6.5 Executive Functions

Studies of executive functioning (EF) in children with ALL have frequently focused on aspects of working memory, behavioral inhibition, self-monitoring, and mental flexibility using a variety of instruments. In a meta-analysis conducted by Campbell et al. [68], researchers found differences between groups on objective measures of working memory (WISC-IV/WAIS-III WMI); but not on measures from the D-KEFS, including Color-Word Interference, Sorting Test and Tower Test. In addition, subjective complaints of EF deficits were obtained by parent completed Behavior Rating Inventory of Executive Functions (BRIEF) scales and no differences between groups were found. ALL children scored within the average range on all measures, though a modest effect size (Cohen's $d = -0.75$) was found on the WMI of the WISC-IV/WAIS-III.

In the Copeland et al. [101] study, serial assessments of ALL children treated with IT chemotherapy were completed at baseline and three subsequent intervals. Patients with ALL or lymphomas and IT chemotherapy ($N = 51$) were compared to other cancer groups treated systemically ($N = 48$). Measures of phonemic fluency and Trails A and B were completed. Patients with CRT were eliminated from the study. Results from the long term (5–11 years) follow up indicated no significant differences in EF measures used between groups at baseline or any follow up point. However, among those patients from either group, a modest decline in EF skills was noted over time with both groups declining slightly less than 0.5 SD over the ≥5 interval. No other interactions with other demographic variables were found [101].

A chemotherapy-only, prospective study of children with ALL was conducted by Kingma et al. [25] in which some specific measures of EF were included. Twenty patients underwent a series of three evaluations with a median range of follow up lasting 7 years. Results from the ALL patients were compared to a cohort of 225 Dutch control students demographically matched. Results indicated that the ALL group scored in the normal range and did not differ significantly from the NC group on Trails A & B. However, by the third evaluation, the ALL group scored significantly lower than NC on Trails B (NC = 38.2 s, ALL = 47.0 s, $p = 0.009$) and 3 out of 20 patients scored below the 5th percentile on the test. No significant demographic factors were noted. Although limited in subject size and test selection, declines were evident in EF from baseline. All other neuropsychological measures in this study were non-significant except a slight drop in VIQ on the WISC-R [25].

A small study (N = 15; ALL = 8, Matched Controls = 7) conducted by Robinson et al. [105] evaluated neurocognitive functioning from several survivors of IT-chemotherapy and healthy matched controls. Clinical subjects were selected based on the relative severity of their cognitive deficits compared to other ALL subjects. All subjects were administered the WISC-IV and selected measures from the D-KEFS (Color-Word Interference, Sorting and Tower tests). All subjects also underwent fMRI while undergoing tasks of selective responding (N-back task) to assess regions associated with working memory. Results indicated that the ALL subjects did show significantly lower scores on measures of working memory and executive functioning. However, they also showed deficits in FSIQ relative to controls. FMRI data indicated that ALL survivors displayed significantly greater activation in areas underlying working memory (dorsolateral and ventrolateral prefrontal cortex) and error monitoring (dorsal and ventral anterior cingulate cortex) as demands on tasks measuring these brain areas increased. The authors concluded that ALL survivors may show specific deficits in tasks related to the appraisal, selection and incorporation of information needed for everyday decision making at least among the most impaired children following prophylactic IT chemotherapy. As noted earlier, Carey et al. [71] found decreased white matter in two frontal regions (right middle and superior frontal gyri) and subsequent deficits on some D-KEFS measures (Trail Making Test-4 and Verbal Fluency—Category Switching Correct); however, as with the Robinson et al. study, significantly lower FSIQ was found in the ALL group. Overall, results from combined neurocognitive and neuroimaging studies reveal specific areas of dysfunction in frontal lobe systems that subsume working memory and executive control.

15.6.6 Memory

The analysis of memory functioning in survivors of ALL is complicated by varying instruments used in different studies and at different ages. However, memory deficits were among the most salient findings in early research studies on the neuropsychological functioning of children with ALL. Brouwers, Riccardi, Fedio, and Poplack [27] evaluated 23 ALL children in continuous remission treated with IT-chemotherapy and CRT. CT imaging and neuropsychological testing were used and results indicated that neuropsychological deficits correctly predicted the presence of CT abnormalities with 87 % accuracy. In addition, subjects with CT abnormalities recalled fewer items than those without on the Wechsler Memory Scale (WMS) and showed greater attrition between immediate and delayed trials.

In the previously discussed study by Copeland et al. (1996), serial assessments of ALL children treated with IT chemotherapy were completed at baseline and three subsequent intervals. Memory was assessed using verbal and nonverbal selective reminding tests. Results from the short term (3 years) and long term (5–11 years) follow up indicated no significant differences in memory measures used between groups at study termination; and, in fact, the ITC group outperformed the NITC group (though all scores were average to above average). However, among those patients

from differing treatment protocols, a modest decline in memory was noted at baseline and time three for one protocol, possibly owing to a higher chemotherapy dose and/or younger age at diagnosis. No other interactions with other demographic variables were found [101].

Similar studies using verbal supraspan measures (Rey Auditory Verbal Learning Test—RAVLT) or broad memory measures (Wide Range Assessment of Memory and Learning—WRAML) found no differences between ITC, NITC or ITC + CRT groups when controlled for IQ and demographic variables [24, 25]. In addition, when these broad memory measures were administered along with MRI volumetric measures no differences were found in hippocampi volume nor neuropsychological measures between ITC and healthy controls [105]. However, slightly lower scores on verbal memory measures were seen in a small group of ALL children treated at a young age with chemotherapy, including oral dexamethasone and high cumulative doses of vincristine sulfate (68 mg/m^2) compared to healthy control subjects [84].

Rodgers et al. [88] compared 64 ALL and solid tumor survivors treated with either 18 or 24 Gy cranial radiation with sibling controls. Memory and related skills were assessed using the Cambridge Automated Neuropsychological Test Battery (CANTAB). No difference in overall IQ scores was noted. There were no significant differences between patients and sibling controls on reaction times or delayed matching to sample. In addition, when immediate recall was examined no significant differences were found. However, when the number of items correctly recalled during the delayed test was examined, the ALL patients in both the 24 and 18 Gy groups were found to recall significantly fewer items than sibling controls (24 Gy, $F=6$, $p=0.01$; 18 Gy, $F=4\text{-}6$ $p=0.05$). There was no such difference in delayed recall in the group with solid tumors. Finally, the results also indicated that ALL subjects employed fewer and less well developed rehearsal strategies than their siblings or those subjects treated for solid tumors. In other words, the memory deficit present in the ALL population appears to be of meta-memory nature rather than a perceived structural defect. The potential importance of these findings is that they suggest that children with this type of deficit may be amenable to intervention and training in rehearsal strategies [88]. Studies have also shown that ALL children with ITC score slightly higher than ITC + CRT on some nonverbal memory tests [82] further implicating radiation therapy as the likely causal factor. Waber et al. [24] found that specifically, ALL children receiving ITC + CRT had significantly more difficulty completing the copy and immediate memory portions of the Rey Complex Figure Test and that these deficits could be ameliorated with metacognitive strategies when provided [106].

15.7 Conclusions and Assessment Strategies/Recommendations

Despite continued improvement in the safety and tolerance of current treatment protocols for ALL, the literature suggests that many children will experience declines in neuropsychological functioning following contemporary treatments. Neuropsychological assessment plays a valuable role in the treatment process in that it can aid in the identification of specific deficits, and development of accommodations and learning strategies. Clinicians help guide families through expected outcomes and aid schools in implementation of metacognitive strategies for attention, executive functions, and memory.

Overall, the data available suggests general and specific declines in several neurocognitive areas. IQ scores following treatment for ALL suggest slight declines in ability in ALL patients over time when compared to their baseline and to normal controls. Sibling and clinical non-CNS children also performed significantly better though many studies found long-term scores still within the average range. Evidence of focal deficits in processing speed were common in ALL patients. There appears to be a negative impact in the use of CRT when compared to chemotherapy alone. Lower scores on measures of academic achievement were noted in most studies for ALL groups regardless of treatment modality.

However, results indicated that the protracted nature of CNS treatment may have contributed to academic declines due to increased absenteeism. ALL children appear to show more deficits in areas of mathematics.

Studies have shown specific deficits in attention and working memory with some studies finding improvement on standard doses of MPH and cognitive training programs. Significant declines in visuomotor integration and motor coordination have been noted in the literature. Deficits in executive functions have also been seen in ALL following all forms of treatment and possibly owing to decreased white matter in frontal regions. ALL survivors also show fewer and less spontaneous use of metamemory strategies during recall tasks.

15.8 Case Study

The following case study of "CM" illustrates the general and focal deficits often seen in ALL patients. In addition, secondary deficits related to abnormal imaging are presented to illustrate the use of deficit-focused treatment planning.

15.8.1 Reason for Referral

CM is an 11-year-old Caucasian female who was seen for a neuropsychological evaluation. She has a history of acute lymphoblastic leukemia with treatment using intrathecal MTX and ARAC for 3 years. She also has had subsequent seizures and some abnormal T2 intensity on MRI around the hippocampus. The evaluation was requested by her oncologist to provide some estimation of her cognitive and emotional functioning and treatment recommendations.

15.8.2 Background Information

CM was diagnosed with ALL at age 5 and began treatment using intrathecal MTX. Baseline IQ was obtained just after her sixth birthday. Somewhere in the following year she had a generalized tonic-clonic seizure and was placed on Dilantin. She continued on Dilantin for several years although the MTX was switched to ARAC. Her final round of chemotherapy was at age 8.

CM was off of all medications for several months prior to the neuropsychological evaluation and then had another seizure and went into status epilepticus. She was hospitalized and then placed on Keppra. Since then, she has had some breakthrough seizures. Her Keppra dose has been titrated over time, and this has been somewhat helpful.

She has had three MRIs. The first in year 2 of chemotherapy indicated mild increased T2 signaling in the deep hemispheric white matter bilaterally. This was thought to be secondary to the chemotherapy. She also had some possible scar tissue around the body of the left hippocampus. It was thought that the volume and architecture of the hippocampus was normal. There was a follow up MRI done 1 year later. The same findings were evident; however, there were some changes in the T2 signal in the periatrial white matter along the frontal horns of the lateral ventricles, possibly reflecting some demyelination. The final MRI was conducted 2 years later and appeared to be consistent with previous findings with the aforementioned T2 weighted signal from the mesial aspects of the left temporal lobe surrounding the hippocampus. The most recent EEG indicated some questionable slowing in the left temporal region, although there were some significant artifacts from the study.

Her parents indicated that she has difficulty with reading comprehension and to some degree memory. She is serviced under a 504 Accommodations Plan as part of the Rehabilitation Act (discussed Chap. 23). She repeated first grade and received additional help, mainly in terms of extra time on standardized testing. She also has some obsessive-compulsive disorder-like symptoms. She is fairly order driven and likes to keep a running track of all of the things that she is going to do in a day. She gets a little bothered if that is not done. She has some sensory difficulties with her feet and insists on wearing shoes wherever she goes.

15.8.3 Neuropsychological Assessment Data

Name: CM	Age	Gender	
	11	F	
WISC-IV	**Scaled score**		**Scaled score**
Verbal Comprehension	**Age 6/age 11**	**Working memory**	
Similarities	10/7	Digit Span	11/7
Vocabulary	10/3	LN Sequencing	10/8
Comprehension	12/11		
Perceptual reasoning		**Processing speed**	
Block design	12/10	Coding	12/12
Picture concepts	12/10	Symbol Search	12/10
Matrix reasoning	13/12		
	Index score	**Percentile**	
Verbal comprehension	102/83	55/13	
Perceptual reasoning	115/104	84/61	
Working memory	102/86	55/18	
Processing speed	112/106	78/66	
Full scale	119/92	90/30	
Woodcock–Johnson (WJ III)	**Grade equivalent**	**SS (95%BAND)**	**Percentile**
Broad reading	3.9	85 (80–90)	15
Broad math	5.7	97 (91–103)	42
Math calculation skills	5.6	96 (87–105)	39
Letter-word identification	3.6	84 (79–89)	14
Reading fluency	5.1	93 (83–103)	32
Calculation	4.4	85 (74–96)	16
Math fluency	10	117 (112–122)	88
Passage comprehension	3.8	89 (80–98)	23
Applied problems	5.7	98 (92–104)	45
BEERY VMI	**Standard Score**	**Scaled Score**	**Percentile**
VMI	103	11	58
Visual perception	92	8	30
Motor coordination	91	8	27
Children's Memory Scale (CMS)	**Scaled score**		**Scaled score**
Visual immediate		**Verbal delayed**	
Dot location total	9	Stories delayed	2
Faces immediate	9	Word pairs long delay	3
Visual delayed		**Learning**	
Dot location long delay	10	Dot location learning	9
Faces delayed	9	Word pairs learning	3
Verbal immediate		**Verbal recognition**	
Stories immediate	2	Stories recognition	7
Word pairs total	2	Word Pairs recognition	3
	Index score	**Percentile**	
Visual immediate	94	34	
Visual delayed	97	42	
Verbal immediate	51	0.1	
Verbal delayed	54	0.1	
General memory	63	1	

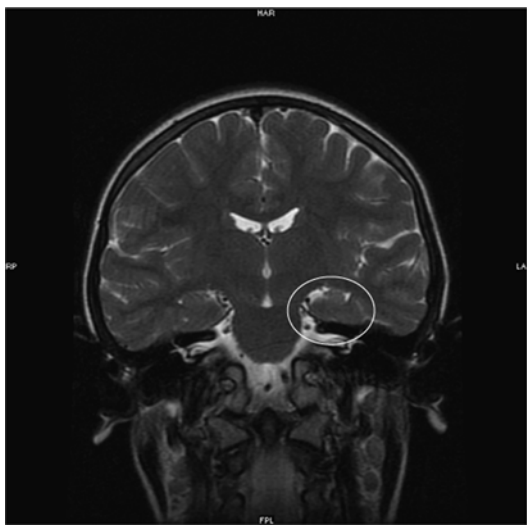
(continued)

(continued)

Name: CM	Age	Gender
Learning	75	5
Delayed recognition	69	2
Conners' CPT-II		
Profile matched	Clinical	
DFA percentile	54.00 %	
SCAN-C	**Standard score**	**Percentile**
Filtered words	7	16
Auditory figure—ground	8	25
Competing words	9	37
Competing sentences	10	50
Composite standard score	90	25

15.8.3.1 MRI Images

Description: T2 Coronal Image with evidence of left hippocampal scarring.



15.8.4 Case Summary

Results from the neuropsychological evaluation indicated a global drop in overall IQ from baseline assessment at age 6. Results also indicated focal deficits in Verbal IQ, verbal memory, reading, math calculation and some areas of auditory processing. This cluster of deficits is consistent with radiological findings on MRI and EEG. She has white matter abnormalities in the left mesial temporal lobe and suspected scarring around the left hippocampus and thus the verbal memory deficits are not surprising. In addition, left temporal lobe slowing was found on her EEG and is consistent with more broad deficits on verbally mediated tests. Diffuse deficits also were found in attention and working memory and full scale IQ.

It was recommended to the family that results from the testing be shared with the school to facilitate an Individual Education Plan (IEP). Specifically, metacognitive strategies and mnemonics were suggested for encoding of new information. Instructions were requested with visual aids to serve as reminders and frequent check-ins were requested to ensure she stayed on tasked. Given the working memory deficits, instructor notes were requested prior to class lectures so that she could highlight salient material while tracking orally presented information.

At the feedback session, CM admitted that much of her "obsessive" note taking and emerging rigidity about routines stems from her progressive memory loss though it was less clear whether she appreciated the declines at the time. CM was tried on a low dose of methylphenidate, which proved helpful.

CM sustained damage to regions along the course of the left hippocampus without substantial volume loss or architectural changes. This likely reflects mesial temporal scarring resulting from chemotherapy. This case illustrates the impact of ALL treatments on neurocognitive functioning and the need to track changes over time. Clinicians should familiarize themselves with trends in the literature regarding deficits from the various ALL protocols and attend to relevant demographic variables such as age at treatment, type, length and complications related to treatment. Strategies to accommodate emerging deficits should be implemented and reevaluated yearly.

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Neuropsychological Effects of Pediatric Brain Tumors and Associated Treatment

16

Karin S. Walsh and Iris Paltin

16.1 Introduction

Long-term survival in the pediatric brain tumor population has become increasingly common with significant advances in treatment approaches over the past several decades [1, 2]. Approximately 74 % of children with central nervous system (CNS) malignancies achieve 5 year survival [3]. Over the past 10 years, there has been a significant increase in the appreciation and understanding of neurocognitive outcomes in pediatric brain tumor survivors. About 5–40 % of survivors exhibit significant, functionally disruptive neurocognitive impairments [4] that negatively impact overall quality of life. In fact, these outcomes have led to therapeutic modifications and the development of novel treatment protocols. We will review research on primary and secondary factors related to neurocognitive outcomes as well as common functional impairments that those caring for survivors of pediatric CNS tumors should recognize.

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16.2 Neurocognitive Late Effects

Pediatric brain tumor survivors exhibit a unique pattern of emerging neurocognitive impairments over time that place them at risk for increasing problems in day-to-day living [5]. Unlike other acquired neurological insults in children (e.g., traumatic brain injury, stroke), which often result in immediate neurocognitive changes and afterwards recovery [6], the course of emerging impairments in brain tumor survivors are distinctive in that the presentation's trajectory is protracted. The pattern of decline appears to be age-dependent, such that younger patients show a more immediate decline with attenuation over time, while older patients demonstrate a more protracted decline, with evaluable deficits typically not present until 18–24 months post-treatment [7, 8].

In addition to the documented changes in global intellect, more recent research has focused on documenting the presence and role of specific neuropsychological impairments among brain tumor survivors. Processing speed, executive functions (including attention), and memory have been demonstrated to be the most vulnerable neurocognitive domains affected over time [7–14]. The disruption of each of these functions

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hinders learning [15], particularly in children with concurrent seizures requiring medication, and children with third ventricle or cerebellar tumors [16].

Some recent studies have highlighted the lack of baseline data in studies of neurocognitive late effects, citing possible premorbid deficits, which may be related to the primary disease [17] or other developmental disruptions unrelated to the disease. Establishing a "true" baseline level of functioning in these children is difficult, as treatment is expedited from the moment of diagnosis. In some cases, the initial assessment occurs during the course of chemotherapy (usually maintenance), which poses its own challenges, as children may feel ill and suffer significant somnolence. At other times, an estimate of premorbid functioning is gathered after chemotherapy has been completed, but before radiotherapy. In all cases, it is considered important to establish a baseline estimate prior to radiation therapy, as such treatment has been associated with the highest risk for neurocognitive disruptions.

16.2.1 Neuropathological Mechanisms

One of the primary neuropathological mechanisms associated with these functional deficits appears to relate to secondary vascular insufficiency, with particular effects on cortical white matter in various brain regions [18–21]. In patients treated with radiation, approximately half will show progressive white matter changes over time [22], which appears to be dose dependent [23]. Extreme cases of white matter disease are observed in some treated with radiation therapy, manifesting in leukoencephalopathy and/or cerebral atrophy. Animal models have demonstrated that demyelinating processes and necrosis in rats treated with various doses of radiation are evident as early as 1 month post radiation and intensify for up to 6 months. Neural stem cell and progenitor cells were specifically affected, which may be related to diminished brain growth and subsequent dysfunction [24]. Functionally, white matter volume loss, secondary to radiation and chemotherapy, has been demonstrated to be related to global intellect [25].

16.2.2 Risk Factors Related to Outcome

There is a complex interplay of risk factors related to outcome in these pediatric cancer survivors, and a model of primary and secondary causes provided by Maureen Dennis provides a useful conceptual framework [26] (see Fig. 16.1). *Primary* considerations relate to biological risk, development, time, and reserve (cognitive, social, and physical). In general, pediatric brain tumors equate to higher biological risk, primarily related to treatment approaches more than the tumor itself (with the exception of supratentorial tumors). In addition, *secondary* effects of the tumor and associated treatments, including hydrocephalus and seizures (and antiepileptic drugs), further increase the biological risk when present. Development (age at onset), time since onset, and treatment factors are predictors of long-term outcome as is a child's premorbid level of functioning.

A number of known primary and secondary factors have been demonstrated to impact neurocognitive outcomes in children with tumors of the CNS. Primary factors include treatment dynamics (surgery, chemotherapy, radiotherapy) and disease or tumor characteristics. Secondary factors include individual patient characteristics such as age and gender, elapsed time since treatment, and neurological sequelae (e.g., hydrocephalus, seizures).

16.2.3 Primary Factors

Surgery. Surgical resection of tumors is not typically discussed as one the most prominent factors associated with functional outcomes, and the lack of assessment of pre-surgical functioning is limiting. Nonetheless, there has been some suggestion of disruptions in verbal memory, visuospatial skills, and motor functions [27] in a group of children treated with surgery exclusively. Approximately 25–33 % of patients undergoing resection of posterior fossa tumors (primarily medulloblastoma) suffer cerebellar mutism syndrome (CMS), a complication considered to be related to surgical intervention [28].

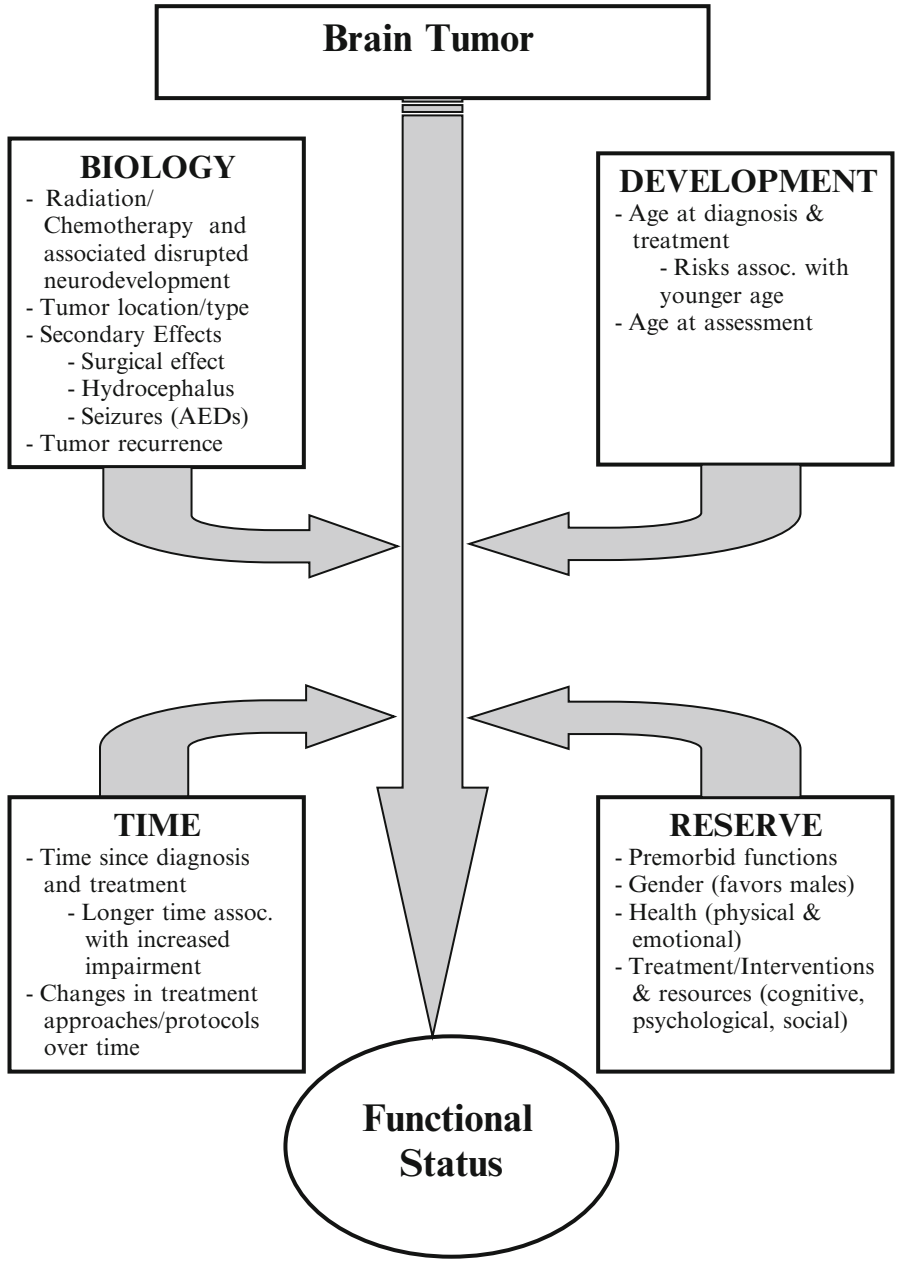


Fig. 16.1 Interactions related to functional status of brain tumor survivors based on Dennis' multifactorial model [26]

Transient features of this syndrome include acute mutism, irritability/agitation, ataxia, and hypotonia that typically emerges 2–3 days after resection and can last from days to months. The length of these symptoms relates to outcome, such that longer time to resolution relates to greater long-term impairments. Beyond the acute symptoms of CMS, various neurocognitive deficits persist, including executive dysfunction, particularly related to attention, cognitive and behavioral flexibility, strategic planning, and initiation [28]. While the cause of this complication in some pediatric patients remains elusive, young patients who developed CMS following surgery for

medulloblastoma were more likely to exhibit brainstem and cerebellar medullary angle involvement pre-operatively [29]. There is also evidence of significantly greater atrophy of the total cerebellum, vermis, and brainstem in the children with CMS compared to those without CMS 1 year post-operatively. A difference of 15 IQ points between the groups on average was evidenced, and 60 % of the CMS group measured in the impaired range, compared with only 14 % in the non-CMS group [29]. These findings hint at a pathologic mechanism involving disruption of the dentatothalamocortical outflow pathway, which may relate to the more chronic functional impairments in CMS, namely the neurocognitive and behavioral sequelae. This is a reasonable hypothesis given the recent understanding of the relationship of the cerebellum to higher order cognitive functions, including executive functions, and emotional regulation [30].

Chemotherapy. Assessing the role of chemotherapy exclusively in pediatric brain tumor patients is difficult, and occluded by the involvement of multiple simultaneous treatment approaches (e.g., multi-agent chemotherapy, radiotherapy). Nonetheless, the Head Start II study suggested that within the first 2 years post-treatment, young children with malignant brain tumors treated with chemotherapy and autologous hematopoietic cell transplantation (AuHCT) were spared some of the neurocognitive consequences associated with early radiation therapy [31]. Similarly, children with medulloblastoma treated with chemotherapy alone were shown to function significantly better than children who received radiation, although still significantly worse than normal controls [32].

One study attempting to evaluate the effects of chemotherapy regimens in patients with medulloblastoma revealed significant neurocognitive susceptibility in patients treated with intrathecal methotrexate (MTX) compared to those treated with intravenous MTX or controls [33] as they performed significantly worse on all neuropsychological measures. However, another small study of children with chiasmatic-hypothalamic tumors reported no significant change in IQ over time related to MTX delivery methods [34].

The timing of chemotherapy, specifically MTX, has also been shown to relate to outcome, and the effect is pronounced in females, as well as in the younger cohort. Specifically, the greatest functional impairments are observed in children who received concurrent MTX and radiation therapy versus those who received MTX prior to radiation [35, 36]. Further, IT MTX is more commonly associated with the development of leukoencephalopathy, which also impacts neurocognitive functioning [37].

Radiation. Radiation therapy (RT) has been demonstrated to be a major factor in neurocognitive outcomes in pediatric neuro-oncology and treatment approaches have been altered over the past decade in an attempt to minimize these sequelae, while still contributing to survival. Specifically, reduced doses and volume considerations (focal or conformal approaches) have been the focus of research.

Establishing the lowest curative dose through reduced-dose craniospinal and whole brain RT has been a target of research [38, 39], as a clear dose-dependent relationship with cognitive functions in this population has been established [40–43]. Children receiving conventional craniospinal radiation dosing (55 Gy) more often have a high level of cognitive morbidity, and significant deterioration in global intellect over time, in some cases in excess of 25 IQ points [44–46]. About 23–50 % of survivors receiving high radiation doses demonstrate IQ's less than 80 (≥1.5 SD below the mean) at follow-up [47, 48]. Additional areas of neurocognitive impairment have also been demonstrated to be related to higher radiation doses [49], including diminished processing speed [41, 43], attention, verbal reasoning and memory [43], visual-perception, language, and academic functioning [42, 50]. When radiation at higher doses (>45 Gy) involves total brain, supratentorial regions, and particularly the left temporal lobe, there is a higher susceptibility for greater neurocognitive declines [51, 52] including poorer intellectual outcomes [52].

Less radiation-related neurotoxicity has been demonstrated in reduced-dose RT studies, primarily related to global intellectual outcomes. However, even reduced doses carry some morbidity, and

average IQ decrements of four points per year have been documented [53]. Comparisons made between craniospinal radiation doses on functional outcomes reveal greater neurotoxicity at 36 Gy, than 23.4 or 18 Gy. Patients treated with 36 Gy perform an average of 8–13 IQ points lower than those receiving 23.4 Gy [38, 40]. Douw's study comparing low grade glioma patients with or without low-dose radiation therapy revealed significantly poorer executive functioning and processing speed in the radiated group, while core memory and motor functions did not appear to be affected [54]. Neuroanatomically, acceleration of white matter volume deterioration has also been linked to doses of 36 Gy even compared to 23.4 Gy [20].

Beyond differences in radiation doses comparisons between craniospinal RT or whole brain, and focal radiation reveal differential outcomes in intelligence and other neurocognitive domains, primarily with regard to *severity*. In contrast to the 25 point decline in IQ documented in the groups of patients requiring craniospinal RT/whole brain doses, an average 6–11 point IQ decline has been demonstrated in partial brain radiation [55]. Jalali and colleagues [51] reported a >10 % diminishment in IQ in a third of patients in their study, 2 years after focal radiation (primary diagnosis was craniopharyngioma). Compared to children receiving only focal posterior fossa radiation, craniospinal doses of 36 and 24 Gy resulted in 21 and 13 IQ point differences, respectively [40]. Other neurocognitive and functional domains are also impacted by focal approaches, including processing speed, attention, auditory and visual learning/memory, academic skills, adaptive functions, and behavior [55–57]. This again highlights that although the *severity* of neurocognitive impairments may be diminished with focal radiation, there remains a notable number of neurocognitive sequelae over time.

Several factors mediate the relationship between radiation and neurocognitive outcomes. Age has shown to account for more variance than radiation, and when combined, represent an additive effect on outcome [51]. These effects are particularly salient for those patients diagnosed and treated at younger ages [42], and it has been suggested that long-term IQ can be predicted by baseline intellect, radiation dose, and age at time of radiotherapy [38]. There is currently no conclusive evidence that reduced doses result in better outcomes in older children [58, 59].

Technological advances have resulted in the increased knowledge and availability of proton beam radiation therapy [60, 61]. Proton radiation allows for both higher doses of treatment to the tumor (compared to photons) and increased sparing of normal tissue [62]. This is possible as photon radiation delivers the greatest dose at the entry point, where proton radiation delivers its greatest dose at the target location. Significant structural sparing was identified when treating childhood ependymoma with proton-versus-conventional or conformal Intensity Modulated Radiation Therapy (IMRT) [63]. Similarly, proton treatment reduced the radiation dose to the temporal lobes and cochlea in treating medulloblastoma [64], which is important as the inadvertent involvement of healthy tissue even in the most advanced conformal techniques has been shown to relate to neurocognitive and functional deficits [65, 66]. As the hippocampus is known to be sensitive to radiation, and hippocampal injury is particularly associated with cognitive changes, reduced risk of insult to the hippocampus may likely preserve cognitive (especially memory) functions [62]. Laffonde and colleagues reported that in a cohort of craniopharyngioma patients receiving proton therapy between 1995 and 2007, evaluated approximately 4 years post-therapy, approximately 33 % were reported to have significant executive dysfunction [67]. While the potential benefits of proton beam radiation on neurocognitive outcomes has yet to be fully demonstrated, it is expected that minimizing exposure of healthy tissue to radiation may positively impact outcomes. This new technology may allow for radiation therapy in the youngest patients, potentially increasing survival rates, while limiting the disruption in neurocognitive development. Furthermore, proton therapy is posited to reduce the rate of secondary malignancies [62].

Molecular genetics is becoming an increasingly important focus of research in the area of long-term functional outcomes in children treated with radiation. There is some evidence showing

that specific genetic polymorphisms (*GSTM1* and *GSTT1*) are related to poorer neurological and neurocognitive outcomes in medulloblastoma survivors [68]. Patients with the most significant post-radiation sequelae have been shown to have greater than four single nucleotide polymorphisms (SNPs) in candidate genes [69]. Further, Svensson and colleagues documented crude differences in gene expression profiles between patients with and without severe adverse effects from radiotherapy over time [70].

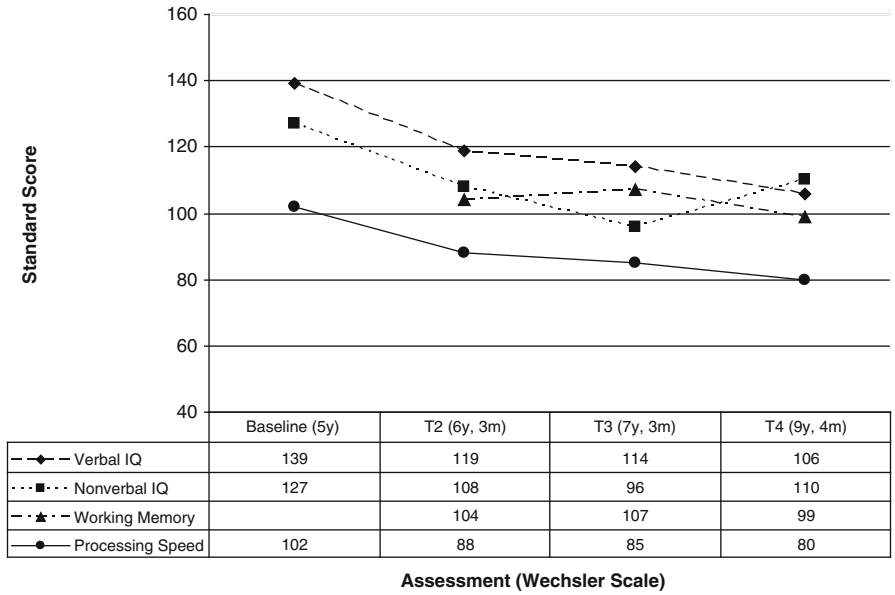
Tumor-Related Factors. While tumor location has not been the primary target of research on neurocognitive outcomes in pediatrics, the studies that have been carried out have produced mixed results. Several studies have revealed evidence of particular susceptibility for tumors of the supratentorium, especially those involving the left hemisphere [48, 71]. However, other studies have failed to identify any differences in neurocognitive outcome between supratentorial and infratentorial tumors [27, 72, 73] or greater impairment with tumors of the posterior fossa [74, 75]. Patel and colleagues found greater neurocognitive and behavioral impairment in children with infratentorial tumors [76]. Attention, working memory, and language-based reading impairments were significantly more affected in the infratentorial group, even after controlling for the age at diagnosis. Nonetheless, both groups showed equivalent deficits in cognitive efficiency (processing speed), verbal learning/memory, and nonverbal intellectual functions. In addition, when assessing neurocognitive functions beyond global IQ in patients with cerebellar astrocytoma, specific impairments in processing speed, attention, executive functions, memory, and visuospatial skills were documented [72, 77]. Third ventricle tumors (e.g., craniopharyngioma, hypothalamic glioma) have also been documented to be susceptible to greater functional impairments based on tumor location [47, 48]. In one study of pre- and post-operative neurocognitive status, evidence of impairment prior to any treatment was found, and predictors of increased risk included severe pre-operative hydrocephalus, diagnosis of medulloblastoma, and brain stem infiltration [17].

Tumor Recurrence. Children who suffer tumor recurrence have not been well-researched, which may relate to lower survival rates in part. We know little about the differences between those who have recurred and those who have not, although there is some basic evidence to suggest that they are at higher risk for more significant functional disruptions than those in which the initial tumor was eradicated [78]. This is most likely related to the necessity for additional treatments, including repeat surgery, chemotherapy, and sometimes additional radiation [78].

16.2.4 Secondary Factors

Age and Time Since Treatment. A well-documented factor in outcome has been patient age at the time of diagnosis and treatment. The most devastating outcomes are observed in the youngest patients. Different cut-offs have been used, but in general, treatment initiated prior to the age of seven has been shown to have a negative impact on neurocognitive outcomes [9, 10, 52, 79, 80]. These findings have prompted changes in treatment approaches, most notably related to the initiation of radiotherapy in the very young (3 years and younger) [81]. Current approaches to treating the very young include delaying radiation as long as possible by initiating an intensive chemotherapy regimen [1, 82]. Sparing of long-term IQ changes has been demonstrated in patients treated with combined chemotherapy and reduced or no radiation compared to those treated with conventional radiation [50].

The time since diagnosis and treatment of brain tumors is negatively correlated with neurocognitive outcomes [9]. Early research on global cognitive development in this population revealed a diminishment of full scale IQ in the years following the end of treatment at a rate of 2–4 IQ points per year [7, 8, 10, 38, 83–86]. Studies have demonstrated more rapid decline in the first few years following treatment, followed by a leveling off over time [7, 43]. However, this trajectory is moderated by age, as those younger at the time of treatment take longer to reach a plateau [11]. In general, these declines continue for more than a



	Baseline (5y)	T2 (6y, 3m)	T3 (7y, 3m)	T4 (9y, 4m)
Verbal IQ	139	119	114	106
Nonverbal IQ	127	108	96	110
Working Memory		104	107	99
Processing Speed	102	88	85	80

Fig. 16.2 Intellectual trajectory of medulloblastoma patient treated with craniospinal radiotherapy and chemotherapy following resection

decade following treatment [11, 12]. However, this is rarely related to a loss of previously acquired skills, rather the pattern exemplifies a lack of appropriately paced development over time relative to the normative population [11] (Fig. 16.2).

Gender. Gender has also been demonstrated to be a factor in neurocognitive outcomes in some studies [87–90], with females being particularly susceptible to the effects of treatment for brain tumors. However, this potential difference has not prompted gender-specific treatment approaches to date.

Hydrocephalus. Hydrocephalus is a complicating factor in outcomes for pediatric brain tumor survivors. Children who have untreated hydrocephalus or require permanent shunt placement are at higher risk for long-term neurocognitive deficits [91]. The presence of hydrocephalus at the time of diagnosis results in significantly lower IQ at baseline, and the most opportunity for improvement following treatment [80], suggesting a reversibility of the effects of hydrocephalus when appropriately addressed. However, there is evidence that compared to medulloblastoma patients without shunts, those with ventriculoperitoneal (VP) shunts exhibited significantly lower IQ, academic skills, and visuomotor functions [92].

Seizures. The presence of seizures has been documented to be another complicating factor in outcomes for pediatric brain tumor survivors. A significant proportion of children with seizures demonstrate global intellect significantly below expected levels [78]. Klein documented greater neurocognitive impairment in patients with low-grade glioma who required treatment with antiepileptic drugs (AEDs) [93]. The presence of seizures and AEDs in patients with third ventricular tumors was also demonstrated to negatively impact verbal memory more severely than those not requiring medical treatment for seizures [16].

16.3 Education and Employment Outcomes

There are obviously many sequelae associated with treatment of CNS tumors in childhood, which can affect the survivor's ability to transition successfully into adolescence and adulthood. This particular

topic will be more fully covered in this manuscript, but a summary of issues as they related to CNS tumors will be reviewed here. The full extent of these relationships is yet to be fully determined. However, several researchers have begun to explore this topic, with one of the longest and most successful being the Childhood Cancer Survivor Study (CCSS), discussed elsewhere in this manuscript as well. Briefly, the CCSS includes a cohort of over 14,000 survivors of childhood cancer, including CNS tumors, who are followed over time with questionnaires assessing physical, neurocognitive, social-emotional, and socioeconomic outcomes. Research emerging from the parent study repeatedly highlights increased rate of impairment in brain tumor survivors, consistent with lab-based research presented above. Specifically, these studies repeatedly highlight that brain tumor survivors have increased rates of impairment compared to controls for attention, processing speed, working memory, and long-term memory (Task Efficiency and Memory subscales on the CCSS Neurocognitive Questionnaire—NCQ) [3, 94]. This risk of impairment was increased for those who received RT, required a VP shunt, suffered a stroke, or evidenced other neurological disturbances such as hearing or vision impairment or paralysis [3, 94]. Further, lower neurocognitive ratings have been associated with reduced educational attainment, employment, and income status [94].

A crucial step in achieving independence in adulthood is completion of secondary and post-secondary education. Compared to all other cancer survivors, brain tumor survivors are the least likely to attend college, and 11 % less likely to do so than their siblings [95, 96]. The CCSS study has documented that nearly a quarter of survivors (compared to 8 % of sibling controls) were reported to receive special education services [97]. Despite this increased use of supportive special education services, CNS tumor survivors were more likely to repeat a grade and have been shown to perform more poorly in Math, English, and Science courses than their peers [98]. Additionally, completion of high school and post-secondary education was less likely, and there were higher rates of unemployment and diminished income levels compared to controls [99].

As teens transition to adulthood, the measure of age appropriate development often includes employment. Survivors of childhood cancer have been shown to be twice as likely to be unemployed compared to healthy controls, especially later in life [100]. Results from a meta-analysis revealed that survivors of CNS cancers were five times more likely to be unemployed than controls, with an unemployment rate ranging from 25 to 50 % [100]. Within the general cancer survivorship population, younger age at diagnosis, radiation treatment, lower baseline IQ, female gender, physical health, including pain, neuromotor, and neurosensory impairments, were significant predictors of limited employment and ability to maintain independence [100].

A number of non-cognitive factors further complicate the educational and employment trajectory of many survivors. Particularly limiting is the presence of neurological, sensory, musculoskeletal impairments, and chronic pain associated with survivorship of cancer and associated treatments. Those with such physical limitations (reported as upwards of 20 %) are more likely to require special education services, less likely to graduate high school and be employed, and less likely to have a household income greater than $20,000 [96]. The impact of poor health status (such as pain and neurosensory difficulties) was most limiting in the amount and type of work attainable in this population both in the years immediately following diagnosis and over their working lifetime [101]. These findings remain even after controlling for demographic (e.g., gender), emotional (e.g., depression), and neurocognitive factors [95]. Please see Chapters 24 and 29 for a more in-depth analysis of these issues.

16.4 Neurocognitive Interventions/Cognitive Rehabilitation

16.4.1 Cognitive Rehabilitation

Some attempts have been made to develop non-pharmacologic intervention approaches to addressing the various neurocognitive impair-

ments commonly present in survivors. A tripartite model incorporating rehabilitation, clinical psychology, and special education paradigms has been proposed and is currently being evaluated by Butler and colleagues [102], and is discussed in this manuscript in more detail. Briefly, the model includes individual training in the areas of attention and metacognition. Cognitive-behavioral therapy (CBT) is also provided. Early results indicate some immediate improvement on quantitative neuropsychological measures, although no improvement in academic achievement was shown. This highlights the challenge of developing interventions with ecological validity.

Another emerging therapeutic program that has recently been piloted with pediatric cancer survivors is the Cogmed® program [103]. It is a web-based computer training program specifically targeting working memory impairments. Research to date in children with attention and working memory impairments from various etiologies (e.g., AD/HD, etc.) has revealed improvements in working memory, with sustained benefits to as long as 6-months post-training [104, 105]. Please see Chap. 26 by Dr. Askins and colleagues for a more detailed description of the available cognitive remediation programs.

16.4.2 Pharmacotherapy

A number of trials have evaluated the efficacy of stimulant medications in brain tumor survivors given the similarities in symptomatology to children with developmental attention disorders. There have been mixed results [106–108], although there is some suggestion that methylphenidate in particular may be beneficial in addressing deficits in focus and sustained attention [109–111]. In Conklin's study, medication response was predicted by higher intellectual ability, male gender, and older age at treatment. There is little to no research to date on the effects of stimulant medication in adult survivors of pediatric brain tumors [111]. The use of pharmacotherapy is discussed in Chap. 27 by Dr. Anna Muriel in more detail.

16.5 Conclusions

Significant gains have been made in the diagnosis and treatment of brain tumors in children. With increasing survival rates, the long-term functional toll of necessary treatments has become an important focus of survival. Appreciation of the individual and treatment-related risk factors has emerged over time, although the majority of research has focused on macro systems of functionality, such as intelligence. Only recently has an appreciation for higher-order neurocognitive factors emerged, and exploring the multifaceted neurocognitive factors involved in diminished functioning in pediatric brain tumor survivors will contribute to improved identification of risk factors as well as more focused interventions. In contrast, no research to date has evaluated *neurocognitive* protective factors or mechanisms that lead to relatively typical development and functioning.

It has been demonstrated that the failure of a patient's ability to advance and attain developmentally appropriate goals begins soon after diagnosis of a brain tumor [112], highlighting the importance of early and consistent neurocognitive assessment and intervention. An appreciation of the need for understanding the longer-term outcomes in survivors of pediatric cancers is emerging, but still in its infancy. As many more children are surviving brain tumors and reaching adulthood, they will present with unique challenges, needs, and supports related to these life transitions. They are at elevated risk for complicated medical presentations such as secondary cancers, endocrine deficits, obesity, neurological impairments, neurocognitive deficits, increased fatigue, and poor sleep hygiene [108]. Further, engagement in health maintaining behaviors such as adequate physical activity, dental care and health screenings are reduced in this population [108]. In addition, there is also the significant risk for poor educational and employment attainment, which can reduce their access to appropriate health care resources (i.e., public/government versus private/employer-based insurance). Social-emotional challenges may further reduce

the survivor's ability to adequately advocate for him or herself, limiting independence, and this topic is addressed more fully in other chapters in this text. Many survivors have undergone neuropsychological assessments over time, however, children from smaller, rural areas, and those from disadvantaged backgrounds may not have had access to these services. This places them at greater risk based on limited awareness of long-term sequelae of pediatric brain tumor and limited connections to community resources. Understanding the needs of our pediatric survivors and developing supports and interventions to increase their independence and self-advocacy will be vital in producing more productive, mentally and physically healthy adults.

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Part IV

Psychosocial Factors and Quality of Life

17 Psychological Challenges and Adaptation in Long-Term Survivors of Childhood Cancer

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17.1 Introduction: Cancer Is a Stressor

The diagnosis and treatment of childhood cancer is a major challenge to the family and the diagnosed child. Treatments are often physically and emotionally arduous and the illness typically disrupts the child's normal school, social, and developmental context. While many patients show signs of psychological distress or acute stress reactions at some point during their treatment [1, 2], most will successfully adapt to these challenges and be able to establish positive psychological outcomes during and after treatment. In fact, studies of long-term survivors of childhood cancers generally indicate that the vast majority do not suffer from severe psychological distress and go on to experience positive adaptation in adulthood [3–5]. At the same time, cancer and its associated late-effects increase the risk of children having more adaptive challenges and psychological symptoms later in life. In this chapter, we focus on understanding the psychological and adaptive challenges that arise in this population, risk factors and high risk survivor groups, and the role of professionals in identifying and addressing these issues (Table 17.1).

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Understanding how an individual's adjustment and quality-of-life are tied to a cancer experience that may have occurred a decade or two before is not straightforward. Individual development is so multiply determined that pinpointing individual causes of psychological and social adjustment is probably impossible. In addition, adjustment difficulties and some psychological symptoms are common in the general population, so reports of these problems and disorders in survivors may only reflect the background level of disorders expected in the general population. To address this concern, we rely whenever possible on research findings, particularly from studies of large groups of survivors to provide objective information about the kinds of challenges survivors, as a group, are most likely to face. At the same time, we also present information in the text and case examples that are drawn from our own clinical experience to complement the research results and to illuminate the effects of cancer on individual survivors. (Names, ages, gender, and other details of the survivors presented in the cases studies may have been changed to protect their confidentiality. Details from more than one individual may be combined into a single case for ease of presentation.) Given the variability in childhood cancers and individual differences in children, presentation of these topics is not intended to be exhaustive, but rather to provide an introduction to the most common issues that arise among long-term survivors of childhood cancers.

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Table 17.1 Case Example: Anna, a 26 year-old leukemia survivor

Medical History: Anna was treated at age 3 for Acute Lymphoblastic Leukemia with chemotherapy and cranial radiation known to affect cognitive function in later-life. At age 26, Anna is referred for a psychological assessment because of depression, frustration with her work and school ambitions, and conflict with her parents.
Psychosocial Adaptation: Anna denies most symptoms of depression, but writes at the bottom of a depression screening measure, "it's not that I am suicidal, it's just that sometimes I think it would be better if I had not survived the leukemia." She describes a history of school problems starting in seventh grade that took many years to be diagnosed. Anna feels her parents were slow to get her evaluated because they did not want to admit she is "damaged goods." Anna began college hoping to study accounting, but found this too difficult even with supportive education services, and left college after 3 years with only 2 years of credits. Currently, she lives with her parents and works part-time at a local bookstore. Her sisters have graduate degrees and work in financial services, as do both her parents. She is disappointed with herself and angry that her parents are disappointed with her.
Over many months of therapy, Anna works on mourning the losses associated with her treatment, including the loss of learning potential and changes in her relationship with her family. She also acknowledges that it is not her family's judgments that are most problematic, and makes use of cognitive-behavioral strategies to alter her own harsh self-criticism. Where previously she either went to school taking a full-load of challenging courses, or dropped out and declared herself a failure, Anna is now able to devise a plan to take single college courses supplemented by tutoring and learning supports. She comes to see this plan not as admitting to being "damaged goods," but as a shrewd strategy for achieving her goal of completing college. In family therapy, Anna is struck by the level of estrangement between her parents, most notably when her mother comments "arguing about Anna is the only thing we have left to talk about." Anna also has to confront the fact that as angry as she is with her parents, she chooses to remain dependent on them and to serve as a distraction from their long-standing marital conflict. Eventually Anna chooses to leave the family home and the family therapy sessions. She says with humor, "if I had known how great it would feel, I would have divorced my parents years ago."
Comments: Many survivors' learning problems may not come to light until many years after treatment and even families who are knowledgeable of treatment late-effects may be resistant to acknowledging them because of stigma. This case is unusual for the high level of family conflict that became associated with Anna's learning difficulties, but it is a good example of the role of pre-existing family problems, and the extent to which cancer treatment and medical late-effects can become entwined with individual and family dynamics.

17.2 Psychosocial Outcomes

17.2.1 Psychological Distress

Research on medical and psychological outcomes of pediatric cancer survivors has benefitted from efforts to assemble large cohorts of survivors treated at multiple centers [3–6]. Making use of standardized assessments of outcomes in these large samples, studies of these cohorts have attempted to overcome the limitations common in smaller studies at individual treatment sites (e.g., poor generalizability, lack of power, selection bias) [3]. Because it includes psychological outcome data from a control group of non-treated siblings, findings from the Childhood Cancer Survivors Study (CCSS) [7] have also addressed the lack of controls and questions about the adequacy of normative data that limited many previous studies. Overall, studies from the CCSS and other large survivor cohorts have demonstrated that the majority of survivors of childhood cancers do not experience significant psychological difficulties after treatment. However, as a group, survivors have been found to be at increased risk for psychological distress compared to their peers, and a significant minority of survivors experience symptoms of maladjustment. For example, studies from the CCSS have shown that most survivors do not experience significant impairments in mental health functioning, although 17.2 % do, and survivors are more than twice as likely to have elevated levels of psychological symptoms compared to their siblings [4]. Similarly, results from the Swiss Childhood Cancer Survivors (SCCS) study have shown survivors are at increased risk for high levels of psychological distress. In both the CCSS and the SCCS, survivors were at increased risk for anxiety and depression symptoms [4, 5]. Survivors in the CCSS have also been found to have elevated rates of suicidal ideation [8], and post-traumatic stress symptoms [9]. Taken

together, these studies cited above provide some of the strongest evidence that prevalence of psychological distress and adaptive problems is increased in adult survivors of childhood cancers. However, it is important to note that this research focuses almost solely on prevalence of psychological symptoms and not of diagnosable psychiatric disorders. This reflects both the relative difficulty of measuring psychiatric disorders in survey research, and the desire to report on psychological distress rather than exclusively on psychiatric diagnosis. Appreciating this distinction has important implications both for understanding the research on survivors' psychological late-effects and for planning appropriate assessment and intervention programs. It bears noting that evidence of survivors' elevated symptoms of distress does not necessarily mean they have a greater prevalence of mental disorders as defined in the psychiatric nosology. Criteria for a psychiatric diagnosis typically include a minimum number of key symptoms that endure for a minimum amount of time, and are associated with at least some amount of impairment. Some survivors with elevated symptoms of distress may not have symptoms of sufficient severity or with sufficient associated impairments to qualify for a particular diagnosis, and others may have severe symptoms that simply do not coincide with the patterns derived from study of mental illness. For a complex diagnostic category like posttraumatic stress disorder (PTSD), the correspondence between symptoms and diagnosis can be particularly difficult to discern since the diagnosis requires not only a particular constellation of symptoms, but also evidence they are all associated with a specific past event and cause current functional impairments. Evidence of higher levels of posttraumatic stress (PTS) symptoms from surveys of childhood cancer survivors may not indicate these survivors have higher rates of posttraumatic stress disorder, and the proportion of survivors who are found to have higher than expected PTS symptoms varies widely depending on how the constellation of PTS symptoms is defined [9–11].

Both investigators and clinicians intentionally adopt a symptom focus rather than mental disorder focus, in part to insure a broad assessment of survivor functioning. Following recommendations from the National Comprehensive Cancer Network (NCCN) [12–14] and others [15, 16], psychological and behavioral symptoms that cause subjective distress are assessed and targeted for intervention, whether or not a psychiatric diagnosis is present. As we discuss in assessment and intervention sections below, clinicians working with long-term survivors should not expect that all of those who report symptoms of psychological distress will have a psychiatric disorder or necessarily require mental health treatments. As we highlight below, understanding factors associated with poor psychological adjustment in survivors can help providers focus on those survivors who are at highest risk.

17.2.2 Quality of Life

Studies of quality-of-life (QOL) in cancer survivors generally focus on health-related QOL, a concept that aims to reflect the impact of health on the individual's functioning in physical, emotional, and social domains [17, 18]. Given their risk for medical late-effects described in previous chapters in this book, and their risks for psychological and social challenges described here, it should not be surprising that childhood cancer survivors also report impairments in their QOL, particularly in physical health domains [3, 19, 20]. Compared to their siblings, survivors in the CCSS have lower average scores for QOL in the physical but not emotional functioning domain [19]. Differences between mean scores for sibling and survivor groups were not large and survivors' scores were only slightly lower than expected population norms. However, when the proportion of individuals with very low QOL scores was examined, a large proportion of these survivors showed significant impairment in problems related to fatigue (47 % of females and 32 % of males compared to the 16 % that would be expected in the general population [19]). This was similar to findings from the British Childhood Cancer Survivor Study (BCCSS) which also reported a higher than expected proportion of

survivors with very poor physical health functioning [20]. Similarly, in a CCSS study examining health problems that interfere significantly with activities of daily living, 12 % of survivors compared to only 2 % of their siblings reported these problems [4]. Survivors were also significantly more likely to report limitations in their physical activities and general health [4, 9, 21], compared to controls [4, 19].

17.2.3 Social Adaptation and Functioning

Although many childhood cancer survivors are able to adapt and experience success within the domains of school, work, and interpersonal functioning, there is evidence that childhood cancer survivors can experience a number of medical, neurocognitive, psychological, and/or physical challenges that can impair their ability to attain developmental milestones [22]. There are circumstances in which even relatively minor changes in neurocognitive functioning can have a significant impact on a survivor's adaptation and can increase their risk of psychosocial issues. Learning difficulties, combined with the symptoms of depression or anxiety, can create even greater barriers to success around social roles and have a negative impact on school performance, employment, and interpersonal relationships. Beyond learning issues, the ongoing medical follow-up needed and the real possibility of additional medical problems are other stressors survivors are managing in the context of trying to maintain "real world" expectations.

The literature has highlighted the neurocognitive issues associated with treatment to the central nervous system (CNS) and readers may refer to the other chapters in this book that address this more throughly. Patients who have received radiation therapy or intrathecal chemotherapy may be at greatest risk for learning difficulties. The CCSS data has indicated that the utilization of special education services has been significantly higher for survivors (23 %) when compared to sibling controls (8 %). Patients with brain tumors, Hodgkin lymphoma, and leukemia, and patients diagnosed before the age of five, were identified at greatest risk for needing special education services [23]. These findings are similar to the results of a Canadian cohort study in which survivors were reported as more likely to be retained, needing special education programs, and having educational/school problems when compared to controls. Patients who had been treated for CNS tumors, leukemia, and neuroblastoma were identified as groups with significant risk factors around educational achievement [24].

Given the issues many cancer survivors experience as a result of learning deficits or ongoing medical concerns, it is not surprising that finding and maintaining employment can be a challenge. While this is addressed in more detail in Chapter 24 of this book, briefly, the issues survivors experience around securing employment can be associated with physical health difficulties [25] or neurocognitive issues. Results from the CCSS indicated that survivors with poor physical health were eight times more likely to be unemployed than healthy survivors, with health related concerns reported as the barrier to employment [26, 27]. The risk for unemployment increases in relation to the chronic medical conditions experienced by survivors post-therapy and this is particularly important given that 73.5 % of the CCSS survivors reported at least one chronic medical condition 30 years after cancer diagnosis [28]. Unemployment also has significant implications for health care access given that in the United States health insurance coverage is typically attained through one's employer. Data from the CCSS has shown that survivors are more likely than siblings to have difficulty acquiring health care coverage [29] and to have Medicaid or Medicare as their insurance carrier. Lack of insurance can significantly impair a patient's ability to receive appropriate follow-up care and the additional stress associated with limited access may increase vulnerability to psychological distress.

The multifaceted issues faced by survivors of childhood cancer can also have an impact on interpersonal relationships. It is not unusual for survivors to report difficulties associated with social relationships, dating, and a lack of

Table 17.2 Case example: Jenna, a 26 year-old osteosarcoma survivor

Medical History: Jenna's osteosarcoma was in her left arm and required surgery, radiation, and chemotherapy.
Psychosocial Adaptation: At 26, Jenna has returned to the U.S. after living abroad as an aid worker. A driven and high achieving High School student, she won a scholarship to a prestigious college but dropped out after her first year. She spent the next five years working in a variety of human services jobs eventually completing her college degree overseas and joining the Peace Corps. Now she is taking pre-medical courses at her original college and hoping to enter medical school next year. According to Jenna, she arrived at college and hated it. "I had seen a lot of life you know in the cancer hospital and I did not want to sit around reading poetry with a lot of privileged kids. I knew life could be short and I wanted to get out and *do* something, and working in shelters and soup kitchens felt much more real to me. A lot of people feel the same way in college, but maybe I felt it more and I knew I could do something about it. Cancer gave me the courage to do something different. It is not that I think it made me stronger than other people—I think everyone has a lot of inner strength—it's just that I had been tested so I *knew* my strength at an early age. That's what let me take this crazy and great ride across the world and back. No one can believe that I am back taking the same science classes I dropped out of eight years ago, but here I am. Probably without the cancer, I would be a doctor already by now. It would have saved a lot of time, but I know so much more about myself and the world and why I want to be a doctor now than I ever could have at 18."
Comment: Jenna's experiences illustrate the increased sense of "inner strength" that many survivors attribute to overcoming cancer. Jenna appreciates both how the cancer experience complicated her life course and it enriched it. Interestingly, Jenna does not think the cancer strengthened her as much as it made her aware of her inner strengths.

intimacy. The social challenges can lead to subsequent delays around psychosexual development, independence, and identity. In a study of Dutch survivors, those with slower psychosexual development were more likely not to be married and those with slowed autonomy were less likely to be living independently. As with other studies, brain tumor survivors were identified as a high-risk group and documented as being more likely not to meet developmental milestones according to a typical trajectory (Table 17.2) [22].

A number of large cohort studies have identified childhood cancer survivors as being less likely to be married when compared to the general population [30, 31]. As with other social adjustment data, survivors of CNS tumors are at greatest risk for not becoming married. Late effects of radiation, such as short stature, neurocognitive deficits, and poor physical functioning contributing to marital status [32]. Issues associated with neurocognitive functioning and the ability to live independently clearly impact ability to marry [33] as do physical functioning limitations/restrictions [34]. Interestingly, of those survivors that do marry, divorce rates do not significantly differ from the general population [35].

In social and sexual relationships other than marriage, survivors of childhood cancer can also experience a number of obstacles, frequently based on disease burden [36]. Issues associated with potential sexual dysfunction secondary to cancer and its treatment pose significant barriers to intimate relationships and create a potential vulnerability to anxiety and distress. In addition, for those who are able to develop intimate relationships, the issues associated with possible infertility as a result of cancer treatment create another obstacle. It is not uncommon for young adult survivors to have questions regarding their sexual functioning and fertility, and to need assistance with communicating concerns to their partner. This is an area that can be particularly difficult to broach with a medical provider, but if left unaddressed, can lead to significant psychological distress and the potential loss of a relationship.

17.2.4 Risk Factors

Given that only a minority of childhood cancer survivors will be expected to have significant psychological late effects, many studies have attempted to identify important risk factors for psychological distress in this population. Since the relevance of specific risk factors can vary across types of cancer, age groups, and even social and cultural contexts, an exhaustive treatment of risk factors is beyond the score of this

Table 17.3 Factors associated with adjustment problems after childhood cancer

Personal factors	Disease factors	Physical factors
Female gender	Brain tumor or CNS-directed therapy	Poor health status
Pre-existing conditions—mental illness, functional limits	Prolonged or intense treatments (e.g., bone marrow transplant)	Chronic medical conditions
Limited education or income	Cranial or pelvic radiation	Pain or disfigurement
Lack of social support	Residual disease/recurrence	Functional limitations (e.g., ambulation, communication)
Life stressors (e.g., divorce, unemployment)	Problems adjusting or adhering to treatment (e.g., medication non-compliance, substance abuse, extreme emotional distress)	Difficulties in self-care (e.g., dressing, eating, bathing)
Disabled status		

chapter. Instead, we present an overview of the risk factors most important for understanding and assessing childhood cancer stress along with our interpretation of the ways in which these factors may influence development and adaptation in individual survivors. Risk factors can be an important guide to assessing and monitoring survivors, however, it is important to appreciate that the course of cancer survivorship is dynamic and individuals who may initially present with no risk factors require ongoing monitoring and evaluation as their risk status and emotional outcomes can change significantly over time (Table 17.3).

In terms of demographic factors associated with psychological adjustment, female survivors have been found to be more likely to report psychological problems [3, 4], a finding consistent with studies in normal populations [37, 38], suggesting that females may be more vulnerable to distress or more willing to report psychological problems when they occur. Other demographic variables such as lower income, lower education, disability status, and unmarried status, have been associated with poor psychological and QOL outcomes in a number of studies [4, 19], but it is important to note that these factors may be both the result of poor psychological adaptation, as well as contributors to it. For example, depression would be expected to impair functioning in a way that makes it difficult for survivors to function in work and school environments, while problems with work and the stress of low income would also be expected to contribute to depression [39]. Although the precise relationship of these sociodemographic variables with psychological adaptation may not be known, their relationship with adaptation problems makes them important indicators of groups of survivors who should be considered at higher risk. Background factors or pre-existing conditions such as psychiatric history and pre-morbid functioning are important to consider, as these are known or suspected to be associated with poor outcomes after cancer. Similarly, extreme emotional or behavioral reactions that occurred during treatment suggest increased vulnerability to future psychological distress and should be considered risk factors for future adjustment problems.

Specific aspects of a child's cancer and cancer treatments are also thought to increase risk for long-term psychological adjustment problems. Conceptually, we would expect intensive treatments to result in later adjustment problems if these treatments increase distress or developmental disruption during treatment, disrupt the ability to learn or acquire certain skills, or increase the risk for medical late-effects including cognitive limitations, physical limitations, physical disfigurement, secondary cancers or chronic conditions—and there is data to support this expectation. Within cancer-related factors, a brain tumor diagnosis is one factor consistently found to be associated with psychological symptoms, poor functional outcomes, and poor QOL [3, 8]. This association is likely due in large part to the negative impact that CNS

tumors and associated treatments can have on learning, educational, and social skills later in life (described below). Survivors of bone tumors have also been found to be at higher risk for psychosocial problems in some studies, which may reflect the impact of physical mobility problems and pain on both physical and emotional quality of life [40]. Radiation therapy which can disrupt normal development of treated areas in later life has been associated with psychological problems, poor functional outcomes, and reduced QOL, though the effects will be different across types of radiation and types of cancers [3]. Cranial radiation, for example, can cause neurocognitive late-effects and growth deficiency, while pelvic radiation can also cause problems with growth, as well as mobility and fertility; radiation to each of these fields have been found to increase risk of adaptation problems later in life [3, 41]. Similarly, chemotherapy generally, especially in intensive chemotherapy regimens, has also been associate with greater likelihood of impaired QOL and psychological functioning [4, 42, 43]. Age at diagnosis might be expected to affect risk of long-term psychosocial complication since it could affect both the child's experience of treatment, disruptions to their developmental course, and their sensitivity to the effects of specific treatments. Several studies have not supported relationship between age of diagnosis and later adjustment [8, 19], indicating no particular age group should be considered to be at increased risk. Nonetheless, clinicians working with individual survivors should consider how age at time of treatment may affect survivors differently. For example, those diagnosed at younger ages may be less likely to recall their treatment and less likely to identify as "survivors" than those diagnosed in their teenage years [44].

As noted, the effects of childhood cancer treatments on later psychological functioning may be due, in part, to their effects on long-term physical health, and poor physical health functioning has been noted to be strongly associated with poor psychological functioning in this population. Survivors with multiple medical problems have been found to report more psychological distress [19, 45], and a study of suicidal ideation among survivors [8] showed that poor health outcomes, including pain, are associated with greater likelihood of reporting suicidal ideation even after adjusting for depression. Survivors with poor physical health were also noted to be less likely to be employed, married, or have medical insurance, and more likely to have low educational attainment, and at least one major medical condition [19]. This, too, is consistent with previous research showing that medical problems, especially chronic conditions that are likely to interfere with routine functioning, are associated with significant psychological morbidity. Childhood cancer survivors are vulnerable to a number of medical late-effects (described in previous chapters) which would be expected to carry this kind of psychological burden as seen in other groups. In particular, physical symptoms that lead to loss of important aspects of individual identity—sexual dysfunction, problems with bladder or bowel control, as well as disfigurement, fatigue, and cognitive changes—can be particularly burdensome and lead to increased psychological distress. Similarly, the loss of independence associated with not being able to participate in age appropriate activities or work, or any condition that limits independence should be considered a likely risk factor. Because survivors are likely to be diagnosed with chronic conditions at a much younger age than their peers [28], they may have fewer coping resources and their educational, career, and relationship plans may be more vulnerable. Developing a chronic condition while still young, many survivors feel unfairly burdened, a sentiment sometimes expressed as "I am too young for this!" Some survivors find the diagnosis of a treatment-related condition extremely anxiety provoking, raising fears that they may be never feel at ease with their health again, especially if the new condition is chronic and unlikely to be cured. "It's not over when it's over," is a phrase commonly heard from survivors expressing a feeling of resignation that they are still not free from the negative impact of cancer despite having been cured of their disease.

17.3 Vulerable Periods and Populations

17.3.1 CNS Treated Survivors

The literature has focused on identifying survivors of childhood cancer who are at greatest risk for psychological distress, and though findings can be inconsistent, survivors of pediatric brain tumors are consistently noted as a high-risk cohort for psychological morbidity. The significant burden of disease location, treatment intensity, and treatment toxicity all contribute to this finding. The neurocognitive, physical functioning, and medical issues that can arise from having a brain tumor can be significant and the types of issues experienced relate to diagnosis and tumor location. Surgery is the most optimal choice of up-front therapy for children with brain tumors and the extent of resection attained has been related to cure of disease [46]. While many surgeries are successful and patients experience minimal to no post-operative complications deficits, there are a subset of patients who have neurological impairments either as a result of the tumor pressing on important areas of the brain pre-diagnosis, due to the surgical resection itself, or complications from surgery. Although we have mentioned throughout the chapter that those survivors treated with more intensive treatments are at greatest risk for the development of medical, physical, and emotional difficulties, research has demonstrated that even patients who are treated for brain tumors with surgery as their sole form of treatment have been identified as having impaired IQ, academic achievement, and adaptive behavior as compared to the normative population [47] and have high utilization rates of special education services (Table 17.4) [48].

Table 17.4 Case example: John, a 27-year-old brain tumor survivor

Medical History: John was diagnosed at the age of 8 and underwent a partial resection of a midbrain tumor followed by radiation therapy. At the age of 11 he developed a seizure disorder requiring ongoing medication. His neurocognitive profile demonstrates Average IQ, with variability in performance. Significant problems with impulsivity, organization, processing speed, and memory were noted.
Psychosocial Adaptation: John attended a high school program which emphasized vocational instruction as well as independent living skills. John graduated from the program at 22 and secured a job working in the culinary field. He was extremely proud of his employment status, but clearly challenged by the demands of working in a fast-paced environment and interacting with customers. John was able to live independently, but required supervision from his parents around finances. He had some close friends and dated, but had significant insecurity about his neurocognitive status. With his family and medical providers he would frequently ask if what he said was "dumb" or he would apologize for asking questions. John viewed his brain tumor history as a significant barrier, stating "why would anyone want to spend time with me?" or "once someone finds out the truth about me they will leave." His dissatisfaction with his social functioning at that time often led to thoughts of suicidal ideation with no plan or intent. John consistently presented to his brain tumor follow-up appointments with symptoms of depression and was treated with antidepressant medication and psychotherapy in the community. At age 26, John began to experience sudden and progressive hearing loss secondary to his radiation therapy. This was extremely upsetting to him and he began to experience significant anxiety associated with his overall well-being, asking "am I going to go blind too?" At the same time he experienced two additional losses, first when he was laid off from his job and then when the girl he had been dating terminated the relationship. In response to these multiple stressors, John attempted suicide by overdosing on a number of his medications. Subsequently, he participated in an intensive day treatment program and was followed closely for individual therapy and psychopharmacology. He had to move in to his parent's home in order to be adequately supervised, and was able to secure part-time employment in a job, but reported low job satisfaction and though he continues to attempt dating through dating websites, he continues to feel somewhat hopeless about finding a romantic relationship.
Comment: This case demonstrates how the dynamic relationship between medical, neurocognitive, and psychosocial issues can severely impact quality-of-life. For John, the cumulative stress of medical late-effects that impaired his cognitive and social functioning contributed to frustration and a profound sense of isolation. With much effort on his part and ongoing support from his parents, he was able to function relatively independently. In the face of new medical complications, and additional losses however, he became acutely distressed and suicidal, and subsequently had difficulty returning to his previous level of functioning. This case highlights the fragility of some survivors' adaptation after cancer, and the potential impact of worsening medical condition of psychological functioning.

In addition to the challenges posed to patients as a result of surgical intervention, the actual location of the tumor and the tumor diagnosis are of great significance in terms of survival and quality of life. For instance, craniopharyngioma is a tumor with a high cure rate and these patients tend to be treated with surgery and/or radiation therapy. While a curable disease, the location of this tumor comes with significant morbidity [49]. Survivors must cope with memory issues, sleep disturbance (narcolepsy), mood issues, and certain endocrinopathies, such as hypothalamic obesity that can severely impact physical appearance. These are patients who are seen in the clinic setting for whom it may be difficult to find an appropriate school placement due to the complex learning, medical, and behavioral issues experienced. It is not uncommon for families to report to clinicians the need to lock kitchen cabinets due to insatiability associated with the disease. The psychosocial challenges facing these survivors such as significant academic needs, physical appearance changes, behavioral issues that impact social functioning, and fatigue that can negatively impact employment, leaves this subset of patients at a particularly high risk for developing depression and/or other psychological adjustment issues.

In addition to tumor location and diagnosis, the treatment utilized for CNS tumors such as cranial radiation, intrathecal chemotherapy, and high-dose chemotherapy with stem cell rescue, increase the number of learning, physical, and medical problems [23, 24, 50] and leave survivors vulnerable to psychological distress. The effect of multiple medical issues is dynamic and can have a negative cumulative impact on psychological adaptation over time. For instance, school-aged survivors who struggle academically despite receiving special education services are at-risk for depression and anxiety. It is not unusual to hear of patients spending 4–5 hours on homework a night as a result of slowed processing speed. The time spent on homework and the stress associated with academic success can leave survivors with anxiety and significant social isolation. These students are then ill-prepared to manage the social demands at the higher education level and tend to experience failure when they transition to college. Such failure can lead to disappointment, feelings of helplessness and hopelessness, withdrawal, and subsequent depression. There are other situations in which patients have difficulty accepting the help that they need and continue to struggle with their academics and psychological adjustment, despite schools and teachers being willing to accommodate their learning needs. The "rejection of help" can have a cumulative impact on mood and self-esteem over time and set survivors up for failure as the academic demands increase in later grades. For instance, one pre-teen survivor felt so strongly that she did not want to be different from peers that she insisted on completing all the homework that was assigned to the class. She presented with significant anxiety, stress, and low self-esteem, and due to the hours she was spending on homework, she was also socially isolated. This situation occurred despite the fact that she had a special education plan that provided homework modifications, supportive teachers, and strong parental advocacy. Her unwillingness to accept help was the barrier to success.

For CNS survivors who are young adults, the challenges around finding employment, social difficulties, and/or an inability to live independently increase the number of risk factors for psychological distress and affect survivors' ability to meet age-appropriate developmental goals. Implications of the neurocognitive limitations on education, employment, and independent living can be significant as highlighted in a study of 1,101 adult survivors of pediatric brain tumors that reported that 26 % were unemployed, 74 % were unmarried, and 28 % had incomes of less than $20,000 per year [23]. As mentioned previously, low income and minimal social support are risk factors in the general population associated with psychological distress. There are also minimal resources available to help these young adult survivors. Many of them do not meet the eligibility criteria to attain services through state agencies, so they tend to have limited options in terms of supportive services to help ameliorate the stress associated with medical and social challenges. Resources at the end of this manuscript

provide the practitioner and their patient with those support networks and systems that are available.

On top of the issues around learning and adaptation, survivors of pediatric brain tumors often experience a number of medical issues that can lead to significant limitations in meeting goals and ongoing challenges associated with psychological adaptation to chronic illness. The very real worry regarding disease recurrence or secondary malignancy risk can lead to anxiety issues that can impede a survivor's overall functioning. In addition, as survivors get older, they are faced with additional ramifications of their disease and treatment that may not have been particularly salient at earlier developmental levels. Research has demonstrated there are numerous factors associated with treatment, tumor histology, and tumor location that can contribute to the incidence of seizures, even many years after the completion of treatment [51]. The impact of a seizure disorder can be significant for overall psychological adaptation and research in patients with seizure disorders has shown an increased risk of suicide ideation [52]. As medical and adaptive difficulties accumulate, CNS survivors can experience changes in their ability to cope and subsequent psychological problems that make survivorship all the more challenging over time.

17.3.2 Bone Marrow Transplant Survivors

The process of going through bone marrow transplant can be extremely stressful for patients and families. In order to understand this at-risk group, it is important to recognize the context in which survivorship has occurred. The consent process associated with bone marrow transplant is extensive and reviews the multitude of side-effects that can occur during the treatment and following the treatment. These side-effects include hearing loss, infertility, renal failure, cardiac dysfunction, growth and gonadal failure, secondary malignancies, neurocognitive delay, and possible death. Discussion of the potential risk of death is part of the consenting process and indicates the intensity of the treatment and the potential psychological trauma that can result for both patients and parents. The stress associated with finding an appropriate donor and in some cases, identifying sibling donors, makes this treatment even more challenging for the family as a whole. Moreover, once patients make it through the actual treatment, there are a number of restrictions, including social restrictions that can be in place for up to 6 months. During that time frame, patients are seen frequently for medical appointments, take multiple medications, and are not able to attend school. These patients are at-risk for a number of medical conditions, including graft-versus-host disease (GVHD), which is reviewed in Chap. 13.

Given the intensity of the treatment, the significant limitations placed on daily functioning as a result of the treatment, and the very real possibility of disease relapse despite the treatment, it is understandable that survivors of bone marrow transplant are a cohort of patients who may be at-risk for increased psychological distress. With that being said, there is literature that demonstrates that survivors of bone marrow transplant have a good health-related quality of life (HRQOL) 4–12 months post-transplant and HRQOL that is similar to population norms 6 months to 8 years post-transplant [53]. There are also studies that show that HRQOL can be significantly lower for BMT survivors when compared to healthy siblings [54]. Parental coping is understandably associated with child adjustment [55] and the literature has also noted that parental psychological adjustment to bone marrow transplant can follow a similar course to patients. Parents may experience elevations in distress during the acute phase of transplant, but the distress typically resolves approximately 4–6 months post-transplant. Families with lower socioeconomic backgrounds have been noted to be at increased risk for psychological distress [56].

While the literature is inconsistent, there are certain cohorts of patients who have received bone marrow transplants who may be at increased risk for psychological distress. Similar to the CNS survivors, BMT survivors are coping with the cumulative effect of their intensive treatment in

terms of long-term medical problems. For those who are dealing with debilitating side-effects such as GVHD and its treatment, quality of life certainly can become an issue. Results from the Bone Marrow Transplant Survivor Study (BMTSS), indicated that active chronic GVHD was associated with somatic and global psychological distress. Patients treated with prednisone for the management of chronic GVHD demonstrated elevations in psychological distress across all domains [57]. The use of corticosteroids has been shown to be associated with increased rates of depression in the general population, as well as other chronically ill populations [58].

Patients impacted in ways that affect physical appearance or that severely limit physical functioning are certainly at higher risk for quality of life difficulties and psychological distress. In a study using data from both CCSS and BMTSS, survivors of bone marrow transplant were more likely than sibling controls to have severe/life threatening conditions, two or more medical conditions, functional impairment, and activity limitations. These findings were also consistent when bone marrow transplant survivors were compared to other childhood cancer survivors [59]. Ongoing medical issues, pain, fatigue, and/or physical functioning deficits are barriers to employment and meeting appropriate developmental milestones. The BMTSS showed that low annual income amongst the survivors was associated with global distress, anxiety, depression, and somatization [57].

17.3.3 Periods of Vulnerability

While physical and psychological adjustment often improve after completion of cancer therapy and survivors return to "normal life," subsequent life periods and transitions can be associated with greater vulnerability to psychological distress and adaptive problems. From a developmental perspective, Erikson's theory of adolescent development [60] provides a useful framework for understanding how each new developmental period provides opportunities for reworking unresolved issues related to cancer. As cognitive capacities increase and social relationships change, the survivors may be prompted to think about their cancer experience in new ways. For most survivors, this reworking of the cancer experience may be subtle and lead to a sense of growth, but for others there is the possibility that aspects of the cancer experience may reemerge later in life to promote maladaptation and the development of symptoms. Most survivors will pass through these vulnerable periods (summarized in Table 17.5) without excessive problems, but these are considered to be times during which survivors, including those who had a sustained period of healthy recovery and good psychosocial adjustment, are at risk for new problems with psychological adaptation.

For some survivors, the completion of therapy itself is an unexpectedly stressful time. Survivors who are greatly relieved to complete their medical regimen, may also feel some anxiety at being let loose in the world with less medical oversight, and some uncertainty at leaving the "patient role" to take up the regular expectations of school and

Table 17.5 Common periods of vulnerability

Life transitions
• Transition off-treatment
◦ Decreased contact with medical professionals
◦ Greater integration with home and school routines
◦ Increased expectations/loss of special status
• Move to a new environment
◦ Loss of special status
◦ Questions about disclosing cancer history
• Career changes
◦ Questions about insurance and employability
• Developing Intimate Relationships
◦ Questions about disclosing cancer history
◦ Concerns about body image, sexuality and fertility
Health related
• Medical care and information
◦ Regular medical follow-up/surveillance
◦ Illness in friends/family
◦ Notable cancer-related media event
• Physical health changes
◦ Change in health status or functional status
◦ New diagnosis of medical condition
◦ Recurrence of cancer or secondary cancer

Table 17.6 Case example: Tina, a 23 year-old lymphoma survivor

Medical History: Diagnosed at age 14, Tina had a long course of treatment, which included radiation and chemotherapy and lasted for much of her high school years. She relapsed at age 16 and needed a stem-cell transplant.
Psychosocial Adaptation: At 23, Tina is returning to college after dropping out and being dismissed several times. Despite being extremely bright and an excellent student in High School, she had a terrible time adjusting to college, something she attributes to her cancer experience and its aftermath. "I was not really depressed or anything during my treatment, I was a pretty happy camper considering, but I look back and think of that time as my 'lost years.' When I got sick and left school everyone was starting to play spin the bottle, and when I got better and came back it was like everyone was dating and having sex—I couldn't figure out what I missed and couldn't figure out what I was supposed to do about talking to other kids much less dating. College was a total disaster. I went from being in a protective bubble surrounded only by doctors, nurses and my family, to being dropped in a huge college campus that was like one big frat party. I couldn't relate to anyone but drinking and drugging turned out to be a great way to break the ice and try to fit in. I know I am not the first person to screw up in college—believe me I knew all the other screw-ups, but I see now that cancer really messed with my adolescence in ways I never understood and it really set me up to fail in college." Eventually Tina left college, was treated for depression and found a job at which she excelled. With 2 years of job and personal success under her belt she is returning to school more confident and happy than she has felt in years. "Now I know who I am, what I want, and what I am doing at school."
Comment: Tina's case demonstrates the extent to which a prolonged illness can effectively remove a child from the normal social and developmental context. Even as Tina coped well with the challenges of her treatment, her social and psychological development was significantly disrupted, though this would become evident only when she returned to "normal" life. Perhaps because of her long treatment and the extended period of isolation after her transplant, Tina's difficulties with readjustment were more significant than for most survivors. While experimenting with alcohol and drug use is not uncommon in young adults, Tina ties her substance use to feelings of isolation due to her illness, and her medical treatments may leave her more vulnerable to the health effects of alcohol and drug use.

society. In some cases, survivors and their families speak of treatment as being such a central focus of their lives that it is only after completion of all medical treatments that they really process some of the emotional components of the cancer. This may lead to an increased sense of loss or depression. If the survivor has had a long treatment period during which they interacted predominantly with adults, they may feel ill-at-ease with peers and unfamiliar with the latest trends within their peer group, and this too may increase feelings of isolation and depression. For many young cancer survivors, the experience of returning to their regular school or peer group can feel bewildering, as they move from a context where they are a focus of intense attention and concern, to being just one of the crowd. For young children, this loss of special status may present in the form of behavioral problems (e.g., defiance, tantrums, withdrawal) as they resist the reintroduction of expectations and consequences that may have been suspended during the illness. For teenagers, problems in this transition period can include feeling isolated and misunderstood (Table 17.6).

Many survivors welcome an opportunity to move to a new school or living situation where their cancer history is not widely known as they feel it helps them move past being "the kid with cancer." For others, however, moving into a new environment means having to give up a special status they may not have recognized they had, as well as new concerns about how and when to talk about their cancer history. As one 22 year old survivor John, recalls:

> "When I got to college I was just one of a sea of new students. I thought that would be great, but the work was really hard, and I started to realize I wasn't prepared. My teachers and tutors in High School had cut me a lot of slack because of my cancer, and suddenly that help and support was all gone. Then when I tried to get to know people it seemed like cancer always came up. What sports did I play, what was that scar from—inevitably I had to keep "coming out" as a cancer survivor and that was weird. At home everyone knew me and I had never once had to tell anyone I had cancer, but in college I was on my own and some people had really weird reactions. It became a big problem for me adjusting to college and I ended up seeing a counselor first at the cancer center and then at school."

Developing intimate and sexual relationships presents challenges for most young adults, and in addition to all these expectable challenges, some survivors will need to confront ways in which

their body image, sexual function, or fertility have been affected by cancer. Even in the best of circumstances, when these issues are talked about openly as part of treatment and follow-up care, survivors who are entering into a new romantic relationship have to take new risks such as talking with their partner about their concerns, or possibly seeking medical consultation about sexual function or fertility. Other major life changes can also prompt some new reflection about their health and questions of whether their cancer history can be a liability. For example, taking on a major new job role, or becoming a parent can be a time that survivors find themselves worrying or reflecting on their health. As one survivor put it:

> "I never really thought much about my cancer, but when I got pregnant it all came up. For 20 years the fear that I might get sick again was way in the back of my head, and I did not even know it. Once I found out I was going to be a mom, it all came up and I kind of freaked out. I had to educate myself, see my doctors, and make sure I was really healthy and taking care of myself."

Not surprisingly, new or ongoing medical concerns are a common source of stress for cancer survivors. Close medical follow-up is recommended for most survivors many years after their treatment; these visits, tests and waiting for results can be a source of significant anxiety as well as a catalyst to recalling their cancer treatments or triggering new health anxieties. The impact of some symptoms or limitations may not be fully experienced in the immediacy of the end of treatment, but become more of a problem in the context of later development. For example, a young boy who was happy to be excused from gym in middle school may feel frustrated that he can't participate in team sports in high school, or angry and depressed in college to learn that a manageable medical condition may affect his ability to apply for certain jobs or special training in the armed forces. Because of their intensive medical treatments, childhood cancer survivors are at increased risk for the development of a variety of medical late-effects [28], and any new health problem may be a source of significant anxiety and distress. New physical symptoms, exams to work up suspicious findings, or a new diagnosis may be significant triggers that can spike preoccupation with symptoms, anxiety, fear of cancer recurrence, and sadness. Survivors with new medical complications may need additional education, reassurance, and support from medical providers to understand their new condition and its implications for their health. If the condition is serious, debilitating, or life threatening, such as a diagnosis of a new cancer, survivors may need more intensive support such as a referral for support groups or professional counseling. In addition to personal health problems, learning of a peer's recurrence or even the diagnosis or death of a celebrity due to cancer can have a significant impact, potentially jarring an individual survivor from an otherwise healthy adjustment into a period of psychological distress (Table 17.7).

17.4 Identifying Survivors with Adjustment Problems

Given the various kinds of adaptive problems and psychosocial distress that cancer survivors can experience, we advocate efforts to monitor their psychological adjustment in a variety of settings, including oncology and general medical practice care as well as in educational and supportive care programs. Cancer survivors are often interested in talking about these issues, but often wait for professionals to raise them or signal an interest in hearing about them [61–63]. While the specific methods for inquiring about survivors' emotional health will vary across settings and survivor populations, basic evaluation of adjustment can be integrated into a variety of programs and services aimed at childhood cancer survivors. With knowledge of the common medical and psychological challenges childhood cancer survivors may face, and openness to learning about their experiences, those working with survivors can be prepared to talk with them about their adjustment and quality-of-life. Using this information, simple, direct questions around the potential areas of distress, like those in Table 17.8, can be integrated into an assessment or evaluation. This approach is not intended as a comprehensive assessment of survivors' emotional health, but rather as a way to "start the conversation" and

Table 17.7 Case example: Don, a 34 year-old survivor of Rhabdomyosarcoma

Medical History: Diagnosed at age 10, Don was treated with intensive chemotherapy which included drugs known to confer risk of long-term heart problems in some patients. He is referred for a psychological assessment in the context of a worsening cardiac condition
Psychosocial Adaptation: Don is an outgoing and charismatic person who has been a successful business man since he started his first business in college. He is single but has a large group of friends and has been active in community organizations. Changes in his cardiac test results were noted by his physicians for several years, though Don has been able to continue in his activities until the past year. Now he is often fatigued, and cannot maintain his usual schedule of work and social activities. He is very worried about the likely diagnosis of heart failure, and feels depressed at the thought he will become "an invalid." He can't believe that "after everything I went through this is what I get!" He is particularly frustrated and angry with his cardiac care, feeling that he is getting worse and no one seems to care. He makes frequent visits to the pediatric cancer follow-up clinic even though he knows the adult cardiology specialists are best suited to help him. Don feels helpless as a medical patient, and notes, "I can talk to anyone, negotiate and wheel and deal my way around a board room or a bar room—why can't I talk to these doctors?" Over a course of a few therapy sessions, Don comes to realize he is treating his cardiac specialists with the same deference and awe he had toward his oncologist at age 10, and is expecting to have his cardiac care plan completely mapped out and managed. Unlike his cancer care which was aimed at cure and followed a highly specific treatment protocol, his cardiac condition is chronic and there is no definitive treatment plan that his care will follow. This realization helps him become more active in his medical care, and he comes to feel more like "himself," as a competent assertive adult. He selects a new cardiologist with whom he feels he can have a good relationship. While he is very reluctant to join a support group for cardiac patients, when he does, he engages very actively and becomes something of a "leader" in the group, eventually using it to help him face his fears of losing the work and other activities that give his life meaning.
Comment: The onset of serious treatment-related conditions can arouse intense feelings for survivors. In addition to the emotional issues facing anyone with a serious medical condition, survivors may find themselves recalling and even re-experiencing some aspect of their childhood illness which can complicate efforts to cope with the new illness. Don's case is remarkable both because he slipped so profoundly into a child's role which increased his feelings of being overwhelmed, but also because he was able to recognize his situation and overcome it so quickly.

Table 17.8 Sample questions to inquire about survivors' adaptation and quality-of-life

• What is it like for you coming back to (school/work/medical environment) now that your cancer treatment is over?
• Overall, how do you feel things are going for you in your life right now? Do you have any questions or concerns about your physical or emotional health?
• Are there certain goals you are working on in your (school/work) or personal life?
• How about your mood and emotional health, how is that going for you? Are you having difficulties with your concentration, sleep, pain, or fatigue that concern you?
• Do you find yourself thinking about cancer frequently? Do these thoughts ever bother you or get in the way with your sense of pleasure, sleep, daily functioning?   ○ Have you ever received any counseling or support for these concerns? Do you ever think you might like to have someone to talk to about these experiences?
• Whom do you talk to when you have questions or concerns about being a cancer survivor?
• As they get older, some cancer survivors wonder if their cancer may affect their sexual health or their fertility. Has this been a question for you?
• Is there anything else about how you are feeling emotionally, getting along at home or at (school/work) that we should talk about?

begin an ongoing dialogue with survivors about their evolving adjustment.

Programs or medical settings that already use some written self-report checklist or medical history forms as part of their intake procedures may also want to include items addressing emotional health, economic, social, and functional status in the assessment forms completed by survivors. Self-report assessment has the advantage of being simple to incorporate into each visit and presenting relatively little burden to providers and survivors. It also insures that these topics are addressed, and "primes" survivors and professionals to discuss these issues. At a minimum, these items would include 6–10 questions about general emotional functioning, including depressed mood, anxiety, feelings of hopelessness and suicidality, as well as other symptoms or functional limitations. Self-report rating scales that have been previously validated can also be important tools for screening cancer survivors. In settings where they are appropriate, such as in survivorship clinics, they may be included as part of an assessment of psychological functioning. Validated rating scales have the advantage of being standardized so that information can be compared to some normative

data that facilitates interpretation and comparison with the general population. However selection of an appropriate measure, as well as scoring and interpretation, often require expertise in implementing this kind of mental health screening in a clinical environment. For example, reliability and validity of tests will vary in different populations, and several studies have indicated that previously validated tests may operate differently or require different cut-off scores to be used in cancer patients or survivors [64–66].

Whenever written assessment is used, reviewing responses and discussing them directly with the survivor is essential. By way of introduction, a provider may simply ask, "When you completed the questions about mood and emotional functioning, did any of those questions seem to apply to you?" The provider can then quickly scan the responses to the self-report items and inquire about any that were endorsed. Assuming that no significant emotional issues were raised, a final question, such as, "Is there anything else about how you are feeling emotionally, getting along at home or at work that we should talk about?" may help to encourage reticent survivors to bring up any other emotional concerns, or to close the topic and provide a segue to the next area for discussion.

Ongoing monitoring of psychosocial adjustment can be helpful to all survivors, and should be incorporated into routine survivor care, both as a means of identifying survivors in need, and of communicating to survivors that their psychosocial well-being is important and will be attended to if they begin to experience difficulties at a later date. Because survivors' adjustment can change over the course of development, it is important that this kind of assessment be ongoing and available to survivors across the survivorship trajectory.

Depending on the survivor population, between 10 % and 30 % of survivors can be expected to indicate they are experiencing some adjustment problems or emotional health concerns, and they will require further assessment and/or referral to a mental health or medical professional. In talking with survivors about their symptoms, it is important to acknowledge that everyone experiences normal variation in mood, especially during adolescence. Since medical visits can be a source of anxiety, it is important that providers distinguish between anxiety related to a follow-up visit versus anxiety that is more lasting and potentially impairing a survivor's functioning. Assessment should focus on symptoms that are lasting and cause distress or impaired functioning. Because of their risk of medical late-effects, evaluation of depression, anxiety, and other psychological symptoms in childhood cancer survivors should include an investigation of medical conditions or medications that may be contributing. Cancer treatments may have medical late-effects affecting hormonal, cardiac, pulmonary, and neurological functioning, and effects of these systems may be associated with psychological symptoms. Similarly, many commonly prescribed medications may cause symptoms of depression or anxiety, and a careful medication history may reveal possible associations with medications. For some survivors who experience minor adjustment problems, reassurance that their experience is normal may be sufficient to help maintain psychological well-being. Recommendations for self-care, education, and support strategies may also be beneficial. For those indicating more distress formal referral to mental health professionals for further evaluation and treatment is warranted, as described elsewhere in this manuscript.

17.5 Conclusions

As discussed in this chapter, the majority of childhood cancer survivors will have successful psychosocial adaptation after treatment of childhood cancer. However, there are many factors that affect adaptation to the myriad challenges survivors often face years after treatment has ended. The risk factors that have been identified include lower income, lower education level, disability status and marital status, as is being of female gender. Health status is also a major variable, and individuals who experienced more intensive chemotherapy during treatment, who have long-term physical health issues, multiple

medical problems, and pain, and were treated for CNS cancers, are more susceptible to experiencing difficulties successfully adapting to life's transitions. Given these risk factors, providers should be mindful that the long-term follow-up of childhood cancer survivors extends beyond medical needs and includes identifying and responding to psychosocial needs and vulnerabilities.

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Resiliency in Childhood Cancer Survivors: A Clinician's Perspective

18

Frances Wollman Baumgarten

18.1 Introduction

The patients who walk into my office present with a multitude of problems. The survivors of childhood cancer and their parents all have several things in common: they are actively trying to navigate through life after cancer, and develop happy, successful, fulfilled lives, as well as satisfying relationships with each other. Parents are often times confused and taken aback by the presence of problems that may be connected to long-term consequences of the treatments, and they can certainly feel unprepared to deal with them. Survivors frequently are unaware that the symptoms they are experiencing are connected to the side effects from the treatment, and subsequently are not likely to implement the most effective management tools.

As clinicians, our role involves teaching and coaching the survivors and their family members on how to achieve their common goals. The clinical work is a combination of healing and growth. It allows for a safe place to identify and acknowledge the pain, trauma, and struggles of having a diagnosis of cancer, having endured the grueling diagnostic tests and treatment regimens, transitioning from patient to survivor, and dealing with the emotional, psychological, physical and cognitive side effects from the treatments and the lifelong issues of survivorship. All the while, they must encourage the reframe and development of new and appropriate expectations for life goals, and what I later describe as "resiliency." For many parents, psychotherapy is their first real opportunity to process the trauma and pain of having experienced their child suffer through the diagnostic process and cancer treatments. Significant survivor parental discussions include: education on how the cancer treatments have impacted their child's developmental process, issues around their child's self identity, which may now include a self-image of being a cancer survivor, and what meaning and consequences may be attached to that label, the impact of any ongoing physical changes, and how parenting styles and attitudes can be affected by being a family of childhood cancer survivors. Because childhood cancer has an enormous impact on the infrastructure of a family, it can challenge one's parenting notions and values. Working together as a cohesive team (clinician, survivor, parents and family members), we set a framework and put in place tools and skills that these children and their parents can use for a lifetime.

Having worked with children and families for many years, I'm known for my ability to "pull a rabbit out of a hat." I create sessions in which reframing, changing agendas, setting limits,

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handing out homework assignments, playing games, having serious discussions, tolerating lots of tears, pain, yelling, and laughing result in the acceptance of new perspectives and insights. With these creative interventions, and a basic belief that we can accomplish anything, symptom relief is always in the forefront. I am relentless in finding ways to meet these goals and will not settle for less than an agreed upon satisfactory result. My love and enjoyment for my work, these patients and their parents is contagious. The therapeutic interactions that I employ encompass the cognitive attitudes, beliefs, and tools that formulate the basis for the operational definition of resiliency presented in this chapter. These interactions afford survivors and their parents an opportunity to experience and try out new ways of thinking and responding. The more successful these interactions are, the more reinforcing they become outside of the clinical setting.

This chapter is organized to offer a clinically applicable framework in which to discuss the most effective ways of working with childhood cancer survivors and their parents in building and enhancing resiliency. The discussion involves the review of effective treatments and research which addresses the struggles and challenges of survivorship, identifying the protective factors and strengths which are most useful in dealing with adverse life situations, and discussing the theories that propose models for resiliency and adaptive functioning, combined with the wealth of information shared by survivors and family members within the clinical settings.

As clinicians, it is expected that our work is grounded in theory, research, practical clinical experience, and effective treatment strategies. Our success is dependent on our ability to communicate this knowledge in ways that are clear and easily understandable for our patients. In discussing theory and treatment strategies I will try to stay as true to this as possible. Although using jargon is easy to fall into, our task is to translate that jargon into usable, concrete concepts and examples. It is in these easy-to-understand translations and examples that our patients learn the "when" to use and apply tools and skills, the "why" these tools and skills are important and relevant, and the "how" these tools and skills actually improve life. The experience in our clinic of working through an issue in this systematic way through the organization of thoughts, problem solving, and response sets becomes a model that is replicable, for a lifetime, outside of the therapy environment.

18.2 Conceptual Framework

When children are diagnosed with cancer they are forced to deal with medical procedures that reach far beyond any imaginable stress or trauma. Parents are charged with the responsibility of being their child's support system, their safety net, and their protector. At the same time, parents have to absorb the pain and suffering of their child, as well as their own overwhelming emotional pain and fear. For parents, there isn't anything more difficult or heart breaking than feeling helpless in one's ability to make the world safe for one's children. The grueling diagnostic tests and cancer treatments that their children are forced to participate in are accompanied by overwhelming and extreme fear, anxiety, and helplessness, for both the children and their parents.

Mental health providers offer these children and their parents support, tools, and skills to help them manage through this medical crisis. During the active phase of treatment, parents are focused on getting through the treatments with the fewest medical problems and complications, just wanting and waiting for the day that their child is back home safe and sound, alive, healthy, and finished with treatments. Children are grateful for the times and days that they can play and be with their friends again, anxiously awaiting their freedom from doctors and procedures.

As these children and families transition to life after cancer treatments, the challenges and demands change, and goals now involve dealing with the aftermath of the treatments and recovery. The issues and realities of physical, academic, emotional, behavioral, cognitive, and psychological side effects are new areas to be dealt with. Reintegrating back into school settings, peer groups, and activities can be surprisingly stressful

and disappointing, especially after having longed, dreamed, and waited for the freedom to return to life as it was before treatments. In addition, regular medical follow-up visits entailing scans, blood work, and physical exams, as well as waiting for the results, are ongoing stressors that can make recovery difficult and problematic. How well children and their parents are able to navigate through these issues will depend on a concept called *resiliency*. Resiliency is defined by Masten [1] as: "…good outcomes in spite of serious threats to adaptation or development" (p. 228), and by Walsh [2] as "…the ability to withstand and rebound from crisis and adversity…" (p. 1). Additionally, Walsh presents the concept of family resilience, which encompasses the concept that how a family deals with a crisis is "… crucial for individual and family recovery" (p. 1) [2].

When mental health providers work from a resiliency model, they can offer education and guidance which will help maximize the entire family's recovery by assisting them in developing a framework for successful pathways into their future. Parenting a child who has survived cancer treatments involves thinking about parenting in new and innovative ways. With support, education, and skill building, parents can learn about their child's needs, and become empowered to fulfill their desire and need to raise emotionally, academically, and psychologically sound children.

Relevant research in the field of young adult survivors of childhood cancer, which address developmental issues and functionality, helps to increase understandings of the challenges survivors face [3, 4]. In addition, when childhood cancer survivors identify the late-effects of cancer treatments, their struggles, and emotional responses, it elevates our awareness of how young adults identify stress-related long-term consequences of their treatment. However, it is in the narratives, the stories that the survivors and their families share in the clinical setting and in interviews as found in books like *Childhood Cancer Survivors; A Practical Guide To Your Future* [5], where some of the most relevant information is attained.

As families transition from active treatment to survivorship, important parenting questions arise. What do I need to know? What should I be doing? What can I do? When should I ask for help? Where do I go for help? If these questions are not being asked, parents should be encouraged to start thinking in these proactive terms. Childhood cancer challenges parental role shifts from compliance with the medical team, to one of coach, treatment planner, problem solver, advocate, and therapist, in a way that is different from typical parenting. Parents cannot be expected to predict or anticipate academic, social, or psychological difficulties, or how to address them.

Clinicians can play an important role in offering a continual, comprehensive follow-up which provides ongoing support and education, for both survivor and parents, throughout their lifetime. Research by Kazak and colleagues [6] outlines the need for a "developmental trauma" model that follows patients and families from diagnosis through survivorship. Combining research and clinical findings, Kazak and colleagues propose that, "The normative and understandable experience of a trauma reaction after childhood cancer is not always a pathological response or one with singularly negative implications" (p 1102). This developmental model allows for psychosocial interventions aimed as a prevention model "…in an attempt to prevent long-term distress" [6].

18.3 Definition and Benefits of a Resiliency Framework

The goal of this chapter is to offer an operational, working definition of resiliency that is useful and successful for the challenges that survivors and their families face. For this purpose I describe resiliency as a cognitive developmental process involving a combination of attitudes, beliefs, self-talk, and life evaluations of "I can" and "I will" determination. The foundation of this approach can be found in the positive psychology theories presented by Seligman [7] and Dweck [8]. When patients adapt these attitudes and beliefs, their behaviors demonstrate effort and motivation in finding ways to live, enjoy, and succeed to their fullest capacity regardless of the physical, academic, emotional, or psychological

challenges of having endured cancer treatments, and/or the possible lifelong side effects. This includes developing skills that help manage a life that includes awareness, diligence, stress, and worry that is associated with a watchful eye for future developing cancers or side effects.

This working definition encompasses the ability to enjoy things even if you are not the best, to challenge oneself to one's personal best, to be able to see accomplishments that are not fulfilled, the way we had hoped for, as a challenge to try again, or sometimes to be satisfied with what we did accomplish, and to find the things that are good fits for us (which are usually things we enjoy and do well). Resiliency, in this definition, is personally defined by each survivor and each family member. Successful outcomes are found in family systems which develop a general sense of satisfaction in how life is managed and lived. This definition also helps survivors and parents set a framework in which to plan their lives. It can offer a picture of words that is personalized and easy to use. Putting into words these common goals and feelings empowers everyone. Placing control back into a system that had lost all control can be achieved by designing a deliberate and well thought through plan of how to move forward. For many survivors, this can be a launching pad into their new normal life as a cancer survivor.

18.4 Challenges of This Resiliency Definition

For cancer survivors, the challenge of living life with this resiliency definition and reaping its benefits requires: (1) coming to terms with the realities of the cancer experience; (2) being able to reconcile the treatment phase which involves almost complete surrender of any control and being able to identify this time of helplessness as very specific to the treatment demands; and (3) having a strong, realistic, flexible treatment plan which allows for a successful transition from patient to survivor, and the appropriate support systems to implement this plan). The helplessness that encompasses cancer treatments has the potential to be overpowering and life-lasting when it is not framed in a perspective that is cognitively manageable, putting survivors at high risk for depression, anxiety, and the disabling symptoms that accompany trauma.

18.5 Theories and Approaches That Support Resiliency

Cognitive tools that enable survivors to deal with the trauma of the cancer treatments and effectively move through life with a resiliency lifestyle are based in the works of Ellis & Ellis [9], Beck [10], and Seligman [7], and confirmed by such research projects as *Surviving Cancer Competently Intervention Program* (SCCIP) [11].

Rational Emotive Behavioral Therapy, as first presented in the 1950s by Albert Ellis [9], is based on a humanistic outlook that is enriching and self-empowering. It encourages the unconditional acceptance of one's self, others and life, while offering a way to deal with adversity. It encourages choice, high frustration tolerance in light of human frailty and adversity, and re-education rather than removal of symptoms. Using concepts of insight, realistic perspective, reasoning, and logic, people can reconstruct their thoughts and dialogues about their lives and ultimately impact their emotions and behavioral responses. Impacting perceptions of events through words allows the possibility for emotional response to be altered, providing choices for more positive behavioral outcomes [9].

Cognitive therapy, as formulated by Aaron Beck [10], offers a therapeutic model whereby a person's perceptions and thoughts about a specific situation influence their behavioral and physiological reaction. Under stress, thoughts can be distorted, leaving one even more distressed. Being able to identify and evaluate these thoughts while exploring alternative explanations can relieve the emotional and physiological responses of distress and lead to more successful behavioral choices [10].

Martin Seligman [7] uses these concepts as a platform in his development of *learned optimism*. Learned optimism is a motivational skill set that outlines ways to teach optimism to young adults

and children as a way to prevent depression and enhance self-esteem. The first skill set helps children and young adults learn how to see the connections between adversity and beliefs (our thoughts about what is happening that is adverse), and consequences (negative interpretation of the event). The second step involves learning how to dispute the negative thoughts with challenging questions such as: would you interpret these beliefs in the same way for everyone? This challenge allows for the gaining of a *distant perspective*, which lends itself to a process he calls *energization* (new thoughts that help calm the system, reframe and tolerate the adversity) [7].

Carol Dweck, in her book *Mindset* [8], presents a theory outlining how one's beliefs about oneself permeate just about every part of one's life. From how you think about yourself, what you describe as your personality, to whether you are successful or prevent yourself from fulfilling your potential. She proposes that in addition to understanding your personal beliefs about yourself, learning about mindsets helps to understand others too (friends, partners, kids, bosses, and superstars in science, arts, sports, and business.) Ultimately, her goal is to teach people how to improve their lives by understanding their belief system, and changing these beliefs using the mindset skills outlined in the book [8].

18.6 Clinical Application of Cognitive Theories for Survivors

If we accept the undisputable premise that cancer, the diagnostic tests, and treatments are about as traumatic an experience a child and family can have, placing everyone in a vulnerable emotional, physical, and psychological position, the question then becomes: what helps strengthen and secure a solid emotional future for these youngsters and their families? Ultimately, it is their ability to move through the disease process and manage life afterwards, using the very skills that Ellis, Beck, and Seligman so eloquently describe. Of course, the more debilitating the after effects of cancer the more of a challenge this entails.

These cognitive theories offer cancer survivors methods of tolerating, processing, and dealing with the trauma of the treatments and any long-term side effects, while maintaining the ability to function in the world to their fullest capacity. Once survivors learn that they can control their emotional destiny by their internal dialogue, and understand that this internal dialogue of thoughts and perceptions cultivate matching emotional responses, they can be empowered with a choice about how they want to feel and how they want their lives to look. Implementing the behaviors that reflect this life attitude takes time, practice, support, and mentoring. It is difficult enough under normal conditions to make behavioral changes; given the challenges of the disease, this process can feel overwhelming.

Adopting this attitude and life view is extremely empowering and self-fulfilling. With a foundation of insight, acceptance of their experience, realistic plans and goals, acceptance of themselves in realistic terms, and focusing on the future rather than what could have been, survivors can gain control of their destiny, improving their quality of their lives. The ability to learn and use the outlined skills of accepting reality, developing insight, reframing one's thoughts, and challenging one's irrational beliefs, are important emotional and psychological developmental tasks, especially in light of research which suggests that a survivor's perceptions and beliefs about treatment medical events, and its effects can impact their level of psychological distress [4, 12]. For successful outcomes in this area, having strong solid support systems (which include heath care providers, family, and friends) are identified as key factors in emotionally and cognitively managing the disease [13].

18.7 Clinical Challenges of Implementing Cognitive Tools

One challenge for survivors in the use of these cognitive tools is how emotions tend to be labeled negative and positive, and how the display of emotions and reactions to adversity can be labeled weak or strong. Although cognitive

theories address a realistic evaluation of thoughts, life situations, and emotions, these labels are pervasive in the culture, potentially leaving some survivors feeling isolated, embarrassed, and ashamed when they are struggling. During the active phase of treatment, being told you are strong and using powerful superheroes is one method of helping children tolerate the treatments. But, there are times that may feel more vulnerable, and living up to these images can feel like an impossible feat. In addition, even the most well-adjusted childhood cancer survivors can struggle with issues about "why me" and grieve over lost time and the remaining side effects, as well as grieve the loss of other childhood cancer friends who did not survive [5].

Survivorship can present these children and families with the dilemma of living with contradictory thoughts and emotions. It can be very confusing to feel joy and happiness, while also sporting sadness. Learning how to live with what is perceived as contradicting thoughts and emotions requires the realization that these cognitions and their resulting emotional responses can live side by side, and can be managed.

In the clinical setting, families often report that during the active phase of treatment, mood swings are easily accepted by friends and extended family as part of the struggles of dealing with the grueling treatments. However, as the children and teens feel better, start to play, socialize, and reenter their lives in general, it can be interpreted as everything is fine and back to normal, rather than the momentary break that it is. As side effects of treatments become less noticeable, the support of outside friends and family may diminish in both time and understanding of any long term emotional or psychological stress. Therefore, the emotions that linger in survivorship are more difficult to explain and understand. For children and teens, behaviors that may demonstrate these emotions can be misinterpreted as laziness, day-dreaming, defiance, anger, or oppositionality. For the children that look and sound as if everything is fine, it is equally, if not more important, to have a communication system that allows for their inner most thoughts and feelings to be expressed. Adolescence, in and of itself, has its own developmental and social challenges. If stressful behaviors are demonstrated in externalizing responses, for example angry outbursts and defiance, it is easy to recognize and deal with. However, when adolescent survivors "look fine" and appear problem free, we can't assume that they are not distressed or internalizing their sad and disappointing emotions or struggling with issues like body image, self-perception, and social interactions [14, 15]. Survivorship can be complicated and complex and present a confusing picture [5]. Being knowledgeable and respectful of the cancer experience, from diagnosis through survivorship, provides an awareness that highlights the need for evaluating the emotional status of these youngsters, so that if they are struggling, they are not left alone suffering in silence.

During active treatment, behavioral interventions such as hypnosis, self imagery, distraction, and emotive imagery (fantasy) are effective methods used with youngsters to help them tolerate and reduce the pain and anxiety that accompanies grueling cancer treatments [16]. In the clinical setting, we sometimes face a more subtle problem when the very cognitive tools of self-hypnosis and imagination that helped survivors through grueling cancer treatments become the very cognitive processes that isolate them from their peers. We see this happen when children deal with socially difficult situations by isolating, withdrawing, daydreaming, and fantasizing, as a way to retreat to some internal safe place when life feels overwhelming. Although using these cognitive tools can be very helpful in decreasing anxiety or distress from uncomfortable situations, developmentally learning how to tolerate some distress of everyday life and incorporate skills that allow for continued interaction, rather than withdrawal, is essential for positive interactions and relationships.

Observational research on childhood survivor's quality of close friend interactions outlined their vulnerability toward disengagement during stressful play times [17]. Observing childhood survivor's difficulty dealing with uncertain or negative affect situations makes us aware of how this disengagement, if left unchecked, can lead to

social isolation. The research addresses how survivors can struggle with sustaining play periods when they are faced with stressful feelings, and suggests that the subtle differences in peer play may not be as apparent to teachers and parents when questioned about social interactions as is the expression of negative affects [17].

In addition, when we consider the enormous stress on a child's system from tolerating the traumatic treatments, along with long periods of separation from friends and schoolmates, childhood survivors can find themselves returning to situations in which they may be lagging in some social and developmental skills. As clinicians, this is another example of the importance of evaluating these youngsters accurately and meeting them at their emotional level so that we can help them catch up.

One clinical goal addresses re-educating survivors and their families in how they define the emotional pain, memories, and re-experiencing the cancer, from statements such as: "It's all over, therefore, I should feel better and be happy," to learning how healing is a *process*, and how emotions tied to this traumatic experience are normal, and expected to wax and wane at sporadic or seemingly unpredictable times after the completion of treatments. The developmental process of growing up can help by bringing a new light of insight into this earlier experience, new definitions, emotions, strengths, and challenges [18].

Self-identity and peer acceptance are major developmental tasks of childhood and adolescence. In the clinical setting survivors talk about some of the challenges of fitting in after treatments. They have had this life-altering experience that their friends and peers cannot come close to understanding. They describe conflicting feelings of wanting to talk about having cancer, or at the very least some recognition of having had the disease, but of course their peers don't know what to do with the information or how to react. At the same time, they report not wanting to be different. Either way, this dilemma can lead to feelings of isolation and loneliness. The cognitive challenge is one of formulating a self-identity that has an internal dialogue, which reinforces the strength that they possess having had this cancer experience. Understanding that self-identity is now fuller, more inclusive, rather than limited; that is the task. Expanding self-identity to include cancer survivorship as a part, but no longer as the central theme of their identity, allows survivors to focus on other areas of self-identity that can be far stronger and more rewarding. Survivors talk about how helpful it is to have interactions with other survivors, whether in social settings or groups, in order to discuss the issues of survivorship, or simply to just be around peers who understand. These types of connections, even in simple socialization settings, can bring a level of comfort in knowing as you look around the room that everyone understands without having to speak a word.

Recovery, reentering the world after cancer treatments, and moving forward as a survivor has no special delineated trajectory. These challenges can be overcome and mastered, with the exposure and learning experience afforded by the cognitive behavioral theories and approaches described above, and solid support systems that allow for the expression of emotions and thoughts so that these cognitive tools and a resiliency life-style model can be implemented.

18.8 Research Supporting the Use of Cognitive Skills for Survivors

The *Surviving Cancer Competently Intervention Program* (SCCIP) [11], introduced earlier, demonstrates this usage. It is an invaluable tool for providers who want an evidence-based, effective treatment intervention for childhood cancer survivors ages 11–18, and their families. SCCIP targets anxiety, social support, beliefs about the cancer and its treatments, and family communication. Within a group setting consisting of four sessions of adolescent cancer survivors, their parents and siblings, cognitive behavior techniques and family therapy were shown to improve hyperarousal symptoms (anxiety, difficulty falling asleep, irritability, outbursts of anger, difficulty concentrating, etc.) in adolescent survivors. Although SCCIP was used in group settings, it offers a basic framework to be considered for clinical practice.

Based on two decades of research and clinical work conducted in the Division of Oncology at Children's Hospital of Philadelphia, Kazak et al. [6] present a "blueprint" that focuses on preventing long-term distress in childhood cancer survivors and their families through interventions that are evidence-based in research and applied practically in a clinical setting. This "blueprint" integrates the Pediatric Psychosocial Preventative Health Model (PPPHM) and Medical Traumatic Stress Model to differentiate the needs of families and children from time of diagnosis through survivorship. Using a developmental approach for understanding the experience of families spanning the trajectory of childhood cancer allows for the building of interventions that are individualized and appropriate to each family's needs, for example, The Surviving Cancer Competency Intervention Program, as adapted for newly diagnosed patients and their families (SCCIP-ND) [6]. Although Kazak and colleagues are respectful in discussing their experience and results as based in their cancer center; their theories, models of evaluation and treatments offer providers a proactive evidence based approach for prevention and treatment of distress and trauma for our childhood cancer patients and their families.

18.9 Thriving in Childhood Cancer Survivors

Adopting a positive psychology framework, Phipps [19] offers an insightful review of studies of children with cancer who report positive psychosocial adjustment (low levels of self-reported depression, anxiety, posttraumatic stress symptoms, and in general less distress) and how they make use of an adaptive and repressive adaptive style to deal with their cancer. The concept behind the theory of *repressive adaptation* is that repressors tend to think about themselves as well adjusted and act accordingly. Phipps suggests that these childrens' use of repressive adaptation is in part what might account for their lower levels of distress and reported good adjustment. In addition, he reports being unable to find any significant physiological costs to the system in the use of this adaptive style. In this review Phipps sites studies that replicate these findings in long-term childhood cancer survivors [19].

A heartwarming and interesting study exploring how childhood cancer survivors thrive in light of their diagnosis, treatment, and recovery is presented by Parry and Chesler [18]. The goal of this study was to gather information of if and how lives positively changed, how losses are integrated into life stories and how survivors find meaning and transformation after the challenging experience of cancer. Adopting a narrative approach, in open-ended semi-structured interviews, Parry and Chesler had the opportunity to gain rich information that is often not accessible through questionnaires. Participants had the opportunity to explain how they felt, and were able to reflect back on their cancer experience and life since active treatment. The authors addressed how the thriving narrative of the participants was a complete picture of pain, loss and struggles alongside the courage, strength, and wholeness that grew out of their experience. Participants discussed how difficult it was to have cancer, as well as the positive outcomes of psychological maturity, greater compassion and empathy, new values and priorities, new strengths (self-reliance and belief in one's ability to handle life), and the recognition of vulnerabilities and struggles, coping skills, and defining life's meaning. The authors also addressed the opportunity that adults have in helping to shape children and adolescents' interpretation of having cancer and surviving cancer, their self-perceptions, and ultimately finding meaning in their lives.

In this study, as in many others, participants reported the importance of family, social support, and the medical community in their journey through this disease [18]. The reports of feeling loved, taken care of, and hope and belief in the future is touching, and reinforces the importance of these messages throughout the treatment process and cognitive beliefs as a means of tolerating and getting through the harrowing treatments, in addition to the power and meaning that these messages hold as they become a central part of one's future life story.

18.10 Developmental Issues

In looking at these theories and tools as a way to process and deal with having had cancer treatments and all that it entails, developmental stages will determine how best to use these tools. Research has been able to help us identify how childhood cancer survivor's reactions to the treatments differ as they grow from their childhood responses through adolescence and into adulthood. It is certainly no surprise that as children mature, the meaning of having had cancer changes in significant ways, and that for some children as they grow this trauma will have profound effects emotionally, socially, psychologically, and physically [4].

In one study, albeit a small sample of 21 adolescents who had been off treatment the longest, had more negative perceptions about their body image, self-worth, and social anxiety compared to a healthy comparison group of 21 control subjects [14]. Additional research with adolescent childhood cancer survivors (with a mean age of 15 and favorable prognostic indicators) found that although some psychological and body image disturbance were reported, for the most part these youngsters had a vested interest in presenting themselves favorably [20]. Similarly, the adolescent survivors presented with higher social desirability levels (more compliance in social and interpersonal situations) than the control group. The authors suggest that having lived through a cancer experience, survivors may have developed an increased maturity with more adult like coping strategies, use denial as a coping skill, have a desire to avoid conflict, have self-images of vulnerability, and have developed an overall increased tolerant attitude. How well these coping strategies work for adolescents in light of the disturbances they did report are significant developmental issues. Recognizing and understanding the long term impact cancer has on the developmental challenges of adolescence accentuates the importance of early intervention strategies that can prevent, reduce, and halt the development of trauma symptoms and mood difficulties, and use of less effective coping strategies in other challenges they may face. The issue becomes one of not waiting for problems to surface [20].

18.11 Resiliency

General research in the field of resiliency with high risk youngsters consistently identifies important factors associated with resiliency to include: supportive adults that are actively involved in their lives, motivation, achieving some level of competence, and the opportunity to participate in enjoyable, rewarding experiences. Self-regulation and self-esteem are individual qualities often described as important resiliency factors [1, 21]. These very basic needs of all children can be especially challenging for survivors facing long-term effects from cancer treatments. Creative solutions, cognitive tools, and strong supportive networks can add the positive elements necessary to maximize their quality of life.

In exploring a posttraumatic growth framework, adolescents who were at least one year post-treatment and had been diagnosed after age five were found to process their cancer experience with a response set of complex emotions and insights [22]. As they were further away from treatment, their recall of the cancer experience was accompanied by a greater awareness of the struggles they endured during treatment, resulting in some posttraumatic stress symptoms. On the other hand, they also reported a greater appreciation and acknowledgment for how they adapted to the treatments, and for the support and encouragement they received during treatments [22]. This study is enlightening in helping providers understand how adolescents process the cancer experience retrospectively and reinforces the need for using cognitive tools in helping minimize the predictable, typical, normal responses of sadness and grief that accompany any trauma, and even more poignantly, a medical trauma as presented in cancer treatments. In addition, this study offers providers insight into the positive growth that can accompany trauma as survivors get older, and gain distance from the trauma.

18.11.1 Importance of Building Resiliency

There is a significant amount of research that has addressed post-traumatic stress symptoms and/or post-traumatic disorder in childhood cancer survivors and their families [4, 23, 24]. Although resiliency research continues to report that a substantial majority of childhood cancer survivors report few if any emotional or psychological distress, there is a subset of survivors who report significant difficulties [23]. As health care providers it is important to be able to recognize if the symptoms that patients are presenting with are different from typical developmental struggles, or possibly more severe due to cancer treatments. Recognizing these distressed symptoms, and their prevalence in this population, allows for thorough evaluations. Although building resiliency is vital, this cannot be done to the exclusion of addressing real common concerns of depression, anxiety, arousal, fears, phobias, re-experiencing, and avoidance behaviors associated with health care and illness, social difficulties, attention and concentration difficulties, irritability, and anger.

Specific evidence based research studies will be highlighted which explore the issues that affect this vulnerable population subset, as a way to acknowledge the importance of addressing resiliency building for children surviving cancer and their parents, and as a reminder that these difficulties need attention. The majority of the recent studies have been formulated from the work of the Childhood Cancer Survivor Study (CCSS) [25]. CCSS is a landmark multi-institutional project, funded by The National Cancer Institute, involving 26 clinical research centers in the United States and Canada, involving over 20,000 childhood cancer survivors diagnosed before 21 years of age, between 1970 and 1986 and some 4,000 siblings.

One study, using the resources of the CCSS, found that young adult survivors of childhood cancer reported significantly more difficulties than a control group of healthy siblings [23]. In looking at what may account for these differences in this subset, this extensive piece of research suggests that clinical distress, functional impairment, and symptoms of post-traumatic stress may emerge as survivors are faced with negotiating the developmental tasks of young adulthood, especially if they are challenged with late effects of treatments. The researchers also question the possibility that the survivors having the most difficulty did not sustain their participation in the study [23]. It makes clinical sense that anyone having psychological and or emotional difficulties would find it distressing to face their feelings and thoughts in a self-report measure or in interviews. It is also possible that the survivors, who could not sustain their participation, simply did not have the energy or emotional strength to endure the stress that accompanies this type of introspection.

In another report generated from CCSS, data collected from parental reports examined the behavioral and social outcome of adolescent survivors of childhood cancer compared to their siblings. Parents' perceptions were that survivors struggled more in the area suggestive of internalizing difficulties leading to distress that is less noticeable than acting out externalizing behaviors [3]. If these parent assessments are accurate, there is possibly an entire population of childhood cancer survivors who are not being identified as struggling. By not being identified as struggling, these survivors are at risk for developing more intense psychological difficulties around depression and anxiety, especially if their lives present unsuccessful or unfulfilling results. Without this important clinical information, clinicians are at a great disadvantage in helping these youngsters resolve their difficulties, and are further more handicapped in developing preventive steps and interventions for future generations of young survivors. This makes it all the more important for those working with childhood cancer survivors to be mindful of this vulnerable subset of individuals, and regularly screen for internalizing symptoms that may require mental health referrals and intervention.

One such screening tool is the Beck Youth Inventories of Emotional and Social Impairment (BYI) [26], a self report measure designed for youngsters ages 7–18. The BYI offers a comprehensive assessment of thoughts, feelings and

behaviors associated with emotional and social impairment by measuring for depression, anxiety, anger, self-concept and disruptive behavior. In the clinical setting, I find that most youngsters do not mind taking the time to fill out this inventory, are receptive to discussing their answers, and ultimately share clinical information that may have never surfaced otherwise. This clinically rich exchange allows for a deeper understanding of the struggles that these youngsters are experiencing, allows an avenue for them to express and address underlying issues, and offers us the ability to make meaningful interventions.

Research findings by Hobbie et al. [4] support the conclusion that long-term survivors of childhood cancer are experiencing higher levels of distress than had been reported by earlier studies. Furthermore, they suggest that by combining their interview with standard research questionnaires, young adults had an opportunity to describe the illness experience in a way that allowed for reporting of post-traumatic stress symptoms, which under other conditions, might have been underreported. The emergence of post-traumatic stress symptoms as childhood cancer survivors enter young adulthood and its effect on future functioning is important for the medical team to assess, as an intervention for distress as well as a preventive measure to facilitate competence.

Recklitis et al. [27] reviewed adult survivors of childhood cancer responses to a survey question from CCSS on suicide ideation. Analyzing data from CCSS, they report that adult survivors of childhood cancer were at risk for suicide ideation when psychological and most importantly, medical problems were prevalent, even many years after treatment. This report highlights the importance of follow-up medical care to either ameliorate or manage chronic medical conditions. An additional goal of this follow up care is to avoid or alleviate depression and feelings of helplessness/hopelessness that can accompany long term physical challenges. Please see Recklitis & Liptak's Chap. 17 in this manuscript for a more in-depth discussion on the psychological outcome of childhood cancer survivors.

An early retrospective review of suicidal histories of ten pediatric cancer patients ranging from ages 10 years to 27 was conducted in order to identify potential suicide risk factors [28]. Depression, hopelessness/helplessness, and stressful familial events i.e. parental divorce, parental illness, and financial problems, in addition to medical factors were identified as risk factors. The authors concluded that medical stressors alone cannot account for these suicidal events, suggesting the need for more research to help identify the interrelationship between medical and psychosocial stressors for both pediatric cancer patients and pediatric cancer survivors, as well as considering the effect of accumulated chronic stress from dealing with cancer [28].

18.12 Protective Factors

18.12.1 Parental Relationships and Resilience

The one consistent factor in all of the resiliency research, whether it is general child and family resiliency research, or specific to children with cancer or childhood cancer survivors, is the role that caring, supportive adults play in maximizing resiliency. These adults are described by survivors as adults who supply endless strength, encouragement, direction, belief in them, and a willingness to advocate in their behalf. Although this can be satisfied by any caring significant adult, for most children, it is their parents that fulfill this role [1, 21]. There is some speculation that it is the active engagement with supportive systems, and not simply their availability, which is the protective factor in resiliency that prevents the development of post-traumatic stress symptoms [29]. Qualities that are consistently found to influence a family's functioning level and basic well-being are their interactive qualities of cohesion, flexibility, open communication, and problem solving skills. Additionally, the support found in relationships with extended family members, friends, the community and social networks, were also identified as important [2, 15, 30].

McCubbin [13] using semi-structured interviews with parents of childhood cancer survivors, and a theoretical model derived from *The*

Resiliency Model of Family Stress, Adjustment, and Adaptation, report similar findings on resiliency in long-term cancer survivors [13]. The resiliency process involves accepting the diagnosis, understanding the impact of the trauma, formulating new life meanings, and accommodating the enormous challenges that cancer has brought to their lives. These insightful growth patterns, described in this retrospective manner, should not be a surprise given this shared journey by child and parent, and given our premise that parents are influential in what children ultimately believe and think about having cancer. The things that parents describe as supportive in the reorganization of their lives to accommodate taking care of the child in treatment, as well as the children at home, are the family's flexibility and adaptability to schedule and lifestyle changes, and active support and help from extended family, friends, neighbors, and colleagues at work. All of these factors were reported as playing an important part of the family's ability to recover, to move through and on after active treatment [13].

Orbuch [31], using data from self-report measures from long-term adult childhood cancer survivors (ages 16–28, and at least three years post treatment), explored how these survivors felt about their relationships with their parents and how they assessed the quality of their lives. Their findings are consistent with other research delineating the important role that parental relationships play in children's emotional and psychological well-being when dealing with cancer. It is always interesting, as found in this study, when adolescents and young adults affirm these findings, and attribute the impact parents have on their emotional well-being, how they think and approach life, and how they deal with physical and medical issues.

18.12.2 Primary Care Physicians/ Pediatricians/Family Physician

Although primary care physicians are not usually identified as a protective factor for survivors, some recent attention to their importance in lifetime follow-up care brings this issue to the forefront. Primary care physicians, for many survivors and their parents, become the first line of providers to be sought after when day to day medical issues surface. Pediatricians, family doctors, and general primary care physicians usually provide a long standing comfortable environment of familiarity, so that patients depend and confide in them easily. These intimate relationships offer physicians a unique opportunity to recognize the onset of long-term effects, enabling them to deal promptly with the problems while offering support and appropriate referrals. Therefore, their knowledgebase and understanding of cancer treatments and late-term effects is vital to survivors' continuing to get appropriate lifetime care [32].

18.12.3 School Reintegration

Although the primary focus of this chapter is centered on the emotional and psychological aspects or resiliency, it would be amiss if academic and school reintegration for this population was not addressed. Please review Kirkpatrick's chapter in this manuscript for more thorough review. In terms of adjustment, the challenge of transitioning back to school is an enormous task. As patients, these children's lives have been interrupted, causing them to be absent from school for significant amounts of time. Given the pace of most academic programs, catching up with their peers requires an understanding of how to accomplish this so that these children and adolescents have successful outcomes. Transitioning from patient to survivor can involve physical as well as learning challenges. The physical challenges of fatigue and exhaustion that accompany the treatments and recovery process can affect the rate of learning, concentration, attention, recall, and memory. These learning challenges also include any neurological deficits that may have been exacerbated or acquired. These challenges can require special needs at school and readjusting expectations for academic performances. The emotional toll of returning to school and not being able to fit right back in to one's peer group, grade, and performance level can have significant self-esteem consequences. Clinical experiences

with survivors reveal their desire to get back to a normal life, simply wanting to fit back into their peer group and life schedules. Unexpectedly, for survivors, some of the long-term difficulties can become more apparent years after treatment, as performance does not return to pretreatment levels, and certain aspects of learning do not seem to keep up with the expected developmental trajectory. Teachers, school psychologists, and school liaisons comprise some of the supportive adults, identified by survivors, as vital to the success of this transitional period and continued growth and adjustment [33–35].

We can only imagine the stress of not being able to return to life with peers and school as these children and adolescent survivors have been waiting for so long to do. The potential difficulties of reentering school and peer groups with physical and academic challenges, highlights the role that the resilience life style model can play in offering relief and potentiating a more successful outcome.

18.13 Clinical Application

The operational definition of resiliency that is presented here allows for a dynamic, fluid, developmental process of attitudes, beliefs and behaviors that survivors and their families can develop and use for their entire lives. This framework, based on strong cognitive theories, learned optimism, and backed by its effectiveness in research lends itself to a useful therapeutic model of resiliency.

While many of these techniques are used with the general population dealing with trauma, depression, and anxiety, the cancer experience is unique in its physiological, neurological, life-threatening nature, as well as the emotional and psychological long-term side effects. Even though many survivors fair well after treatment, the ability to use these cognitive tools can only enhance their lives. For others, having cancer becomes a new life identity. Regaining stability and normalcy is forever marked by the disease and the traumatic treatments. These survivors and families are resigned to life being "less than." They have not yet found their way out of the helpless "hook" of the cancer treatments and are especially in need of cognitive interventions.

For any therapeutic intervention to be effective, understanding and appreciating the challenges facing survivors is imperative. As providers, credibility is found in this knowledge, and clinical effectiveness is found in the ability to communicate clearly, using words to create pictures for the future, and role modeling how to integrate this knowledge while developing new attitudes and beliefs, which result in rewarding responses and behaviors. For many patients it is about lending our experience, strength, determination, creativity, and foresight when survivors and their families are in turmoil and/or distress and unsure of how to move forward. For all survivors, cancer goes from actively running their lives and taking precedence over everything else, to either a chronic medical condition requiring attention similar to other chronic diseases, or a lifelong medical condition, that cannot be ignored, but hopefully is not in need of much attention. However, the follow-up physician visits, scans, and blood work tend to thrust many people into memories or re-experiencing the active time of the disease. These connections are so strong that, for example, the smell or sight of familiar medical procedures can cause an automatic physical and emotional response [4]. The anticipation of these visits can induce sleeping problems, nightmares, flashbacks, distractibility, memory problems, concentration problems (which can interfere with learning and retaining school information), irritability, hyperactivity, and increased emotional reactions. If survivors are prepared for these experiences they can better tolerate their appearance and handle their reactions with less distress. Knowing they are not the only ones having these reactions can be an enormous relief. This knowledge also opens the door for learning how others handle these re-experiences and implementing proactive strategies to minimize their disturbance.

In addition, as discussed earlier, having solid, strong adult support is clearly found to be one of the most important factors in resiliency for survivors. Children and teens are especially

dependent on parents for their support and care when enduring cancer treatments and the side effects. Children are naturally amenable to believing what their parents tell them, and rely on their input and accept their words as the truth. Although adolescents tend to challenge parents, they find comfort in their love, support and belief in them. For adolescents, other peer survivors and other adults, such as teachers, doctors, nurses, and therapists, can supply this needed determination and hope for the future, as well as a reinforcement for the same parental messages.

For parents to be emotionally and psychologically available for their children, it is helpful for them to have supportive and safe environments to process their pain and trauma, as well as having the learning opportunities to develop or enhance their resiliency skills. As parents receive this support, it is easier for them to address the emotional and psychological challenges that their children faced as they endured the cancer treatments, and now as survivors, the emotional and psychological side effects of the treatment and follow-up care, and are, therefore, better equipped to help their children use the tools outlined in this chapter. The more solidly based parents are able to impart their sense of "We can" and "We will" determination to help their children grow into productive adults, regardless of the stress and trauma of the treatments and any long-term side effects, the more their children will assimilate these attitudes and beliefs and appropriate behavioral responses. This is especially true if parents assess their child's abilities accurately, encourage and help set goals that are realistic and attainable, and support their children when activities seem to be a stretch for them. Parenting with an attitude of "We can" and "We will" also involves setting loving limits, learning when empathy is good and when it is debilitating, when to push and when to back off, what is developmentally appropriate, and how to help their children reach these goals.

Helping parents understand the possible repercussions of the cancer experience calls for important discussions that include: education on how the cancer treatments may have impacted their child's developmental process, helping parents to understand that their child's self-identity may now include a self-image of being a cancer survivor (the negative and positive aspects) and what that might mean, discussing the impact of any ongoing physical challenges due to the treatments, and discussing how parenting styles and decision-making processes can be affected by being a family of a childhood cancer survivor.

Ultimately the goal of any intervention includes the development or enhancement of family communication about the cancer experience and now survivorship, the pain, struggles, and difficulties along the way, in addition to identifying the emotional and psychological individual and family strengths, the growth benefits from having survived cancer, and a continued determination for future learning and implementation of successful resiliency strategies. This is accomplished through the process of sharing thoughts, feelings, stories, memories, and future plans and goals, as well as recognizing and taking pride in the enormous amount of strength that is needed to become a survivor who has lived through cancer treatments and has gained resiliency strategies for the future, for themselves and as a family.

18.14 Conclusions

There is strong support in theoretical orientations, in clinical therapeutic settings, and reinforced by research, that childhood cancer survivors' lives are positively impacted when a resiliency life style model is embraced. By using the resiliency framework outlined in this chapter, survivors, and their parents can develop thoughts, beliefs, attitudes, and behaviors that enhance their lives, are self-fulfilling, and can be used across the lifespan.

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Cultural and Linguistic Issues in the Assessment and Treatment of Pediatric Cancer Survivors

19

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19.1 Introduction

According to the Centers for Disease Control and Prevention, in excess of 16 out of every 100,000 children and adolescents are diagnosed with cancer in the United States, representing significant incidence and morbidity [1]. The most common cancers among pediatric populations include leukemia and those involving the brain and other central nervous system (CNS) substrates. With regard to mortality, the CDC reports that three out of every 100,000 children and adolescents perish from the disease and/or its complications [1, 2], making pediatric cancers the second greatest cause of mortality among children ages one to 14 years, the most lethal only after incurred accidents [3]. However, similar to other diseases in recent years, including large-scale, global, epidemic infectious diseases [4, 5], the mortality rate associated with childhood cancers has decreased, in spite of the fact that their incidence rate has slightly increased over the years [1, 2]. Improvements in the diagnosis and advancements in the treatment of childhood cancers have led to enhanced survival rates and a dramatic increase in the prolongation of life. For example, according to the National Cancer Institute's Surveillance, Epidemiology and End Results Program (SEER), between 1978 and 1980, the 5-year survival rate among 0–19 year-olds diagnosed with brain tumors was approximately 58 % [6]. In contrast, SEER data indicates that 75 % of individuals diagnosed with a brain tumor between 0 and 19 years of age experienced a 5-year survival rate, an increase of approximately 18 % [6]. In addition, such rates have remained hovering around 77 % or greater since 1998. Therefore, and in spite of the fact that survival rates vary depending on the specific type of pediatric brain tumor (e.g., PNET v. Glioblastoma), perusal of these data reveals that the majority of childhood cancers have become chronic, treatable illnesses leading to increased survival rates. Such decreases in mortality rates and prolonged longevity have led to the increased emergence of late effects associated with pediatric cancers, and their CNS expression, coupled with the effects of their powerful treatments.

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Neurocognitive consequences associated with cancers, including CNS neoplastic growths, and their complex pharmacological and/or radiological treatments, unfortunately are not uncommon in pediatric patients. In addition, they are frequently observed with a delayed onset, long after remission and survival already have been established subsequent to such interventions. Such sequelae has been shown to have significant impact on adaptation, emotional functioning, quality of life variables, socialization, and other factors impacting pediatric patients and their families, as well as brain-behavior relationships, dictated by complex genetic (host) and environmental factors, in conjunction with the disease process and potent treatments. More important, as pediatric cancers are increasingly being considered a chronic disease, particularly in resource-rich areas throughout the world with advanced medical management, it is critical to examine the presence of subtle neurodevelopmental involvement. These issues are commonly expressed in emerging higher order skills, and while controlling for putative confounds, it is possible that psychosocial factors may partially account or contribute for a large proportion of such effects rather than the primary impact of the disease process alone. As pediatric survivors mature, these variables likely have a significant impact on academic, leisure, personal, and vocational functioning, such as coping skills, medication adherence, and avoidance of risk behaviors. Therefore, neuropsychology, the science of brain-behavior relationships, and its applied clinical skills and research methods has been appropriately surmised with the task of assessing such neurocognitive sequelae and to be part of a multidisciplinary approach to treatment and scientific investigations.

Aside from other complex clinical requirements encountered and well-elucidated in the literature, from a neuropsychological and sociocultural standpoint involving assessment and treatment, there are theoretical and applied factors to consider when evaluating children and adolescents who have survived childhood cancer, including cultural and linguistic variables. Such factors are critical from various perspectives: (1) cultural and linguistic variables impact neuropsychological performance during the course of assessment [4]; (2) culture and language impact the development of the tests and norms that are used to evaluate the neurocognitive effects of cancer with ethnic minority populations and their families [4, 7]; and (3) disregarding ethnic, cultural and linguistic factors, as has been shown for other diseases and conditions [8], has significant implications for neuropsychological assessment and treatment outcome in pediatric patients with cancer [9].

This chapter will succinctly address issues associated with ethnicity, culture and linguistic variables in pediatric cancer. It will initially provide an overview of important definitions and general health care issues associated with culture and language. It will then focus on patterns of American immigration and their impact on the acquisition and application of normative data for tests used with pediatric cancer patients, followed by factors associated with linguistic variables in greater detail. Finally, the chapter will present other critical information associated with culture and ethnicity including applied factors, with the overarching goal of providing the clinician with a multicultural framework to better understand their patients' expenence of illness.

19.2 Definition and Importance of Culture

The term culture can be defined in several ways. It has been described globally by the American Psychological Association [10] as "the embodiment of a worldview through learned and transmitted beliefs, values, and practices, including religious and spiritual traditions. It also encompasses a way of living informed by the historical, economic, ecological, and political forces on a group" (p. 380) [10]. Culture embodies and influences all facets of an individual, including cognition. "Differences in cultural background include, not just language differences, but also differences in group identity, beliefs, and values" [11]. All of these influence the patient's utilization of services and presentation of symptoms, the assessment techniques utilized, as well as most aspects of treatment, including neuropsychological rehabilitation.

The term "culture" unfortunately has been used interchangeably with the terms "race" and "ethnicity." This has been a source of significant confusion, as well as frequent debates, as there is no established consensus for the definition of these terms [4, 12, 13]. Historically speaking, racial categories have generally been defined on the basis of perceived physical or "biological" characteristics [12, 13]. These characteristics are not thought to be learned or changeable [14]. Ethnicity, on the other hand, can be considered as similar to culture, as both are considered learned, flexible, and passed on from generation to generation [15]. Markus [13] defines ethnicity as "a dynamic set of historically derived and institutionalized ideas and practices that…allows people to identify or to be identified with groupings of people on the basis of presumed (and usually claimed) commonalities including language, history, nation or region of origin, customs, ways of being, religion, names, physical appearance, and/or genealogy or ancestry…" (p. 654).

These distinctions are critical if we are to understand the specific factors that influence assessment and treatment. For example, the term "Hispanic" has been used to reduce a very heterogeneous group into a specific racial, rather than an ethnic, category [16]. Harris and Llorente [16] note that this "panethnic label" fails to "capture the unique attributes" of an individual including his or her unique ethnic and racial background. Even when referring to a specific Hispanic group, such as Mexican, there are several attributes to consider, including: place of birth, ancestral background, level of acculturation, and dominant language. For the purpose of this chapter, however, we will be referring mostly to the term "culture" and "cultural minorities" as outlined in the APA Guidelines cited above and in the work by Markus [13].

When examining the critical aspects of multicultural assessment and rehabilitation in pediatric cancers, it is also essential to understand patterns of American immigration. Over the past 25 years, there have been significant changes in the ethnic diversity of the United States. Over the course of two decades (1980–2000), minority populations (non-"Caucasian") have grown 11 times faster than the "Caucasian" population [17], and immigration and population growth have dramatically increased the racial and ethnic diversity of the country, producing significant increases in all minority groups [18]. The US Census Bureau predicts that by the year 2050 the percent of population by race will represent 46.6 % Caucasian, 13 % African-American, and 7.4 % Asian, with 5.4 % of the population being identified as having "two or more races" [18]. The percent of Hispanic individuals is expected to be close to 27.9 % [18]. These predictions note marked increases in all minority groups.

More importantly, as it relates to psychological and neuropsychological intervention in childhood cancer survivors, patterns of American immigration, moderating the demographic variables of large numbers of individuals, are not the result of mechanisms driven by chance processes. The nonrandom nature of these mechanisms is the outcome of specific and selective influences affecting host and sending countries, be it humanitarian concerns, occupational needs, or geopolitical turmoil [19]. In addition, the proportion of immigrants from specific regions living in the U.S. or from foreign countries may vary substantially over large periods of time [7, 20]. This inter- and intra-variability in immigration patterns is particularly important for key demographic variables, as gravitation exists towards specific residential areas, occupations, and educational attainment [4, 7, 20]. Ultimately, these factors moderate the utility of data obtained during the course of test standardization, as well as neuropsychological assessment and treatment planning [16, 21]. In summary, the current and predicted changes in the racial and ethnic diversity of the U.S. population underscore the ever increasing importance of understanding the dynamics between culture and health care.

19.3 Culture and Health Care

Within the health care setting, it has been found that cultural, socioeconomic and ethnic factors influence a patient's seeking and receiving treatment, as well as impact adherence and response to treatment. Minority patients in the United States unfortunately are more likely to have a poorer

health status [22]. Latinos, Native Americans and Asian Americans have also been found to receive less treatment and/or prevention services in the U.S. [23]. The risks are worse for minority members with lower socioeconomic status, as well as those with limited English proficiency [23]. Limited English proficiency in parents has been found to correlate with poorer health status and greater odds of inadequate medical care in children [22]. This makes it necessary to have interpreters available in health care settings such as hospitals and clinics for clinical services, if using such linguistic resources is appropriate and necessary. However, the availability of interpretive services is often limited [24], and may even be unavailable for some minority patients.

19.4 Barriers in the Assessment and Treatment of Minorities

In addition to this, many barriers can affect the process of assessment and treatment with minority populations, including families of children and youths with cancer. Some of the barriers that have been found, particularly when working with minority patients diagnosed with cancer, are identified below.

19.4.1 Language

Language is frequently cited as a significant barrier encountered by health care providers treating pediatric patients with cancer [25]. Language differences may hinder the communication process between patients and health care providers. In terms of assessment, language proficiency may affect the results from individualized assessments and rating scales created primarily in English. Pfefferbaum et al. [26], for example, found that Hispanic parents of children diagnosed with cancer have been found to encounter more difficulties when completing scales designed to measure variables such as anxiety and language use.

19.4.2 Differing Expectations and Cultural Beliefs

Cultures may differ in the process of providing information about diagnosis, treatment plans and prognosis. For example, cultural differences have been found in physicians' attitudes towards disclosing diagnostic information to child patients, as well as family members. Parsons et al. [27] found that, fueled by their sense of responsibility to inform, 65 % of physicians sampled from the U.S. reported always informing underage patients of their cancer diagnosis. In contrast to this, only 9.5 % of Japanese physicians reported doing so, stressing the importance of issues such as parental burden, stigma, work culture, and patient variables. Culture may also underlie beliefs about illness and disability, as well as its meaning. Whereas personal independence is highly valued in Western culture, it is not necessarily a goal in other cultures, which often have different beliefs about: (a) a person's degree of responsibility and control over health, and (b) the role of family in dealing with illness [28, 29]. These factors may influence the amount of medical information available during intake, and must be taken into account when offering feedback and recommendations.

Similarly, cultural differences are apparent within the expectations of health care providers and patients throughout the assessment, diagnosis and treatment process. A national study found that racial and ethnic minorities held more negative views of physicians than European-American patients, even after controlling for socioeconomic status and education [30]. The authors of this study hypothesized that this may be due to the differing expectations between physicians and patients, or to physicians misunderstanding the views held by minority patients. With regard to general treatment adherence, the literature suggests that cultural minority patients are more likely to end treatment prematurely, due to frustration, misunderstanding, and role ambiguities in treatment [31].

19.4.3 The Presence and Treatment of Pain

Most children diagnosed with cancer experience some amount of pain during the course of their illness, be it due to the disease itself or to the effects of the procedures and powerful therapies (e.g., chemotherapy or/and radiation) used to treat it in some instances [32]. In adults, the presence of severe pain has been found to have a negative impact on performance in neuropsychological assessments [33]. Pain is also likely to have a negative impact on children's performance and effort during the evaluative process. Anderson and her colleagues (2004) found that physicians underestimated baseline pain for more than 50 % of a sample of African-Americans and Latino outpatients with cancer [34]. This led physicians to under-prescribe analgesics for this population. Consequently, minority patients have been found to receive inadequate pain management in some settings [35].

19.4.4 Parental Stress

A diagnosis of pediatric cancer can produce significant levels of stress, as well as depressive symptoms, in both children and parents. Parental reactions, as well as stress management, during the process of diagnosis and treatment of cancer has been found to be related to anxiety and post-traumatic stress symptoms in the family after treatment ends [36, 37]. Symptom severity and management have been found to show some variations related to educational level, ethnicity, and gender [38]. Pfefferbaum et al. [26] for example, found that Latin-American parents expressed feeling more stress in relation to their children's illness, when compared to parents from the United States. This finding is significant, as other studies have found that mothers who report higher levels of anxiety during their child's treatment have been found to show more avoidant behaviors, such as missing post-treatment follow-up appointments [36].

19.4.5 Treatment Adherence

Early studies suggested that multicultural clients are more likely to prematurely end treatment, due to frustration, misunderstanding, and role ambiguities of treatment [31]. Sohlberg and Mateer [39] note that identity and self-concept are influenced by culturally-mediated norms about assertiveness, aggression, emotional expression, and individual goal attainment versus sacrificing for the greater good. Culture may also underlie beliefs about illness and disability, as well as its meaning. Whereas personal independence is highly valued in Western culture, it is not necessarily a goal in other cultures, which often have different beliefs about (a) a person's degree of responsibility and control over health and (b) the role of family in dealing with illness [28, 29].

19.5 Multicultural Assessment and Diagnosis

The ever-increasing ethnic diversity of the U.S. population emphasizes the need to account for the role of culture in diagnosis, assessment, and interventions. Many studies examining performance on neuropsychological tests have found differences in performance between cultural minority groups, despite matching for relevant sociodemographic factors [40]. Various factors have been hypothesized to influence this, including structural brain differences, clinician and patient cultural and language proficiency, as well as the constructs measured by the tests themselves. Years of education, acculturation level and reading ability have also been found to have significant effects on performance in neuropsychological tests for ethnic minorities [41].

The patient's level of acculturation and linguistic dominance is critical to assess prior to selecting a test battery and commencing an evaluation. Furthermore, measurement of a patient's level of acculturation and linguistic dominance is vital to the validity of an evaluation, as it informs the clinician of the best manner in which to

approach the assessment process, including which language and measures to use during the assessment. Depending on a client's level of acculturation and language skills, the clinician should tailor the evaluation for the individual, or choose to refer a client to another clinician with expertise in that particular person's culture and/or dominant language. For example, the interested reader is referred to Ostrosky-Solis and Oberg's [42] review of the similarities and differences in performance on various tests across languages and cultures. For information specific to the Hispanic population, the reader may want to review the work of Llorente [4] and Marin and Marin [43]. During the clinical interview, the neuropsychologist must gather information that will inform him or her as to the best way to proceed, including test selection, and whether the client needs a referral to a more appropriate professional. To determine how to proceed, the evaluator must inquire about the demographic characteristics of the client. Equally important is the collection and review of collateral sources of information. This information can include the patient's own verbal report, past personal and family history, and cross-informant reports [4]. Specifically, the evaluator would benefit from learning the client's level of education in the U.S. and elsewhere, the length of time they have lived in the country, what language(s) are primarily spoken in the home, whether the client participated in English as a Second Language (ESL) classes in school, and specifically, how bilingual they are. Do they write in only one language, but speak both? If they speak multiple languages, which one do they prefer?

While subjective information obtained through the clinical interview is vital to an evaluation, the neuropsychologist should also conduct a *formal* assessment of acculturation and linguistic dominance and competence. Making judgments about acculturation and linguistic skills solely from simple conversational interactions during the clinical interview is egregious. Fortunately, objective measures of these variables have been developed to assist the neuropsychologist in making important decisions about minority clients. Formal acculturation scales can tap into the client's preferred language across a variety of settings, including home, leisure, and more formal settings. Remarkably, such acculturation scales are effective in predicting generational cohort and degree of acculturation [44]. For example, the acculturation scale developed by Marin et al. can be reliably used with the Hispanic population and encompasses seven simple questions to which the client responds [44]. These acculturation scales take into consideration variables that include the timing of immigration, generational differences in migration, ethnic identification, and length of U.S. residency [44–46].

The Latino Consortium of The American Academy of Pediatrics' Center for Child Health Research found that one of the most pressing issues concerning Latino Health is the scarce availability of adequately validated research instruments for this population [47]. This can also be said to be true for members of other minority groups. Similarly, neuropsychological assessment instruments that are adequately adapted and standardized for distinct minority groups are limited. As a result, many neuropsychologists are forced to use interpreters, or translated versions of tests and procedures which have limited cultural norms. As explained by Ardila et al., translations of English-based tests, without proper cultural adaptation, may be biased by the requirement of prior knowledge on particular concepts, cultural references and conventions, and even phoneme usage [48, 49]. Thus, simply translating tests can result in assessment inferences that are invalid and unreliable due to cultural ignorance [50]. Geisinger [51] suggests that the reliability and validity of a test must be re-established whenever a test is altered for use with a specific population. This is necessary in order to ensure instrument accuracy when assessing selected variables within that population [51, 52]. Recently, test standardizations have begun to include small samples of cultural minorities in the data collection process, providing some advancement in culturally sensitive neuropsychological testing. However, care should be taken when using certain norms, as they may not reflect the specific demographics of an individual from a

given cultural group, which may lead to inaccuracies in the interpretation of the acquired data [53].

Even though an interpreter represents another attempt to adapt the evaluation for patients who speak another language, this method should be avoided at all costs [4, 54–56]. Cross-cultural bodies of research suggest that evaluations which utilize an interpreter may be invalid, unethical, and when used for forensic purposes if they should ever reach a legal setting, are easily challenged in a court of law [56]. As evidenced by the American Psychological Association's (APA) Ethical Principles and Standards, the neuropsychologist is ethically responsible for maximizing the validity of the parameters of the evaluation [52, 57]. Thus, given the strong support from multiple, prevalent bodies of research, the use of an interpreter may represent an egregious ethical error in the course of a pediatric forensic neuropsychological evaluation.

The only situation in which the use of an interpreter during a neuropsychological evaluation would be acceptable is when the client speaks a very rare language, and the clinician's attempts to locate and refer the client to a more appropriate clinician or neuropsychologist who speaks that language are fruitless. Still, test results and conclusions drawn in the evaluation would be of questionable validity, and the clinician is obligated to emphasize limited confidence in test results in the written report. In the rare occurrence wherein an interpreter must be used, the neuropsychologist is implored to follow certain guidelines in order to preserve the validity of the evaluation as much as possible [4]. Specifically, the interpretative services should be of high quality and should utilize trained professionals, preferably specialized in the psychological sciences. Individuals with mental health training are most preferred, as they are more likely to be familiar with the parameters of the assessment situation [4]. Clearly, a client's family member or associate should never be utilized as an interpreter during the neuropsychological evaluation for obvious reasons [58]. Although the problems with the use of family members serving as interpreters should be self-evident, they deserve emphasis here. Family members do not have proper training in the ethical guidelines and proper procedures of interpretation, their own levels of acculturation and language proficiency can impact the quality of their interpretation, and their use can lead to bias, given their inevitable vested interest in the results and outcome of the evaluation [59].

Cultural awareness and understanding clearly need to be considered an integral part of a clinician's knowledge base when called upon to assess, diagnose, and provide consultation and follow-up care with children and adolescents with cancer [60]. Groce and Zola [61] noted,

> "An individual's culture is not a diagnostic category; no cultural heritage will wholly explain how any given individual will think and act, but it can help health care professionals anticipate and understand how and why families make certain decisions."

Rivera Mindt et al. [62] describe the importance of developing linguistic and sociocultural competency in neuropsychologists and psychometricians. They also recommend the integration of multiple factors into case conceptualization, including, but not limited to: country of origin, level of acculturation, education, socioeconomic status, social support, and nutritional history. The presence of barriers inherently associated to a diagnosis of cancer, such as pain and parental stress, should also be considered during the process of assessment, diagnosis and intervention with pediatric patients from cultural minorities. Although taking these factors into consideration is critical, the most essential component in this process is an ethical and culturally sensitive stance towards the assessment and rehabilitation of these populations.

Multi-culturally sensitive neuropsychological intervention poses unique challenges to practitioners, given the limitations in our assessment tools that guide this intervention, the need for developing a greater understanding of the impact of culture on one's practice, and interpreting the results of our findings within a culturally sensitive context [63]. Groce and Zola [61] propose that this cultural sensitivity begins with self-reflection:

> Everyone has a cultural heritage that influences his or her health beliefs and practices. It is thus not practical to learn in detail the infinite details of

> specific cultures, but rather to assume that such variations occur and learn how they might affect one's health practices. Rather than teaching every health practitioner to be a mini-medical anthropologist, it is more important for practitioners to be sensitive to the patient's heritage, to their own heritage, and to what happens when different heritages and belief systems come together (p. 1054).

Fadiman [64] exemplifies what can occur if there is a lack of understanding of different cultures in the medical setting including the rehabilitation milieu. This book examines the potential cultural conflict between Western beliefs and individual culture when a seizure disorder is perceived as a "gift" within a specific culture, but as a disorder in Western medicine. The author provides some questions to ask to promote greater understanding of a patient's culture: (1) What do you call the problem?; (2) What do you think has caused the problem?; (3) Why do you think it started when it did?; (4) What do you think the sickness does? How does it work?; (5) How severe is the sickness? Will it have a short or long course?; (6) What kind of treatment do you think the patient should receive? What are the most important results you hope he/she receives from this treatment?; (7) What are the chief problems the sickness has cause?; and (8) What do you fear most about the sickness? Additional studies have supported the use of similar questions in understanding a patient's perspective of illness, disease, and disability, within their culture [65].

19.6 Linguistic Considerations

Although a detailed examination of the issue relating language to cancer and common treatments is difficult to address due to the lack of available research, it is still important to touch upon. First, however, a broader overview of how culture and language are related is necessary, particularly given the fact that many individuals from such minority backgrounds may possess complete or partial fluency in more than one language.

Cultural factors modulate biologically-based responses and behavior, including the biological predisposition of infants to develop language, and the specific language that infants and young children eventually learn heavily depends on their culture [66, 67]. Nevertheless, these findings support the fact that everyday brain functions derived from cultural influences, such as using an abacus to count, can lead to culture-based brain differences. Such influences impact the functional anatomy of the brain and underscore the need to take linguistic variables into consideration when evaluating neurocognitive functioning during the course of pediatric assessments.

To scientifically illustrate the impact of language on the human brain, Tang and colleagues [68] revealed differences in functional magnetic resonance imaging (fMRI) between native Chinese and English speakers on tasks which evaluated foundational arithmetic skills and targeted the brain's occipitoparietal region. The native English speakers demonstrated increased left perisylvian activity, while the native Chinese speakers showed increased activity in the premotor cortex. Tang et al. proposed that these differences directly related to the greater demand on visuospatial skills within the Chinese language [68]. They cited a relative advantage for Chinese speakers who learned to effectively utilize an abacus for counting, compared to the less effective English speaker's method of processing number symbols. Moreover, this anatomical difference may explain why Chinese-speaking children often perform better than their English-speaking counterparts on mathematics tests [69].

An individual's language background also bears weight on neuropsychological test performance. In a subtle example, Mok et al. [50] studied the effect of language background on two different trail making tests with Chinese dominant, English dominant, and Chinese-English bilingual groups of children. The study results showed that the Chinese dominant group outperformed both the English dominant and Chinese-English bilingual groups on measures of speed and executive functions. The authors concluded that language background exerts differential performance on tests of executive functions, in particular trail making tests. In another study documenting the effects of language spoken in the home, reliable discrepancies in test performance between individuals with

similar as well as different ethnic backgrounds were documented, even after accounting for variability derived from demographic factors such as age, education, gender, and income [70].

Although the majority of research investigating the effects of language background has been conducted with adults, research with pediatric populations has also demonstrated that language background impacts neuropsychological test performance. In the study by Harris and Llorente, language spoken in the home was the only variable able to completely account for differences in the performance on the Wechsler Intelligence Scale for Children, Fourth Edition of Hispanic children who spoke either English or Spanish at home when compared with the "White" sample [16, 71]. Therefore, language can significantly affect test results and subsequent interpretations.

Complex linguistic abilities, such as bilingualism, reflect additional factors for consideration in neuropsychological assessment of childhood cancer survivors. Bilingualism involves the ability to speak two (or more, in the case of multilingualism) languages. However, bilingualism is more complex than merely monolingual skills in two languages; rather, the development of a second language directly relates to the bilingual individual's need to communicate in different contexts, with different individuals, and for specific purposes [72]. Notably, individuals who admit to speaking multiple languages often vary greatly in their fluency and competency in each. Encompassing linguistic, communicative, and sociocultural aspects, bilingualism can range from the individual who has expertise in their native tongue and near-native knowledge in another language, to someone who has only basic conversational ability in their second language [73].

Early studies considering the relationship between bilingualism and test performance emphasized bilingualism's negative effects on cognition. For example, Barke and Williams asserted that the introduction of a second language inhibited continued development in the first language [74]. To the contrary, contemporary research indicates that bilingualism can be advantageous to cognitive functioning. Specifically, Garratt and Kelly reviewed research that indicated a bilingual advantage when compared to monolinguals in the following cognitive domains: development of reading skills, metalinguistic ability, phonological awareness, concept formation, divergent thinking skills, symbolic development, working memory, attention and impulse control [73]. Despite these promising findings, bilingual normative data to which a neuropsychologist might compare his or her client is scarce, if nonexistent.

Research investigating the proposed reasons behind the differences in test performance between bilinguals and monolinguals implicate two competing cognitive mechanisms: competition or interference between languages and the reduced frequency of language-specific use [75]. The former mechanism explains the process by which a bilingual individual inhibits use of one language in order to more effectively use a second language. Typically, the dominant language is more readily accessible and its use must be suppressed during non-dominant language use [75]. The latter mechanism is based on the notion that because bilinguals have two languages at their disposal, their use of words within each language is less frequent. Words that are used less frequently have fewer established neuronal connections required for effective retrieval. Both principles ultimately impact a bilingual individual's proficiency in the languages they use.

19.7 Specific Issues Related to the Pediatric Cancer Survivor

There are a variety of deficits that may be seen in survivors of childhood cancer. Neuropsychological functioning, especially cognitive ability, has been the topic of much research, and is addressed more fully in other chapters. It has been found that slightly more Hispanics have more problems related to cognition and other neuropsychological variables when compared to "African-Americans," "Whites," and others. Additionally, cancer survivors frequently report learning difficulties and hyperactivity [76].

Lofstad et al. [77] found that individuals that have undergone chemotherapy treatment have an

average IQ that is 13 points lower when compared to healthy individuals, with comprehension and arithmetic being the most striking group difference. Additionally, deficits were seen in attention, verbal functioning, visual-spatial abilities, and processing speed. Lofstad et al. indicated that the rapid development seen in the brain of young individuals, especially the frontal lobe, makes these areas particularly vulnerable to effects of chemotherapy [77].

A study conducted by Conklin and colleagues [78] found that attention was troublesome among individuals that underwent chemotherapy treatment. Also, it was found that the more intense the chemotherapy the worse the performance on processing speed and academics. Attentional and memory skills were worse for the patients that were exposed to chemotherapy at a younger age. Overall, treatment for cancer can have a significant impact on an individual, and affect cognitive functioning, including attention and concentration. Therefore, it is very important to be aware of different interventions and rehabilitation options available for this population in order to attempt to lessen these deficits.

19.8 Culturally Sensitive Interventions and Rehabilitation

Pontón et al. describe a cultural-based intervention used in the rehabilitation of a Hispanic population who experienced brain injury, which may be partially applicable to children with cancer and their families [79]. Four well-grounded therapeutic techniques are utilized as intervention: symptom validation, journaling, structuring, and reframing. Symptom validation is defined as, "to verbalize concretely the subjective experience of vague and diffuse symptoms and to make the patient feel understood" (p. 515) [79]. This technique involves active listening and informing the patient about the symptoms commonly experienced in brain injury rehabilitation. Journaling involves recording symptoms and subjective experience ("How does the symptom make you feel?") with reasonable frequency in order to define the symptoms, provide a baseline of symptoms, foster a positive coping style, and to provide a concrete measure of progress. Structuring involves establishing or returning an individual to a routine to increase his or her productivity and adjustment. It is defined as,

> "a predictable, purposeful set of activities that allows patients to channel their energy productively. It gives them a sense of control over their immediate environment, provides them with positive feedback on their progress, and helps them achieve short-term realistic goals" (p. 522) [79].

Finally, the purpose of reframing is defined as, "shifting the perspective of the process—from tragedy to challenge, from future to present, from unmanageable issues to manageable issues" (p. 524) [80]. This technique involves paradoxical/cognitive behavioral interventions (e.g., guided imagery), as well as reframing of spiritual issues ("spiritualizing"). The authors describe three case studies in which these techniques were used and found to be effective [79]. They also discuss the limitations to these specific techniques.

Unfortunately, the majority of the empirically validated treatments have been based on European-Americans, and do not reflect the cultural diversity of the United States. Christophersen and Mortweet note the lack of empirical data (e.g., base rates, treatment efficacy) on cultural diversity, which makes it difficult to estimate when and where cultural differences are important [4, 80]. Guidelines to improve cultural awareness and understanding were created by the American Psychological Association [10] due to:

> . . .the continuing evolution of the study of psychology, changes in society at large, and emerging data about the different needs of particularly individuals and groups historically marginalized or disenfranchised within and by psychology based on their ethnic/racial heritage and social group identity or membership (p.377).

These guidelines recognize the importance of influences of the larger environment (e.g., social, political, historical, and economic) on one's behaviors: (1) Psychologists are encouraged to recognize that, as cultural beings, they may hold attitudes and beliefs that can detrimentally influence their perceptions of and interactions with

individuals who are ethnically and racially different from themselves. (2) Psychologists are encouraged to recognize the importance of multicultural sensitivity/responsiveness to, knowledge of, and understanding about ethnically and racially different individuals. (3) As educators, psychologists are encouraged to employ the constructs of multiculturalism and diversity in psychological education. (4) Culturally sensitive psychological researchers are encouraged to recognize the importance of conducting culture-centered and ethical psychological research among persons from ethnic, linguistic, and racial minority backgrounds. (5) Psychologists are encouraged to apply culturally appropriate skills in clinical and other applied psychological practices. (6) Psychologists are encouraged to use organizational change processes to support culturally informed organizational development and practices.

With regard to interventional outcomes, the literature supports the fact that racial-ethnic differences exist in outcomes. For example, in a recent study published by Hanks et al. [81], data supported the fact that ethnic and racial minorities experience greater frequency of traumatic brain injury (TBI) associated with violence than Whites. In fact, they showed rates of violent TBI to be approximately twice as high in ethnic minorities (74 %) compared to Whites (46 %). Most important, these results suggested the presence of poorer outcomes in minorities as a result of violent TBI. It should be noted that this disparity is similar, for example, to that for strokes in African-Americans populations. One of the most comprehensive studies assessing TBI outcome to date [82] was sponsored by the National Institute on Disability and Rehabilitation Research (NIDRR), Traumatic Brain Injury Model Systems, established in 1987 to establish a national TBI database, and to demonstrate the benefits of a coordinated system of neurotrauma and rehabilitation care, as well as support innovative research on all aspects of care for those who sustain traumatic brain injuries. In this study, a comparison was made again between the ethnic "minority" group (African-American, Asian/Pacific Islander, etc.) and Whites. This investigation revealed the presence of poorer outcome as measured by the Community Integration Questionnaire assessing role performance in the community, with the "minority" group scoring lower than whites after significant analyses were made to covariate for various potential demographic and injury confounders including age, gender, and trauma cause and severity [82].

In a study recently published from existing Veterans Administrations records, they note the importance of appropriately documenting ethnicity as it has high significance in stroke rehabilitation [83]. More important, they note the pitfalls associated with methodological issues when using ethnicity as a predictor with dichotomous response variables. Similar findings have been obtained for other outcome measures in other studies for various types of brain injury and its rehabilitation but their detailed examinations are beyond the scope of this chapter [84]. Furthermore, a U.S. volunteer surgical team performed approximately 100 craniofacial surgeries to repair cleft lip/palate in the Middle Amazon region of Brazil, which is composed of mixed Amerindian, European, and African ancestry. The team inquired, through a Portuguese translator, about the patient's and their family's expectations after surgery, traditional beliefs, attitudes toward surgical intervention, and outreach efforts. The study found that growing international clinical exchange programs to provide services to under-served populations in less developed countries can potentially make significant contributions; however, authors caution, they must understand the patient's sociocultural matrix in which the meaning of the condition they are treating and the future they face are determined by a host of factors over and above the specific procedures they are performing [60].

Additional support for culturally-sensitive approaches to intervention was examined by Zhimin [85]. This study examined the interplay between Western and Chinese traditional medicine and education to promote increased adherence through self-care practices in Chinese school-age children with primary nephrotic syndrome. Results of the study indicated high levels of self-care (90 %) for children ranging in age from 6 to 12 years of age, and the older children were most adherent to their self-care regimen.

19.9 Conclusions

Those affected by pediatric cancer are susceptible to the emergence of cognitive deficits, along with emotional and psychosocial sequelae, due to the cancer and subsequent treatment experience. In order to adequately assess which areas are most affected, neuropsychologists must investigate using applied clinical skills, and consider cultural and linguistic issues in order to provide effective, culturally-sensitive assessment and treatment for the childhood cancer survivor. In addition to how one defines culture, individual experiences of immigration, and access to health care, it is important to consider the barriers that may affect the process of assessment and treatment with minority populations such as differing expectations and cultural beliefs, parental stress, and treatment adherence. Measurement of a patient's level of acculturation and linguistic dominance before commencing an evaluation is very important and will increase the validity of the evaluation. This chapter touched upon other ways to increase the validity of an evaluation, such as the use of interpreters or translating test measures.

However, as stated, these two options should be used sparingly and with extreme caution. Overall, this chapter provides an overarching view on culture and language and how they are related to each other, and how they relate to the assessment and treatment of those affected by pediatric cancer, in order to elucidate the challenges that minority patients face. When using these considerations, the survivor has the opportunity to see long-term improvement in many areas, including cognitive abilities, emotional and adaptive functioning, and quality of life.

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Quality of Life During Palliative Care

20

Gay Walker

20.1 Introduction

This chapter will explore the expertise, principles and value of Pediatric Palliative Care (PPC) as it applies to quality of life (QOL) in childhood survivorship of cancer and other life limiting diseases.

It is estimated that approximately 1 million children in the United States live with serious chronic medical conditions. Approximately 53,000 children under the age of 19 years die each year in the United States [1] while an estimated 270,000 children have been identified as pediatric cancer survivors [2].

In the course of developing plans of treatment for each category and stage of illness, PPC has emerged in response to the continued demand for improvements in the care and support of children and their families facing these life limiting and life threatening illnesses. With the cancer survivor, given the risk of relapse or onset of second cancers, cardiomyopathy, renal dysfunctions, musculoskeletal problems, and the addition of psychosocial needs, the expertise of PPC is increasingly applicable.

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20.2 Definitions

20.2.1 Palliative Care (General)

As defined by the World Health Organization, palliative care is an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, including physical, psychosocial and spiritual [3].

20.2.2 Palliative Care (Pediatric)

In the same token, the World Health Organization defines palliative care for children as the active total care of the child's body, mind, and spirit, and also involves giving support to the family. It begins when illness is diagnosed and continues regardless of whether or not a child receives treatment directed at the disease [3]. The National Hospice and Palliative Care Organization (NHPCO) defines Pediatric Palliative Care in the following terms:

> Pediatric palliative care is both a philosophy and organized program for delivering care to children with life-threatening conditions. This care focuses on enhancing quality of life for the child and family, minimizing suffering, optimizing function and providing opportunities for personal growth [4].

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The Institute of Medicine (IOM) expands on these definitions as follows:

> Pediatric Palliative Care seeks to prevent or relieve the physical and emotional distress produced by a life threatening medical condition or its treatment, to help patients with such conditions, and their families live as normally as possible, and to provide them with timely and accurate information and support in decision making. Such care and assistance is not limited to people (children) thought to be dying and can be provided concurrently with curative or life-prolonging treatments [5].

20.2.3 Hospice Care

Hospice is a form (or subspecialty) of palliative care that provides end of life comfort care across a variety of settings, based on the philosophy that dying is a part of the normal life cycle. Hospice promotes the concept of "living until you die." The hospice model was developed to address the specific needs of the dying and of the families who had long been neglected by the medical system of care. It functions through an interdisciplinary team of professionals that supports the child and family through the later phases of illness and dying process and the surviving family through the bereavement processes [6]. Dr. Cicely Saunders, a pioneer of the modern hospice movement describes the perspective and motivation of all hospice care: "You matter because you are you, and you matter to the last moment of your life. We will do all we can to help you, not only die peacefully but live until you die." [7]

20.2.4 Quality of Life (QOL)

Measuring health as it relates to the changes and frequency of disease is not easy compared to measuring well-being and quality of life (QOL), particularly in relation to children. The World Health Organization provides a general definition of QOL:

> Quality of Life is an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns. It is a broad ranging concept affected in a complex way by the person's physical health, psychological state, level of independence, social relationships, personal beliefs and their relationship to salient features of their environment [7].

QOL is a personal concept with varied meanings for each child and family. It is important to examine aspects of each dimension from the child and family's perspective. Patient QOL is strongly related to family caregivers' QOL. The Model of QOL as stated by the End of Life Nursing Education Consortium (ELNEC) outlines the physical, psychological, social, and spiritual well-being factors associated with overall QOL [8, 9] (Fig. 20.1):

It is important to note that the specific definition of QOL as it applies to children and their families/caregivers will change with time, as treatment changes, stages of disease progression/regression, age of patient, and numerous other factors influence QOL issues.

20.2.5 Pediatric Survivorship

The National Coalition for Cancer Survivorship and the National Cancer Institute give us this definition of survivorship:

> "An individual is considered a cancer survivor from the time of diagnosis through the balance of his or her life. Family members, friends, and caregivers are also impacted by the survivorship experience and are therefore included in this definition" [10].

It is important to note that regardless of the duration of a child's survivorship, the value and impact of quality palliative care techniques are profound, long term and far reaching. The essentials of palliative care—attention to physical pain and suffering, including existential distress; the inclusion of the family as a unit of care; and interdisciplinary care—are all relevant to and needed by the cancer survivor [11].

Survival after a cancer diagnosis often comes at a great price. Medical, psychological, social, and spiritual issues all impact the life of the child for as long as they live. Chronic pain, fatigue, anxiety, and social reintegration, as a result of

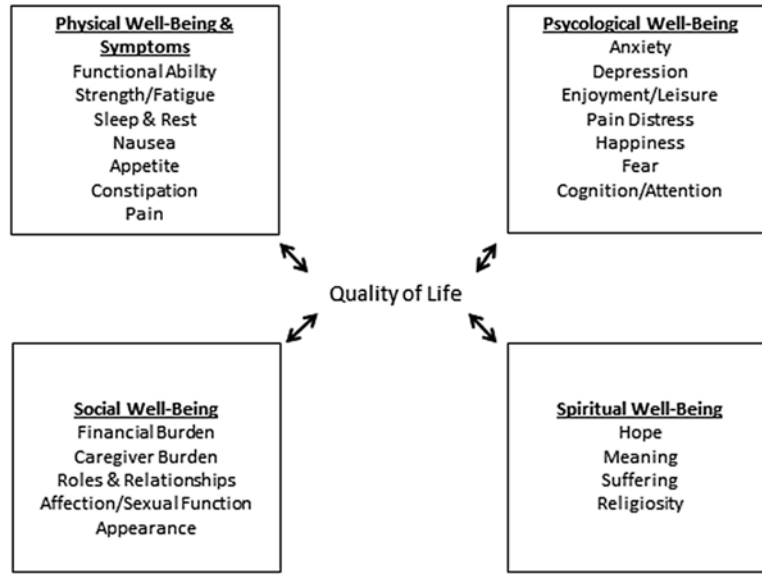

Fig. 20.1 Quality of life model. City of Hope Medical Center. http://prc.coh.org. Reprinted with permission [10]

survivorship will have their impact on the child's quality of life. The application of palliative care strategies has been developed to address and reduce or eliminate those burdens. In general, the terms "supportive care" and "palliative care" may be used interchangeably. By definition, palliative care is not just for hospice and end of life care, but for any child suffering from a debilitating or chronic illness.

Unlike Hospice, the use of palliative care does not require a terminal illness diagnosis. On the contrary, palliative care (PC) is offered to patients undergoing curative treatment and who have long-term prognosis, such as cancer patients or those suffering from multiple sclerosis or cystic fibrosis. The PC model evolved from the traditional hospice perspective addressing QOL for those living with prolonged illness using an interdisciplinary team approach to care.

> "Pediatric Palliative and/or Hospice care are recognized as the BLENDING of the two specialties, being both a philosophy and an organized method for delivering competent, compassionate, and consistent care to children with chronic, complex and/or life threatening conditions and their families. This merging of principles allows for increased access to care and ensures palliative treatments and support are available in all settings throughout the illness/dying trajectory" [12].

This "blending" of specialties could describe hospice as being the intensifying of PC as the child moves closer to death. Ideally children and families who live with chronic or progressive disease are receiving PC throughout the course and treatment of the child's life, however long it may be. As they come closer to death and hospice is required, the child and family can be seamlessly transitioned to such programs.

20.2.6 Concurrent Care

In accordance with section 2302 of the Patient Protection and Affordable Care Act, any Medicaid eligible recipient younger than 21 years of age and certified by a physician as having a life expectancy of six months or less may elect to concurrently receive hospice care in addition to curative treatment of the hospice related diagnosis [13]. This was passed by Congress on March 23, 2010. It is often referred to as the "2302 care provision." This provision has greatly helped to change the 'either hospice or curative treatment' dilemma. Although this provides care for only those with Medicaid at this present time, several private insurances are now beginning to work with benefits to securing this care as well. The concurrent

care provision is a vital piece of legislation that the pediatric hospice and PC communities have been championing for years. This will allow many children to receive all services that are related to the treatment of his or her life limiting illness. Providing palliative and hospice care services while they are receiving other disease-modifying treatments is a much-needed advance [4].

20.3 Purpose and Goals of Pediatric Palliative Care (PPC)

As described by the American Academy of Pediatrics, the goal of Pediatric Palliative Care (PPC) "is to add life to the child's years, not simply years to the child's life" [14]. The relief and prevention of suffering and enhancing quality of life along the illness trajectory for the children and their families is the primary purpose of PPC. The child and family are considered the unit of care, and their goals change frequently as children advance through disease survivorship or death. In order to meet the family's changing needs, inter-disciplinary team (IDT) involvement is essential to bring consistency, continuity and compassion. The family and child direct the care with the guidance of the palliative team in collaboration with other primary service teams involved.

"Care is focused on enhancing the quality of remaining life by integrating physical, psychological, social, and spiritual aspects of care as defined by the family" [15]. Care is given in a manner that reflects the personal, emotional, cultural, and religious values, wishes, and goals of the child and family. Approach and interventions affirm life and neither hasten nor postpone death [16].

Within the IDT, the skill sets and support of members of differing disciplines and volunteers are critical to the care of the child and family as well as the effective functioning of the team itself. In the traditional hospice model the core disciplines include Medical Director (MD), Nurses, Social Workers, Chaplains, Home Health Aides, Bereavement Counselors and Volunteers. They are available 24 h a day, 7 days a week to respond to the needs of the child and family through providing pain and symptom management, emotional support, psycho-social needs, spiritual concerns and developing long-term goals of care.

In the broader application of PPC, other specialists such as Childlife, Pharmacists, Expressive Therapists, Dietitians, Psychologists, Teachers, Physical/Occupational/Respiratory and Speech Therapists may be included. All play a part in ensuring quality of life for the child and the family during illness, survivorship or the dying processes.

Figure 20.2 shows the traditional model of PC in the adult patient. Curative and palliative/hospice/supportive care are not concurrent. Oftentimes, families receive much needed palliative care too late. The "too little too late" access to care often results in needless suffering for the patient and their families. Figure 20.3 shows us the more progressive model. Curative therapies are pursued along with the introduction of PC from the time of diagnosis for adults with life threatening illness. It is vital to remember that some will have only a limited need for palliative care whereas others will need more intense involvement as the curative focus begins to change to supportive/end of life care. If the family has been introduced to PC early on during treatment the transition to support or hospice care is not so

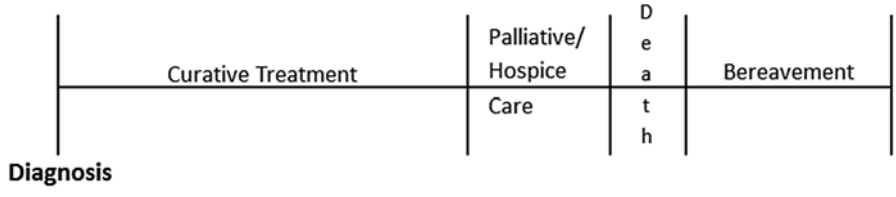

Fig. 20.2 Traditional model of palliative care

Fig. 20.3 Alternative model of palliative care

Fig. 20.4 Pediatric model of palliative care

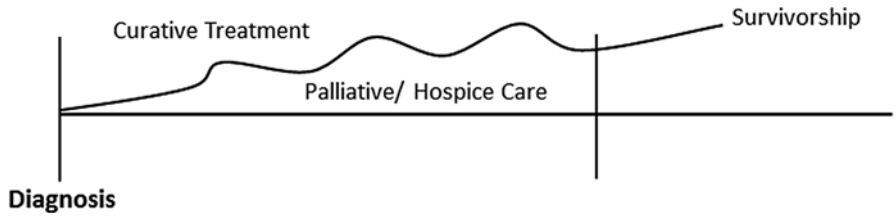

Fig. 20.5 Pediatric model of palliative care and survivorship

disruptive. A more seamless bridge prevents needless suffering and enhances quality of life for the patient and their family. The patient and family are more likely to view PC and even hospice care as not "losing hope" as much as "redefining hope." If death occurs, for grief to progress and the tasks of mourning to be accomplished, bereavement support is essential to be provided.

Notice now the difference in the pediatric palliative care model in Fig. 20.4. "Children are not little adults" as demonstrated by the wavy line depicting their journey through illness. The introduction of PPC is ideally at time of diagnosis for children with life threatening or life limiting illness. The uncertainty of prognosis and a child's physiologic resiliency makes predictions about survival and outcomes difficult [16]. The degree to which PC is needed is often changed and realigned with the child's status. This being the case, it is vitally important that the application of PC to "prevent, relieve, reduce, or soothe symptoms" produced by serious medical conditions or their treatment is provided for children. Avoidable distress and preventable suffering of the child and their family are central goals of PC. If death occurs, the unique needs for bereavement of siblings, parents, grandparents, and extended family members are provided.

The final Fig. 20.5 includes the model for the pediatric cancer survivor and those children with chronic illness. Needs such as chronic pain and its management are well addressed by palliative efforts throughout the child's life. Once again, curative approach and palliative care work together to enhance the quality of life for each child and his family throughout survivorship and cure.

20.4 Barriers to Successfully Addressing Palliative Care

Despite recommendations to refer children to palliative care early in the course of life limiting illness, health care providers vary in how they define Pediatric Palliative Care (PPC), how they access services, and when they would refer a child with a specific disease [17]. The following are the most common barriers.

1. *Uncertain prognosis*. Uncertainty may confuse the goals of care, resulting in dichotomous cure versus palliative care thinking, rather than encouraging the two types of therapy to coexist. Pediatric providers must realize that uncertainty may be unavoidable in the care of seriously ill children. An uncertain prognosis should be a signal to initiate, rather than to delay, palliative care [18].
2. *Ineffective communication*. Ultimately, communication is the cornerstone of quality of life and quality patient care. Quite often the well-intended professional may believe that effective communication will just happen. A commonly accepted definition of effective communication is the transmission of information, such that, what is in the speaker's head gets somehow magically transported to the listener's head so that both agree about the content of the message. We suggest that communication is, instead, the mutual creation of meaning by both communicators [19]. Communication is a complex process in all circumstances, but becomes truly challenging in a time when a child's life is threatened by disease. Parents tell us that what they expect from us are clear, honest words no matter how hard they may be. In a Stanford study they found 30 to 70 % of healthcare providers admitted to being inexperienced in having difficult conversations with families [20]. Ongoing education to teach skills in communication is a goal for all professionals working with children with life threatening illness in order that further suffering may be avoided.
3. *Lack of understanding of PC and families' reluctance to accept PC*. In a survey of pediatricians in Florida and California, the two greatest barriers were related to families' reluctance to accept PC (95 %) and families viewing PC as giving up (94 %) [21]. This may have a direct correlation to the way in which we are educating the healthcare professionals who refer or suggest PC services. The pervasive stigma of what hospice and palliative care mean to the general public and health care professional remains a major obstacle for accessing pediatric programs.
4. *Reimbursement and Regulations*. Reimbursement for children suffers in comparison with that for adults. Financial and policy obstacles interfere with the establishment and delivery of palliative and hospice care to children in the United States [18]. Caring for children with life limiting illness is expensive and although we are making progress with new policy for pediatric palliative care, the reimbursement rates from Medicaid or private insurances do not cover costs. Much is being done through philanthropic efforts to support and establish pediatric palliative care for these children and their families during a time when they need the care the most. One example of a positive outcome was reported in a policy brief examining the Partners for Children Waiver (PFC) in California. This is California's public, pediatric, community-based palliative care benefit to children living with life-threatening conditions and their families. Preliminary analysis indicates participation in the PFC program improves quality of life and reduces by one-third the average number of days spent in the hospital, resulting in a cost savings of $1,677 per child per month. This constitutes an 11 % decrease in spending on a traditionally high cost population [22]. Much advocacy yet is needed.
5. *Limited access and availability*. The advancement of palliative care as a model for care and for professional development in the United States has reached unprecedented levels in

many types of settings. Following that surge is now a robust effort to develop and integrate programs and services for those facing life-threatening diagnosis [24]. In 2000, the American Academy of Pediatrics issued recommendations for an integrated PC model beginning at diagnosis, emphasizing curative therapies and comfort measures to enhance quality of life throughout the trajectory of disease [14]. To date there are only five pediatric palliative fellowships available in the United States to train physicians in this specialty. Although board certification for physicians, certifications for RN's, MSW's, and Advanced Care Practitioners are emerging, many children do not have access to this care. Due in part to geography, (e.g. rural areas) lack of trained pediatric palliative and hospice experts in the community, regulatory restraints, and institutional buy-in, availability for this care remains a challenge.

20.5 Conclusions

The National Coalition for Cancer Survivorship and National Cancer Institute state that an individual is considered a cancer survivor from the time of diagnosis through the balance of his or her life [5]. Family members, friends, and caregivers are also impacted by the survivorship experience. The application of the philosophy and organized programs of pediatric palliative care will work toward securing the highest quality of life during that "balance" however long it may be.

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Part V

Re-Entry After Treatment

Lifestyle Factors and Health Risk Behaviors

21

Vida L. Tyc and James L. Klosky

21.1 Introduction

Despite advances in medical treatments for childhood cancer, many pediatric cancer survivors are at risk for developing treatment-related late effects and second cancers [1–3]. As many cancer-related complications do not become apparent until the survivor enters adulthood, the implementation of timely interventions is critical in preventing or ameliorating late treatment sequelae and their adverse effects. In a recent report from the Childhood Cancer Survivor Study (CCSS), the largest cohort of cancer survivors assembled in the U.S., it was estimated that 42 % of pediatric cancer survivors will experience a serious or life threatening illness by 30 years post-diagnosis, including cardiovascular disease, stroke, pulmonary disease, kidney failure, or second malignancies. In fact, cancer survivors are 8 times more likely than their siblings to experience many of these severe or life threatening health conditions [4]. The practice of unhealthy behaviors such as substance use, poor diet, and inadequate levels of physical activity, can further compound these risks.

As it is now typical for survivors of childhood cancer to live well into adulthood, prevention of adverse late effects and second malignancies, through adoption of healthy lifestyles, is a key component of survivorship care [5]. Long-term health issues, specific to cancer survival, are fast emerging as a public health concern [6]. This chapter will highlight areas of the health behavior profile of childhood cancer survivors that call for intervention and examine promising behavioral lifestyle interventions that may potentially minimize the risks associated with the late effects of cancer treatment. Where possible, we will review current behavioral guidelines and provide specific recommendations for promoting healthy behavioral changes in childhood cancer survivors in the healthcare setting.

21.2 Behaviors that Put Survivors at Risk

21.2.1 Smoking

Cigarette smoking is the single most dangerous behavior associated with preventable causes of cardiac, pulmonary, neoplastic, and other major diseases [7]. Several antineoplastic therapies used to treat pediatric malignancies, including

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radiation therapy and cardiopulmonary toxic chemotherapies, have been associated with organ dysfunction that can be potentiated by cigarette use [4]. Specific to cancer survivors, tobacco use increases the risk of lung cancer among Hodgkin lymphoma survivors treated with chest irradiation by 20-fold [8]. Because of its relevance to a patient's immediate medical condition, smoking status has often been included as one of the "vital signs" [9].

Smoking rates among adult survivors of childhood cancer are slightly lower than that of their healthy counterparts. According to a report from the CCSS, 28 % of cancer survivors reported "ever" smoking and 17 % were current smokers [10]. The prevalence of current smoking was approximately 20 % in a population-based cohort in the United Kingdom, the British CCSS [11]. Similar smoking rates have been reported in smaller survey studies of young adult survivors [12, 13]. These rates are particularly concerning in that survivors are less likely than their peers to successfully quit smoking once having started [14–16]. Smoking is also associated with the practice of other risky health behaviors. For example, an assessment of 796 childhood cancer survivors enrolled on a smoking cessation trial revealed that 31 % of the sample engaged in one or no health risk behaviors in addition to smoking while 63 % engaged in two to three additional health risk behaviors [17]. Approximately 8 % of smokers also reported engaging in risky alcohol use.

Approximately half of childhood cancer survivors who smoke are trying to quit, despite high levels of nicotine dependence which are often reported [18]. Quit attempts were common among survivors in the CCSS cohort with 58 % of current smokers reporting a quit attempt in the previous year [19]. Among survivors who contemplated quitting, not all were confident that they could successfully quit. Characteristics of survivors who made more quit attempts included younger age, increased social support for quitting, perceived vulnerability to smoking-related illnesses, and social networks comprised of non-smokers. Survivors with more smokers in their social networks smoked more heavily. Exposure to household smoking bans and restrictive workplace smoking policies also affect the survivor's smoking behaviors and increase the likelihood of quitting [18]. Based on the reported correlates of smoking among survivors, approaches that increase the survivor's social support for quitting, capitalize on their perceived risk, and engineer their social environment in ways that constrain their smoking behavior appear to be the most promising [18].

21.2.2 Interventions and Recommendations: Smoking

To date, only a limited number of smoking cessation interventions have been empirically evaluated among young adult cancer survivors and these have demonstrated that tobacco use can be reduced in this high risk population. Emmons and colleagues [20] conducted the first randomized smoking cessation trial (Partnership for Health; PFH) with young adult cancer survivors enrolled on the CCSS. In this trial, participants were randomized to either a self-help or peer counseling program that included up to six peer-delivered telephone calls, tailored and targeted written materials related to their smoking behavior and cancer history, and free nicotine replacement therapy (NRT). The peer-delivered intervention focused on building the survivor's self-efficacy and reducing barriers to quitting. A doubling of quit rates at 8-months (16.8 % vs. 8.5 %; $p<0.01$) and 12-months (15 % vs. 9 % $p<0.01$) was observed in the peer counseling condition relative to the self-help condition, and this intervention effect was sustained over time [21]. Although quit rates were higher overall and among NRT users in the peer counseling condition, no significant interactions between NRT use and intervention group were found. These study findings suggest that survivors may benefit from tailored interventions that increase their self-efficacy and behavioral skills to successfully quit smoking. Results also highlight the effectiveness of peer-to-peer counseling as an intervention strategy for smoking cessation that could have

broader application for health promotion interventions conducted with survivors.

Building on the findings from the first trial, a follow-up study was conducted (PFH-2) to examine delivery of intervention components in a more disseminable self-guided format [22]. In the PFH-2 study, participants were randomly assigned to either a web-based intervention or a print materials condition that included provision of self-help materials organized by levels of readiness to quit smoking. Both conditions focused on survivorship issues and included key components of the original PFH-1 peer-delivered intervention, including a letter encouraging smoking cessation from the site oncologist and free pharmacotherapy for participants and their spouses/partners. Smokers who were childhood or young adult cancer survivors were recruited from five cancer centers in the US and Canada.

Equivalent rates of cessation were reported for the two groups (16 %) at a 15-month follow-up; these rates were comparable to the quit rates achieved in the more intensive peer-delivered counseling intervention. Both interventions were viewed as substantive and appealing and were relatively comparable in terms of "dose" based on participant report of use. The use of pharmacotherapy was low in this sample of survivors (requested by 12 % of sample with no differences between the intervention conditions) despite its availability at no cost. Results are promising and suggest that survivorship programs can offer cessation services in either the print or web-format without sacrificing effectiveness. The ability to disseminate effective interventions and provide survivors with options in programming based on their preference is especially important to the survivor community who may not have regular access to treatment facilities or survivorship care.

Results from several studies also highlight the need for routine screening of known risk factors during childhood and adolescence that are associated with later smoking. Klosky et al. [23] demonstrated that intentions for future smoking, reported as early as age 10, was a significant predictor of later tobacco use among adult survivors of childhood cancer. Similarly, childhood attention problems were predictive of smoking in adulthood survivors [24] when assessed nearly a decade later. A nearly threefold increased risk of adult smoking has also been reported among survivors who display antisocial behavior during adolescence [25]. These risk factors may serve as good behavioral markers that inform prevention efforts by health care providers. Cognitive [26], educational [27, 28] and behavioral risk counseling interventions [29] have proven to be beneficial in reducing short-term smoking risk among adolescents with a cancer history. More studies that establish the efficacy of pediatric interventions in preventing smoking onset and progressive smoking during the young adult survivorship years are certainly warranted.

Health care providers can build on the existing literature to address the survivor's smoking by using available systems of care. A strong message from the health care provider to not start smoking, to quit smoking, and to avoid secondhand smoke may motivate behavioral change among cancer survivors. An approach that uses a combination of evidenced-based brief behavioral cessation counseling, pharmacological management of tobacco dependence, and proactive referral to free regional and national tobacco quitlines (e.g. 1-800-QUITNOW) or web-based cessation services may be most effective [30–32]. Free stop smoking quitlines are now available in 50 states and can assist the smoker in forming a quit plan, offer nicotine replacement therapy, and arrange for follow-up contacts. Enrolling smokers in multi-session telephone counseling as an adjunct to face-to face provider-delivered counseling ensures that smokers receive professional, evidence-based ongoing counseling services that may not be otherwise possible. In fact, smokers who use telephone counseling are more likely to achieve long-term cessation compared to those who do not [33]. Treatment components of the current U.S. Public Health Service (PHS) guidelines and the abridged guidelines for physicians are publicly available for review [30–32].

Despite the availability of national guidelines for smoking cessation, rates of tobacco-control service delivery are low within survivorship care settings. A recent survey of 132 institutions with survivorship programs reported that survivors

may not have access to recommended smoking services or resources that could help them successfully quit [34]. Surprisingly, only 3 % of programs screened patients for tobacco use at every visit, 39 % of sites offered smoking prevention, and 25 % offered smoking cessation services. This is in sharp contrast to the PHS guidelines for the treatment of smoking in the healthcare setting that call for routine assessment of smoking status, prevention, and cessation as the standard of care for all patients [30, 31]. Survey respondents clearly acknowledged the significance of the health care provider in the delivery of smoking cessation services as a part of the survivor's ongoing care and rated smoking cessation as more important than cancer screening and other prevention-oriented activities. However, staffing, time constraints, cost of services, and level of interest among survivors emerged as barriers to offering services. In order to improve compliance with PHS guidelines, survivorship programs must first develop an effective organizational infrastructure that allows for identification and tracking of all smokers and promotes consistency of anti-tobacco messaging. Given the evidence that young cancer survivors are more likely to smoke than older survivors [35, 36], delivery of these services early in the survivorship continuum may be necessary.

As in the clinical arena, changes in smoking status are monitored in very few survivorship research trials despite emerging evidence of the effects of smoking on a number of cancer outcomes (e.g. treatment efficacy, toxicities, and morbidity, quality of life, survival time, recurrence) [37]. Lack of adequate support for collection and storage of data is often cited by institutional and cooperative groups as the primary reason for this exclusion. Gritz and colleagues [37] advocate for systematic collection of smoking history and smoking status as core data in all oncology clinical trials. They have identified a list of standardized items used to classify smoking status in both research trials and clinical practice. This important information could add to interpretation of trial outcomes affected by smoking and enhance scientific knowledge in this area.

21.2.3 Illicit Drug Use

Marijuana is the most commonly used illegal drug in the US, and is considered by adolescents and young adults (AYA) to be the drug with the lowest health risk [38]. Yet, several lines of research suggest that marijuana use is a predictor for the development of certain cancers. In a cohort study of 64,855 Northern California Kaiser Permanente subscribers aged 15–49 years, Sidney et al. [39] found that among non-tobacco users, marijuana smokers had a threefold increased risk for developing prostate cancer, and a 1.4-fold increased risk for developing cervical cancer. Using the same cohort, Efird et al. [40] also found a 1.9-fold increased risk of developing adult-onset glioma in individuals who have smoked marijuana, compared to those who never smoked marijuana, after controlling for sex, race, education, smoking status, alcohol consumption, and coffee intake. Although findings are more mixed when considering smaller case control studies, associations have also been identified between marijuana use and head and neck squamous cell carcinoma [41] and lung cancer [42, 43]. The ill effects of marijuana use extend within families as associations between parental marijuana use during the gestational period and childhood cancers including leukemia, astrocytoma, and rhabdomyosarcoma [44–47] have been identified. As one in ten survivors of childhood cancer will experience a subsequent malignant neoplasm in adulthood unrelated to their original diagnosis [48], avoiding marijuana use is important to reducing their risk of future cancers.

Survivors treated with alkylating agents (such as Busulfan, Carmustine, and Lomustine), anthracyclines (such as Danorubicin, Doxorubicin, Epirubicin, and Idarubicin), anti-tumor antibiotics (such as Bleomycin), radiation therapy (including cardiopulmonary organ exposure), hematopoietic cell transplant (with or without chronic graft-versus-host-disease), and specific surgical procedures are already at high risk for cardiac- and pulmonary-related late effects, and marijuana use may further exacerbate these vulnerabilities. For example, in Wolff and O'Donnell's [49]

review of adverse pulmonary effects of illicit drug use, inhaled marijuana use was associated with increased airway inflammation, acute bronchospasm, airflow obstruction, diffusion impairment, emphysema, impaired immunity, and tumor production. Similarly, Tetrault et al. [50] found marijuana use associated with bronchodilation (short-term effect), as well as chronic cough, phlegm production, and wheezing (long-term effects). When compared to tobacco only smokers or non-smoking controls, marijuana users also experienced increased risk for tar exposure, alveolar macrophage tumoricidal dysfunction, oxidative stress, and bronchial mucosal histopathologic abnormalities [51]. Considering these findings, survivors of childhood cancer should avoid marijuana use to protect themselves from further health risks.

Specific to survivors of childhood cancer, historical estimates of marijuana use among AYAs have been reported to be as high as 49 % [52], with more recent studies reporting rates of 10 % for current (within the past 30 days) use and 34–46 % for past/ever use [13, 53]. Findings have been mixed when comparing rates of marijuana use between childhood cancer survivors and their peers. For example, Thompson et al. [53] found that adolescent survivors were less likely to have tried marijuana as compared to race and gender matched classroom peers (34 % vs. 53 %), but no group difference emerged among those with a history of marijuana use in regard to frequency of lifetime, past year, or past month usage. In contrast, significant differences for marijuana use were not found between survivors and siblings [15]. Furthermore, risk factors for ever engaging in marijuana use among adolescent survivors include higher reported number of best friends, being rated as less prosocial by peers, being less sensitive-isolated, and having a history of alcohol, tobacco and illicit drug use [53]. Among cancer specific risk factors, only older age at diagnosis has been positively associated with self-reports of marijuana use.

Although not as prevalent as marijuana use, Bauld et al. [52] reports that 24 % of young adult survivors of childhood cancer have engaged in cocaine and/or methamphetamine use which was captured by the category "other illicit drug use" in their study. More recently, between 0 % and 8 % of adolescent/young adult (AYA) survivors of childhood cancer report current illicit drug use including cocaine, heroin, methamphetamine, illicit steroids, or glue/aerosols sniffing [13]. However, adolescent survivors are just as likely as race- and gender-matched classroom peers to have tried illicit drugs (27 % vs. 24 %) in the past [53]. Of those survivors and peers who reported illicit drug use, the median categorical frequency of lifetime use endorsed by these adolescents was 20–39 times, with median frequency categories of use within the past year and month being 3–9 and 0–2, respectively. Those with a history of using illicit drugs reported having used, on average, three illicit drugs other than marijuana in their lifetime. In addition to tobacco and marijuana use, risk factors for ever having used "other" illicit drugs included increased peer acceptance, higher leadership-popularity scores, and lower sensitive-isolated ratings by classmates [53]. Older age at diagnosis was positively associated with self-reports of illicit drug use, with male survivors being more likely to report high illicit substance exposure as compared to female survivors.

Whereas marijuana use has primarily been associated with pulmonary complications, cocaine and methamphetamine use promotes cardiac problems. Specific complications associated with cocaine use include dilated cardiomyopathy, left ventricular dysfunction, cardiac arrhythmias (including sudden cardiac death), and myocardial ischemia [54–56]. Methamphetamine use increases heart rate and pressure (resulting in irreversible damage to blood vessels in the brain, often producing stroke), and hyperthermia which may result in cardiovascular system failure and death [57–59]. Because survivors of childhood cancer may already have cardiac- and pulmonary-related late effects associated with their cancer treatment, illicit drug use would place this already vulnerable population at high risk for primary and secondary health complications.

21.2.4 Intervention and Recommendations: Illicit Drug Use

The Children's Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers (version 3.0) provides recommendations for the screening/management of late effects based on treatment exposures received during pediatric cancer therapy [60]. The guidelines are organized by therapeutic agent, potential late effect, host/treatment/behavioral risk factors for developing the specified late effect, highest risk factors, along with recommendations for periodic evaluation based on the specific treatment exposure and potential late effect. Illicit drug use is included as a behavioral risk factor for the development of several late effects based on referenced evidence from the literature. For example, in Section #28 (Chemotherapy/Anthracycline Antibiotics) and #71 (Radiation Therapy/Potential Impact to Heart), drug use (including cocaine, diet pills and ephedra) is included as a risk factor for cardiac toxicity, whereas section #36 (Chemotherapy/Plant Alkaloids – vinblastine and vincristine) includes illicit drug use as a risk factor for vasospastic attacks. Clinicians and survivors can refer to these guidelines in managing survivorship care, while accessing the Patient Education Materials or "Health Links" [61] to assist in healthy living after treatment for childhood cancer. More traditional approaches to intervening with those engaging in illicit drug use, drug abuse, or drug dependence may also be necessary in this population. When these cases arise, it is important that the treating clinicians/facility be informed/provided details about the patient's treatment exposures, current late effects, and history as a pediatric cancer patient. This way, safe and appropriate clinical management of the patient's drug problem can be provided.

21.2.5 Alcohol Use

Alcohol has been classified as a Group 1 carcinogen by the World Health Organization [62], and alcohol consumption has been linked to a variety of malignancies including oropharyngeal, esophageal, liver and stomach cancers [63–66], breast and ovarian cancer in women [67, 68], and colorectal cancer in men [69–71]. Risk of alcohol-associated cancer appears to be positively associated with frequency and volume of alcohol consumption, with heavy drinkers being at highest risk for health problems [72]. Although the mechanisms of alcohol-related carcinogenesis are unclear, theories have ranged from alcohol's role in increasing adipose tissue, alcohol's effect on hormonal functioning, cellular vulnerability secondary to alcohol metabolism, and complications in DNA damage/repair [73, 74].

Alcohol may also contribute to the risk of second cancers among survivors [75], and when combined with tobacco use, places drinkers at even higher risk for cancer [76].

Excessive alcohol consumption is already linked with several serious medical conditions including hypertension, stroke, liver cirrhosis and coronary heart disease. Therefore, survivors with chronic hepatitis C, hepatic steatosis secondary to total body or cranial irradiation, anthracycline-related cardiomyopathy, and liver dysfunction after abdominal irradiation are at increased risk for alcohol-related problems [77–79]. As survivors of childhood cancer are often prescribed medications for the treatment/management of various late effects secondary to cancer treatment, alcohol use may be contraindicated in these survivors due to potentially serious alcohol/medication interactions [80].

Previous research describing alcohol consumption among survivors of childhood cancer has been mixed, and definitions of alcohol outcomes (i.e. current drinking, binge drinking, risky drinking, excessive drinking) have varied. Compared to controls (which have ranged from community peers, siblings, or population norms), survivors have been described as engaging in less frequent alcohol use [52, 81–83], equivalent use [84, 85], or increased use [86]. Among adolescent survivors of childhood cancer, Klosky et al. [87] found in age and sex adjusted models that survivors were less likely to engage in current use of beer/wine or binge drinking when compared to siblings,

but were just as likely to consume mixed drinks/hard liquor. When considering young adult survivors participating in the CCSS, Lown and colleagues [88] found that survivors were less likely to report risky or heavy drinking as compared to siblings, but were more likely to be current drinkers as compared to population peers. These findings highlight differences that can result when different control groups are employed in this research literature.

A variety of demographic, psychosocial, and medical/treatment variables have also been identified as being risk or protective risk factors for alcohol use. In regard to demographic factors, being male [86, 88], lower educational attainment [82, 86, 88] and younger age [88] has been associated with increased/risky alcohol consumption, whereas having an African American background [89] and older age at cancer diagnosis [88] has been found to be protective among survivors of childhood cancer. Psychosocial variables such as depression, anxiety (both generalized and specific to cancer), somatization, increased life stressors, life dissatisfaction, activity limitations, and perceptions of poor health have all been linked to increased/risky alcohol consumption among survivors [82, 88]. In terms of cancer specific variables, a diagnosis of brain tumor or leukemia, or cognitively compromising treatment have all been found to be protective of alcohol use [81, 88].

21.2.6 Interventions and Recommendations: Alcohol Use

The American Cancer Society (ACS) recommends that alcohol should be limited to no more than 2 drinks per day for men and 1 drink per day for women [90]. Women have a smaller daily allowance for alcohol consumption because of relatively smaller body sizes, and slower metabolism of alcohol. This recommendation is complicated in that low to moderate alcohol use has been associated with decreased risk of heart disease. However, there are more effective ways of lowering heart disease risk including avoiding tobacco use, maintaining an active/healthy lifestyle (including physical activity, healthy weight, and diet low in saturated and trans fats), along with controlling blood pressure and cholesterol [90]. As such, survivors who do not drink alcohol should not start, and those who do drink should limit their alcohol consumption. For those survivors whose drinking has escalated to include alcohol abuse or dependence, more traditional intervention approaches to address this problem may be necessary. For more information regarding alcohol intervention options among medically vulnerable populations, refer to the National Institute on Alcohol Abuse and Alcoholism webpage at www.niaaa.nih.gov.

21.2.7 Physical Activity

Physical inactivity has been demonstrated to increase risk of metabolic syndrome, type 2 diabetes, cardiovascular disease, hypertension, and osteoporosis in the general population [91–94]. Childhood cancer survivors, particularly those who have been treated for ALL, are at particular risk for these health problems if they adopt an inactive lifestyle. Given their elevated risk of anthracycline-induced cardiac toxicity, childhood ALL survivors must be diligent about meeting recommended levels of physical activity [4, 95–97]. Decreased levels of physical activity, combined with the effects of some pediatric cancer treatments, can also result in many survivors becoming overweight or obese [98, 99].

Although there is considerable variability in the levels of physical activity reported by childhood cancer survivors across studies, they generally appear to be more sedentary than their siblings or peers without cancer [100–102]. Finnegan and colleagues [100] found that young adult cancer survivors were 1.2 times less likely than sibling controls to meet the previous Centers for Disease Control (CDC) recommendations for physical activity defined as 30 min of moderate intensity activity per day on at least 5 days each week or 20 min of vigorous intensity physical activity on 3 days or more per week.

Based on data from the CCSS cohort, 53 % of childhood ALL survivors reported not meeting these same guidelines, and 23 % reported being physically inactive [101]. In a smaller study, 63 % of survivors of different types of cancer were not meeting CDC guidelines for physical activity [12]. The current CDC recommendations for physical activity differ from those that were previously in place at the time most of the research was conducted on this topic. The CDC now recommends that, each week, adults perform 150 min of moderate-intensity aerobic activity or 75 min of vigorous-intensity activity and at least 2 days of muscle strengthening activities [103].

Survivors who engage in low levels of physical activity are likely to be female, older, a racial or ethnic minority, less educated or unable to work, depressed, underweight or obese [101, 102]. Those who received cranial radiation therapy (CRT) or amputation are also more likely to be physically inactive [101, 102]. The long-term effects of CRT have been associated with obesity, growth hormone insufficiency, and problems with balance and posture and these have been linked to physical inactivity [101]. Medulloblastoma and osteosarcoma survivors are at highest risk for physical inactivity. Survivors who smoke are also less likely than nonsmokers to meet CDC guidelines for physical activity [102]. In terms of social-cognitive variables, survivors who report more cons to physical activity are less likely to be active while those with higher levels of self-efficacy for physical activity are more likely to have adopted a physically active lifestyle [100]. Survivors with neurocognitive problems are also less likely to meet the current CDC guidelines for weekly physical activity [104]. Given the inverse relationship between physical activity and neurocognitive impairment [104], it may be that interventions that increase exercise can improve cognitive skills among survivors with deficits, similar to what has been demonstrated with aging adults. Many factors associated with physical activity levels may be modifiable with appropriate interventions that address them as barriers to participation in regular physical activity.

21.2.8 Interventions and Recommendations: Physical Activity

There have been a limited number of interventions to promote physical activity among childhood cancer survivors and most have yielded only moderate success [105–109]. Outcomes have varied across studies and have included cardiovascular endpoints, total exercise time, perceived exercise tolerance, muscle strength, functional mobility, and fatigue. Most studies have relied on self-report measures of physical activity and interventions have been relatively short-term (10–16 weeks).

Features of successful approaches aimed at increasing physical activity levels of survivors have included integration of exercise into their ongoing daily activities in the home setting as opposed to more formalized, structured exercise programs. Home-based exercise programs offer a more appealing and practical option than formalized, structured exercise programs for adult survivors who often report limited time availability as a barrier to engaging in regular physical activity [110]. Using an original home-based exercise intervention for severely fatigued survivors of childhood cancer, Blaauwbrook and colleagues [105] provided participants with pedometers and encouraged goal setting and completion of daily activity logs. Participants also received regular telephone counseling related to physical activity goals that incorporated problem-solving, instruction on lifestyle changes, and self-regulation strategies. Within 10 weeks, significant increases in physical activity and reduced fatigue were reported pre-post intervention and at follow-up. Similarly, improvements in functional capacity, as well as exercise time and tolerance, were reported among survivors exposed to a combined regimen of structured exercise and home-based physical activity [108]. Less robust effects have been reported for survivors who participate in structured exercise programs alone [106].

Given the variability in cancer treatments and types of exercise individuals can do (e.g. aerobics,

strength training, flexibility), it may not be feasible to expect that general training programs or evidence-based exercise guidelines will be developed and universally applicable to all survivors across ages and diagnostic groups. Little information is available about the clinical characteristics of survivors that can predict who will likely benefit from certain exercise training programs with improvements in exercise capacity [111]. There is also insufficient evidence to determine the dose–response relationship between exercise and the management of/or prevention of later health problems [112]. Additionally, challenges remain including how to assist survivors with maintaining high levels of motivation, preventing boredom, overcoming fatigue and achieving long-term participation in physical activity [113]. Therefore, it is likely that interventions will need to be individualized to survivors based on age, gender, functional status, time availability, exercise experience, and personal limitations [113].

Encouraging survivors to engage in regular exercise that promotes achievement and maintenance of adequate fitness levels should become part of routine survivorship care [114]. If it is determined that the survivor is physically deconditioned through exercise testing, it is important to examine whether the deconditioning is due to inactivity, nutritional status, medications, or disease or treatment-related pathophysiology [111]. Recommendations regarding the type, frequency, intensity, and duration of physical activity that will optimize the survivor's long-term health should be considered when designing an individual survivor's exercise prescriptions. Lower aerobic capacity and reduced muscle strength have been reported among children, adolescents, and young adults who have survived cancer compared to their peers who have never had the disease [115–117]. Therefore, it is possible that survivors may report higher fatigue levels, slower recovery times, and slower adaptation times [111]. Adverse effects of treatment (e.g. cardiac compromise secondary to anthracycline exposure) may also require caution in considering exercise type and intensity [116]. Longer exercise programs, however, may be beneficial for survivors with weight management goals. Provision of information about the potential benefits of regular exercise, activity-related side effects, and strategies to overcome perceived barriers to exercise may be necessary to promote more frequent exercise among this vulnerable cohort [118].

21.2.9 Nutrition

Healthy nutritional practices can help prevent or ameliorate obesity, cardiovascular disease, osteoporosis, and secondary cancers [64, 119–121], complications often associated with treatment for childhood cancer [4]. Yet, the nutritional habits of many childhood cancer survivors are not consistent with dietary recommendations that may help reduce their risk of these health problems and other chronic diseases. Overall, survivors report dietary behaviors that are similar to those in the general population [122–127]. Many survivors consume high fat diets, do not maintain adequate fruit and vegetable intake, and do not meet recommended dietary intakes for vitamins D, Calcium and other important nutrients [122, 125, 127]. One study reported that although half of their sample of adult survivors of childhood ALL met the minimum daily goals of fruit and vegetable consumption and dietary fat restrictions, participants reported dietary sodium and added sugar intake that exceeded recommended levels as well as low consumption of dietary fiber [125]. Adherence to dietary guidelines was not associated with either body mass index (BMI) or waist circumference in this study. Another study of long-term survivors of childhood ALL [127] found that reported carbohydrate and fat intake exceeded recommendations in 38 % and 47 % of the participants, respectively, at the expense of foods high in nutrients important to bone health.

To date, the dietary research with childhood cancer survivors has been characterized by a number of methodological limitations. Studies have been cross-sectional in design, are based on small samples, and few include adequate control groups or standardized measures of dietary intake [3, 122, 125]. The literature has demonstrated, that like healthy populations, survivors who eat a

healthy diet are likely to be younger, female, more educated and from higher SES backgrounds, and non-minority status [83, 118, 122]. Dietary patterns of minority survivors have also been largely ignored [126].

21.2.10 Interventions and Recommendations: Nutrition

Intervention research in the nutritional arena has been limited in quality and quantity such that little specificity is provided regarding the unique dietary needs of various cohorts and minority survivors [128]. These limitations should not diminish the importance of educating survivors about a healthy diet, which is an integral part of comprehensive care for the childhood cancer survivor. Current dietary guidelines for cancer survivors closely mirror the recommendations for primary cancer prevention [64, 129]. Several private organizations and federal agencies [64, 129, 130] provide nutritional guidelines that can promote health and reduce risk of chronic disease.

Like their healthy peers, cancer survivors may benefit from health messages and behavioral interventions that promote increased nutrient density of their diets while encouraging a healthy body weight. Additionally, development of evidence-based and risk-based guidelines that recommend healthy food choices associated with reduction of serious treatment-related late effects are clearly warranted. Low consumption of fruits and vegetables, low dietary fiber intake (e.g. few whole grains), and increased sodium and sugar provide targets for intervention. Likewise, dietary interventions should focus on minimizing intake of foods high in saturated fat and refined carbohydrates while ensuring adequate intake of vitamins D, potassium, magnesium, calcium, and folate [127]. Cohen and colleagues [131] reported that a large proportion of childhood cancer survivors, less than 13 years of age and less than 5 years from completion of treatment, were consuming more than their recommended energy requirements, placing this group at risk for obesity and associated endocrine and metabolic disorders over time. Additionally, adolescent studies provide evidence that ALL survivors who are at increased risk for being overweight are those who are overweight (BMI for age $\geq$ 85th percentile) at the end of therapy [132]. These findings suggest that preventative interventions, which promote good nutrition and minimize weight gain among young survivors, be initiated early in treatment to soon after treatment, to prevent potential late effects.

21.2.11 Sun Protection

Non-melanoma skin cancer [NMSC] (including primary basal cell carcinoma and squamous cell carcinoma) is rapidly increasing in the U.S. and represents the most common form of cancer diagnosed today [133–135]. If not detected early, lesions associated with NMSC are often locally invasive and responsible for considerable morbidity and significant health care costs [136]. In the general population, an increased likelihood of developing skin cancer is related to genetic predisposition and exposure to environmental risk factors. Ultraviolet (UV) radiation, from sun exposure, and non-solar forms of ionizing radiation are well known risk factors [137].

According to the CCSS report, skin cancer is the most frequent occurring subsequent cancer in the survivor cohort with NMSC accounting for 41 % of all confirmed subsequent cancers and melanoma for 3 %; 46 % of patients have had multiple occurrences. Although NMSC is a diagnosis primarily of older adults, it was found to occur at a much younger age in the CCSS cohort than expected in the general population, with nearly half of cases occurring in patients less than 30 years of age [136]. Ninety percent of tumors occurred on areas of the skin previously exposed to radiation therapy [136] and radiation therapy was associated with a 6.3-fold increase in risk. Long-term childhood cancer survivors with a history of radiation therapy are at highest risk for developing NMSC and may further increase their risk through sun exposure.

The impact of sun exposure can be dramatically reduced by practicing protective behaviors such as wearing protective clothing, using sunscreen, and

avoiding sunbathing and artificial tanning. An examination of sun protective behaviors among cancer survivors in the CCSS cohort, compared to their siblings, found similar self-reported patterns of sunscreen use and lower rates of sunbathing and artificial tanning behaviors in the previous year among survivors [138]. Most notably, 61 % of CCSS survivors and 60 % of survivors with a history of prior radiation therapy, engaged in sunbathing at least once in the previous year, thereby increasing their exposure to UV radiation. Compared with survivors who did not receive prior radiation therapy, those with radiation therapy exposure showed increased use of sunscreen and less sunbathing and artificial tanning practices. Given that risk-based recommendations are more likely to be provided to survivors at highest risk (those previously exposed to radiation therapy) [139], the better sun protective behaviors practiced by high risk survivors may reflect compliance with these recommendations and suggest an association between perceived risk and lowered engagement in risky behaviors. Increased use of sun protective behaviors among survivors was associated with lighter skin complexion, being female, having had a previous examination for skin cancer, and a history of sunburn. These same characteristics are associated with increased use of sun safety behaviors among the general population [140]. Because of the survivors' increased risk of skin cancer from therapy-related exposures, intervention aimed at reducing their UV exposure and promoting adherence to risk reduction practices is clearly warranted [138].

21.2.12 Intervention and Recommendations: Sun Protection

Promoting sun protection practices, regular skin cancer screening, and careful skin cancer examinations, are reasonable risk reduction strategies for survivors. However, there have been no randomized trials testing these outcomes in childhood cancer survivors. Approaches that have been effective in promoting screening and sun protection behaviors in the general population provide evidence for utilization of similar strategies (e.g. free skin cancer screening, provision of sunscreen, and promotion of routine skin self-examination) in high risk populations. A few randomized trials have targeted adults at high risk for skin cancer [141–143], and concluded that low-cost, tailored risk communication about skin cancer prevention practices can improve sun protection and skin self-examination behaviors. Interventions have typically consisted of some combination of tailored print materials, personalized telephone counseling, links to free skin screening programs, provision of skin self-examination instructions and practice tools, as well as discussion of barriers to better sun protection and strategies to motivate oneself to engage in greater protection. Although the effects from these studies have been modest and behaviors have been difficult to sustain, these interventions merit consideration for use in high risk survivor populations.

For example, Manne and colleagues [143] compared a tailored intervention, consisting of three print mailings and one telephone session, to a generic intervention including these same components, delivered to first degree relatives of melanoma patients who were non-adherent to practices associated with skin cancer risk reduction. Although both interventions resulted in increases in total cutaneous skin examinations (TCE) by a health care provider, skin self-examinations (SSE), and sun protection habits assessed at a 6 and 12 month follow-up, the tailored intervention yielded stronger effects. An almost two-fold increased probability of having a TCE was noted in the tailored intervention group with effects of lesser magnitude reported for SSE and sun protection behaviors.

Using a similar tailored messaging approach, Geller et al. [141] conducted a randomized trial to improve early detection and prevention practices among siblings of recently diagnosed melanoma patients. In this study, investigators evaluated an intervention that included telephone counseling and individualized educational materials tailored to the participant's level of engagement in three target behaviors (e.g. skin self examination, physician screening, and sun protection),

self-efficacy, and beliefs based on responses to a baseline survey. For the usual care condition, melanoma patients were advised by their physician to notify their family members of their diagnosis and encourage screening for family members. Compared to the usual care condition, higher rates of skin self-examination were reported among siblings in the intervention group at 12 months. Improvements in the quality of skin self-examination were also noted. Rates of physician examination and use of sunscreen increased in both groups but there were no group differences in these behavioral practices at 12 months relative to baseline. The higher standard of care used in this study may have lessened the observed intervention effect and contributed to the lack of group differences from baseline to follow-up for these two primary outcomes. Other studies have demonstrated that the use of pictures and photographs, paired with written educational information or a nurse-delivered intervention, may increased patients' adherence to performing skin self-examination [144] and affect one's perceived benefits of engaging in sun protection behaviors [145].

In the absence of proven therapeutic interventions for childhood cancer survivors, health care providers can, at minimum: (a) provide personalized risk information to their patients, (b) encourage regular surveillance for the development of NMSC, and (c) verbally promote increased utilization of sun protection precautions and avoidance of exposures that increase their risk of NMSC. Early detection is also an important tool in skin cancer control, particularly for fair-skinned and sun-sensitive survivors at increased risk due to previous radiation therapy. Delivery of prevention messaging through provision of brochures, tailored materials, instructional sheets, and referral to websites containing "how to" instructions with pictures for performing quality skin self-examinations, is an inexpensive and practical intervention. Information that is tailored to the survivor's treatment history, beliefs, and current behaviors is likely to be viewed as personally relevant and more motivating [146]. Identification of sun protection intentions, perceived benefits, and self-efficacy as mechanisms for change in the practice of skin cancer reduction behaviors [143] has important clinical implications for survivors. It may be important to increase the survivor's confidence that he/she can incorporate protective behaviors, such as sunscreen use, into their daily routines. Intentions could also be targeted by requiring the survivor to commit to times and places to conduct self-examination or undergo an examination by a health care provider [143]. Further testing of convenient, low-cost tailored communications, that address the benefits and barriers of behavioral practices, will be important in achieving optimal skin cancer risk reduction in the childhood cancer survivor population.

21.2.13 Risky Sexual Behavior

Risky sexual behavior has recently been highlighted as a prioritized area of study among survivors of childhood cancer due to its discovered association with sexually transmitted infection (STI) and cancer. Genital human papillomavirus (HPV) is the most common STI [147, 148] and will affect the majority of sexually active people in the US [149]. Among females, for example, up to 80 % will experience lifetime HPV-acquisition [150–152] with prevalence reported at 40 % among 14- to 19-year-olds and 49 % among 20- to 24-year-olds [153] among sexually active AYAs. Oncogenic HPV strains have been linked to cervical, vaginal, vulvar, penile, anal, and oral cancers. Cervical cancer is the second most common cancer among women worldwide and the leading cause of cancer-related deaths in developing countries [133]. Regular screening using the Papanicolaou (Pap) test has been the most successful method for identifying cervical intraepithelial neoplasia, a precursor to cervical cancer. Because engagement in cervical cancer screening is variable, and cervical cancer is typically asymptomatic until it has progressed beyond the point of effective treatment, primary prevention of cervical and other HPV-related malignancies is the logical next step. Both males and females experience complications related to HPV infection, but the primary health threat is

for women. As such, the bulk of this review will focus on risky sexual behavior and HPV-related complications among females surviving childhood cancer.

Women surviving childhood cancer are at increased risk for HPV-related complication due to a variety of medical, cognitive, behavioral, and demographic factors. Children and adolescents with a history of hematopoietic stem cell transplantation (HSCT), for example, experience extreme immunosuppression as a result of pretransplant conditioning. Although most patients achieve immune reconstitution by 2 years post-transplant, many do not. Slowed or complicated immune recovery in these survivors increases the likelihood of infection from bacteria, fungi and viruses, such as HPV [154]. Similarly, generalized immune suppression is a classic disease feature of Hodgkin lymphoma and this immune deficiency is worsened by cancer treatment, often persisting long after treatment [155–158]. Women with a history of pelvic irradiation are also more likely to experience HPV-related cervical and vaginal dysplasia and carcinomas of the genital tract with the etiology being attributed to recurrence of original malignancy, mutation of cervicovaginal mucosa cells due to radiation exposure, natural HPV dysplastic processes, or a combination of these mechanisms driven by treatment-induced immunosuppression [159, 160].

Sexual behavior is a necessary cause of genital HPV infection, but it has been suggested that survivors of childhood cancer are at decreased risk for STIs secondary to decreased engagement in risky sexual behavior. Recent data suggests that this may not be the case. When risky sexual behavior was examined among a large cohort of adolescent survivors of childhood cancer and their siblings, no differences were identified across groups in regard to history of sexual intercourse, age at first intercourse, lifetime number of sexual partners, or method used to prevent pregnancy or STD at last intercourse [87]. However, Sundberg and colleagues [161] examined differences in sexual behavior across adult survivors and community control groups and found that female survivors reported experiencing fewer sexual partners in the last 12 months, and fewer partnered relationships. Male survivors reported fewer lifetime sexual partners (8.6 vs. 12.6) as compared to controls. Across diagnoses, males with a history of CNS tumor had fewer sexual partners within the last 12 months and in lifetime compared to other diagnostic groups but no differences were found across women.

It is also important to note that survivors who perceive themselves to be infertile may be at particularly high risk for engaging in riskier sexual behaviors, which in turn, increases HPV exposure risk [162]. Survivors are more likely than non-cancer population controls, for example, to report having experienced a high risk HIV transmission situation [84]. Cognitive deficits, including inattention and hyperactivity, are commonly reported late effects of cancer treatment [163, 164] and may also contribute to engagement in risky sexual behavior. Evidence linking inattention and/or hyperactivity to increased risky sexual behavior (e.g., earlier initiation of sexual activity, increased number of partners, increased casual sexual encounters) has been established among those with a history of ADHD [165]. As survivors of childhood cancer are at risk for experiencing executive dysfunctions of this nature, they are consequently at increased risk for unplanned/impulsive engagement in risky sexual behavior (with or without being influenced by alcohol and/or illicit drugs) and contracting STIs, such as HPV.

In population-based studies, the expression of cervical cancer has been associated with lower education, lower household income, and Hispanic ethnicity [166]. Socioeconomic differences in male and female sexual behavior, along with access to cervical cancer screening, have been suggested to potentially explain these findings [167]. Among childhood cancer survivors, women who are college educated, medically insured, and older are more likely to have undergone Pap testing within the previous 3 years as compared to survivors who are less educated, without insurance, and younger [168]. As survivors of childhood cancer are more likely to report unemployment, lower educational attainment, and lower annual incomes as compared to their siblings [169], they are at increased risk for cervical

cancer and suboptimal cervical cancer screening as a socioeconomic consequence of their childhood cancer treatment.

21.2.14 Interventions and Recommendations: Risky Sexual Behavior

Despite their increased risk for cervical dysplasia and cancers, female survivors of childhood cancer are not engaging in cervical cancer screening at rates recommended by the American Cancer Society. After adjusting for age, ethnicity, education, income and health insurance, women surviving childhood cancer are less likely than their healthy siblings to have undergone a Pap smear within the previous 3 years [168], with Hispanic survivors being the least likely to have undergone this screening [89]. Survivors of childhood cancer without insurance and those over the age of 30 years are already less likely to report secured medical care, and this risk increases as the survivor ages and time since diagnosis increases [170]. Although interventions are needed to increase cervical cancer screening among survivors, increased attention has been placed on primary prevention.

Recent efforts to reduce cervical cancer have led to the development of vaccines to protect against HPV, which are currently available and have been demonstrated to be safe and clinically effective [171–173]. In June of 2006, the U.S. Food and Drug Administration [174] approved Gardasil (Merck & Co., Inc.), a quadrivalent vaccine developed to protect females aged 9–26 years from HPV types 6, 11, 16, and 18, which together account for 70 % of cervical cancers and 90 % of genital warts [175]. Then, in October of 2009, Gardasil was approved for use in U.S. males 9–26 years of age to protect against genital warts, and in 2010 this indication expanded to include protection against HPV-related anal cancers [176, 177]. Also in 2009, Cervarix (GlaxoSmithKline), a bivalent vaccine that protects against HPV types 16 and 18, was approved for use among U.S. females [176]. In clinical trials, these vaccines, when administered as directed, were efficacious in providing safe and effective protection for males and females against the specified HPV types [173–180]. Based on these favorable findings, routine HPV vaccination is currently recommended by the Advisory Committee on Immunization Practices (ACIP) for adolescent girls aged 11- and 12-years [173], and girls should initiate the vaccine series prior to the onset of sexual activity due to the mechanism of HPV transmission [174]. Based on this and other evidence, the *Children's Oncology Group's Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent and Young Adult Cancer Version 3.0* has recommended HPV vaccination for all eligible females surviving childhood cancer [60]. The endorsement of the HPV vaccine by these guidelines is an important first step in addressing the need for HPV vaccination in childhood cancer survivors, but interventions are needed to translate these recommendations into a successful HPV vaccination strategy.

21.3 Conclusions

Although engagement in healthy lifestyles could prevent or reduce the impact of some chronic health problems associated with childhood cancer treatment, findings across studies demonstrate that childhood cancer survivors are no more likely than their siblings or the general population to engage in health protective behaviors. The fairly high rates of tobacco use, physical inactivity, inadequate nutrition, and heavy alcohol use are disappointing, particularly if survivors have been informed of their treatment exposures and related risks during routine medical care visits and risk-based long-term follow-ups. Results from health behavior studies also suggest that individual-level factors such as knowledge and perceived risk are not sufficient to motivate change among survivors. Although not adequately studied, interpersonal, community, and environmental influences may be more important predictors of behavioral change among survivors.

While the current literature provides a good description of health behaviors among childhood

cancer survivors, relatively few specific recommendations for effective behavioral risk-reduction approaches have emerged. Overall, studies that have evaluated the impact and durability of targeted behavioral interventions have not been impressive. Unfortunately, the methodological weaknesses of these studies limit their impact such that there remains an unmet need for more rigorous behavioral interventions, with proven efficacy, in various high risk survivor populations. Limitations have included single site convenience samples, lack of appropriate comparison groups, lack of theoretical frameworks to guide methodology, and use of non-standardized measures [126]. Most studies have limited information on racially diverse populations, as most have included an over-representation of white non-Hispanic participants. Additionally, the majority of interventions have largely focused on a single health behavior. As risky behaviors typically co-occur, it remains to be seen if interventions that target multiple behaviors are more effective.

As the health behavior profiles of childhood cancer survivors resemble, but are not identical to those of their healthy counterparts, it is not clear whether survivors would benefit from the same interventions developed for their peers without a cancer history [181]. Additional research on whether the factors that facilitate or impede behavior change are similar between survivors and their healthy peers, and how much of a role their cancer status plays in health behavioral outcomes, may shed light on this question. Based on some of the successful research conducted to date, is likely that promotion of healthy lifestyles in the survivor population will require development of uniquely targeted interventions [181]. Whether these interventions are effective in promoting biomarker-validated behavioral changes that ultimately impact health status and other disease-related endpoints has yet to be determined. Despite these remaining questions, opportunities exist for health care providers to make use of existing findings cited in this chapter to inform their practices and promote lifestyle changes that may improve the health and quality of life for survivors. For additional information, clinical practice guidelines for screening and management of potential late effects resulting from treatment for pediatric cancer are available through the Children's Oncology Group Long-Term Follow-Up Guidelines [182].

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School Issues and Educational Strategies for Survivors of Childhood Cancer

22

Kathryn M. Kirkpatrick

22.1 Introduction

The concept of a "truly cured child" was presented by van Eys [1] and defined as "the hope that he will eventually die of old age from unrelated causes," but even more than that, "…even the children who will die are treated as individuals and accepted as normal among their peers" (p. 166). A cure is never guaranteed for the child with cancer and even with a cure to the disease there are chronic, long-term impacts of having lived through the diagnosis and treatment experiences. Some of those impacts are directly related to academic and social functioning. If a child is expected to have a shortened life and is not treated with normal expectations and opportunities, he cannot be truly cured, even when the disease is no longer an active menace. Emotional, social, and mental development may be distorted by the lack of normalizing childhood experiences.

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22.2 School Transition and Interventions

The importance of school for survivors of childhood cancer has gained attention over the last few decades as long-term survival rates have increased. Five-year survival rates for children diagnosed with cancer at the age of 14 or younger have climbed from approximately 58 % in the 1975–1977 era, to nearly 83 % in the 2002–2008 timeframe [2]. School intervention and re-entry programs for childhood cancer patients have also grown and there is little debate about the value of such programs [3–6]. School intervention programs are typically designed to provide education to peers, teachers, and other school staff about cancer treatment and consequences experienced by the patient/student, and to provide support for the student during the process of reintegration to daily school life after an extended absence [4–8]. Researchers have found that peer education makes the student's transition back to school more successful [4, 5, 9, 10]. Teachers and other school personnel benefit from education about the disease, treatment, physical and cognitive side-effects, and psychosocial issues as it may reduce some of their own anxiety about a child's return to school after a long absence related to serious illness [9–13].

There are a variety of resources available that outline components of successful school reintegration and intervention programs [3, 4, 8, 14].

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Some of the recommended components of any program include education, collaboration, and long-term monitoring of academic progress. Information for parents and patients about the potential cognitive effects of treatment, education, and disability rights and an understanding of ways to advocate for the child's needs are all important elements of any program. School staff and peers also need education about the disease and treatment effects to calm any anxious misconceptions and to help the relationships retain as much normalcy as possible. Collaborative efforts between the medical team, school personnel, and family are important to insure adequate academic progress and access to any necessary supports for the student [3, 4, 15, 16]. School intervention programs often include a school liaison based at the treating medical center to provide the education for peers and school staff. The liaison may also be available to help advocate for the needs of the cancer survivor in the school setting. School psychologists are also able to fill the liaison role by collaborating with the medical team and providing support to the student and family. The medical team, both specialty and primary care, can help monitor for cognitive late effects and make early, appropriate referrals for assessment. School personnel can also monitor closely for cognitive late effects and can have a low threshold for referral to the assessment system within the school structure at early signs of struggle. Collaboration of local care providers and school personnel may be especially important when the survivor's treatment is complete and they transition back to the general medical community for long-term care.

Researchers have also focused on the academic prognosis or outcomes for students with a history of childhood cancer [11, 17–23]. Some of the specific mechanisms of cognitive late effects have been reviewed in other chapters of this volume. In this chapter, our intention is to review basic information and discuss how those effects disrupt the typical development of a child in ways that can interfere with the course of schooling and plans for young adulthood. It is important for parents, medical providers, school personnel, and other care providers in the community to understand how the interruptions might impact academic performance, motivation and long-term outcomes. It is important to identify any concerns early so interventions can be put into place and optimal outcomes can be promoted. All caregivers involved with the survivor should have some awareness of school related issues and remedial resources so early referrals for intervention are possible.

As students move through the multiple transitions related to schooling during their treatment and survival of a pediatric cancer diagnosis, stages and phases of development impact the adjustments that must be made. At this point, for reference in thinking about the challenges the students must navigate, we will review some basic elements of psychosocial and cognitive development, as well as a theoretical framework for academic motivation. Students are negotiating these phases of development while they carry the history of their disease through their academic career.

22.3 Erikson's Theory of Psychosocial Development

Erikson's theory of psychosocial development [24, 25] provides grounding for understanding the social and emotional changes experienced by children as they move from preschool and early elementary school age to adolescence and then on to the world of a young adulthood. There are four stages of Erikson's developmental progression that are particularly relevant for students from preschool age through young adulthood: initiative vs. guilt (3–6 years); industry vs. inferiority (6–12 years); identity vs. role confusion (12–20 years); and intimacy vs. isolation (18–25 years).

22.3.1 Preschool

Preschool children and those ready to enter kindergarten are typically working on the task of developing initiative in exploring the world rather than experiencing guilt around interfering with others. During this phase, it is important for young children to experience opportunities to interact

with others and explore their world to learn about how they can have an impact without developing a sense of self-doubt. When children successfully negotiate the initiative vs. guilt stage, they will move on with a sense of being a capable self.

When a preschool child is diagnosed with cancer they are faced with many painful procedures and isolation from social and community learning experiences. It is the work of creating a sense of initiative and purpose that is interrupted. The young child will likely be denied opportunities to interact with typical peers, non-related adults, and experiences with the world that could allow the building of a sense of being a capable individual.

22.3.2 School-Age

Negotiating the stage of industry vs. inferiority is the task of elementary school age children who are learning to do many new things and do them well. A sense of industry develops when the child is able to practice tasks that are useful and develop a mastery of those tasks or skills for both the purpose of self-satisfaction and to show important adults how capable one is of meeting the demands of the world. Interactions with parents, peers, and other adults in the community help with the development of social skills during this phase. Children have generally mastered a sense of industry and feelings of competence (or conversely, developed a sense of inferiority if the life experiences have been negative or thwarting) by the time they reach puberty [24]. After successful development of a sense of industry, the young adolescent will move on to the work of identity development.

If a child is undergoing treatment for a pediatric cancer diagnosis during the early elementary school years, they may have limited opportunities to practice new skills and behaviors. Without the practice they may have difficulty moving successfully through this stage without feeling less than capable in many areas of life. Children who are experiencing cancer treatment during the early elementary years may become very competent in treatment related behaviors (pain management, self-control, and communication with adults), but they miss the opportunity to develop age appropriate skills in a setting with same-age peers.

22.3.3 Adolescence

The major psychosocial task of the adolescent is the resolution of a developed sense of identity versus role confusion, with of goal of establishing a personal sense of well-being. This work must happen in the social milieu of the young person moving through middle school and high school. It also happens while young adolescents are experiencing changes in physical bodies. Adolescents in this stage of psychosocial development may be preoccupied with the perceptions they believe others have of them and how those perceptions fit with the beliefs they hold about themselves. As the young person works to integrate the different ideas of who they seem to be, they develop an ego identity—an understanding of their own needs, beliefs, abilities, interests, and resources. Much of this work involves opportunities for experimentation, choice, and decision during a period that Erikson [26] says allows the adolescent to "find a niche in some section of his society, a niche which is firmly defined and yet seems to be uniquely made for him" (p. 225).

Diagnosis and treatment during the period of adolescence may interrupt the process of identity development and, if the child has not mastered a sense of industry and competence at the elementary level, may cause difficulty for settling on an identity that is satisfying. There are many potential treatment related changes in physical appearance that must be incorporated into a sense of self.

Marcia [27] extended Erikson's concept of identity development and defined four potential identity statuses that can be incorporated by a young person, typically toward the latter end of the adolescent period. The "identity achieved" status represents a state in which the young person has explored viable options for him or herself, chosen his or her own vocational path and belief systems, and moved into a state of commitment to the chosen identity. A "foreclosed identity" exists when the adolescent follows a

direction in vocation and belief systems that have been imposed by parents, without any exploration or challenge of the parental choice. "Identity diffusion" is characterized by a lack of direction or ideology, even if there has been an exploration experience. There may actually be a pause in active identity development, during which an adolescent actively seeks out vocational or ideological direction. This pause is considered a "moratorium" status that puts the formation of identity on hold for further exploration.

Arnett [28, 29] has suggested that adolescence gives way to a stage of "emerging adulthood," a period of psychosocial development between adolescence and young adulthood. Emerging adulthood is a phase of development that can only occur in cultures that allow for the extended period between adolescence and adulthood; it is generally an available avenue of development for those aged 18–25 in the United States and Europe. Emerging adults are working on continuing identity development but are doing so with some release of restraint that is present in adolescence. Young people in this age range are generally more independent of their parents and have more autonomy in personal, relational, and vocational decisions. Arnett divided young adulthood described by Erikson into two distinct phases with the first part being emerging adulthood and the later part (late 1920s and 1930s) classified as young adulthood. The identity statuses defined by Marcia [27] also tend to agree with a period of emerging adulthood. Madan-Swain and colleagues [30] reported that chronic illness may have negative impact on identity formation. They found a higher rate of identity-foreclosed status in childhood cancer survivors than in healthy controls. However, there was no difference in achieved status between the two groups, perhaps suggesting that some survivors may choose a foreclosed identity status rather than challenge and explore in a stage of moratorium. When survivors of childhood cancer are preparing to move on to an independent lifestyle they may face cumulative concerns from the previous stages of interrupted learning and development. They may need time to adjust and recoup missed life lessons and experiences.

22.3.4 Adulthood

After resolution of the identity vs. identity diffusion stage, adults move into a stage of development that involves the task of creating intimacy vs. isolation [24, 25]. It is helpful to think about some of the tasks of this stage as preparing for long-term relationships and quality of life outcomes. Young adults are moving into a career/job that they have chosen as a part of the identity development process and now their energy moves toward the task of building intimate relationships with others or moving toward a state of isolation. Intimate relationships include elements of mutual trust, sexual gratification, and responsibility, without which the young adult will likely withdraw into isolation or self-absorption [25]. Thwarted resolution of intimacy and affiliation qualities will likely lead to a more rigid, less warm style of interaction with others that prevents the development of fulfilling relationships [24].

As an individual moves through the stages of psychosocial development, ideally a sense of competence and self-understanding will evolve, one that can fuel motivated behaviors and growth toward each new stage of life. During the same years of growth, cognitive development is taking place, allowing for problem-solving skills to emerge.

22.4 Piaget's Theory of Cognitive Development

Piaget's theory of cognitive development [31–33] outlines stages the child must progress through to have an adult understanding of the world. Progressing through the sequential phases is a product of individual qualities interacting with the world outside the self [31]. It is in this interaction that knowledge is constructed and the individual develops cognitive capacity. The theory identifies four specific factors which contribute to the construction of knowledge or intelligence and allow the individual to internalize the information provided by the world in new ways: maturation of the individual, experience with the physical environment, action within the social

environment, and equilibrium or self-regulation [31]. The factors play a collaborative role in the cognitive development of the individual.

22.4.1 Sensorimotor Stage

Infants to the age of approximately 2 years are learning about their own body and the world through direct experience. A young child will only be able to reference what they can feel, see, hear, and taste—anything in the abstract does not yet exist in the mind. A child in this stage will be learning about how their own body can be directed to act and how it can interact with the world around to cause desired outcomes. When an infant undergoes the treatment required for a cancer diagnosis, the experiences of pain and other adverse effects can be confusing and frustrating because the experiences do not submit to the typical cause-effect rules or relationships the child is learning. The incongruence can lead to distrust or anxiety because the world is not consistent. The infant will likely need extra amounts of reassurance and security to continue exploration of the world.

22.4.2 Preoperational Stage

Cognitive skills of preschool and very early elementary age children are generally developing in the preoperational stage. In the stage of preoperational cognitive processing, a child is very egocentric. The child cannot mentally manipulate information and cannot perceive information from another's point of view. Children in this stage of development learn by pretending or imitating the world they see around them. They are also using experience with the world to learn about the concept of conservation (i.e., that things can look different but still maintain basic qualities).

During the course of treatment for a pediatric cancer diagnosis, a preschool child may need many opportunities for medical play or may benefit from reading stories to help acclimate to the environment. They may experience unrealistic fears (i.e. all their blood will come out during a lab draw) and can benefit from routine. Magical thinking is prevalent during this time, leading to many different ideas about causes and effects. If a child of early elementary age is experiencing cognitive late effects they may not have full memory of their previous treatment and may need reassurance that they are not at fault for their struggles. Sometimes the traumatic experiences of treatment may lead to higher levels of anxiety for a child and they may need support for fears that are a result of the previous medical experiences.

22.4.3 Concrete Operational Stage

The stage of concrete operations begins to emerge at approximately 6 or 7 years of age and generally lasts through age 11 or 12 years [31–33]. It is during this stage that children begin to use reason and logic in their thinking. A child at this stage can consider an experience on a mental level and is able to use (internal) operations such as classification, conservation, transformation, and reversibility. Although a child in the concrete operational stage is becoming a better problem-solver, it is still necessary for the problem to be visible or real. A child at this stage cannot use the operations on hypothetical or abstract problems or to solve problems with many variables that must be represented mentally in the process [31, 33]. This is also a stage of becoming less egocentric and more social. The child in a stage of concrete operations can begin to understand that others in the social environment have different thoughts or conclusions to be considered and they learn to understand the differences through social interaction and discussion [33]. This reduction in egocentric thinking allows the child to work cooperatively with others and to identify autonomous activity and self-regulatory practices [33].

The elementary age child may become very proficient at cooperating with a treatment regimen but may also continue to have unrealistic beliefs about the cause of the cancer diagnosis, symptoms or late effects. Children at this stage of thinking need clear explanations of procedures and symptoms and need the opportunity to

explore questions. They are beginning to be able to use planning and rehearsal to prepare for unpleasant events with appropriate guidance.

22.4.4 Formal Operational Stage

Piaget's stage of formal operations emerges at age 11 or 12 years and is generally developed by the time an adolescent reaches the age of about 15 years [32, 33]. Formal operational thinking is not universally accomplished; some adults never fully reach the ability to use the formal and hypothetical reasoning involved [33]. The formal operational stage is characterized by the ability to use operations to solve hypothetical or verbal problems. The formal reasoning that is accessible to the adolescent at this stage allows planning and deduction of potential consequences. The adolescent or young adult can use information from the past, present, and future to solve hypothetical or abstract problems [31–33]. A formal operational thinker also has the ability to identify opinions of the self and others, understand concepts such as justice and morality, and use propositional logic [32, 33].

Adolescents are developing the ability to consider how their medical situation will impact other aspects of life, both present and future. However, when a patient experiences active treatment prior to adolescence, it is possible that they will still be working on the preoperational skills of the younger child well into adolescence. If a patient is diagnosed and treated during early or middle childhood, and not given opportunity to practice competence and develop independence, it may take them longer to develop the skills of formal operational thought in later adolescence. Formal operations need a base of experience before hypothetical thinking can take place.

Peers and adults who act as models and provide the interaction for cognitive stimulation are important to the cognitive development process. Vygotsky identified this phenomenon as the "zone of proximal development" [34, 35], a place of learning close enough to reach but far enough to stretch. Young children need role models to imitate as they come to understand how their world works. The isolation that is medically necessary during treatment may interfere with the young child's opportunity to spend time in a preschool learning environment. While the child can learn academic concepts at home, the interaction and practice within a zone of proximal development will be interrupted. Cognitive effects of treatment may also impact the development of the abstract thinking processes involved in defining a self and understanding others. As adolescents are moving away from childhood they will need interactions with important adults and capable peers within the cultural/social milieu so they learn to solve problems, develop social skills, and use the tools of the culture to develop functional ways of finding a quality of adult life they desire.

Both psychosocial and cognitive development can be disrupted by the complications of cancer diagnosis and treatment. Table 22.1 can be used as a reference when considering the age of diagnosis and treatment as well as the current age of the pediatric cancer survivor. The development that was interrupted during diagnosis and treatment may be continuing to impact the survivor in ways that are not manifested until later in life, making long-term monitoring essential. The survivor may have negotiated previous stages successfully but be working on a current phase of development with interference from treatment late effects. Understanding typical ages and stages can help a caregiver consider appropriate interventions when concerns arise.

22.5 Academic Motivation

The self-processes model of human motivation [36–39] and the self-determination theory of motivation [40–43] both implicate basic human needs as the impetus for motivated behaviors. The basic psychological needs of competence, relatedness, and autonomy, and the level at which those needs are satisfied or frustrated for an individual, drive motivated behaviors and lead to a state of well-being [37, 41–43]. The needs are innate and are important at each stage of development [36, 43]. Competence [43] has been defined

Table 22.1 Key issues related to ages/stages of development

	Age 0–2	Age 3–7	Age 6–12	Age 11–16	Age 15–25
Age of student/ school environment	Infancy	Preschool and beginning elementary	Elementary school	Middle school and early high school	High school and emerging adulthood
Psychosocial development	Trust vs. mistrust Autonomy vs. shame • Count on adults for safety and comfort • Develop sense of physical control and independence from others	Initiative vs. guilt • Find a sense of purpose • Experience control over environment • Initiate activities and exploration	Industry vs. inferiority • Find sense of competence through practice • Like to show skills to adults	Identity vs. role confusion • Find direction in personal endeavors • Decide how to define self • Work to identify future roles	Intimacy vs. isolation • Find friendship and love • Practice building long-term relationships
Cognitive development	Sensory • Learn by touching, tasting, hearing, smelling • Develop object permanence • Integrate sensory and motor functions	Preoperational • Begin symbolic thinking, make-believe play • Language development • Remain egocentric • Develop understanding of conservation	Concrete operations • Develop ability to classify • Can do mental operations with concrete concepts • Begin to use generalizations but need many specific examples	Formal operations • Develop abstract thinking • Ability to take perspective of others • Can imagine future and consider plans • Hypothetical thinking	
Neurocognitive brain development	Gross motor skills • Expressive/receptive language • Verbal memory	Regulation of attention and emotion • Fine motor skills • Visual memory • Visual processing • Visual-spatial skills • Visual-motor control	Progression of cognitive abilities • Organization and planning • Processing speed for visual and auditory information • Increased storage capacity and retrieval abilities		

Note: The ages are somewhat arbitrary as stages can overlap depending on the individual child. When diagnosis and treatment interrupt any given stage it may need to be revisited or it may take longer to accomplish

as "feeling effective in one's ongoing interactions with the social environment and experiencing opportunities to exercise and express one's capacities … not an attained skill or capability, but rather a felt sense of confidence and effectance in action" (p. 7). Relatedness [43] is "feeling connected to others, to caring for and being cared for by those others, to having a sense of belongingness both with other individuals and with one's community … tendency to connect with and be integral to and accepted by others" (p. 7) and, in the context of academic and vocational outcomes, will be reviewed here as school belonging. Autonomy [43] is defined as "being the perceived origin or source of one's own behavior … acting from interest and integrated values" (p. 8). Basic needs are addressed and served in the social context and are developed in relationships with others. The level of support for the needs in the social environment will promote either engagement in valued activities or disaffection and lack of motivated behaviors [37, 38, 41, 43, 44].

As students, children and adolescents need experiences with competence, relatedness, and autonomy in order to nurture a self-directed level of motivation for social development and academic achievement [40–44]. It is also helpful to keep in mind that needs can sometimes compete with one another and compromise an individual's well being in doing so [45]. An example might be that a person's need for competence could lead to such driven behavior that relationships are ignored and the need for relatedness would suffer.

The self-processes model of motivated behavior includes basic needs for autonomy, belonging, and competence as they impact engagement or disaffection in the social milieu [38, 46–50]. Furrer and Skinner [48] define engagement as "active, goal-directed, flexible, constructive, persistent, focused interactions with the social and physical environments" and disaffection as "alienated, apathetic, rebellious, frightened, or burned out" (p. 149). Engagement or disaffection can serve as a mediator between the satisfaction of a student's basic needs and academic motivation [46, 48–51]. Academic motivation then leads to more positive outcomes for the student. Skinner et al. [50] suggest that the self-system processes of competence, belonging, and autonomy are facilitators of the engagement process, and not internal indicators of the product (engagement or disaffection). They found that autonomy, competence, and relatedness mediate the pathway between contextual factors of school, including relationships with teachers and peers, and engagement or disaffection.

Newmann and colleagues [49] describe educational engagement as a product of school membership and authentic work opportunities, both of which promote satisfaction of an individual's need for competence and relatedness. School membership "develops when students establish affective, cognitive, and behavioral connections to the institution" (p. 20) and is most likely to develop when students feel a sense of clear purpose, fairness, and personal support. Authentic work is that which is "considered meaningful, valuable, significant, and worthy of one's effort, in contrast to those considered nonsensical, useless, contrived, trivial, and therefore unworthy of effort" (p. 23). When a student experiences both membership and authenticity in the school environment they are more likely to become engaged in the world of school and value the outcomes promoted by the school environment. Engagement leads to the motivation and investment that is necessary to persist and be successful with academic endeavors.

Finn [46, 52] developed a model of engagement that involves a process of participation and identification. The participation component can be considered the level of belonging experienced by a student. Once the student becomes an active participant in the school environment, both behaviorally and emotionally, they are more likely to become engaged and begin to identify with the values and expectations of the school setting. If the student does not perceive themselves as belonging to the school environment, they are more likely to begin the process of withdrawal—either emotionally, or more literally, by dropping out of school. There are two components to the state of identification with school. Finn [46] states: "First, students who identify with school have an internalized conception of belongingness—that they are discernibly part

of the school environment and that school constitutes an important part of their own experience. And second, these individuals value success in school-relevant goals" (p. 123). Relatedness or belonging is important to that sense of being a part of the school community.

Self-determination theory of motivation assumes humans actively seek to define their sense of self and to meet basic psychological needs through challenging, interesting, and accomplished experiences [40–43]. The theory is presented as a dynamic interaction between individual and environment with the primary force of motivation being the basic human psychological needs of competence, relatedness, and autonomy. Satisfaction of the basic needs comes from interpretation of contextual or environmental factors by the individual, and level of need satisfaction can lead to support for or interference with an individual's motivation, performance, and well-being. One's environment offers opportunities for personal growth or thwarting of development, and the person's level of self-regulation and interaction contributes to the benefit or deficit garnered from the environmental context.

22.6 Competence

Competence involves feelings of effectiveness, self-efficacy, or confidence in one's efforts to intentionally impact the environment [45, 53, 54]. The need is innate and the feelings develop over time, within a variety of contexts and relationships, and they contribute to both social and cognitive development [45, 53, 55]. The concept of competence has also been discussed as self-efficacy or personal agency [56], a mechanism involving "people's beliefs about their capabilities to exercise control over their own level of functioning and over events that affect their lives. Efficacy beliefs influence how people feel, think, motivate themselves, and behave" (p. 118). Efficacy beliefs [56] also "influence aspirations and strength of goal commitments, level of motivation and perseverance in the face of difficulties and setbacks, resilience to adversity, quality of analytic thinking, causal attributions for successes and failures and vulnerability to stress and depression" (p. 1206). When an individual does not develop a strong sense of competence or self-efficacy, there is a higher risk of experiencing anxiety, depression, or withdrawal from the environment [53, 56, 57]. High levels of competence or efficacy have been linked to internalized levels of motivation, engagement, and academic achievement [39, 44, 53, 56, 57].

Competence can also be conceived as the sense of "perceived control," the ability of the individual to impact the environment and achieve a desired outcome [39, 57, 58]. Perceived control involves three different sets of beliefs [39, 57]. Control beliefs are those about whether one can influence successes rather than failures. Strategy beliefs are those about whether there are effective strategies to create desired outcomes. Capacity beliefs are those about whether or not the individual has the capacity to implement the strategies that might be successful in the given situation. Higher levels of perceived control promote engagement, which can then lead to achievement of goals. Perceived control is influenced by social relationships and by environmental contexts.

An individual's beliefs about controllability may influence the degree of effort expended to master a skill or change an environment versus a decision to tolerate an adverse situation [59]. Perceptions about controllability change with development; children develop the ability to differentiate chance or luck from skill and ability by the age of 11–13 years [59]. By then, children have a greater ability to use problem-focused coping with efforts to manage or master an element of the environment seen as stressful.

22.7 Relatedness and School Belonging

Belonging has been defined as a basic human need, important for optimal functioning [60–63]. People need to have an integrated and reciprocal relationship with others in the community. A child's primary community outside the family is school. School environments with characteristics such as high academic standards, high levels

of teacher support, a community where relationships between students and adults are caring and respectful, and school safety have been identified as promoting school connectedness for students [62, 64, 65]. Connectedness is important for students of all ages [63, 66–68]. Many benefits of school belonging for student success have been noted, including social, behavioral, and academic [61, 62, 64, 65, 69]. When children feel as though they belong they are able to pull from a stronger set of inner resources, perceiving themselves as more competent. They may also suffer when they anticipate isolation by experiencing decrements in reasoning and thought processing [70].

Teacher-student relationships have been shown to have a clear impact on positive school belonging for students [61–63, 71–76]. Teachers can impact their students through caring, treating the students fairly, providing specific support, and actively engaging them in learning. Libbey [62] noted, "student relationships with their school often were operationalized as their relationship with their teachers" (p. 281). Goodenow [61] noted that teacher support explained over one-third of students' assessment of value and interest related to their academic work.

Pedagogical caring [71, 77, 78] is a concept that involves the ways that students perceive care from their teachers. Behaviors of teachers that suggest pedagogical caring include modeling caring behaviors, democratic communication style, treating students as individuals, structure and expectations, and a nurturing manner. When students feel cared for by their teachers, they are more likely to be academically motivated, experiencing autonomy and competence, and pursuing prosocial goals [71, 78].

Wentzel [76] looked at the impact of support from peers, parents/family, and teachers. She found that, while each component of the adolescent's environment provides some support for academic success, it was perceived teacher support that provided the most impact for classroom functioning and interest in class. Others have also come to the conclusion that supportive relationships between teachers and students influence children's social, emotional, and academic adjustment and achievement [73, 75]. However, Rosenfeld et al. [75] found that, although perceived teacher support was a necessary condition for success, it was not sufficient on its own—partnerships with parents, other teachers, peers, and other members of the students' environment were also important.

22.8 Autonomy

Autonomy involves a perception of being responsible for one's own actions and choices and the perceived ability to act from one's own interests or values. Autonomy is not the opposite of independence, but rather, it is the opposite of coercion and its development requires support in the social environment [38, 42]. Individuals seek to be the origin of their own behavior rather than a pawn to external forces that cannot be controlled [38, 79]. Autonomy is related to the concept of "locus of causality," with self-regulation more related to an internal locus of causality—when the reasons for acting come from within the individual [36, 80].

Parent support for autonomy through the use of an authoritative parenting style, including qualities of firm control and psychological autonomy, has been found to promote self-reliance and independence in children [81]. Grolnick & Ryan [81] define parental autonomy support as the "degree to which parents value and use techniques which encourage independent problem solving, choice, and participation in decisions versus externally dictating outcomes and motivating achievement through punitive disciplinary techniques, press, or controlling rewards" (p. 144).

The importance of competence, relatedness, and autonomy in stressful conditions (i.e. serious or chronic illness) may be especially important. Children with chronic illness are often absent from school, experience significant pain, or have low levels of energy; these issues are likely to create a sense of isolation and academic struggle [13, 82, 83]. The effects of chronicity and absenteeism over time can have cumulative effects and can lead to consequences such as difficulty completing school work and keeping up with assignments, weaker relationships with teachers, and lower levels of academic success [82]. Ross [10] summarized the impact by concluding "serious illness threatens the child's self-confidence,

interrupts school attendance, interferes with developing social and academic skills, and disrupts important relationships with other children and adults" (p. 84).

Perceptions of competence, belonging, and autonomy can all be altered by the experience with a serious medical condition. Competence is developed by many opportunities to practice and explore options to solve everyday situations of life. The absence from school and missed opportunity for other typical interactions can also make it difficult for a child to develop a strong sense of being able to impact the world around them. Svavorsdottir [84] found children with chronic illnesses reported lower school connectedness and lower positive feelings about their school than did their healthy peers. The lack of control that accompanies any treatment regimen of pediatric cancer can impact a child's sense of autonomy. Adults regularly demand certain behaviors, including submission to painful procedures and restriction of activity. Side effects of treatment such as fatigue and malaise also curtail a child's ability to act on their own desires or goals.

Feelings of autonomy may function as a protective source of energy during times of stress or distress, as the sense of autonomy may counteract the inherent feelings of helplessness that can accompany difficult life events [38]. The social context can provide feedback to frame a stressful event as a challenge or a threat. Autonomy support may help the individual cope with both the chaos (loss of control) and coercion (loss of choice) in ways that lead to better adjustments [38].

A motivational model of stress and coping [38] suggests that stressful situations or contexts can threaten an individual's ability to meet psychological needs. The appraisal of any given stressful situation will elicit certain ways of acting in an effort to meet one's basic needs. Children and adolescents undergoing such stress may have a need for more deliberate activities that promote competence, relatedness, and autonomy. The long-term impact of the stress of managing a life-threatening illness on academic motivation should be an area of assessment by caregivers and educators so interventions can be implemented as needed.

22.9 Health Impact on Academic Outcomes

When any part of the body is exposed to the consequences of disease or chronic illness, it is possible that other parts of the body, including the brain, may be affected [85]. The disease process itself, the necessary treatment, or psychosocial and coping capacity may all impact the total outcome. Children with chronic illness have consistently demonstrated lower levels of academic or vocational achievement, even when global IQ scores are similar to those of healthy peers [15, 85–90]. These children also experience lower educational trajectories and lower socioeconomic status in adulthood [89]. There is some evidence that children with chronic medical conditions reach developmental milestones later than their healthy peers [91] and are less likely to complete high school on time [87]. Children with chronic medical conditions have also been noted to have higher levels of behavioral and emotional problems than their healthy peers, with decreased peer interactions and increased dependence on adults [91–94].

Effects of health on academic performance may be directly related to cognitive impact of disease and treatment or a result of indirect factors [7, 95]. Factors that can directly affect academic outcomes include fatigue, pain, and cognitive changes that result from the disease and treatment. Indirect effects arise via school attendance patterns and related missed instructional time, alterations of teacher and parental expectations for academic achievement, or other psychosocial adjustment issues such as the development of school phobia or separation anxiety [88, 90, 95, 96].

Academic struggles can occur acutely as a result of disease symptoms and treatment side effects or they can emerge later, when the child reaches an age at which affected skills would be expected to emerge developmentally [15, 18]. Acute interference with academic progress is often a result of pain, fatigue, lethargy, general malaise, or medication side effects [7, 83, 97]. When cognitive effects of disease and treatment appear over time, they do not represent deterioration of previously accomplished milestones, but

rather are a result of impact on the rate of brain growth and development of complex structures within the brain [12, 18, 22, 98]. Neurocognitive sequelae can include impact on cognitive ability, attention, processing speed, memory, visual-motor integration, school performance, social interactions, and adaptive behaviors [18, 92, 93, 97, 99, 100]. The neurocognitive deficits can interfere not only with academic progress, but also with development of competence and social skills [100]. They can be observed by parents and teachers in the classroom as failure to compete work, slowness with approaching and accomplishing work, periods of inattention, fine motor deficits, or difficulty with development and maintenance of peer relationships [5, 19].

Maslow and colleagues [90] identified school connectedness as a protective factor related to academic attainment for students with chronic illness. Social isolation can be a greater concern for students with medical conditions and it may be that lack of connectedness is related to lost opportunities for development of competence and social relationships. Peer interaction and teacher-student relationships may be especially important for students with chronic illness, as they can foster a sense of school belonging just as they do for healthy, typical students [10, 101–103].

22.10 Academic Impact of Childhood Cancer and Treatment

School absence, pain, and fatigue that accompany the intense treatment of any pediatric cancer can impact both academic and social outcomes in the short term [7, 20], and cognitive late effects add to the impact as they emerge over time. Some childhood cancer diagnoses and treatment regimens create a higher risk of cognitive difficulties than others [9, 12, 17, 19, 22, 104]. The diagnoses found to have the highest risk of cognitive late effects, and consequently, interference with academic progress and psychosocial skills, are those that involve the brain or central nervous system (CNS). This group includes children diagnosed with brain and spinal tumors and those diagnosed and treated for acute lymphoblastic leukemia (ALL). Treatment for brain tumors can include a combination of surgery, chemotherapy, and radiation to the brain and spine [105]. Acute leukemia and lymphoma treatment regimens involve intrathecal chemotherapy (medication delivered directly into the spinal fluid) and high dose chemotherapies that can cause cognitive late effects [9, 17, 85]. Children with high-risk leukemia or disease that has spread to the CNS are also likely to receive craniospinal radiation therapy as a part of their treatment regimen [17, 20]. Other, more rare, diagnoses also involve treatment regimens that include high doses of chemotherapy or radiation to the neck and head [98].

Children who have survived a leukemia diagnosis and have received intrathecal chemotherapy have a higher risk of developing neurocognitive late effects than those children whose cancer does not involve the CNS or need for intrathecal treatment [9]. Brown and his colleagues [9] found that children who had received intrathecal chemotherapy had specific cognitive deficits in non-verbal learning, visual-motor performance, attention, memory, and mathematics skills. Madan-Swain and colleagues [5] also note major deficits to include processing speed, ability to transfer learning, attention, concentration, memory, visual-spatial, and visual-motor skills. The difficulties seem to be greater for those children who were further removed from their treatment course. The deficits experienced by children seem to appear and expand in the years after treatment has been completed [5, 106]. For a more thorough review, please see Chaps. 15 and 16 in this manuscript.

Childhood ALL survivors have been found to have poorer educational outcomes than their typical peers, including more frequent failure and retention, and higher levels of behavior difficulties [4, 5, 20, 107]. Mulhern and Butler [17] have suggested that as many as 20–30 % of children with acute lymphoblastic leukemia who are treated with intrathecal chemotherapy will develop cognitive dysfunction. Some of the critical academic skills that can be affected for brain tumor and ALL survivors include attention, memory, processing speed, planning and organi-

zational skills, fine motor skills (that can affect writing or copying speed and accuracy), visual learning, mathematics skills, and reading comprehension [4, 85]. Some children also experience declines in general intellectual functioning as a result of their disease and treatment [85].

In a study that included childhood cancer survivors with and without CNS impact of disease, as well as a healthy comparison group, Buizer et al. [108] noted that students with CNS treatment were not enrolled in special education at any higher rate than peers but they did experience lower school performance, more frequent retention, and more frequent identification by teachers as displaying behavior difficulties, attention concerns, and underperformance. It is concerning that the children may have been misidentified and were really experiencing consequences of their CNS treatment that interfered with school performance. Those children may have benefited from special education services if they had been properly identified with neurocognitive late effects of CNS treatment.

In contrast, Haupt et al. [107] found that ALL survivors had higher rates (three and one-half times) of enrollment in special education programs but similar rates of high school graduation, college admission, and college graduation as their healthy siblings. They also noted that the rates of special education enrollment and gifted and talented program enrollment for cancer survivors were similar to that of healthy siblings prior to diagnosis and that the levels of gifted and talented enrollment stayed the same after diagnosis. Only the rate of special education enrollment in the survivor group was significantly increased. Mitby, et al. [109] looked at a large sample of childhood cancer survivors and found that, although children who had been diagnosed with ALL prior to their fifth birthday were four times more likely to be enrolled in special education services, children with a cancer history were no less likely to graduate from high school than children without a cancer history. In each of these studies it is likely that the additional support of special education services helped those students graduate and move successfully forward at rates similar to their healthy siblings and peers.

Brown and colleagues [9] found that the group of students who had received CNS prophylactic treatment in their study had some difficulties with non-verbal learning and fine motor skills but they did not experience lower levels of academic achievement than controls. It is notable that more than one-third of the ALL survivors in this study were enrolled in special education services. It is possible that this group represents the 20–30 % of ALL survivors that Mulhern & Butler [17] found are likely to develop cognitive late effects of treatment. Therefore, special education services may have addressed cognitive difficulties as they arose and allowed for typical academic achievement in these children.

In meta-analysis of studies that examined the academic outcomes for ALL survivors, Campbell et al. [110] found evidence of consistently poorer outcomes for the ALL survivors than for their healthy peers or control groups using children with diagnoses that did not affect the CNS. There were significant deficits in overall cognitive functioning, academic achievement, and specific neurocognitive abilities for the students with a history of ALL treatment.

Robinson et al. [105] performed a meta-analysis of brain tumor survivors. Although they found samples from the various studies to be heterogeneous and warrant further study, they did observe that overall, “children treated for brain tumors tended to exhibit pervasive and substantial deficits along a range of broad and specific neurocognitive domains, including overall cognitive functioning, academic achievement, attention, psychomotor and visual-spatial skill, verbal memory, and language” (p. 528).

One predictor of cognitive difficulty is younger age at diagnosis [9, 22]. When young brains are still developing, the interruption of the maturation processes has the potential to cause greater difficulty with yet undeveloped areas of the brain involved in higher order thinking skills [22]. Armstrong and his colleagues have described a developmental approach to understanding neurocognitive late effects of CNS treatment [11, 19, 106]. They note that declines in academic functioning over time do not really represent deterioration but, rather, demonstrate a

slowing of the development of abilities, which widens the ability/performance gap between children treated with intrathecal chemotherapy and typical peers. They suggest that treatment affects brain structures and functions developed after treatment but not those already established prior to treatment. This developmental approach would account for the findings that younger age of diagnosis and treatment is related to greater disability over time. It could also explain why deficits appear to increase over time.

Educators, psychologists, medical caregivers, and others involved in caring for cancer survivors need to have an understanding of how typical developmental milestones and the development of self-determined motivation can be impacted by disease, treatment, and resultant interruptions to schooling. Overall, the experience of childhood cancer diagnosis and treatment has the potential to impact areas of development relevant to school success, as well as the potential to interfere with the development of competence, relatedness, and autonomy necessary for self-determined academic motivation. The areas of concern interact and intertwine, and difficulties present or expand over time.

22.11 Strategies and Recommended Practices for Intervention

Strategies for promotion of academic progress and long-term success are best considered in phases and as a long-term endeavor. Important transition points during the course of treatment are the time of diagnosis, school re-entry after treatment related absence, completion of treatment, and long-term survival. There is a small body of research aimed at identification of specific school interventions to support childhood cancer patients/survivors [6, 8, 10, 111]. The general consensus regarding school intervention work is that collaboration and cooperation of the various members of the child's ecosystem is critical for the optimal outcomes to occur [3, 5, 7, 12, 96, 98, 100, 112, 113]. A child with a history of cancer will be closely involved with family, school, and the medical community. School systems and medical systems focus on different aspects of a child's well being, but it is imperative that the systems work together to promote optimal outcomes for the total child [100, 114].

The *Association of Pediatric Hematology/Oncology Education Specialists* (APHOES), a national organization of professionals from multiple disciplines, has developed a handbook of practice recommendations for school transitions of students with hematology and oncology disorders [14]. Transitions begin at the time of diagnosis and continue to occur as the child moves from one stage of development to the next or from one phase of treatment to another. Repeated and ongoing assessment of academic progress is important at every stage. The assessments will require regular communication between home, school, and medical care providers. Checklists of issues to be considered at each stage are included in the APHOES publication [14].

An important part of any reintegration or adjustment process for a child with a cancer diagnosis involves the education of the various elements of the child's educational community, including peers, teachers, coaches, and counselors [3, 5, 14, 96]. Ongoing and updated education is important at each transition during the various phases of treatment and survival. Peers need an understanding of the cancer diagnosis and treatment effects so they can provide empathic interaction with the student and accommodate social needs. Teachers need support and guidance about what to expect from the student undergoing treatment or who is experiencing late effects as a result of past treatment [8, 10, 17, 83, 112, 115]. Educators, school nurses, and guidance counselors all have an opportunity to promote academic success for the student if they understand the needs and recognize their own anxieties about having an ill child in the classroom [16]. Teachers may worry about the risk of an emergency in the classroom or they may worry about the amount of time an ill child will require and how that will impact the needs of the healthy classmates [13]. However, with appropriate support of their own, a teacher can be a crucial element in the adjustment of a child living with a cancer diagnosis.

After treatment has been completed, it is likely that the relationship with the oncology treatment center will become less intense and the survivor and family will have stronger ties to their primary caregivers in the community. Community providers in the medical and school arenas will then need to assume the necessary monitoring for late effects of treatment and consequences for academic and vocational outcomes.

Because deficits seem to develop over time, repeat assessments and close monitoring are necessary to recognize the evolution of any cognitive late effects [5, 11, 17, 19, 20, 106]. The assessments need to include specific measures of the neurocognitive effects of treatment experienced by the childhood cancer survivors [17, 106]. The developmental model for monitoring academic progress can be a foundation for anticipation and early identification of problems for the effected children. Armstrong, et al. [106] suggests that serial assessment can lead to targeted and preventive intervention in response to the emergence of difficulties. Mulhern & Butler [17] speak strongly about the need for proactive intervention to address potential neurocognitive deficits long before a child is considered a long-term (greater than 5 years) cancer survivor. Early intervention will make it more likely that children can be successful in school and subsequent adulthood.

22.12 Conclusions

Children who have experienced a cancer diagnosis, treatment and long term survival have developmental, social, and academic needs much like those of healthy peers. School is the center of their everyday world. However, long-term cancer survivors have an added burden to manage as they move through the typical stages of development and invest in academic endeavors on the way to adulthood. Long periods of school absence, physical consequences of disease and treatment, and cognitive late effects all have the potential to disrupt the academic journey. It is important for the childhood cancer survivor to have broad-based support from a variety of sources to promote successful academic outcomes.

Both medical caregivers and school personnel need to understand the ways diagnosis, treatment, and long-term effects can impact learning and academic outcomes for students who have experienced a pediatric cancer diagnosis. Collaboration between the family, school, and medical care provider can facilitate that understanding. Recognizing academic difficulties, both cognitive and social, makes it more likely that comprehensive evaluation and appropriate interventions can be implemented in a timely and effective fashion, leading to more positive academic outcomes and successful adult lives.

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Special Education Laws

23

Michael E. Jewell

23.1 Introduction

Federal and state law both play a role in educating a child with a disability. The confines of this publication only permit a very general overview of federal law with no specific discussion of its application to any particular state since variations exists among the states. As this is an overview of applicable law, it is intended for general information purposes only and is not intended as legal advice. Any liability that might arise from use or reliance on this information in this chapter or on the websites referenced herein is expressly disclaimed.

23.2 Section 504 of the Rehabilitation Act of 1973

23.2.1 Background

Section 504 of the Rehabilitation Act of 1973 ("Section 504") prohibits discrimination for a "physical or mental impairment which substantially limits one or more major life activities".[1] Section 504 applies to any entity which receives funds from the U.S. Department of Education, including private institutions.[2] From an educational standpoint, it is designed to ensure that the individual has appropriate access to his or her education. It can affect preschools through colleges.[3] It applies to public school districts and may apply to private educational institutions.

This section will focus on the requirements applicable to public elementary and secondary school districts. While Section 504 requires that an individual receive a free appropriate public education ("FAPE"), the provision of an Individual Education Plan under the Individuals with Disabilities Education Act (see below) is only one way that an entity may meet this requirement. When looking at how a child should be supported and/or accommodated to ensure progress in the educational setting, a determination should be made whether the child is entitled to Individualized Education Plan ("IEP") or a 504 plan. Generally speaking, an IEP is a more detailed document with more exacting procedures (see below), while a 504 plan is principally designed to adapt a class or program to the child.

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[1] 34 C.F.R. 104.3(j). Impairments which are "transitory and minor" whose "actual or expected duration" is 6 or fewer months, do not qualify. 42 U.S.C. §12103(1) and (3)

[2] 34 C.F.R. §§ 104.1–104.3.

[3] 34 C.F.R. §104.2 and §104.31.

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23.2.2 Process

Individuals eligible under Section 504 may be entitled to receive a "504 Plan". This is a plan designed to ensure that the individual has an equal opportunity to access his or her education. A 504 plan *adapts* a program for the individual (e.g., reducing the amount of work the student must perform, changing the class schedule, allowing the student notes from other students or from the instructor, and providing specific seating in the class or additional time to complete classwork, assignments or homework). Unlike an IEP (discussed in more detail below), a 504 plan does not offer supportive services like therapy from a professional (such as, a speech and language therapist, occupational therapist, etc.).

A child must be evaluated to determine whether he or she is eligible for a 504 plan. The evaluation should use testing by qualified individuals with tests designed to evaluate the "areas of educational need" and which "accurately reflect the student's aptitude or achievement level."[4] A meeting is held with parents and school staff to discuss whether the child is eligible for a 504 plan. If the child is found eligible, a written 504 plan is developed by the participants in that meeting. Upon receiving written consent from the child's parents, the 504 plan should be provided to all those individuals who might be responsible for implementing the plan. A meeting should be convened at least once a year to review the 504 plan and make appropriate changes. Revisions to the 504 plan can be made as the child's needs change.

23.2.3 Role of Professionals

Professionals wishing to help a family to obtain a 504 plan should prepare written information for the school district staff identifying the impairment which limits one or more life functions describing the impact of the impairment and outlining what steps can be taken to accommodate the student. There are many resources available on the Internet (including state department of education websites; please see the Resources section at the end of this manuscript), which identify some accommodations that might be available to a child who qualifies for a 504 plan. If time and circumstances permit, an observation of the child in the educational setting as well as input from school district staff who work with the child in the educational setting can be very helpful to the professional in formulating what accommodations might be appropriate for the child. Professionals should consider participating in the 504 meeting (either in person or by telephone) to discuss their professional opinion regarding the needs of the child and the accommodations necessary for the child to be successful.

23.3 Individuals with Disabilities Education Act

23.3.1 Background

The Individuals with Disabilities Education Act, or "IDEA" (20 U.S.C. §1400 *et seq*.) is designed to ensure that each child receives a "free appropriate public education that emphasizes special education and related services designed to meet his or her unique needs and prepare him or her for further education, employment, and independent living."[5] The IDEA makes federal funds available to public school districts to help accomplish its purposes and its implementing regulations may be found at 34 U.S.C. §300.300 *et seq*. (please see Resources chapter). (Of note, Congress's initial effort to address the educational needs of disabled children was through the Education for All Handicapped Children of 1975.)

23.3.2 Process

To be eligible under the IDEA, a child must have a disability which impacts the child *educationally*. The educational impact may not be the result of "lack of instruction" in reading or math

[4] 34 C.F.R. §104.35(b).

[5] 20 U.S.C. §1400(d)(1)(A).

or limited English proficiency.[6] Potential categories of eligibility include "intellectual disabilities, hearing impairments (including deafness), speech or language impairments, visual impairments (including blindness), serious emotional disturbance, orthopedic impairments, autism, traumatic brain injury, other health impairments, or specific learning disabilities."[7] Generally, the IDEA requires that a free appropriate public education be made available to qualified individuals between the ages of 3–21, however, state law may impact eligibility before 5 and after 18.[8] School districts have an affirmative duty to seek out children who might be eligible under the IDEA.[9]

The eligibility process is usually started by a referral for evaluation, either by the family, a teacher or a professional (physician, psychologist, speech therapist, etc.). When requesting that their child be evaluated to determine whether he or she is eligible for an IEP, parents should identify the concerns they have about the child, provide any relevant history of the child and provide any documents that they wish the school district to consider. At the conclusion of this section there is a sample letter that a parent might use to request evaluation for a 504 plan or IEP. To ensure that such important correspondence is received, a parent should consider sending that correspondence via certified mail or hand delivery.

The school district should consult with those individuals involved with the child to design an assessment plan for the child, sufficiently comprehensive to assess "all areas of suspected disability."[10] The school district requires the informed written consent of the parent before it may initiate the assessment process; if a parent refuses to consent, there are administrative procedures which may allow a school district to proceed to assess, however, those are beyond the scope of this chapter. Upon receipt of consent, the school district conducts its assessment and has approximately 60 days to convene an IEP meeting and determine whether the child qualifies under the IDEA (this time period may be affected by state law). The child's parents are entitled to a copy of the completed assessment.

The school district must convene an IEP meeting to review the results of the assessment, determine whether the child qualifies for special education programs and services and, if so, develop an IEP for the child. The IEP team is generally required to be in attendance at an IEP meeting. Such a team consists of the parents, a regular education teacher ("if the child is, or may be, participating in the regular education environment"), a special education teacher (or a special education provider) and a representative of the school district (who is "knowledgeable about the general education curriculum" and "the availability of resources") .[11] Parents may also invite anyone who has "special knowledge or expertise regarding the child"[12] to participate in the IEP meeting, this includes doctors, therapists, or other professionals who have worked with the child.

If a child is determined to be eligible under the IDEA, an IEP is created. The IEP is a written document which includes: "present levels of academic achievement and functional performance;" "measurable annual goals"; a statement of how the child's progress will be monitored; an outline of the special education and related services to be provided; "an explanation of the extent, to any, the child will not participate with non disabled children" (to the "maximum extent appropriate," school district are required to educate special needs children with their typically developed peers[13]); the accommodations for the child; the extent to which "the child cannot participate in regular assessment" and, if the child cannot participate in regular assessment, the assessment that will be done of the child; and, for the first IEP "in effect" when the child turns 16 years old, a transition plan[14] to bridge the child's transition

[6] 20 U.S.C. §1414(b)(5).
[7] 20 U.S.C. §1401(3).
[8] 20 U.S.C. §1412(a)(1).
[9] 20 U.S.C. §1412(a)(3).
[10] 20 U.S.C. §1412(3)(B).
[11] 20 U.S.C. §1414(d)(1)(B).
[12] Ibid.
[13] 20 U.S.C. §1412(a)(5),
[14] 20 U.S.C. §1414(d)(1)(A).

to post secondary activities. It should also be noted that a child who does not have an IEP might still have an opportunity to receive home or hospital education depending on his or her condition and applicable requirements."[15]

23.3.3 Considerations for Parents

Parents are entitled to "participate in the decision making process"[16] for their child. Accordingly, parents should make a written request to the school district in advance of the IEP meeting requesting that they be provided copies of all documents prepared in anticipation of the meeting (i.e., progress reports, present levels of performance, proposed goals, etc.) so that they can fully participate in the IEP process. Parents should also consider whether there are individuals who have specialized knowledge who should be invited to the IEP meeting, such as outside doctors, psychologists, or therapists. If such an individual is not available to attend the meeting in person, parents can request that the individual participate in the meeting via telephone. Some states permit the audio recording of an IEP meeting by parents. Where permitted, this can be a helpful tool to allow the parents to review the IEP meeting, and, if needed, to enforce their child's educational rights.

Before granting consent to any portion of an IEP, the parents should carefully review the document to ensure that the document accurately reflects what the parents understood the school district was offering their child with respect to accommodations, goals, services, etc. Parents are not required to grant written consent to any portion of the IEP as they sit in the IEP meeting; however, parents should be aware that a school district cannot implement a component of the IEP until consent is received. An IEP should be reviewed at least annually, but may be reviewed more frequently.

[15] 20 U.S.C. §1401(29).

[16] 20 U.S.C. §1415(f)(3)(E).

23.3.4 Considerations for Professionals

Professionals who are in a position to assist families are strongly encouraged to familiarize themselves with special education law (at a minimum, the eligibility criteria for a child to be entitled to receive special education). Those who do so are in a much better position to write a beneficial report and assist the IEP team to help the child.

Professionals wishing to help parents in the IEP process can start by writing a clear description of any evaluations which they have conducted, their findings and conclusions and, most importantly, their recommendations to be considered. Often, professionals make the mistake of writing a few words on a prescription pad such as "Child needs IEP" or "Child needs speech" and telling the family to submit that to the school district. While a school district is required to consider outside information, information submitted which does not provide a basis for its recommendations will be given little, if any, weight.

To properly prepare the report for the intended audience (i.e., school district staff members), it may be best for the professional to envision that he or she is sending their patient to a new professional who knows nothing about the child except what is written in the report by the referring professional. In such circumstances, the professional would want to describe how they received the patient, their observations of the patient, any pertinent information they received about the patient from the parents (or others), any testing done of the patient, the results of that testing, the professional's conclusions based on all of the available information and concrete recommendations for the school district to consider. If a professional believes that a child needs goals in a particular area, certain therapies or accommodations or particular supports, the professional should clearly delineate what those are so that those recommendations can be adopted or, if not adopted the parent can show a clear disparity between what was recommended by the outside professional and what was offered by the school district in the IEP.

If time and circumstances permit, it is highly recommended that a professional observe the child in the educational setting (if possible, more than once) and obtain the input of teachers and others who work with the child (either anecdotally and/or through testing and inventories). One of the major complaints of school districts as they deal with outside professionals is that the professional does not understand the educational environment or has failed to take into account those who know the child best in the educational setting.

It is always best if a professional is able to attend the IEP meeting in person since paperwork is often distributed at the meeting and will not be available to the professional if he or she participates via telephone. However, participation by telephone is preferable to no participation at all since parents who provide a professional's report to a school district to be discussed at an IEP meeting are often confronted with this statement, "We would like to consider this, but we have some questions we need answered." (This is not an uncommon response from school district staff and may be used to excuse a thorough consideration of the report.) However, if the professional is available to the IEP team, either in person or via telephone, often, there are usually few questions by the school district and the report receives greater consideration.

Professionals who participate in IEP meetings must be prepared to explain, usually more than once, the basis for their findings, conclusions and recommendations since school district staff may be unfamiliar with terminology or may be suspicious of the professional's information. Professionals who want to help students with their IEPs can best do this by: understanding the IEP process; observing the child in the educational setting and speaking to district staff who work with the child; providing clear written information regarding their findings, conclusions and recommendations which they wish the school district to consider; and actively participating in the child's IEP meeting(s).

23.4 Conclusions

This chapter provides a brief overview of the Federal Laws that pertain to the education of children and adolescents with special needs and/or circumstances that require attention in the educational setting. It should be noted that some, but not all, children with a history of cancer may be eligible for either Section 504 or IDEA, as the determination for eligibility might rest solely on the impact that the cancer and its treatment has had on the student's ability to access regular curriculum within the classroom. Furthermore, the reader is reminded that state laws vary and may come into play when determining a child's eligibility. A sample letter has been provided to assist the professional involved in the survivor's care should they need to be evaluated to determine if additional services or accommodations are warranted within the academic setting. Finally, helpful resources are provided in Section VI of this manuscript that provides additional information regarding these processes.

Appendix

Sample Letter

Director of Special Education
ZZZ School District
Address
City, State Zip

Dear Director of Special Education:

Re: Child's Name & Date of Birth

I believe my child might be eligible for an IEP under the IDEA or for a 504 plan under section 504 of the Rehabilitation Act of 1973. [Relevant history regarding the child, i.e., academic struggles, medical history, behavioral struggles, social-emotional struggles, reports of problems at school from any source, any testing or evaluations done by outside professionals etc.] My concerns for my child include the following: _____. I request that my child be immediately assessed to determine his/her eligibility for either an IEP or a 504 plan. Included with this letter, please find documents regarding my child that I would like considered as part of the assessment. Below, please find my contact information. Please provide written confirmation of receipt of this letter and let me know if there is any additional information you might need. Thank you.

Sincerely,

Parent

Address

Phone #

Email

Enclosures: [Identify by name and date]

Career and Vocational Outlook

24

Sujin Ann-Yi and Martha A. Askins

24.1 Introduction

Most would agree that an individual's career or vocational functioning significantly impacts all aspects of life such as self-identity, overall life satisfaction, physical and psychological well-being, as well as family and social relationships. For most, career and vocational development occurs in concert with formal educational experience and exposure to various careers and work-related opportunities. Educational experience and progress is pertinent and directly related to the successful development of career progress and other social outcomes. For some, however, these career development factors are lacking and result in an interrupted career development process.

It is known that children who are treated for pediatric cancer often experience extended absences from formal school and have to repeat a grade, negatively impacting academic learning and educational advancement relative to their same aged peers [1]. Pediatric cancer survivors generally have commensurate high school graduation rates as their siblings, but necessitate higher rates of special education and learning disability services [2]. Survivors of central nervous system disease and acute lymphoblastic leukemia have been found to be at comparatively higher risk for educational difficulties [3, 4]. Childhood pediatric cancer survivors are generally 1–2 years delayed in educational status due to the increased risk of repeating grades [2, 5, 6]. In addition, survivors have been found to obtain college degrees significantly less than their control group peers. The impact of pediatric cancer on academics, covered in detail in a previous chapter, often serves as the precursor for challenges to the career development process. For example, educational attainment was found to be a significant predictor of employment and securing health insurance as noted in 694 survivors of lower extremity bone tumors [7]. For pediatric cancer patients, one could surmise that the primary reason for career, vocational, and employment difficulties is underachievement.

24.2 Overview of Survivors' Employment Statistics

Historically, survivors of pediatric cancer have reported vocational related difficulties such as obtaining employment, workplace relationship difficulties, work related discrimination, lower

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annual incomes, rejection from the military, and higher rates of unemployment compared to control groups [4, 5, 8–12]. In addition, survivors frequently have reported difficulties obtaining health and life insurance policies commensurate with their control subjects [4, 5, 10, 13–18]. Pediatric cancer survivors also tend to demonstrate lower occupational status in career choices compared to control group peers [5].

In contrast, other studies have reported that, in general, childhood cancer survivors' educational attainment and career success was commensurate with their siblings or control representatives [12–14, 16–20]. A few studies also have found no significant differences in income levels between survivors and controls [19–21].

Of note, these studies had either an underrepresentation or exclusion criteria of brain tumor and central nervous system (CNS) related diagnoses in their samples, which have been a subset of survivors at greater risk of work related difficulties [13]. For example, Green et al. [14] concluded that most pediatric cancer survivors were similar to peers regarding achievement of adult developmental milestones such as employment. This study reported, 93 % percent of the employed survivors reported that their history of cancer had not limited their career progression and 88.8 % of the survivors reported positive career satisfaction regarding their employment. In addition, a minority (10.5 %) of survivors reported discrimination as a direct result of their cancer history, which was significantly lower than what other studies have historically reported. However, their sample consisted of only seven brain tumor survivors out of 227 total participants, which limits generalizability.

Hays et al. [13] also concluded that a sample of 219 childhood cancer survivors were generally more similar than not to carefully matched controls regarding employment issues. However, when they compared CNS survivors to non-CNS survivors, a vast discrepancy was revealed. For example, only 55 % of CNS survivors reported being currently employed compared to 86 % employed of the non-CNS group. In the same study, 14% of CNS survivors reported coworker discrimination compared to only 3 % of the non-CNS group and 23 % of CNS survivors reported conflicts with supervisors versus only 3% of the non-CNS group. Finally, 55 % of the CNS group compared to only 22 % of non-CNS tumor group reported an annual income of less than $15,000.

Further, other variables, such as gender or treatment history, might have contributed to the discrepancies in research findings. For example, Green et al. [14] discovered that gender and age at follow up significantly discriminated between employment statuses. Males and those who were of older age at time of follow up were more likely to be employed in comparison to female survivors. The authors reported employment rates for male survivors that were commensurate with the national average in their sample of childhood cancer survivors, while rates for females were slightly lower, although it was statistically insignificant.

Despite the more overall positive statistics reported by Green et al. [14], still 6.7 % of survivors reported they had been denied a job offer, 3 % were denied promotions, and 3.6 % reported that they were terminated as a direct consequence of their cancer history. However, over 70 % of the sample did not disclose their cancer histories to their employers, which may have positively impacted these findings.

Finally, although the rates of health insurance coverage were not statistically significant when compared between survivors and national same-aged norm groups, the rates of life insurance policies that were obtained by survivors was significantly less than national averages for comparable same aged peers and also for previously reported studies of other sample of childhood cancer survivors [14]. Authors speculate cancer survivors are often denied life insurance policies due to risks associated with recurrence of original cancer or due to the higher chance of development of new cancer or related diseases.

A meta-analysis of employment outcomes of adult survivors of pediatric cancer identified 34 articles published between 1966 and January 2006 which resulted in 40 empirical studies including 24 controlled studies [22]. The results indicated survivors were twice as likely as controls to be unemployed. Central nervous system (CNS) survivors were found to be *five times* more likely to be unemployed compared to healthy controls. Another interesting finding was that

survivors in the United States were three times more at risk of being unemployed compared to no risk for European survivors. One possible explanation for this finding provided by the study authors is that there might be more discrimination towards cancer by employers in the workforce in the United States due to the notion that cancer survivors may not be as productive on the job due to continued health issues or need for time off. Support for this idea is in the discrepant rate of employment rejection for adult survivors of childhood cancer rates with the United Kingdom reporting at 6 % [19] versus the United States as high as 32 % [10]. Obviously, more research is needed in this area in order to clarify this discrepancy.

Other risk factors for unemployment identified by these researchers include: younger age, lower education, lower intelligence (IQ), female gender, motor impairment, epilepsy, and treatment with radiotherapy. Treatment with radiation was also found to be associated with increased unemployment rate in another study of long-term acute lymphoblastic leukemia survivors [23].

Various researchers have attempted to address methodological issues of previous studies that examined employment outcomes that may have accounted for the discrepancies in results such as small sample sizes, mixed samples in terms of diagnoses, differences in types and extent of treatment, and comparisons with demographically appropriate control groups [24]. Several papers have examined employment outcomes in the Childhood Cancer Survivor Study (CCSS) cohort which includes 14,370 survivors and 3,418 siblings from multi-institutional consortium [2, 25].

Childhood cancer survivors were at a significantly higher percentage of unemployment within the past 12 months of participation time in the study compared with their siblings for all diagnostic categories [26]. These findings were consistent with results of a study which consisted of 500 long-term young adult Dutch survivors of childhood cancer [27]. Failure to complete high school, young age (less than 4 years) at diagnosis, cranial radiation therapy (greater than 30 Gy), and female gender were associated risk factors for never obtaining employment [26]. Brain tumor and bone tumor survivors were least likely to be employed after age and gender adjustments were analyzed. Another study of survivors of pediatric lower extremity bone tumors found amputees had significantly lower rates of education, employment, and health insurance coverage compared to siblings [7]. In addition, development of chronic medical conditions after cancer treatment significantly increased the chance for unemployment. Consistent with previous findings, the CCSS cohort survivors also had significantly lower rates compared to siblings of securing health coverage [28].

In general, these findings appear to follow the patterns of children with chronic illnesses [29]. In a study of over 13,000 participants, adults with childhood onset chronic illness (e.g. childhood onset cancer, heart disease, diabetes, or epilepsy) had similar rates of marriage, children, living with children, and quality of romantic relationships compared to those adults without childhood onset chronic illness. However, those with chronic illnesses had significantly lower rates of earning a college degree, being employed, and lower income levels. In addition the chronic illness group had higher rates of being on public assistance.

Besides the obvious financial and social benefits of employment, other benefits include impact to psychological health and quality of life. Another study that examined the CCSS data reported that survivors who were unemployed or unable to work were at higher risk for depression, anxiety, and somatic distress compared to those who were successfully employed [11, 30]. Wilms' tumors and neuroblastoma survivors who were employed reported a higher quality of mental health [31].

Another study compared self-concept and self-worth between adult survivors of childhood ALL and sibling control group [32]. Overall, this study found survivors' global self-worth scores were significantly lower than controls. For the survivor group, unemployed survivors scored lower global self-worth scores than those who were employed. Employment status was not related to self-worth in the control group. Seitzman et al. [32] concluded that unemployment and the belief that cancer treatment limited

employability were predictors of negative self-concept for the survivor group. The belief that cancer treatment limited employability was a risk factor for negative self-concept even in the group of survivors that were employed. Similarly, childhood cancer survivors were less likely to be employed full time, which was a significant risk factor for negative emotional difficulties [11].

Income levels and socioeconomic status have also been found to be related to psychological distress and quality of life. CCSS survivors with income levels less than $20,000 annually had more depressive, anxious, and somatic distress symptoms compared to those survivors with higher income levels [30]. Those with lower level of educational attainment and annual income less than $20,000 were associated with at least one adverse health status domain [33]. Similarly, psychological distress was related to unemployment and those with reported household income of less than $20,000 for both survivors and controls in a sample of solid tumor CCSS survivors [34]. Along the same vein, more depressive symptoms and somatic distress were reported for survivors of leukemia or Hodgkin's disease with reported household incomes lower than $20,000 [35]. Non-Hodgkin lymphoma survivors also demonstrated higher rates of somatic distress for those with lower annual income levels [35]. For brain tumor survivors, those with incomes less than $20,000 reported higher rates of anxiety, those unmarried or not completing high school reported higher rates of depression, and those unemployed reported higher rates of somatic distress [36].

24.2.1 Career Development of Survivors

In considering whether other career development variables qualitatively differ between survivors and their peers, there was no significant differences between survivors and matched peers in terms of employment, termination experience, job performance, and plans to attend college and work post high school in a sample of adolescent survivors of non-CNS pediatric cancer who were not enrolled in special education services [1]. Similarly, there were no significant differences between ALL survivors and a comparison group, which was comprised of Hodgkin and non-Hodgkin lymphoma survivors in terms of employment status, occupational status, and vocational satisfaction [12].

In contrast, there is some indication that pediatric cancer patients experience some delay in achieving major developmental milestones in areas such as autonomy, social, and psychosexual development [37, 38]. For example, both male and female survivors were married at significantly less rates compared to control subjects [39].

Most relevant to the topic of this chapter however, is that developmental delays related to career development or successful employment was also found [39]. Therefore, career counseling provided by a qualified counselor, who is also competent and familiar with the vast array of physical and cognitive sequelae of pediatric cancer, can be instrumental in preventing not only the delay of successful career development but provide timely intervention to nourish successful transitions from childhood to young adulthood and successful career and employment opportunities. In the following section, we will present a model for career and vocational counseling for the pediatric oncology patient, which includes transition planning to young adulthood.

24.3 A Career and Vocational Counseling Model for the Pediatric Oncology Setting

At our institution, MD Anderson Cancer Center, career and vocational counseling services not only include traditional career assessments and career counseling, but also encompass transition planning post high school, college preparation, higher education support services, work readiness skill development, job seeking assistance and work support services. Due to the developmental level of the pediatric cancer survivor population, readiness development support during transitions from high school and college, as well as support during college and graduate school, naturally compliments career planning services.

24.3.1 Transition Planning

Transition planning is an important service that can significantly promote career counseling. Ideally, the seeds of career counseling should be planted prior to transition planning. However, preparing for the next step after secondary school is a perfect opportunity to segue into career planning, which is often synonymous. When working with a high school student, developing goals and plans may include further education, vocational or technical training, or direct entry into the workforce. It will be imperative that the career counselor helps the student explore a wide variety of options while promoting the best match between interests, ability, and goals.

24.3.2 College Preparation

At our institution, career counselors assist high school students interested in pursuing higher education with educational planning in conjunction with career planning. This includes assisting high school students with the college application process including searching for schools, completing applications, financial aid and scholarship searches, and registering for appropriate classes. In addition, counselors help students identify any barriers for academic success, including any physical or cognitive disabilities in order to develop appropriate coping strategies to ensure academic success.

24.3.3 Higher Education Support Services

As previously mentioned, survivors of pediatric cancer patients may develop cognitive or physical disabilities that impact academic functioning. Even if the student was provided special education services or educational accommodations as part of an Individualized Education Plan or under Section 504 of the Rehabilitation Act (discussed in Chap. 23), a college student will have to reapply at the student disability services to qualify at that institution for accommodations based on a disability that impacts academic functioning. As part of identifying coping strategies for possible educational barriers, the career counselor should be able to provide support and advocacy for the student to apply for disability services.

24.3.4 Work Readiness Skill Development and Job Seeking Assistance

Another aspect of career services involves preparing one for employment in the workforce by teaching job seeking skills such as resume development, interviewing skills, and workplace social skills. Due to pediatric survivors having been in treatment during formal education years, they may have missed out in opportunities for volunteering and job experiences which are typical content areas on resumes. Therefore, a counselor can assist the survivor in adapting his/her resume to focus and highlight other positive skill sets while minimizing these weaknesses.

Another common difficulty that survivors encounter is determining whether or not to disclose their cancer history either on a job application or during a job interview. Some studies found that many survivors chose not to disclose their cancer history for fear of discrimination [8, 14, 18]. A career counselor can explore this issue with the survivor prior to the application or interview so that a personal decision can be made and an appropriate response can be developed and rehearsed. Mock interviews that help the survivor rehearse responses to such inquiries can be greatly beneficial and also help to increase interviewing self-efficacy.

24.3.5 Work Support Services

In addition to providing career counseling for purposes of developing career plans, some young adult survivors might already have an established occupation and require support in either working during treatment or returning to their former position. Others might be unable to return to their former positions due to sequelae of their diagnoses and treatments. In these situations, career counseling to explore other career opportunities

or to change careers would be most beneficial. Survivors should be appropriately prepared and equipped to face possible challenges prior to returning to work, based on their health status, disabilities and previous work environment. Tebbi et al. [40] reported that although only 5 % of their sample required a job change as a result of their cancer, 64 % reported that physical accommodations at the job site were required for them to successfully readjust to the workplace and only 16 % reported that no changes or accommodations had been required at their work site. The same study reported that 79 % of the sample believed their adjustment back to work would have been easier if the attitudes of others had been different. In these types of situations, a career counselor should provide education regarding protected time off, which is provided by the Family and Medical Leave Act (FMLA), and work accommodations, which can be requested and supported by the Americans with Disabilities Act (ADA).

24.3.6 Family and Medical Leave Act

The Family and Medical Leave Act (FMLA) protects employees from termination by employers who legally must participate. FMLA allows up to 12 work weeks within a 12 month period of protected time off for personal medical reasons, including the birth or adoption of a child, or for caring for an immediate family member's medical condition. During the leave of absence the employer must continue group health insurance coverage for the employee. However, time taken off is typically unpaid. Please see http://www.dol.gov/whd/fmla/ for more information.

24.3.7 Americans with Disabilities Act (ADA)

The Americans with Disabilities Act (ADA) of 1990 protects an individual with a disability from employment discrimination such as hiring, firing, and benefits if the individual is able to perform the "essential functions" of the job. A disability is defined as a major health impairment that significantly limits the ability of life activities and functioning. All employers with 15 or more employees, state and local governments, legislative and federal government, employment agencies, and labor unions must adhere to the ADA. Please see http://www.ada.gov/pubs/ada.htm for more information.

A cancer diagnosis can be considered a disability if it has impaired a person's ability to perform major life activities and functioning; however, each cancer patient and survivor is considered individually because of the wide variance of the effects cancer and its treatment can have on each individual. For example, a cancer survivor with no apparent side effects of disease or treatment and no impairments to any aspect of his/her functioning would not be considered to have a disability and, therefore, not qualify for protection under ADA.

As a result of ADA, an employer cannot inquire about a potential employee's medical status or history unless it is related to whether the essential functions of the job will be impacted, and a potential employee is not obligated to disclose any medical history. A medical exam can be required of the potential employee provided that this is consistent for all potential employees and part of the employer's standard process for screening all potential employees. Once an employer has made a job offer, it cannot legally be rescinded based on any health information that is revealed.

In addition to protecting persons with disabilities from work discrimination, the ADA also provides "reasonable accommodations" that would not cause "undue hardship" for the employer or coworkers. Examples of accommodations include flexible work schedules, providing breaks during the work day, providing any physical equipment that may aid work duties, and so on. Undue hardships are those that would disrupt or significantly force changes on the normal operations of the business or fellow employees.

24.4 Components of a General Career Counseling Model

Although presenting a specific theoretical conceptualization and intervention of a career counseling model is beyond the purpose and scope of this chapter, a general overview of basic career counseling goals will be provided. Career counseling typically begins with an assessment of the client's current career developmental stage and needs. It is important at this initial phase to explore the following areas: career interests, career aspirations or goals, personality factors, extent of career exploration, previous work experiences, level of career self-efficacy, possible educational or career barriers, and available supports. In the next stage, career counselors will assist in utilizing all the above-mentioned information to define both short and long term career related goals which will then guide planning action steps to accomplish set goals.

During the planning stage, the more concrete and detailed each step towards the desired educational and career goal can be created, the more beneficial it will be for the client. We often use a roadmap approach to plot out all the required education, training, and individual efforts that will be required for the client to achieve his/her goals. In this stage, it will also be beneficial to create alternative plans to provide options and the assurance that the roadmap can be adjusted if needed. Along with the planning, it is also essential to identify possible barriers at each step and to address strategies for coping with or overcoming each of these barriers.

In the final stage of a general career counseling model, it is recommended to have periodic follow-ups with the client to re-evaluate progress and whether adjustments need to be made to his/her roadmap. This can provide accountability to the client and opportunities to process ongoing work towards his/her goals. Having regular check-ins can also provide the opportunity to problem solve any difficulties that may have developed, therefore preventing a crisis that can cause a serious derailment from the career development roadmap (Table 24.1).

24.5 Career Counseling of Pediatric Cancer Survivors

As the literature review indicates, not all survivors of childhood cancer will warrant career and vocational intervention. However, there are subgroups and risk factors for developing career and employment issues that have been identified through research. Knowledge of these can assist in identifying those who might benefit most from career services and interventions, especially as a preventative measure for future occupational problems. Therefore, it is imperative to identify survivors who may be at the highest risk of developing these issues, and utilize a preventative approach to career counseling and intervention.

Table 24.1 General career counseling model

Stages	Goal	Activities
First Stage "Getting to know you"	Exploration/Assessment	• Assess career development stage and needs • Assess career variables i.e., interests, aspirations, personality, barriers, etc.
Second Stage "What are your dreams?"	Develop and Identify Goals	• Concretely define both short term and long term goals
Third Stage "How do we get there?"	Planning Action Steps	• Identify and define behaviors necessary to achieve both short and long term goals • Identify alternate or contingency plans
Fourth Stage "Accountability and encouragement"	Evaluate Progress and Adjust	• Regularly evaluate progress • Identify barriers and develop coping strategies to overcome barriers • Make adjustments to goals and action steps if needed • Provide encouragement to persevere

Following is a list of risk factors that have been previously identified in the literature (not listed in order of significance):

- Brain tumor and CNS involvement diagnoses [13, 22, 26]
- Bone tumor diagnoses [26]
- Chronic medical conditions after cancer treatment [26]
- Motor impairment or epilepsy [22]
- Physical limitations or restrictions [41]
- Young age (less than 4 years) at diagnosis [26]
- Treated with cranial radiation therapy (greater than 30 Gy) [23, 26]
- Female sex [26]
- No high school diploma [26]
- Lower education level achievement [22]
- Lower intelligence quotient (IQ) [22]
- Belief that cancer treatment limits employability [32]
- Maladaptive psychological coping with illness experiences [42]

Our recommended model for career counseling provides basic career guidance support services to all pediatric cancer patients, especially considering that many will miss the opportunity for such services at their home school campuses. Basic career guidance can include education regarding post high school options, assistance with college or vocational school applications, assistance with searching and obtaining financial aid, career assessments, career counseling, education regarding accommodations and rights for disabilities in both academic and employment settings, and so on.

An imperative step in providing career services is to initially educate the medical staff regarding the availability of career counseling services to recruit referral sources. In addition, outreach opportunities such as organizing career or college fairs proximal to the main clinic has been very successful in our setting in terms of providing education, increasing awareness of patients with regards to available career counseling services, and recruiting potential candidates for service. If career counseling is a service that is unavailable, referring patients to the Cancer and Careers website would be an alternative and beneficial resource. Cancer and Careers is a comprehensive website for cancer patients and survivors that provides educational publications, career coaching, support groups and educational seminars for those dealing with cancer and work related issues. Although Cancer and Careers is not specifically for pediatric cancer survivors, it offers a wealth of information, resources, and interactive tools to assist in the career development process. Please see http://www.cancerandcareers.org/en for more information.

Once a patient is referred or identified for services, the next step is to assess the potential risk factors for future educational or career and employment difficulties. During this initial assessment, risk factors identified by the literature, a thorough evaluation of the patient's career development process, potential barriers to career choice, and availability of support and resources should be assessed and evaluated.

In addition to the general career counseling goals, when providing career services to cancer patients and survivors, it is vital to also assess potential effects of the cancer diagnosis and treatment and how these might impact career goals, especially physical and cognitive sequelae. For example, if a patient has a career goal of becoming a professional athlete and he/she is facing lower extremity limb salvage, it will be important to sensitively and respectfully address how this treatment may impact future career plans and goals. Nearly 50 % of pediatric cancer survivors had to change educational plans as a result of their illness and 38 % reported changing their original career goals as a direct result of their cancer diagnosis [37]. The earlier this is addressed and alternative career goals developed, the sooner emotional distress and potential career problems are avoided.

24.6 Case Illustrations

24.6.1 Case Study 1

Steven is a 19-year-old male who was diagnosed with a pineal germinoma brain tumor at the age of 14 years old. Unfortunately, due to several tumor recurrences he had been on treatment for the past several years, which began when he was

in the 9th grade. He was treated with resection and radiation to the ventricles and pineal region, and various chemotherapies. At the time of referral for career counseling, he was declared to have stable disease and continued to receive maintenance chemotherapy.

Most of his high school years were accomplished through homeschooling and online courses. Historically, he was reported to have high intelligence and was a successful student. As a result of excellent academic abilities and extraordinary determination, he graduated with a high school degree and began taking classes at the state university. Despite experiencing significant physical and cognitive side effects of both his brain tumor and treatment, he was attending college classes without any academic accommodations. Unfortunately, he recently became unable to keep up with his classes and began to fall behind. At the recommendation of his nurse, he agreed to a consultation with the career counselor to assist with current academic difficulties and for general academic planning.

Steven is an example of a pediatric cancer patient who continues to receive treatment while simultaneously pursuing academic goals. A career counselor would be ideal in assisting Steven in developing both proximal and distal academic goals that would lead to his future career goals. An immediate and practical need that Steven presented with was to assess his current academic standing and to provide counseling whether it was in his best interest to continue his courses or to consider a medical withdrawal. In situations like these, the decision needs to take into consideration the current time period of the semester (e.g. second week of the semester versus the week before finals), how behind the student is in terms of assignments and exams, and medical prognosis of symptoms (e.g. if side effect symptoms were expected to worsen or improve). If it is early in the semester, than a medical withdrawal might be appropriate, especially if symptoms impacting academic difficulties are not expected to improve. However, if the semester is almost over and majority of assignments and exams have been completed, then the counselor may advise Steven to negotiate "incompletes" with his professors and request additional time beyond the end of the semester to complete the course requirements.

Another priority need that Steven presents with is the need for evaluation for disability services that would provide academic accommodations including a referral for neuropsychological evaluation with a provider familiar with the possible cognitive late effects of cancer and its treatment. Once the results are presented, the career counselor could assist Steven in applying for appropriate educational accommodations and provide advocacy if there are any barriers or resistance. Even if the decision is made to withdraw from courses in the current semester, initiating an application for disability services will ensure that appropriate accommodations will be in place upon his return to school. Many college campuses may be unfamiliar with pediatric cancer survivors' difficulties, many of which can be addressed by the career counselor providing education and advocacy on behalf of the patient.

Finally, career counseling to assess and develop educational and career goals will be beneficial so that Steven is able to concentrate his resources towards his goals. For example, if he is able to declare a major early in his college years, then he may be able to narrow down the number of classes he takes for exploratory purposes. This can also be helpful in terms of planning the courses he takes each semester by attending to factors such as not registering for too many demanding courses in the same semester or taking advantage of alternative course formats such as online courses to increase flexibility and independence of the student.

24.6.2 Case Study 2

Alison is a 22-year-old female who is a long-term survivor of osteosarcoma of the right femur which was initially diagnosed at the age of 13 years. Alison received chemotherapy and a limb salvage procedure at the age of 14-years. At the time of referral, Alison was taking classes at a community college while working full time as a sales representative at a cellular phone service

center and store. Fortunately, her employer provided health benefits which were not typical of most jobs for which she was eligible for. She reported that it was imperative for her to sustain her employment with this company due to the health benefits. Alison's work duties involve assisting customers either on the sales floor or behind a counter, by constantly standing on her feet. She had not disclosed her cancer history to her manager nor requested any accommodations mostly in fear of any negative reactions or repuraussions from her manager and coworkers.

Alison reported that for the past couple of months she has had pain that worsened at the end of the day in her right hip and legs. She was recently evaluated and diagnostic imaging confirmed no evidence of disease in her right leg. Her physician recommended reducing the amount of physical activity, including time spent standing. When Alison disclosed to her nurse practitioner that she was conflicted between wanting to relieve her pain and needing to work, her nurse practitioner recommended a consultation with the career counselor.

Alison reported to the career counselor that despite her discomfort and pain, she was unable to support herself financially if she worked fewer hours. She was also fearful of losing her full time status because she would then be ineligible for health coverage benefits if she worked part time. Alison also struggled with the idea of disclosing her medical history and current pain issues to her manager.

First, the career counselor should provide education regarding the American with Disabilities Act (ADA) including ideas of reasonable accommodations that might assist Alison in being able to continue working full time. Examples of reasonable accommodations may include furnishing a stool for Alison to sit down on, allowing frequent breaks during her shift, or changing work duties to only assisting customers from behind a counter or at a desk, and so on. It will be imperative that Alison comprehends her legal rights afforded by ADA and the implications that will follow if she decides to utilize the law. In order to claim accommodations under ADA, Alison will be required to demonstrate a disability which would lead to the necessity of disclosing her medical history.

Therefore, it will be equally important to explore and problem solve a resolution regarding the disclosure of Alison's cancer history. If Alison prioritizes not disclosing her cancer history, then she will need assistance for alternative solutions such as seeking alternative employment. If she chooses to disclose her health history and apply for accommodations at her current place of employment, then counseling to support her through the process and to cope with her manager and coworkers' reactions would be greatly beneficial.

Finally, the career counselor could help Alison explore her future career goals incorporating her physical limitations into the career choice. In addition, once a career goal is identified, the career counselor can also assist with educational planning and recommend whether she should also apply for student disability services at her campus as well.

24.7 Conclusions

Due to the increased curative rates and advances in treatment methods, more pediatric cancer survivors are entering the developmental stage of young adulthood. A major task of young adulthood is to successfully launch and initiate and develop work and career identities. Literature regarding the employment and career development of pediatric cancer survivors tends to have discrepant findings. However, several important studies have found significant employment issues in the survivorship population and have identified specific risk factors for increased chance of problems with successful employment [13, 22, 23, 26, 32, 41, 42].

As the medical field continues to make advances in the treatment of pediatric cancer, it is imperative that medical providers be mindful of the need for consultation with psychosocial experts who can congruently provide interventions to improve the quality of life of survivors. Providing transition planning and career development services to increase the number of pediatric cancer survivors joining the work force would

not only benefit the individual survivor, but society as a whole, as this would decrease the burden of individuals on public assistance, and instill a sense of independence and a more optimistic future.

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Rehabilitation Consideration in Pediatric Cancer Survivors

25

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25.1 Introduction

Cancer rehabilitation has been broadly defined as "an interdisciplinary team approach to helping patients and their families maximize their level of independence physically, emotionally, and spiritually within the limitations of their disease" [1]. Interdisciplinary rehabilitation team members often consist of many different professionals, such as physicians, nurses, social workers, psychologists/neuropsychologists, child life specialists, and rehabilitation therapists. Specific therapies may include any combinations of services, such as physical, occupational, speech-language, recreation, and other cognitive remediation therapies. More recently, Gamble, Gerber, Spill, and Paul defined the subspecialty of cancer rehabilitation as "any rehabilitation assessment, diagnosis, or functional intervention needed by and provided for any cancer patient at any moment along the continuum of their cancer care" [2].

Given that many pediatric cancer survivors suffer from "late effects" of the cancer and related treatments [3], rehabilitation issues often continue to be important in the long-term well-being of these survivors. Although there have been considerable improvements in survival rates for many childhood cancers, issues of morbidity continue to be of great concern. For example, Lackner et al. [4], prospectively studied 223 childhood cancer survivors and found that 75 % of the children in their long term follow-up group had at least one chronic medical problem. The organ system that was most often impacted was the nervous system (30 %), which has many implications for the need for ongoing rehabilitation services. Thus, therapies to address physical, speech-language, and cognitive functioning are particularly relevant in this population.

It has been known for many years that there is a need for rehabilitation services within cancer survivors, although the need for rehabilitation services has been studied mostly in adults. Lehmann et al. [5] conducted a retrospective chart review of 805 cancer patients from 4 different institutions. The goals of this study were to determine rehabilitation problems by cancer type/site, assess need for rehabilitation services, and to

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assess for gaps in delivering effective rehabilitation services. In the population studied, greater than 50 % had at least one problem defined as a "rehabilitation" issue, including paralysis, paresis, cognitive deficits (i.e., intellectual, perceptual), communication deficits, contractures, pressure sores, difficulties with ambulation or transfers, self care issues, fractures, and lymphedema. Psychological problems were more prevalent throughout the entire population studied, but even more so in those with physical disabilities versus those without (i.e., ~50 % in those with a physical issue and 29 % in those without). The authors noted that many of the subjects did not get appropriate rehabilitation services for their particular issue and that failure to get services often related to a lack of familiarity with rehabilitation services by the treating physician and failure to identify the rehabilitation problems.

Although the Lehmann et al. study was conducted more than 30 years ago, Paul and Buschbacher [6] report that many of the same barriers exist today. These authors note that a significant contributing factor behind skyrocketing healthcare costs in the world of oncology relates to the incomplete detection of rehabilitation, psychological, vocational, and financial needs in the cancer patient which in turn lead to poorer outcomes and quality of life issues. Given these concerns, a recent supplement in the *American Journal of Physical Medicine and Rehabilitation* (Vol 90, No 5) was published with the purpose of "increasing awareness of the role of rehabilitation in cancer care among the public and among medical professionals, as well as to stimulate further interest and training in the field of cancer rehabilitation" [6].

There may be multiple ways in which rehabilitation services can be helpful in the cancer population. Dietz is best known for introducing the idea of adaptive cancer rehabilitation as early as the 1960s. In 1981, Dietz suggested that there are four categories of cancer rehabilitation [7]. These are: *preventative*, where rehabilitation is aimed at improving physical functioning and reducing morbidity and disability; *restorative*, where cure is likely and the sequelae of cancer treatment are to be controlled; *supportive*, where the aim is to lessen disability when cancer is not eliminated but continues with periods of remission; and *palliative*, where there is advanced, active disease and control of symptoms and disability is required. Rehabilitation may also be thought of as treatment for *acute* vs. *long term* or *chronic* issues. For example, children recovering from a surgical resection of a brain tumor may undergo a period of intensive inpatient or outpatient rehabilitation in order to maximize their functioning and return to home and school life. In these circumstances, the goal is to capitalize on the rapid phase of recovery that is often seen in the initial weeks/months following an injury to the brain, such as in the case of a surgical tumor resection. In other cases, the goals of rehabilitation may be to treat more long-term issues, such as impact of limb amputation in an individual with osteosarcoma or in the case of cognitive late effects (secondary to radiation and chemotherapy treatments) seen in children with CNS cancers.

Given that rehabilitation may be helpful across phases of recovery, Heath [8] suggests that rehabilitation services may be beneficial to all childhood cancer patients in order to optimize their functioning and quality of life. This includes all parts of the spectrum, i.e., those in which there is a strong potential to be "cured" (e.g., ALL); those whose health may be maintained with periods of remission and relapse (e.g., childhood brain tumors); those whose cancer is likely to cause significant disability and reduced functioning (e.g., osteosarcoma); and even in those whose cancer is likely to be a terminal illness. Although one may not think of providing rehabilitation to those who have a terminal diagnosis, there may be situations in which such services can be quite helpful. For example, our facility once treated a school-age child with a recurrent brain stem glioma with poor prognosis. This young lady had significant difficulties with mobility, resulting in increasing isolation and loss of independence. In this case, the child benefitted from physical therapy to assist with increasing independence, decreasing isolation, and allowing her more autonomy when coping with end of life issues.

The focus of this chapter will be on long-term rehabilitation needs in survivors of pediatric cancer. It is meant to be a review of some of the most important issues to consider with regard to

mobility, activities of daily living, swallowing, speech production, and language functioning. A few particular pediatric cancers will be highlighted, as these cancers tend to have higher impact on neurological functioning (e.g., CNS brain tumors) and mobility (e.g., osteosarcoma). Particular attention will be paid to posterior fossa tumors, as these are the most common brain tumors diagnosed in childhood. Treatment and surgical resection may result in a group of symptoms known as "posterior fossa syndrome" and are characterized by behavioral changes, irritability, emotional lability, mutism and speech deficits, difficulty following verbal commands, nystagmus, dysphagia or swallow deficits, cranial nerve palsies, and motor deficits, among other signs and symptoms [9].

25.2 Mobility, Activities of Daily Living, and General Physical Activity

25.2.1 Impact of Musculoskeletal Functioning

Adult survivors of pediatric cancer may experience a number of musculoskeletal issues, including amputation, arthritis, osteopenia, and fractures [10]. These are more frequently found in bone-tumor survivors; however, these issues may result in survivors of other types of cancers [11]. This may be in part due to the unintended effects of chemotherapy and radiation on bone and muscle health [12].

Haddy and Haddy [13] noted that the musculoskeletal effects of radiation therapy can be even more pronounced in survivors of pediatric cancer, as the tissues of children and adolescents are still developing and tend to be more susceptible to side effects. More specifically, radiation can cause premature closure of the epiphyses which can lead to limb-length discrepancy [3]. In turn, limb-length discrepancy can lead to functional scoliosis, chronic back pain, or knee and hip pain in the functional limb [14]. Radiation may also lead to spinal deformities (scoliosis, lordosis, and kyphosis) or an overall decrease in bone mineral density [12].

As addressed in a previous chapter, chemotherapy also has detrimental effects on the musculoskeletal system. Chemotherapy agents may also lead to limitations in soft tissue growth, reduced bone density, or osteonecrosis [12]. In addition, corticosteroids can result in decreased bone mineralization, stunted bone growth, or avascular necrosis [10]. Adult survivors of pediatric cancer may not reach peak bone mass as a result of their cancer and/or treatment. This often results in osteoporosis/osteopenia and possibly even osteonecrosis which can lead to fractures, muscle or bone pain, or spinal deformities (scoliosis, lordosis, and kyphosis) [13].

Other musculoskeletal issues related to this area are a result of limb-sparing procedures for osteosarcoma. While there is an obvious initial change after these surgeries, what may be less obvious are the long term effects which may result. According to the Children's Oncology Group, individuals who have undergone limb sparing procedures are at risk for limb-length discrepancy, contractures, or chronic pain [12]. Other possible complications from the surgery include prosthetic loosening (when the implanted joint loosens or wears out) or nonunion (when one or both ends of the bone do not heal properly).

Individuals who have undergone amputation may also deal with complications such as prosthetic issues, skin breakdown, residual limb pain, phantom limb pain, and bone overgrowth [11]. Unfortunately the effects of amputation and limb-sparing surgery are not necessarily limited to the residual limb. The unaffected extremity and its joints may experience increased stress as a result of overuse and may age more rapidly, particularly in weight-bearing joints. According to Gailey et al. [14], amputation and long term prosthetic use can also lead to osteoarthritis, osteopenia, osteoporosis, and back pain. Individuals who have undergone amputation or limb-sparing procedure are also at risk for weight gain and possibly diabetes due to decreased physical activity secondary to increased energy and effort required to perform even simple activities [12].

The musculoskeletal issues caused by childhood cancer can lead to a significant impact on an individual's functioning, including decreased independence with self-care, limited engagement

in education and employment opportunities, and decreased participation in health and wellness activities. Therefore the Children's Oncology Group has outlined specific screening measures and evaluations to ensure these issues do not go unnoticed [12]. Some of the recommendations include spinal exams, bone density evaluations, yearly height and weight measurements, and a history of the patient highlighting any joint pain, swelling, or immobility. In addition for those patients who have undergone limb-sparing procedures or amputations, the residual or affected limb should be periodically examined, as well as the prosthesis when appropriate.

25.2.2 Impact of Neurological and Sensory Functioning

While neurological and sensory issues are more commonly associated with tumors of the central nervous symptom, there is the potential for these symptoms to occur in survivors of other types of cancer as well. Goldsby et al. [15] found that survivors of ALL were at an increased risk for late-onset motor and coordination problems, seizures, and headaches. Survivors may not initially attribute these symptoms to their childhood cancer; therefore it is important for healthcare professionals to be aware of them given their ability to significantly impact functioning.

One sensory system that may be impacted by childhood cancer is the visual system, reviewed in more detail elsewhere. Briefly, radiation, certain chemotherapy agents, and extensive steroid use can predispose an individual to the development of cataracts. Radiation and certain chemotherapy drugs have also been linked to vision loss [10]. Additionally, individuals who have experienced orbital/eye radiation or higher doses of cranial radiation may be at risk for developing ocular toxicity, which can lead to multiple visual problems such as glaucoma, retinopathy, or optic chiasm neuropathy [12]. Therefore, annual eye exams are recommended, as well as a history of the patient highlighting any visual changes. Changes in vision have the potential to impact multiple aspects of an individual's functioning including reduced mobility and greater need for assistance with activities of daily living. Working with an occupational or physical therapist with expertise in vision loss can be quite beneficial in these cases.

Another sensory system that may be affected by childhood cancer is the hearing/vestibular system. Higher dosages of radiation and certain chemotherapy drugs may lead to ototoxicity, which can result in hearing loss (sensorineural or conductive), tinnitus, or eustachian tube dysfunction [12]. Damage to the inner ear can be especially harmful, as this may lead to vertigo and/or changes in balance, which may impair an individual's mobility and put them at an increased risk of falling [16].

One significant neurological effect that may occur as a result of childhood cancer is leukoencephalopathy. As the white matter of the brain undergoes changes as a result of chemotherapy or radiation, various neurological symptoms may occur such as spasticity, ataxia, hemiparesis, or seizures [3]. Certain chemotherapy drugs may also predispose an individual to peripheral sensory or motor neuropathies. Individuals experiencing sensory neuropathies may be limited by pain or dysesthesias, or may be at increased risk for skin issues secondary to decreased sensation. Those experiencing motor neuropathies may be limited by loss of reflexes, decreased strength, or changes in balance or mobility.

These types of symptoms can have a significant impact on an individual's ability to fully engage in day to day activities, and may pose safety risks as well. Therefore, the Childrens Oncology Group (COG) recommends annual neurological exams to screen for these neurological symptoms, as well as a thorough history. If a patient's functioning is being affected by neurological symptoms, they may benefit from a referral to rehabilitation services. For example, an individual experiencing foot drop as a result of a motor neuropathy would likely benefit from treatment from a physical therapist, who can work on strengthening or may recommend an orthosis. Individuals with decreased sensation in their hands may benefit from working with an occupational therapist who can improve what coordination is still available, as well as educate the patient on compensatory techniques [17].

25.2.3 Impact of General Health and Wellness

According to Schmidt et al. [10], nearly two-thirds of survivors of childhood cancer will develop chronic health conditions. For a quarter of these individuals, these conditions will be moderate, severe, or even life threatening. These effects may occur initially after treatment ends, or may not appear for several years. If survivors are made aware that their childhood cancer places them at an increased risk for certain conditions, they may be more likely to engage in healthy behaviors and willing to avoid harmful ones.

Ness et al. [17] examined physical performance limitations among adult survivors of childhood brain tumors. Results indicated that survivors had reduced grip and knee extension strength and lower peak oxygen uptake as opposed to the comparison group. In this particular study, the median age of survivors was 22 years old, but their muscle strength and fitness level was similar to that of the 60+ age group. The authors also determined that survivors had lower physical performance, which was associated with not living independently and not attending college. Obviously, this places this particular group of individuals at risk for a number of challenges that require ongoing evaluation and periodic intervention if needed.

Childhood cancer and its treatment can also lead to various cardiovascular and respiratory issues which can have a significant impact on an individual's general health and wellness. For example, radiation in specific areas of the body and certain chemotherapy drugs can lead to cardiac toxicity, which may present as congestive heart failure, cardiomyopathy, myocardial infarction, or atherosclerosis of the heart. Similarly, radiation and chemotherapy treatments may also lead to pulmonary toxicity, which may present as pulmonary fibrosis, interstitial pneumonitis, or restrictive lung disease [17].

Studies show that survivors are less likely to meet recommendations for physical activity than their sibling counterparts [18]. Additionally, there is a higher rate of obesity and overweight status among survivors of childhood cancer, particularly in those patients treated with cranial radiation. On the other hand, a significant proportion of survivors are underweight as adults [13].

Schmidt et al. [10] lists fatigue as a possible late effect in adult survivors of childhood cancer. Taking into account this symptom, in addition to the myriad of other symptoms survivors are at risk for (musculoskeletal, neurological, cardiovascular, and respiratory), it becomes apparent that survivors may face many challenges in assuming a healthy lifestyle. For survivors whose general health may be at risk, COG recommends providing appropriate education and counseling regarding healthy eating and physical activity to ensure general health and wellness, along with any symptom-specific education which may be applicable.

25.2.4 Swallowing and Related Concerns

Insults to the central nervous system and oral-facial structures put a child at risk for difficulty swallowing (i.e., dysphagia) [19]. In many children, the dysphagic component resolves. However, in some the long-term effects of childhood cancer and/or its treatment result in ongoing swallowing deficits. Often, deficits are related to esophageal strictures, tracheoesophageal fistula, trismus, dry mouth, oral health, and dental development. Patients may be noted with increased coughing while eating, decreased oral opening, a sense that something is "lodged" in their throat or chest, and difficulty chewing food, among other signs and symptoms of aspiration. In these cases, various interventions may be helpful including speech therapy to assist in improving swallowing function.

Dysphagia is a frequent consequence of pediatric brain tumors, particularly when the tumors are located in the brainstem where many of the important structures and nerves important for swallowing are located [20, 21]. Gonglaves et al. [19] conducted a study in which they screened pediatric tumor patients (n = 190) for potential swallowing and other speech-language complaints. Results of this study found that 42 % of

the problems identified through the screening related to concerns with swallowing.

Cancer treatments may also place a child at risk for swallowing difficulties. Although rare, pediatric cancer patients treated with chemotherapy and radiation therapy may develop esophageal strictures or esophageal fistula as a long-term outcome [22]. Esophageal strictures can occur up to 10 years after therapy [23] and are treated with dilation. Research indicates that some patients may require multiple dilations, one study citing a range of 1–50 dilations with an average of 5, before being able to return to a regular diet [22]. Other research indicates that even multiple dilations may not fully resolve esophageal strictures [24].

While esophageal strictures can be managed via dilation, tracheoesophageal fistulae require more invasive remediation including esophageal diversion and secondary reconstruction [22]. One study identifies a cough, particularly with oral intake, in children with esophageal fistula which may be noteworthy for healthcare providers and family of pediatric cancer survivors [22].

Patients who undergo tumor resection, particularly those who are also treated with radiation, may suffer from trismus as a long term effect [25]. In adults treated with radiation therapy for nasopharyngeal cancer, a rapid decrease was noted in maximal interincisal distance in the 1–9 months following radiation treatment [26]. A year following therapy, decreased maximal interincisal distance continue to be noticed, with the rate of change slowing with an average decrease of 32 % relative to initial maximal interincisal space 4 years post-treatment. While the results of adult outcomes cannot be extrapolated directly to children, it appears that trismus may be a long-term consequence in children and adults alike following cancer treatment. Trismus is of particular concern in pediatric patients as it limits oral hygiene and dietary intake, as well as follow-up for oral cancers [25].

Decreased salivary flow rate is documented in adults following cancer treatment and may also be a long-term outcome in some children treated for cancer. In a study of the long-term effects on the oral cavity, children treated with total body irradiation and bone marrow transplantation demonstrated slower secretion rate than children treated with chemotherapy, both of which were reduced relative to healthy controls [27].

In addition to dry mouth, children treated with radiation therapy and chemotherapy may also demonstrate deficits in dental development and oral health. Limited research is available regarding the long term outcomes of dental and oral health in survivors of pediatric cancer, however current findings suggest that patients may suffer from loose teeth, inflamed gingivae, alveolar bone loss, and reduced dental roots as adults despite adequate oral hygiene practices [28]. As such, overall health and oral health status should be monitored carefully in survivors of childhood cancer.

25.2.5 Hearing and Speech Production

25.2.5.1 Hearing Loss

As mentioned above, hearing loss is of significant concern for survivors of childhood cancer, with long term effects likely. Most often, it is not the cancer itself that results in hearing problems, but rather it is a long-term morbidity of cancer treatment and may include hearing loss (sensorineural or conductive), tinnitus, or eustachian tube dysfunction [12]. In a study assessing the long-term outcomes of childhood nasopharyngeal carcinoma treated with either radiation, chemotherapy, or a combination of both, more than 50 % of survivors were noted to demonstrate sensorineural hearing loss in 15 years following treatment [29]. A dose–response relation with radiation was noted, with more severe sensorineural hearing loss associated with increased radiation therapy. Hearing loss can result from ototoxicity following exposure to cisplatin and carboplatin, used in treatment of neuroblastomas, osteosarcomas, hepatoblastomas, germ-cell tumors, and certain brain tumors [30]. “Children are more susceptible to ototoxicity from platinum agents than adults” due to a lower threshold of exposure for “significant hearing loss involving the speech frequencies” [30].

In addition to sensorineural hearing loss resulting from chemotherapy, childhood survivors of cancer are additionally at risk for hearing loss due to radiation therapy. The Children's Oncology Group reports that "approximately one third of radiation-induced ear pathology problems have been reported to occur in the outer, middle, and inner ear, respectively" [29]. Damage in these areas may result in sensorineural hearing loss, conductive hearing loss, or mixed hearing loss. Research also indicates that a combination of both radiation therapy and chemotherapy is more ototoxic than either in isolation and that "radiation before chemotherapy exacerbates risk" [30].

There is currently limited research regarding the long-term outcomes for hearing loss in childhood cancer survivors, however in the general population the affects of hearing loss are well documented. In a study of neuroblastoma survivors (age 8–17), increased risk was noted in the area of reading, math, general learning disability, and special education for those with a hearing loss relative to those without [30].

In a report from the Children's Oncology Group, "yearly evaluations with appropriate risk-based screening for potential cancer-related complications" are recommended [30]. The report also identifies the importance of a speech-language pathology evaluation, as articulation and receptive/expressive language deficits can occur in hearing-impaired children . Involvement of an audiologist may be indicated for amplification, as hearing aids are recommended for 30–40 % of children with hearing loss following childhood cancer. Referral to an otolaryngologist may be necessary to address perforations of the tympanic membrane, refractory cerumen impaction, chronic otitis media or externa, and for additional anatomical abnormalities.

25.2.5.2 Speech Production—Ataxia Following Posterior Fossa Syndrome

Pediatric cancer survivors at highest risk for deficits in speech production are those who have had tumors in posterior fossa. For example, a speech deficit known as ataxia or *ataxic dysarthria*, is commonly noted in children with posterior fossa syndrome and results from damage to the cerebellum. Often, a listener may describe an individual with ataxic dysarthria as speaking with a decreased rate with monotone pitch and monoloudness, harsh vocal quality, articulatory inaccuracy, and unnatural repetitions or dysfluencies, as well as breakdowns in resonance, prosody, and respiration among other deficit areas [31]. A defining characteristic of ataxic dysarthria is in the listener's perception of an individual's speech as having a drunk or slurred quality. Children suffering from posterior fossa syndrome following tumor resection and treatment may also demonstrate a period of mutism, during which time no speech or verbal output is noted from the child.

Recent research suggests that ataxia, dysfluency, and decreased speech rate may be noted in adult survivors of childhood cancer and posterior fossa tumor resection and radiation therapy relative to their adult counterparts [31]. Specifically, survivors of a medulloblastoma had demonstrated "significantly more ataxic dysarthric features" relative to survivors of astrocytomas, likely due to both radiation to the cerebellum in medulloblastomas and/or due to the highly malignant nature of a medulloblastoma [31]. Additionally, medulloblastomas may have more severe outcomes, as medulloblastomas tend to be more central in the cerebellum relative to the more lateral nature of astrocytomas [32]. However, both survivors of medulloblastomas and astrocytomas were noted to demonstrate increased dysfluency relative to healthy controls [31]. Adult survivors were noted to demonstrate a speech rate comparable to that of child survivors, while adult controls were noted to demonstrate an increased speech rate relative to childhood. Additional research suggests that nearly 70 % of children with removal of a posterior fossa tumor may demonstrate a mild dysarthria [32]. This research found that speech deficits may persist 10 years post-surgery in children who did not demonstrate mutism acutely following surgical resection. Of note, unilateral lesions on the right resulted in poorer outcomes relative to unilateral cerebellar lesions on the left, due to the fact that "speech is

controlled by reciprocal right cerebellar/left frontal interactions [32]."

Research currently indicates that there is no clear relationship between age of diagnosis and the severity of long-term speech deficits following treatment for posterior fossa tumors, suggesting that earlier onset in childhood does not necessarily result in more severe long term outcomes [31, 32]. Additionally, there was there a clear association between the years post-treatment and the severity of speech deficits, suggesting little scope for "spontaneous functional sparing beyond the 1 year post-surgery period [32]." Overall, these findings suggest that survivors of childhood tumors in the posterior fossa may demonstrate long term speech deficits including dysfluency, decreased speech rate, and ataxic dysarthria with increased severity for medulloblastomas and exposure to radiation therapy. This is not a universal finding, with some studies noting no difference between survivors of cerebellar tumor resection and controls in the areas of ataxic dysarthria and speech rate. Of note, although some survivors of childhood cancer demonstrate fully intelligible speech, many demonstrate unnatural speech characteristics, including deficits in respiration, prosody, and resonance [32]. Varying assessment measures in research for intelligibility and other speech characteristics, such that one study may assess long-term outcomes of intelligibility, while another may assess listener qualitative perceptions, may explain the varied findings.

As previously mentioned, some children suffering from posterior fossa syndrome suffer from mutism acutely. Although the mutism resolves, these children demonstrate more severe long term ataxic dysarthria relative to survivors who do not demonstrate mutism acutely following cerebellar tumor resection [21]. The overall findings for the long-term effects of posterior fossa tumor resection and treatment appear mixed with apparent worse outcomes for those demonstrating mutism acutely. While findings are mixed, they remain worth noting for caregivers and healthcare providers involved in the care of childhood cancer survivors.

25.2.6 Cognitive and Higher-Level Language Deficits

Problems with cognitive skills and higher-level language in pediatric cancer survivors are complex and will be covered in depth in other chapters in this book. Please see section III of this book for chapters on the neuropsychological impact of both acute lymphoblastic leukemia (ALL) and pediatric brain tumors. We will just briefly mention some of the relevant issues here, as it is likely that treatment by a speech-language pathologist may be helpful in the rehabilitative approach to treating these issues in the long-term cancer survivor. Gonclaves and colleagues [19] highlight that speech and language difficulties, which included both speech issues and deficits in the development of language, writing and reading difficulties, represented 29 % of the complaints identified in their screening. Again, these issues may be particularly relevant in children with tumors in the posterior fossa or other cortical tumors impacting primary language systems (e.g., tumors in the left cortical or dominant hemisphere).

Research indicates that damage to the cerebellum results in cognitive and linguistic changes in children, particularly for high level tasks. One study focusing on language abilities specifically examined language in four children previously treated with surgery and/or radiation therapy of cerebellar tumors [33]. Results revealed that while all of the children's general language ability appeared intact, two of the four children demonstrated breakdowns in high level language skills for linguistic problem solving tasks six months post-treatment, with additional deficits noted 18 months post-treatment in one case.

While right cerebellar lesion results in high level language deficits, deficits for spatial and visual sequential memory are noted for left cerebellar lesions [34]. Damage to the left cerebellum may also influence prosody of speech, which is almost exclusively modulated by the right cerebral hemisphere. Damage to the cerebellum may also influence naming, comprehension, and decreased speed for executive function tasks and time-based attention tasks [34]. The impact of

right cerebellar damage on language and the impact of left cerebellar damage on cognitive tasks is due to the relationship between each cerebral hemisphere and the contralateral cerebellar hemisphere.

Given that problems with cognition and language have been documented in certain types of pediatric cancer (particularly those impacting the CNS), it is also important for individuals treating these patients to consider rehabilitation services to address these concerns. Butler et al. [35] describe several emerging therapies for the designed to improve neuropsychological functioning among pediatric cancer survivors. While some therapies have involved medical/pharmacologic interventions, others include more traditional cognitive rehabilitation approaches. In the late 1990's several case studies documented the use of cognitive rehabilitation strategies (i.e., massed practice, instruction in metacognitive strategies, use of compensatory devices for memory issues) in children with pediatric brain tumors [22, 35, 36]. These researchers developed a particular intervention called the *Cognitive Remediation Program* (CRP) which has subsequently been used in several follow-up research projects including a large clinical trial of 161 pediatric cancer survivors with documented attentional deficits [37]. Research regarding this and other cognitive rehabilitation therapies (such as Cogmed® treatment for working memory deficits) [38, 39] provide some promise in the rehabilitation of the cognitive difficulties seen in pediatric cancer survivors. Please see Chap. 26 of this book for a more in-depth review of the CRP program and other interventions aimed at cognitive remediation of neuropsychological issues in pediatric cancer survivors.

25.3 When to Refer to Rehabilition Therapies

Given all of the issues raised in this chapter, it may be helpful to involve rehabilitation specialists in the long-term care of pediatric cancer survivors. Punzalan and Hyden [40] outline potential triggers for referral to an occupational and/or physical therapist in pediatric and adolescent cancer survivors. Although their work was focused on individuals with osteosarcoma, many of these triggers are more general and can be considered for the survivors of other pediatric cancers. Triggers for referral may include:

- Risk or history of falls
- Impairment of self care activities and mobility
- Deficits in function of an extremity
- Need for Assistive equipment
- Brace/prosthesis training
- Need for splinting
- Community re-entry: needs related to work, school, or leisure activities
- Inability to participate in age appropriate activities

In terms of treatment by a speech-language pathologist, referrals may be made for any number of issues related to swallowing, speech-production, and language development. Potential triggers for referral may include:

- Long term issues with swallowing that have the potential to improve with speech therapy
- Dysarthria or other speech production issues
- Need for the development/expansion of communication systems or a communication device
- Difficulties with expressive and receptive language skills
- Difficulties with academic skills related to language (e.g., reading and writing development)
- Difficulties with higher order skills such as organization or memory

25.4 Conclusions

Even in cases where therapy may not be required, it is critical that the treating team be aware of these long-term rehabilitation issues so that they can best care for the needs of their patients. As outlined by Gamble and colleagues [2], it will also be important for cancer rehabilitation models to be integrated into medical training and future research so that cancer rehabilitation can be at the forefront of acute cancer care and survivorship care.

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26 Neurocognitive Late Effects in Children Treated for Cancer: Psychological Impact, Identification, and Prevention and Remediation

Martha A. Askins, Sujin Ann-Yi, and Bartlett D. Moore III

26.1 Introduction

As noted throughout this Handbook, cure rates for childhood cancer have improved significantly over the past three decades. In the United States, there are an estimated 330,000 survivors of childhood cancer and this number is growing [1]. The ultimate goal of cancer therapy is to cure disease; however, clinicians continuously strive to achieve a balance between effective therapy and acceptable toxicity in an effort to promote a good quality of life for children as they develop and mature into adults [2]. New strategies in radiation therapy such as the use of photons, with their unique depth-dose distribution characteristics, are very promising in the fight against childhood cancer and are expected to contribute to higher cure rates with less morbidity [3–5]. In addition, imaging techniques used in cancer detection and treatment have undergone tremendous growth and now include not only conventional anatomical imaging techniques, but also molecular imaging that allows the visualization of the expression and activity of specific molecules relevant to cancer [6]. These innovations are expected to help physicians and patients decide on courses of treatment that are tailored to patients' individual conditions and needs, thereby minimizing late effects and significantly improving the pediatric cancer survivor's quality of life.

While future childhood cancer survivor cohorts may have fewer persistent problems with health and cognition, at present, 40–60 % of childhood cancer survivors are at risk of developing neurocognitive impairment in one or more specific domains [7–9]; thus, this is an important area of clinical focus and research effort.

Neurocognitive late effects are problems with thinking or learning that can occur in pediatric cancer survivors who have received therapy affecting the central nervous system (CNS) and typically develop two or more years after completion of treatment. Children with brain tumors or acute lymphoblastic leukemia (ALL)—the two most common types of childhood cancer—are at greatest risk for developing neurocognitive late effects [10]. Other childhood cancer survivors who may be at risk for cognitive late effects include those diagnosed with acute myelogenous leukemia or non-Hodgkin lymphoma, those treated with cranial radiation therapy for head and neck tumors, and those who have undergone stem cell transplantation [9]. Whereas these problems are considered chronic, promising cognitive interventions have resulted in modest but important gains in cognitive functioning for childhood cancer survivors.

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Childhood cancer survivors, having lived through the challenges inherent in cancer treatment and facing possible medical and/or neurocognitive late effects, merit proactive clinical and educational interventions that will help ensure the best quality of life possible throughout the lifespan. Several pharmacological and psychological interventions have proven to be successful in ameliorating neurocognitive late effects and/or helping childhood cancer survivors compensate for acquired cognitive weaknesses secondary to cancer and/or its treatment [11]. In addition, adaptable educational interventions that keep pediatric patients engaged in the learning process while undergoing cancer treatment are essential in preventing academic declines.

The purpose of this chapter is to review: (1) clinical approaches to the surveillance for and identification of neurocognitive problems in survivors of childhood cancer, (2) the psychological impact of neurocognitive late effects on children, and (3) the prevention and remediation of neurocognitive late effects in survivors of childhood cancer.

26.2 Surveillance for and Identification of Neurocognitive Problems

All childhood cancer survivors who received CNS therapy, including those who received cranial radiation therapy and chemotherapy that crossed the blood brain barrier and entered the cerebrospinal fluid and brain, need to be screened for neurocognitive late effects. Timely screening is important, because the sooner late effects are identified, the earlier cognitive and educational interventions can be provided in an effort to maximize intellectual and academic outcomes.

26.2.1 Screening Tools

Comprehensive neuropsychological evaluations provide information regarding 10 general domains of cognitive functioning: verbal comprehension, visual-perceptual reasoning, processing speed, academic achievement, receptive and expressive language abilities, attention/concentration, verbal and non-verbal working memory (ability to learn), executive functioning, fine motor skills, and somatosensory processing. The results of neuropsychological evaluations identify patterns of cognitive strengths and weaknesses which are very helpful data for developing individualized education plans, cognitive remediation interventions, and career goals.

Abbreviated neuropsychological test batteries that focus on the domains most often affected by CNS treatment can be used when efficiency is an important consideration in the child's or young adult's clinical care. Alternatively, simply screening for neurocognitive impairment before administering a longer, more complete test battery may prove to be the most practical and economical approach. Krull et al. [12] have developed a reliable and valid method of screening neurocognitive impairment in long-term survivors of pediatric cancer that can be completed in 30 min. In a psychometric study, the screening method accurately predicted global intellect, reading skills, and mathematical ability. Furthermore, the brief neurocognitive screening was a better predictor of cognitive functioning than was a parent's rating, which was only a marginal indicator of global intelligence. Screening can aid the clinician in determining which childhood cancer survivors are doing well cognitively and which survivors will benefit from more comprehensive neurocognitive assessment and follow-up.

26.2.2 Neurocognitive Functioning Following CNS Treatment

The functional neurocognitive domains that are most commonly affected by CNS treatment include attention/concentration, processing speed, visual-perceptual reasoning, executive functioning, and working memory. The resulting impairments may in turn adversely affect academic development and impact career attainment [2, 13]. These effects are largely associated with "white matter changes, calcifications, biochemical changes in the folate pathway, and/or failure

of the development of connecting CNS structures" [9]. Importantly, because the axons of the projection and association areas of the cerebral cortex do not become fully myelinated until the early adult years [14], the brain remains vulnerable to neurotoxic agents during the prime learning period of a child's life [15]. If white matter development is disrupted, cortical and cognitive development will most likely be affected [16, 17]. In addition, cognitive functioning can be affected by factors such as brain tumor location, spread of leukemia to the CNS, damage resulting from diffuse or focal CNS infection, and cerebrovascular events. As elucidated in the chapter by Walsh and the chapter by Dodzik and Fulton, common patterns of neurocognitive findings have emerged in the literature and merit cognitive and educational intervention.

26.2.3 Appropriate Timing of Neuropsychological Assessments

The Children's Oncology Group (COG) guidelines recommend that children at risk for developing cognitive late effects have baseline assessments before, during or shortly after the conclusion of therapy, even in the absence of any overt manifestation of CNS injury, so that potential declines in ability and/or academic achievement can be identified and addressed appropriately [9]. Further, the guidelines advise that any childhood cancer survivor who begins to experience school difficulties, regardless of treatment history, should also undergo neuropsychological evaluation. Recommendations for repeat testing should consider the anticipated trajectory of the emergence of late effects and the child's specific medical and developmental risk factors. Annual reevaluation is recommended to chart the survivor's progress and to identify any potential problems that may arise throughout his or her education. Ideally, the assessment examiner should be a professional familiar with the issues unique to childhood cancer survivors, because he or she will understand how certain treatments and medical factors may affect cognitive functioning.

For children with brain tumors, baseline evaluations at the time of diagnosis, before treatment commences, are useful for monitoring cognitive changes over time which may include both declines and improvements [2]. However, a baseline assessment may not be possible if the child is too sick or impaired to undergo testing which, on the basis of our clinical experience, appears to be the case in a small minority of children newly diagnosed with brain tumor.

26.3 Psychological Impact of Cognitive Late Effects

Psychological quality of life, health-related quality of life (HRQOL) and life satisfaction outcomes are important considerations for childhood cancer survivors. Making sense of a cancer diagnosis and treatment—and appreciating what the cancer journey means in relation to one's identity and personal growth/strengths—is an important foundation for positive psychological adjustment during childhood cancer survivorship. While these issues are discussed in more detail in Chaps. 17 and 18 of this manuscript, an overview will be provided here.

In a study of 335 adolescent and young adult survivors of childhood cancer, Zebrack and Chesler [18] found that both having a sense of purpose in life and perceiving positive changes as a result of cancer were associated with a positive quality of life for survivors. Some of the hopes of our society for all young adults—consistent with their own aspirations—are that these individuals:

- Remain safe and healthy
- Develop positive self-esteem
- Experience and share mutual respect
- Pursue activities and careers that they find meaningful and fulfilling
- Establish financial independence
- Share intimate relationships, i.e., dating and/or marriage
- Enjoy life with family and friends

Any real or perceived barriers to actualizing these life goals can result in psychological distress and/or decreased life satisfaction for survivors.

Unfortunately, some survivors experience lingering anxiety following cancer treatment. In a study by Hobbie et al. [19], one-fifth of a sample of 78 young adult survivors of childhood cancer met criteria for a diagnosis of posttraumatic stress disorder. The disorder was found to be associated with anxiety and other psychological distress. Interestingly, the survivors' perceptions of treatment and its effects were more highly associated with posttraumatic stress than were more objective medical data. Parents also can be affected psychologically as they help their children manage issues related to cancer survivorship and support them in transitioning from adolescence into young adulthood [20, 21].

The Childhood Cancer Survivor Study (CCSS), supported by the National Cancer Institute, has generated over 200 scientific publications, adding greatly to our knowledge of late effects in childhood cancer survivors and the social, educational, and psychological consequences of these effects. The CCSS is the largest multi-institutional research initiative of its kind, and includes 27 participating centers in the United States and Canada. The study cohort consists of 20,346 survivors of childhood and adolescent cancer, diagnosed between 1970 and 1986, and approximately 4,000 siblings of survivors who serve as the comparison group for the study [22]. Because of the significant changes in childhood cancer therapy over the past several decades, the CCSS long-term follow-up study is recruiting new participants to include approximately 15,000 survivors of childhood cancer diagnosed between 1987 and 1999 and an additional 4,000 siblings of survivors. Studies involving future cohorts of childhood cancer survivors will help investigators determine how newer approaches to treatment have helped improve health and quality of life during survivorship as well as define which medical and psychosocial needs remain for this population.

Zeltzer et al. [23] reviewed studies that assessed CCSS data in terms of psychological outcome measures, including the Brief Symptom Inventory [24], the Medical Outcomes Survey Short Form-36 [25], the Cantril Ladder of Life [26], and the CCSS Neurocognitive Questionnaire [27] to describe the psychological status of childhood cancer survivors. The authors concluded that while most groups of childhood cancer survivors are psychologically healthy and report satisfaction with their lives, certain groups are at high risk for psychological distress, neurocognitive dysfunction, and poor HRQOL. Ness et al. [28] found that in a cohort of 7,147 CCSS survivors, 18.1 % reported deficits in physical performance, 10.5 % in emotional health, and 14.0 % in executive functioning. Problems in these three areas were found to be negatively associated with both social role attainment and self-reported HRQOL. In a separate CCSS study, survivors of CNS tumors, lymphoma, and leukemia, and patients treated with cranial irradiation, were found to have the poorest HRQOL [29]. In addition, cancers and treatments that result in CNS impairment or that impact sensory functioning have been found to be associated with greater risk for adverse social outcomes [30]. The risk factors for negative psychosocial outcomes are summarized in Fig. 26.1 on the basis of data from [18, 23, 28–31].

Our understanding of the impact of cognitive late effects on childhood cancer survivors is informed by studies regarding survivors': (1) psychological quality of life; (2) educational indicators such as the need for special education, academic achievement, high school graduation, and college entrance; and (3) realization of experiences related to life satisfaction such as career development and marriage. Studies to date consistently show the link between CNS treatment and cognitive late effects, with more intensive treatments, younger age at diagnosis, and female gender predicting greater impairment. Importantly, cognitive late effects are associated with the need for regular neuropsychological assessment and specialized educational and cognitive interventions that promote academic achievement and social development. When childhood cancer survivors are able to receive and benefit from these interventions, their future outlook becomes brighter. Emotionally, experiencing purpose in one's life as well as finding benefit from the cancer journey appears to enhance the survivors' quality of life.

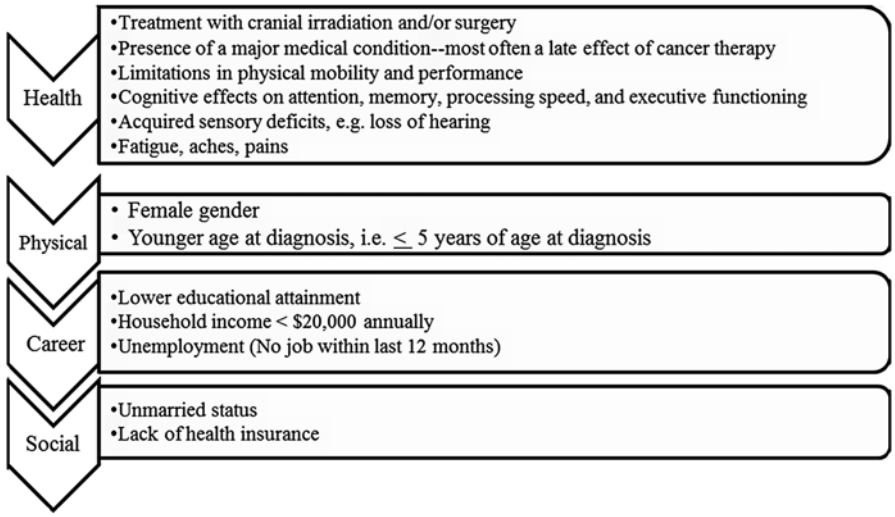

Fig. 26.1 Medical and psychosocial risk factors for negative psychosocial outcomes among childhood cancer survivors

26.4 Prevention and Remediation of Neurocognitive Problems

Many children compensate for specific cognitive weaknesses by relying on areas of relative strength and by using targeted learning interventions and other environmental supports [9]. This section will review pharmacological interventions, cognitive training interventions, and educational interventions that can help improve educational and psychosocial outcomes among childhood cancer survivors.

26.4.1 Pharmacological Interventions

The first efforts to improve neurocognitive functioning among childhood cancer survivors consisted of trials of stimulant medication. This is discussed elsewhere in Muriel's chapter on Psychopharmacology, along with the pharmacological treatment of other psychological symptoms. This chapter will focus on attention deficits as it relates to long-term cognitive difficulties in childhood cancer survivors.

Whereas newer medications have been developed to support individuals with Attention Deficit Hyperactivity Disorder, methylphenidate remains the most studied drug among children and childhood cancer survivors. Early on, DeLong et al. [32] showed that approximately 75 % of survivors who received methylphenidate (Ritalin) exhibited a "good" response indicating that attention functioning improved in study participants; however, that study was not a randomized controlled trial. Nearly a decade later, Thompson et al. [33] at St. Jude Children's Research Hospital conducted the first rigorous clinical trial examining the potential benefits of stimulant medication. For that study, 104 long-term survivors of childhood ALL or malignant brain tumor were screened for deficits in academic achievement (16th percentile or lower in reading, math, or spelling) and difficulties with sustained attention [33]. Thirty-two survivors qualified for enrollment and were randomized in a double-blinded, placebo-controlled trial of methylphenidate (0.6 mg/kg; maximum dose, 20 mg) . Ninety minutes after taking methylphenidate or a placebo, the study participants repeated selected portions of the screening battery. Compared with the 17 patients randomized in the placebo group, the 15 patients randomized in the methylphenidate group showed significantly greater improvement on a continuous performance task as evidenced by fewer errors of omission and a higher overall index, but

not fewer errors of commission (indicative of impulsiveness), or shorter reaction times. The methylphenidate group showed a trend for greater improvement compared with the results for the placebo group; however, no trend was observed for improvement in learning a word association task. No significant side effects from the medication were observed.

The Thompson study was interesting for a number of reasons. First, it demonstrated that stimulant medication could attenuate some of the long term cognitive effects experienced by childhood cancer survivors—a promising finding. At the same time, the fact that some cognitive functions, such as processing speed, did not improve with stimulant medication alone implied that additional interventions such as cognitive remediation and school support would have an important place in optimizing learning and academic achievement. Finally, the multi-disciplinary team that conducted that study consisted of many well-respected specialists in pediatric oncology, who have made numerous contributions to the field, including Laurie Leigh, the School Program Director at St. Jude. Leigh and colleagues had the vision to create the first private in-hospital school in the United States to help meet the unique needs of children undergoing treatment for cancer. Of note, a comprehensive, private in-hospital school is available at the Children's Cancer Hospital at MD Anderson.

Mulhern et al. [34] subsequently published a study of 83 long-term survivors of childhood ALL and brain tumors who were of school age. Ray Mulhern was known not only for identifying the nature of treatment related brain injury, but also for championing rehabilitative strategies, cognitive remediation, and quality of life for childhood cancer survivors and their caregivers [35]. In this 2004 study, participants were identified as having attention deficits with behavioral testing and as having problems with academic achievement according to parent and teacher reports. The study was a randomized, double-blind, 3-week home cross-over trial of placebo, low-dose methylphenidate (0.3 mg/kg; maximum dose, 10 mg), and moderate-dose methylphenidate (0.6 mg/kg; maximum dose, 20 mg). Compared with the results for the placebo group, significant improvements with methylphenidate were reported by teachers and parents on the Conners' Rating Scales [36] and by teachers on measures of social skills. Surprisingly, a dose response relationship was not observed. Among the participants, three demonstrated serious reactions to methylphenidate and nine eventually withdrew from the study, possibly because of medication side effects. The investigators concluded that methylphenidate can reduce some attentional and social deficits among survivors of ALL and brain tumors.

Recent studies have confirmed the benefits of methylphenidate in helping childhood survivors of ALL and brain tumors but have also pointed to some limitations of pharmacological interventions alone. Conklin et al. [37, 38] found that the number of problems endorsed prior to the medication trial (parent and teacher ratings) were predictive of a positive medication response. In a separate, longitudinal study, Conklin, Reddick et al. [39] demonstrated that the attention and behavioral benefits of methylphenidate for childhood cancer survivors were maintained across settings over the course of one year; however, academic gains were not identified.

Pharmacological interventions represent an efficacious step toward helping childhood cancer survivors overcome attention-related cognitive late effects of cancer treatment, but results of studies conducted in this area also demonstrate the need for potentially synergistic neurocognitive and academic interventions.

26.4.2 Cognitive Training Interventions

Butler et al. [11, 40, 41] developed the first comprehensive cognitive remediation program for survivors of childhood cancer. The program's foundation is in pediatric brain injury rehabilitation, which traditionally has involved a multidisciplinary team of professionals providing intensive therapies in an effort to improve neurocognitive, behavioral, and psychosocial functioning. This tripartite model, in addition to incorporating techniques from brain injury

rehabilitation (e.g., massed practice or drill exercises to strengthen neurocognitive function and improve processing speed), the tripartite model also integrates techniques and methods from special education and educational psychology such as meta-cognitive strategies for managing challenging academic tasks (e.g., "check your work"), as well as cognitive-behavioral therapy for enhancing self-confidence with cognitive and academic tasks. The cognitive remediation program approach is innovative not only because of the tripartite model, but also because it is both highly structured and individualized [35], allowing for treatment goals to be determined as particular issues arise during training. For example, if a child were to consistently display anticipatory anxiety before beginning tasks, the goals of improving confidence and mentally preparing for tasks would become part of the child's treatment goals and would be achieved through cognitive-behavioral strategies such as positive self-talk and "putting on one's game face." In the traditional cognitive remediation program, the child participates in 25 two-hour treatment sessions in the clinic setting with a "coach" who has a background in child psychotherapy and who has been trained in the specific CRP methods.

The tripartite Cognitive Remediation Program (CRP) underwear a multicenter, randomized clinical trial [11] and included 161 childhood cancer survivors, ages 6 to 17 years, who had been off treatment for at least one year and who manifested an attention deficit. Two-thirds of the study participants were randomized to receive cognitive remediation and one-third served as controls. All participants were assessed using a battery of academic achievement/neurocognitive tests and parent/teacher measures of attention. Findings showed that the cognitive remediation program resulted in parent reports of improved attention and statistically significant increases in academic achievement. Effect sizes were modest but similar to those reported for other clinical trials of brain injury rehabilitation. Because the traditional cognitive remediation program approach is very time- and resource-intensive, future versions of the intervention might seek to partner with caregivers to help administer the program and incorporate more computerized exercises that can be practiced in the home setting.

The expectation with cognitive remediation is that such programs not only facilitate the behavioral acquisition of attention skills and strategies for academic success, but also change the underlying neural mechanisms responsible for supporting attention and learning, so that the cognitive gains accomplished are enduring and make a lasting contribution to an individual's quality of life. To examine this theory, Zou et al. [42] performed functional magnetic resonance imaging (fMRI) in a subset of 14 CRP participants from Butler's 2008 study and compared their brain activation patterns with those of healthy controls. The researchers reported:

> "The ventral visual areas, cerebellum, supplementary motor area, and left inferior frontal cortex were significantly activated in the healthy participants during a continuous performance task. In survivors, brain activation in these regions was diminished at baseline, and increased upon completion of remediation and at 6-month follow-up (p. 915)."

Remarkably, the fMRI activation index for each region of interest was inversely associated with the Conners' Clinical Competence Index. This pilot study demonstrated that fMRI can be useful in evaluating neural responses to cognitive remediation and provides validation for the concept that cognitive remediation promotes brain injury rehabilitation and neural growth.

With the recent improvements in computer technology and the proliferation of electronic devices, opportunities for "gamification" of educational/training material have become more viable. Children enjoy practicing skills in a gaming format more than rote memorization or by completing paper and pencil tasks. To make education and cognitive training more engaging, computerized cognitive training programs are now being developed. For example, Lumos Labs, Inc. markets validated on-line scientific brain games (www.Lumosity.com) to the public as a way to improve memory and attention [43].

Shelli Kesler at Stanford University recently published a pilot study of Lumosity, an online cognitive rehabilitation program for executive function skills in children, with cancer-related brain injury [44]. In this one arm open trial of 23 pediatric cancer survivors, ages 7 to 19 years, the rate of compliance was 83 % and significant improvements were found in processing speed, cognitive flexibility, and verbal and visual declarative memory scores. Moreover, concurrent neurobiological changes evidenced by fMRI were reported. Pre-frontal cortex activation correlated significantly with improved cognitive test scores. In other recent research, Hardy et al. [45] at Duke University Medical Center pilot tested a 12-week, in-home computerized cognitive training program "Captain's Log" with a small sample (n = 9) of childhood ALL and brain tumor survivors who had deficits in attention and working memory at baseline. The intervention was associated with good feasibility and acceptability. Moreover, significant increases were noted in working memory and parent-rated child attention. Both investigative teams [44, 45] concluded that computerized cognitive training can be successfully implemented at home with young cancer survivors. Thus, computerized cognitive training and remediation represent a promising intervention for survivors with cognitive late effects.

26.4.3 Educational Interventions

The most important educational intervention for preventing or minimizing declines in academic achievement may be the promotion of a student's ongoing participation in education [2, 11]. As noted in these studies, school is important for children with cancer for many reasons which include:

- School settings and structured learning provide normalization.
- When students interact and work together, they develop effective social skills and empathy.
- Educational development fosters self-esteem and autonomy.
- Schooling opportunities provide a meaningful diversion from the pain and discomfort often associated with cancer treatment.
- Continued school participation instills hope for the future.
- Academic knowledge improves one's quality of life during survivorship.

Children are encouraged to remain involved in normal life activities while undergoing cancer treatment. Such involvement provides continuity in learning and friendships, minimizes feelings of isolation, and reinforces the child's belief that he or she is a person first and a cancer patient second. School experiences are not only important for maintaining academic achievement, but also for fostering ongoing psychosocial development and adjustment to the cancer experience. Importantly, school participation signals to children undergoing cancer treatment that healthcare providers, teachers, and parents believe that they will recover from cancer, and want them to continue learning so that they can enjoy a bright future. The importance of ongoing education for children with cancer may not be readily apparent to some individuals involved in his or her care, especially when the child is newly diagnosed and efforts are focused on treatment planning. However, as the family begins to adjust to new clinic and hospital routines and develops trust in the healthcare team, it is important to focus on the child's new school plan.

26.4.4 Continuation of Academic Instruction

Children undergoing cancer treatment have several options for continuing academic instruction. Depending on their health status and requirements for treatment, they may be eligible to attend a community school, a hospital-based school program, or receive homebound educational services. Parents also sometimes choose to provide home-schooling, whereby they follow a curriculum and take responsibility themselves for teaching and monitoring their child's academic progress. More and more common are on-line virtual schools adopted or created by a school district or private educational institution that allow students to access curriculum, instruction, and testing via the internet, earning academic credit as they progress. Placement decisions

regarding whether a child should attend school in a community, hospital, and/or home setting are based chiefly on the child's health and immune system, which fluctuates with some types of chemotherapy. Treatment regimens can affect the student's energy level and time available to participate in school. Placement decisions should take into account whether the child is an engaged student who is able to perform independent work or one who benefits from structured academic guidance and instruction [46].

26.4.5 Importance of a Collaborative Team Approach

The student benefits most when medical and behavioral health care providers, parents, and educational professionals—with their complementary areas of expertise—thoughtfully collaborate on the student's educational goals and learning plan in regularly scheduled meetings. Students themselves can also play an important role in their own educational planning by expressing preferences and advocating for their unique needs. Medical healthcare providers can help others involved in the child's care understand the child's diagnosis, treatment plan, and health considerations as education progresses. Community school professionals need to have the following important information when children with cancer and childhood cancer survivors attend school on campus:

- Cancer diagnosis and date of diagnosis
- Brief description of treatment plan
- Treatment schedule and how it may affect the child's blood counts/immune system
- List of current medications and detailed information for any that are to be given at school
- Anticipated absences
- Seizure precautions
- Recommendations for physical education and participation in sports
- Plan for medical emergencies if and when they occur on the school campus

Behavioral healthcare providers and school reentry specialists (also referred to as counselor-liaisons) employed by cancer centers can provide information about the emotional and cognitive functioning of students and guidance regarding how to prepare the student and classmates for school reentry. These professionals can also provide neuropsychological testing and recommend cognitive and academic interventions. Parents usually know their children best and not only can help educational professionals understand the child's emotional concerns and adjustment, but also can share strategies that best motivate and support the child. Parents typically convey helpful information about the child's learning style as well as academic strengths and weaknesses, on the basis of the child's historical academic performance and their experiences facilitating homework. Parents will remain the child's principal advocates throughout his or her primary, elementary, and secondary education.

Community educational professionals have knowledge about how to assist children with school re-entry and special education needs, and can integrate state educational requirements (when applicable) with a student's learning plan. They have an investment in providing an appropriate education in the least restrictive environment in order to help students with cancer integrate well into the school setting and continue their educational, social, and physical development.

The keys to effective teamwork in educational planning meetings include respect for the unique and helpful contributions each team member brings to the discussions; efficient coordination of efforts (i.e., who is responsible for the various components of the child's education plan and how efforts/results will be monitored); and timely, regular communication regarding the student's health status as well as educational progress and needs.

26.4.6 Protections Afforded by Federal Educational Law

Childhood cancer survivors need to have access to remedial services—when needed—that positively impact educational achievement and maximize opportunities for career development [31]. Mitby et al. [31] reported that among 12,430

survivors of childhood cancer followed by the CCSS, 23 % utilized special education services compared with 8 % of 3,410 siblings. Survivors who were most likely to receive special education services were those diagnosed at ≤5 years of age, and children with a brain tumor, leukemia, or Hodgkin disease. On a positive note, investigators concluded that the use of special education services facilitated high school graduation, because only 12 % of survivors, compared with 9 % of siblings, failed to complete high school. Access to special education services is ensured by federal education law, as discussed in detail elsewhere in this Handbook. Briefly, the specific laws are regularly reviewed, amended, and reauthorized, in accordance with scientific research and contemporary standards in special education.

The Individuals with Disabilities Education Act (IDEA) is a U.S. federal law that governs how states and public agencies provide early intervention, special education, and related services to children with disabilities ages birth to two years of age (IDEA Part C) and ages three to twenty-one years of age (IDEA Part B). IDEA has grown in scope and has been reauthorized over the years, most recently in December 2004, when it was brought into alignment with the No Child Left Behind (NCLB) Act of 2001. The reauthorization revised the requirements for evaluating children with learning disabilities and specified that students with disabilities should be prepared for further education, employment and independent living. It also mandated that school professionals must take a child's disability into account when determining the appropriateness of disciplinary action. IDEA's provisions define eligibility for special education services, provide for the development of an individualized education program (IEP) for each student who qualifies, and address related services as well as procedural safeguards. Under federal law, an IEP must be designed to meet the unique educational needs of the child in the least restrictive learning environment appropriate to the needs of the child. Parents are an equal member of the IEP team. The law specifies who must be present in an IEP meeting, including parents, various school professionals, and an administrator or special education committee representative who has knowledge of the availability of services in the district and the authority to commit those resources on behalf of the child. The U.S. Department of Education has created a website that lists and describes resources related to IDEA and its regulations [47]. The website also cross-references content from other laws, such as NCLB and the Family Educational Rights and Privacy Act that support the rights of children with special educational needs. When a student does not meet the requirements of IDEA, but has one or more of the thirteen disabilities listed in IDEA and as a result of the disability, needs educational support in order to benefit from the general education program, Section 504 of the Rehabilitation Act of 1973 provides for the development and implementation of a dedicated plan. Please see the chapters on Educational Strategies and Special Education Laws for more detailed information on these important topics.

Vocational guidance that emphasizes career opportunities that are an excellent match for the survivor's abilities, personality, work values, and interests can help childhood cancer survivors find rewarding careers. The Americans with Disabilities Act prohibits discrimination against people with disabilities in education, employment and additional activities. Upon college entrance, young adults become their own advocates and can plan individual educational accommodations with the campus office for students with disabilities when needed. This type of educational support is legally mandated for public institutions of higher learning. Many private universities also provide formalized support for students with disabilities. Please see Chap. 24 in this Handbook regarding career and vocational guidance authored by Ann-Yi and Askins for specific information on this topic, as well as the Resources section in this manuscript for helpful websites that address return-to-work issues.

26.5 Conclusions

The remediation of neurocognitive deficits in childhood cancer survivors represents an important area of clinical care and research in pediatric

psycho-oncology. Because 40–60 % of childhood cancer survivors are at risk of developing cognitive impairment, it is critically important to provide psychological and educational interventions that help prevent cognitive and academic declines and remediate areas of deficit or relative weakness.

When cognitive late effects associated with cranial irradiation therapy and intrathecal chemotherapy were discovered in the 1970s and 1980s [48, 49], pediatric oncologists responded by modifying treatment regimens in an effort to lessen the toxic side effects of therapy while still preventing CNS relapse [50]. Whereas those efforts did improve cognitive outcomes, some level of impairment remained for the majority of children who received CNS therapy, necessitating the development of pharmacological and psychological interventions to remediate cognitive deficits and improve quality of life for childhood cancer survivors.

Cognitive remediation programs have yielded positive preliminary results. In contemporary studies, traditional face-to-face cognitive remediation is being supplemented or replaced with computerized programs that guide individuals through exercises designed to enhance attention, memory, and other neurocognitive skills. Computer programs that incorporate gamification are particularly attractive to learners. Despite initial successes in cognitive remediation, more scientific work remains in order to explicate the linkages between training, cognitive improvements and academic achievement. Future research efforts need to be directed towards understanding how cognitive gains acquired during cognitive remediation programs can best be generalized to the academic setting where they can promote achievement, self-efficacy, and ultimately, career development. Educational professionals are key partners in helping childhood cancer survivors thrive in school settings. When needed, U.S. laws are in place to protect the rights of students and workers with disabilities. Cognitive interventions represent one important area of support for childhood cancer survivors who deserve every opportunity to maximize their potential and experience an excellent quality of life.

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Psychopharmacologic Interventions in Childhood Cancer Survivors

27

Anna C. Muriel

27.1 Introduction

Adolescent and young adult survivors of childhood cancers have been shown to have elevated risks of adverse behavioral and social outcomes including depression, anxiety, attention deficits, antisocial behaviors [1, 2] post-traumatic stress [3] and suicidal ideation [4, 5] . These symptoms may lead health care providers to consider psychopharmacologic agents to treat these symptoms and improve function and quality of life in this population. Survivors may also have medical late effects such as endocrine dysfunction [6, 7], insomnia and fatigue [8, 9, 10], as well as increased rates of obesity [11] that may interact with or mediate psychiatric syndromes. Prevalent neurocognitive late effects in survivors [12, 13, 14] also affect educational, health and behavioral outcomes, and may be a common focus of psychopharmacologic intervention. The data on the use of psychotropic use in survivors of childhood cancer is limited to stimulant treatment of attentional and cognitive dysfunction [15]. However, survivors with other significantly impairing symptoms of depression, anxiety, or behavioral dysregulation may nonetheless benefit from psychopharmacologic intervention. Clinicians seeking to treat survivors with psychotropic medications need to consider both their psychological vulnerabilities, and how their medical late effects may impact their treatment responses and their susceptibility to side effects of psychiatric medications.

27.2 General Pharmacologic Considerations

Psychopharmacologic treatment should almost always be considered in the context of other therapeutic psychological, cognitive, behavioral and social/ environmental interventions. Other chapters describe these in detail. Clinicians may turn to medications when other approaches are not achieving needed results, or when the patient's more biologically driven symptoms such as impulsivity and inattention, neurovegetative symptoms of depression, or the hyperarousal of anxiety, are interfering with their capacity to meaningfully engage in non-pharmacologic treatment.

General medical considerations when assessing psychiatric syndromes in cancer survivors should include an evaluation of endocrine function [6] that can mediate mood or anxiety symptoms. Because survivors are at increased risk for cardiac dysfunction [15], clinicians must also assess potential cardiac side effects as risk for sudden cardiac death, arrythmias or conduction abnormal-

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ities can be side effects of certain psychotropics. Increased cardiovascular risks and metabolic issues [16, 17] must also be considered when using medications that may cause weight gain or metabolic syndromes. Co-morbid substance or alcohol use [18] and chronic pain [19] need specific assessment and treatment in the context of psychiatric symptoms. Renal or hepatic dysfunction [20] must also be considered relative to pharmacokinetics.

Primary care clinicians seeking to treat childhood cancer survivors may consider using first line agents for attentional issues, depression or anxiety. However, general medical clinicians may need to seek specific mental health consultation for patients with refractory symptoms, more complex presentations, or primary psychiatric illness such as bipolar disorder or psychosis.

27.3 Neurocognitive Late Effects

27.3.1 Background

Survivors of childhood cancer have well-documented neuro-cognitive late effects [11, 21] that may impact educational, vocational and social functioning [22, 23], overall psychological status, and health-related behaviors [13]. Particular risk has been documented for children who undergo cranial irradiation [24], intrathecal chemotherapy [25], dexamethasone [26], or treatment for brain tumors [12]. It is also important to note that late effects may emerge years after initial treatment [27] and that declines in IQ may be related to difficulties learning at an age-appropriate rate [12].

27.3.2 Treatment

Given the prevalence of core deficits in attention/concentration and working memory, investigators have begun to examine the efficacy of pharmacologic treatment with methylphenidate (MPH) in this population. Among child and adolescent survivors, data now supports the positive immediate effect of a single MPH dose on performance-based measures of attention [28], as well as longer term efficacy in a 12 month open-label trial [14] and in a 3 week, double-blind crossover trail [29]. Response rates were measured in children taking a moderate MPH dose of 0.60 mg/ kg with a maximum dose of 20 mg twice a day. Although the MPH response rates among survivors were not as robust as in general ADHD populations (45 % vs. 75 %), positive observed effects included enhanced attention regulation and social skills, and parent reports of improved executive aspects of school performance, such as planning ahead and remembering to turn in assignments. Lower response rates may be related to differences in the etiology of attentional symptoms, and increased prevalence of co-morbid learning disorders, neurologic impairment, and lower rates of hyperactivity [29].

The safety of methylphenidate in healthy children is well-established [30], and common side effects of insomnia, decreased appetite, headaches or dizziness are for the most part mild to moderate, and dose dependent [31]. However, childhood cancer survivors may experience higher rates of side effects, and medication discontinuation. These rates may be up to 3 times higher in brain tumor survivors, females, and patients with lower IQ's [12, 32]. Methylphenidate labeling warns that sudden death has been reported children and adolescents with structural cardiac abnormalities or other serious heart problems, and clinicians must consider these risks when prescribing stimulants for survivors with these conditions.

27.3.3 Summary

There is good evidence to support the use of methylphenidate to address issues of attention and working memory in childhood cancer survivors. Clinicians seeking to treat survivors with executive functioning deficits, inattention and hyperactivity should follow existing treatment guidelines for stimulants, with attention to patients' cardiac and nutritional risk factors. Patient (and parent or teacher) feedback can be important guides for titration of stimulant dosing to maximize effect and minimize side effects. Individual patient experience will also inform the use of longer-acting formulations or transdermal delivery systems. There is no specific data on the use of stimulant medications other than methylphenidate in survivors, although they may also benefit from amphet-

amine, dextroamphetamine, or atomoxetine, which may require consultation with a psychiatrist familiar with their use.

27.4 Depression

27.4.1 Background

Lifetime prevalence for depression warranting treatment is approximately 16 % of the general adult population [33], making it the second most common chronic condition encountered in general medical practice. When compared to sibling or general controls, adolescent and young adult childhood cancer survivors are found to have even higher rates of depression [1, 2], and mood symptoms may impact their social and educational function, and ultimate developmental trajectory. Although anxiety and depression are not associated with healthcare utilization among childhood cancer survivors, those who reported use of antidepressant medication are more likely to report receiving risk-based healthcare [13].

The DSM-5 [34] defines a major depressive episode according to the following criteria: five or more neurovegetative symptoms must have been present over a two-week period and represent a change from previous functioning, causing clinically significant distress. These symptoms may include changes in sleep, interest, guilt, energy, concentration, appetite, psychomotor activity, or suicidal ideation. At least one of the symptoms must also be either (1) depressed (or irritable) mood or (2) loss of interest or pleasure (anhedonia). See Table 27.1 for full criteria.

Notably, the DSM-5 criteria specifically instruct clinicians not to include "symptoms that are clearly due to a general medical condition." Fatigue, pain, endocrine dysfunction, metabolic issues and obesity or obstructive sleep apnea may affect survivors and complicate the differential diagnosis of depression [8, 9, 10]. Neurovegetative symptoms (e.g., sleeplessness, anorexia, fatigue, and psychomotor slowing) may reflect medical conditions rather than depressive symptoms. Brain tumor survivors may also have primary neurologic conditions that affect mood, affect and expression of emotion [7]. When there is a medical cause for these symptoms, the medical condition should be addressed first, with subsequent reevaluation for depression. In patients with significant medical issues where the cause of neurovegetative symptoms may be difficult to discern, persistent subjective depressed mood, anhedonia, defined as a loss of pleasure in activities, and hopelessness may be the most sensitive clinical indicators of depression warranting specific treatment.

Table 27.1 Criteria for major depressive disorder

DSM-5 major depressive disorder symptoms
• Depressed (or irritable) mood most of the day, nearly every day as indicated by either subjective report (e.g. feels sad or empty) or observation by others (e.g. appears tearful)
NOTE: In children, can be irritable mood
• Markedly diminished pleasure in all, or almost all, activities most of the day, nearly every day
• Significant weight loss when not dieting (e.g. change of >5 % of body weight in a month) or weight gain or decrease or increase in appetite nearly every day
NOTE: In children, consider failure to make expected weight gains
• Insomnia or hypersomnia nearly every day
• Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed-down)
• Fatigue or loss of energy nearly every day
• Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)
• Diminished ability to think or concentrate, or indecisiveness (either by subjective account or as observed by others)
• Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without specific plan, or a suicide attempt or a specific plan for committing suicide

Adapted from American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*. 2013, Arlington, VA

27.4.2 Treatment

Antidepressant medications include: Serotonin-specific reuptake inhibitors (SSRI's) fluoxetine, sertraline, citalopram, escitalopram, paroxetine, fluvoxamine; Serotonin-norepinephrine reuptake inhibitors (SNRI's) venlafaxine, duloxetine, and desvenlafaxine; and atypical agents, bupropion,

nefazodone, mirtazapine, and trazodone. Older agents such as Tricyclic antidepressants (TCA's) and Monoamine Oxidase inhibitors (MAO's) have more significant side effects and drug interactions and are now used infrequently, but may have utility in the treatment of more severe or refractory mood disorders. Choice of anti-depressant therapy should consider efficacy and tolerability, co-morbid medical conditions, and potential drug-drug interactions. The relatively low side effect burden of SSRI's makes then first line treatment for most patients. However, depressed patients with co-morbid physical symptoms such as headache, pain and fatigue may respond less well to SSRI's than those without such symptoms [35], raising concerns that childhood cancer survivors with physical late effects may be at risk for more refractory symptoms of depression.

It is important to note that the onset of effect for SSRI's is usually 2–3 weeks, and it may take 4–6 weeks for full effect. The most common adverse effects of SSRI's include nausea, tremor, headache, excessive sweating, activation or sedation, insomnia, dizziness, rash and dry mouth [36]. Many of these side effects are dose-dependent, and generally subside with time. There is also a rare side effect of toxicity and serotonin syndrome, especially when there are multiple serotonergic agents being taken. Emergence of sexual dysfunction including decreased libido, erectile dysfunction, delayed ejaculation and anorgasmia may occur, and can be a source of non-adherence to treatment [37]. Among the SSRI's, Citalopram is noted to have the fewest inhibitory effects on CYP450 isoenzymes [38], making it potentially useful when these interactions are of concern to prescribers. Recent US Food and Drug Administration (FDA) warnings about increased risk of prolonged QTc at doses above 40 mg may limit use of Citalopram in higher doses among patients with existing cardiac risk factors [39]

In 2003, the FDA in the United States received unpublished data from placebo-controlled trials which suggested that paroxetine taken by pediatric patients with major depressive disorder might be associated with an elevated risk of "suicide attempts" and "possibly suicide-related" events. In 2007, the FDA made revisions to labeling for SSRI's and extended caution to young adults, stating that when compared to placebo, antidepressants increased the risk of suicidal thinking and behavior in children, adolescents, and young adults with major depressive disorder and other psychiatric disorders.

Data from large epidemiological studies examining rates of suicidal behavior have found no statistically significant effect of antidepressants on the likelihood of actual suicide attempt [40]. A study of four older antidepressant medications (fluoxetine, paroxetine, amitriptyline, and dothiepin) also concluded there were no significant associations between the use of a particular study antidepressant and the risk of suicide, although the risk of suicidal behavior was observed to be increased in the first month after starting antidepressants [41].

Although survivors of childhood cancer have increased rates of suicidal ideation that is associated with depression [4, 5], there is no data that SSRI treatment is specifically associated with suicidality in these patients.

27.4.3 Summary

Survivors who present with symptoms of depression require a careful history, consideration of non-pharamacologic approaches and potential medical causes, and close follow-up. General medical clinicians who use pharmacotherapy should prescribe recommended dosing for antidepressants, with specific caution and dose adjustments in patients with hepatic or renal insufficiency, or cardiac risk factors. Patients should be monitored regularly for treatment efficacy, side effects, and suicidal ideation, especially during initial dose titration. Patients with refractory symptoms need re-assessment and likely referral to specialized mental health clinicians.

27.5 Anxiety

27.5.1 Background

Anxiety may present as a transient state of fear that is triggered by a situation, or may be a more pervasive and intense internal experience that is less influenced by the environment. The common experience

Table 27.2 Criteria for anxiety disorders

DSM-5 Anxiety Disorders	
Generalized Anxiety Disorder	Excessive anxiety and worry occurring most days for at least 6 months, about a number of events or activities. Anxiety is associated with at least 3 of the following symptoms: • Restlessness • Fatigue • Difficulty concentrating • Irritability • Muscle tension • Sleep disturbance The person finds it difficult to control the worry and symptoms cause significant distress or impairment in functioning.
Panic Disorder with or without Agoraphobia Agoraphobia: Anxiety about being in places or situations from which escape might be difficult or which might induce panic, e.g. being outside of the house, on a bus or crowded place. These situations are avoided or endured with marked distress.	Recurrent unexpected panic attacks characterized by a discrete, abrupt period of intense anxiety with at least 4 of the following symptoms: • Increased heart rate/pounding • Sweating • Trembling • Sensation of shortness of breath • Choking sensation • Chest pain • Nausea • Dizziness • Derealization or depersonalization • Fear of going crazy • Fear of dying • Paresthesias • Chills/hot flushes At least one of the attacks is followed by at least 1 month of one or more of the following: • Persistent concern about having additional attacks • Worry about the implications of another attack • A significant change in behavior related to the attacks
Specific Phobia	Marked and persistent fear of a specific object or situation that is excessive and is recognized by the person as unreasonable. Avoidance and anxious anticipation interferes with functioning.
Social Phobia	Marked and persistent fear of social or performance situations in which the person is exposed to unfamiliar people or scrutiny by others. The person fears that he or she will act in a way that is embarrassing and becomes anxious or panicky in these situations, and recognizes these fears as excessive or unreasonable. Avoidance and anxious anticipation interferes with functioning.
Post Traumatic Stress Disorder	The person has been exposed to a traumatic event in which he or she experienced a threat of death or serious injury to self or others. The response involved intense fear, helplessness or horror. The event is re-experienced, cues of the event are avoided, or there are symptoms of increased arousal.
Obsessive-Compulsive Disorder	Presence of obsessive thoughts, impulses or images or compulsive repetitive behaviors or mental rituals that are aimed at reducing distress, but are excessive and interfere with functioning.

Adapted from American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*. 2013, Arlington, VA

of worry that most people experience is distinguished from an anxiety disorder that may warrant medication intervention by the intensity and duration of symptoms, and their independence from or disproportionate reaction to external factors. Anxiety disorders are characterized by fears that take on "a life of their own," are not eased by changing situations or reassurance, and significantly interfere with function. Anxiety is associated with cognitive, physiologic and behavioral components. Table 27.2 describes common anxiety disorders that may become the focus of medical attention.

There is significant co-morbidity between anxiety and depression, and survivors of childhood cancer have increased risk for both [1, 2] as well as the specific anxiety symptoms associated with post-traumatic stress [3]. Survivors may also be at increased risk for social anxiety due to changes in appearance related to treatment, or social skills deficits related to neuro cognitive issues or developmental delays. Many medical conditions may also be associated with the physical or emotional symptoms of anxiety, and need to be addressed directly prior to additional psychotropic intervention. Endocrine, cardiac, respiratory and neurologic conditions may all present with anxiety, as can side effects of medications, and recreational drugs or substances such as caffeine and tobacco. Untreated pain may also be a source of anxiety and should be assessed and treated. In post-traumatic stress disorder, anxiety, hypervigilance and avoidance may be directly related to treatment experiences and/ or fears of cancer recurrence.

27.5.2 Treatment

The medication approach for the range of anxiety disorders is quite consistent, and the Selective Serotonin Reuptake Inhibitors (SSRI's) are first line agents for anxiety as well as depression. However, initial titration of these medications can exacerbate anxiety. Therefore starting doses for anxiety may be half of those for depressed patients. Titration can usually proceed to full therapeutic dosing after a week or two of acclimation. The treatment of certain anxiety disorders (OCD or PTSD) may require higher doses and longer trials to achieve full effect. As in the treatment of depression, common side effects for SSRI's are usually dose dependent and subside with time and include nausea, tremor, headache, excessive sweating, activation or sedation, insomnia, dizziness, rash, dry mouth. Sexual side effects may also emerge and interfere with medication adherence. The SNRI Venlafaxine may also be effective in anxiety and should also have lower dose initiation to minimize activation or anxiogenic side effects.

Benzodiazepines are also effective in the treatment of anxiety either as monotherapy or in conjunction with SSRI's especially to mitigate the potential angiogenic effect at initiation. The rapid effect of benzodiazepines may also be useful during the latency to effect of SSRI's, or when anxiety is interfering with medical care or participation in psychotherapy. Short-acting agents such as lorazepam or alprazolam have rapid effect, but may raise concerns about abuse and dependency, due to rebound or withdrawal effects between doses. Higher potency Clonazepam has a longer half-life and minimizes these issues. Side effects of sedation usually attenuate over time, and can be minimized with slow titration. Many survivors may be familiar with benzodiazepines from their cancer treatment and may give a history of positive or negative effects. Although many patients with anxiety can use benzodiazepines safely and appreciate the importance of using the lowest effective dose to minimize tolerance, clinicians must be thoughtful about their use in patients with histories or significant risk for substance abuse. If there is concurrent prescription of SSRI's and benzodiazepines, prescribers may consider tapering benzodiazepines once SSRI's have achieved full effect.

27.5.3 Summary

Survivors may be vulnerable to a range of anxiety disorders that can interfere with function and quality of life. Medical causes of symptoms must also be explored. The mainstays of anxiety treatment are SSRI's and benzodiazepines. Initiation of SSRI's may temporarily exacerbate anxiety, and so initial doses may need to be lower and then titrated up to usual therapeutic dosing. Benzodiazepines are also useful for treatment of anxiety alone or in combination with SSRI's especially during initial latency to SSRI effect. Medication interactions and cautions around renal or hepatic insufficiency, and cardiac risk factors need to be considered, as well as risk for substance abuse when using benzodiazepines. Regular monitoring for both medications is important, and treatment of anxiety may be most effective in conjunction with cognitive-behavioral or other psychotherapies.

27.6 Conclusions

As more children are surviving childhood cancer, the incidence of neurocognitive late effects is becoming more apparent, and has been shown to be responsive to pharmacological intervention. In addition, survivors often experience symptoms of depression, anxiety, or behavioral dysregulation, and many would benefit from psychopharmacological intervention. Clinicians treating survivors should consider the complexity of survivors' medical history and psychological vulnerabilities, and how their medical late effects may impact their treatment responses and their susceptibility to side effects of psychiatric medications.

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28 The Cancer Survivor and Complementary Health Approaches

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28.1 Introduction

The various terms relating to Complementary Health Approaches (CHAs) have been used inconsistently in the literature. Frequently, the terms "complementary," "alternative," "holistic," and "integrative" have been used interchangeably to refer to interventions outside of conventional medicine. The National Center for Complementary and Integrative Health (NCCIH), formerly the National Center for Complementary and Alternative Medicine (NCCAM), at the National Institutes of Health has defined "complementary" therapies as non-mainstream treatments used in conjunction with conventional medicine [1]. "Alternative" therapies are defined as non-mainstream treatments used in place of conventional medicine. True alternative medicine is uncommon in Western medicine, and most individuals utilize non-mainstream treatments in a complementary manner. It is also important to recognize that the distinction between "complementary" and "conventional" has become obscured for some treatments that have gained strong scientific support of efficacy and are now more commonly utilized. This is especially true as medical centers are increasingly adopting an "integrative medicine" or "integrative health care" approach of providing conventional medicine together with complementary therapies.

NCCIH now generally uses the term "complementary health approaches" in reference to the complementary and alternative interventions they study for various health conditions. NCCIH also categorizes these approaches as generally falling into one of two subgroups—*natural products* or *mind and body practices. Natural products* include a variety of products, such as herbs or botanicals, vitamins and minerals, and probiotics. They are widely marketed, readily available to consumers, and often sold as dietary supplements. *Mind and Body Practices* (mind-body therapies) include a wide range of interventions or techniques administered or taught by a trained practitioner or teacher. This category includes: acupuncture, massage therapy, meditation, movement therapies, relaxation techniques

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(e.g., breathing exercises, guided imagery, and progressive muscle relaxation), spinal manipulation, Tai chi and qi gong, yoga, healing touch, biofeedback, and hypnotherapy.

While most CHAs can be categorized into either "natural products" or "mind and body practices," there are other complementary treatment approaches that do not fit precisely into either description. This includes homeopathy, naturopathy, Ayurvedic healing, traditional Chinese medicine (TCM), and traditional medicine/folk medicine. These approaches historically represent separate and complete medical systems with distinct beliefs about origins and treatment of illness that differ from conventional western medicine. In current research and practice within Western medical centers, individual complementary products and therapies are commonly used apart from the corresponding alternative medical system. For example, acupuncture may be used on its own rather than utilizing a whole TCM approach. Likewise, yoga may be used on its own, rather than utilizing a complete Ayurvedic healing approach to care.

Estimates of the use of CHAs range from 2 % in a healthy sample of children [2] to as high as 73 % in children with cancer [3], with estimates suggesting significantly higher utilization in pediatric populations. The 2007 National Health Interview Survey gathered information on CHA use among more than 9,000 children younger than 18 years [4]. Nearly 12 % had used some form of CHAs during the past 12 months. Adolescents aged 12–17 years, children with multiple health conditions, and those whose families delayed or did not use conventional medical care because of cost were also more likely to use CHAs. The most common pain conditions for which CHAs were used in the past 12 months included back or neck pain (8 %), musculoskeletal conditions (4 %), and abdominal pain (1 %), with associated problems including anxiety/stress (5 %), sleep problems (2 %), and depression (1 %). Chiropractic or osteopathic manipulations were used in 3 % of children, deep breathing exercises in 3 %, yoga in 2 %, meditation and massage in 1 % each, and all other modalities were less than 1 %. Integrative care including CHAs is now included in major textbooks of pediatrics [5–7].

Though the use of CHAs in children is increasing internationally, the reported prevalence differs by country, culture, methodology, and populations studied [4, 8–11]. For example, the prevalence of CHA use in the Netherlands in children with cancer was found to be about 40 %, while it was 11 % in a Finnish study based on a national data set of over 6,000 children [12, 13].

As noted, awareness and use of CHAs by cancer patients has increased, with research indicating that childhood cancer survivors are using CHAs to cope with late effects of treatment and to improve their general health. Ndao and associates [14] examined the use of CHAs among childhood cancer survivors in a sample of 197 survivors at the Herbert Irving Child and Adolescent Oncology Center, Columbia University Medical Center (CUMC). Fifty-eight percent of these respondents (115 survivors) reported using CHAs in survivorship. Of these CHA utilizers, 72 % used biologically based therapies, including herbs, botanicals, vitamins, minerals, and other natural products such as herbal ointments or creams. These were typically used for general health, immune support, detoxification, skin/hair health, fatigue, and cancer prevention. Mind-body therapies, including yoga, aromatherapy, and acupuncture, were the second highest reported utilization category of CHAs (reported by 53 % of the CHA utilizing survivors). These treatments were typically used for relaxation and stress management, and were used more frequently by young adults compared to children. Manipulative and body-based therapies including touch therapies, manual healing techniques, pilates, and water treatment/hydrotherapy, were used by 46 % of the respondents who had utilized CHAs. The primary reasons for use were relaxation, stress management, and pain relief, and they were also more often used by young adults compared to children. Thirteen percent of CHA users reported use of energy healing therapies, primarily for general health and/or healing, relaxation, and stress management. Four percent of the CHA users reported usage of alternative medical

systems. These therapies were typically used for immune support. The authors note that respondents in this study generally considered CHA therapies to be very effective.

Despite the high levels of utilization, uses of CHAs are often not reported to treating physicians. Reports indicate that up to half of all adults using CHAs do so without consulting a practitioner ([15]; and some estimate) that CHA use may be reported to physicians even less frequently in a pediatric population [16, 17]. Some research indicates that many parents do wish to discuss use of CHAs with their child's pediatrician [18]. Common reasons that patients do not report use of CHAs include patients' perception that (1) the physician wouldn't need to know this information, (2) the physician wouldn't be supportive of that treatment choice, and/or (3) simply that the physician did not ask about CHA use [19]. This lack of communication regarding use of CHAs is a particular concern given that some CHAs may be contraindicated for an individual patient or even have potentially dangerous interactions with medications the patient is already taking. Thus, it is increasingly important that physicians are knowledgeable about CHAs, and that they initiate open discussions with families in which they ask about CHA use and provide scientifically based recommendations that reflect current data on safety and efficacy.

Over time, there has been an increasing focus on conducting well-designed research studies on these complementary treatments in order to determine clinical effectiveness. Consequently, as scientific efficacy is established, some complementary therapies are becoming much more common and accepted by the medical community. However, given the wide variation in amount and quality of research for different CHAs, it is important for survivors and conventional medical providers to have evidence-based information to assist in making informed decisions about use of CHAs in cancer survivorship.

We provide a summary of the most commonly used CHAs and include a background of the techniques and its uses, mechanism of action, review of relevant studies, risk, and benefits, and our opinion of its efficacy based upon the available research. Where possible, we provide resources to obtain additional information and/or find a provider. Resources are also included in the Resources Chapter in this manuscript.

28.2 Review of Therapies

28.2.1 Hypnosis

Background. Hypnosis and self-hypnosis include the use of various relaxation techniques and imagery, in order to enter a "trance state" of focused attention, with reduced peripheral awareness. In this trance state, the individual is more receptive to suggestion, and the health care provider gives suggestions for changes in subjective experience, alterations in perception, sensation, emotion, thought, or behavior [20]. For example, the health care provider may describe imagery that transforms the individual's pain to cold or numbness. It is usually administered with a trained therapist in the context of psychotherapy.

Potential Indications. Pain reduction, anxiety, stress, depression, insomnia, PTSD, procedural distress, and chemotherapy induced nausea and vomiting; improving immune functions.

Clinical Studies. A clinical review of medical research on hypnotherapy and relaxation therapies with cancer patients was published in 1999 and included three reviews: two randomized clinical trials and one National Institutes of Health (NIH) Technology Assessment, all published before 1999 [21]. The authors concluded that, "There is strong evidence from randomised trials of the effectiveness of hypnosis and relaxation for cancer related anxiety, pain, nausea, and vomiting (side effects of chemotherapy), particularly in children (p. 1348)."

The Complementary and Alternative Medicine Cancer (CAM-Cancer) consortium has completed a peer-reviewed summary of the research on hypnotherapy for cancer patients [22]. Their summary included 16 randomized clinical trials and two controlled clinical trials that included studies on hypnotherapy in anticipatory nausea

and vomiting during medical procedures, hypnotherapy for cancer therapy related pain, and studies of hypnotherapy in other cancer-related symptoms. Their summary states that, "Results show that hypnosis or self-hypnosis can significantly reduce cancer-related pain, antiemetic use, nausea and emesis during medical procedures, as well as anxiety related to all of the mentioned symptoms occurring in cancer patients" [22]. In their review of six studies examining hypnotherapy interventions for anticipatory nausea and vomiting during medical procedures, a significant reduction of nausea was achieved in six studies, a reduction of emesis in five, and a reduction of antiemetic use in one of the included trials. Of the nine studies reviewed for impact of hypnosis on cancer-related pain, eight showed a significant reduction of pain; and another seven also showed a reduction of anxiety or pain-related anxiety when comparing the hypnotherapy group with the control groups. With regards to three other studies examining other cancer-related symptoms, one study showed an increase of self-competence in the hypnotherapy group [22].

A recent review by Jensen and Patterson [23] discussed the clinical implications of research findings for hypnosis in chronic pain management. They note that "the clinical outcome studies on acute and chronic pain as well as neurophysiological studies in the laboratory have demonstrated that hypnosis is effective over and above placebo treatments and that it has measurable effects on activity in brain areas known to be involved in processing pain (p. 168)."

Zeltzer et al. [24] conducted a randomized clinical trial with 54 children undergoing chemotherapy treatment for cancer. The children were randomized into one of three groups: (1) hypnosis intervention, (2) non-hypnotic distraction/relaxation intervention, and (3) attention placebo groups. Findings indicated that children in the hypnosis group reported the greatest decrease in anticipatory emesis.

In an earlier study, Zeltzer and LeBaron [25] conducted a controlled clinical trial with 33 pediatric oncology patients undergoing lumbar punctures and bone marrow aspirations. Patients were randomly assigned to either a hypnosis or a non-hypnotic intervention group. Pain during lumbar punctures was reduced only by hypnosis, and anxiety was reduced by hypnosis and non-hypnotic interventions, but to a greater extent by hypnotic interventions. Pain during bone marrow aspirations was reduced by both hypnotic and non-hypnotic techniques, however, anxiety was reduced only by hypnosis.

More recently, Lang and associates [26] conducted a randomized clinical trial with 201 adult patients receiving a percutaneous tumor treatment. The patients were randomized to receive hypnotherapy, empathic attention, or standard care alone. Results indicated that the hypnosis group experienced less pain and anxiety than the patients in the other groups. Further, the hypnosis patients utilized less pain medication at several time intervals compared to the other groups.

Liossi and Hatira [27] randomly assigned 80 pediatric oncology patients with either leukemia or non-Hodgkin lymphoma who were undergoing lumbar punctures to four different groups. Group 1 received direct hypnosis combined with standard medical treatment; Group 2 received indirect hypnosis with standard medical treatment; Group 3 received attention control with standard medical treatment; and Group 4 received standard medical treatment alone. Results indicated that the patients receiving hypnosis (Groups 1 and 2) reported less pain and anxiety and demonstrated less behavioral distress than those who did not (Groups 3 and 4).

Later, Liossi and associates [28] conducted a randomized clinical trial examining the effectiveness of hypnosis on procedural distress with a sample of 45 pediatric patients diagnosed with leukemia or non-Hodgkin lymphoma. Patients were randomized into one of three groups. All patients had EMLA cream (a mixture of lidocaine and prilocaine) applied to the skin 60 min prior to the procedure. Group 1 received EMLA only, Group 2 received EMLA plus hypnosis, and group 3 received EMLA plus attention. The hypnosis group reported less anticipatory anxiety and less procedure-related pain and anxiety compared to either of the other groups, and they were also rated as demonstrating less behavioral distress during the procedure. Level of hypnotizability

was also significantly associated with the magnitude of benefit seen in the hypnosis group.

The above authors conducted another similar randomized clinical trial examining effects of hypnosis on procedural distress with 45 pediatric cancer patients of various diagnoses [29]. The patients were randomized into the same three groups as above. Patients receiving hypnosis reported less anticipatory anxiety, procedure-related pain, and anxiety. Patients were also rated as demonstrating less behavioral distress during the procedure compared to the other two groups. Parents of children who received hypnosis also reported less anxiety themselves during their child's procedure than parents whose children were randomized into one of the other two groups.

In contrast, some studies have not found significant benefit for hypnosis compared to other interventions (e.g., play, cognitive distraction, or supportive counseling). For example, Wall and Womack [30] did not find significant benefits for hypnosis versus cognitive distraction in reducing pain or anxiety in 20 pediatric oncology outpatients undergoing bone marrow aspiration or lumbar puncture. Patients were randomly assigned to two different groups for self-instruction with hypnosis or with cognitive distraction. Neither intervention was associated with anxiety reduction; however, both hypnosis and cognitive distraction were associated with pain reduction. A "hypnotizability scale" was not associated with pain reduction. Similarly, Katz et al. [31] randomized 36 pediatric patients to either hypnosis or play intervention group. The patients were all being treated for acute lymphoblastic leukemia, had undergone at least three bone marrow aspirations (BMAs), and were scheduled for repeated BMAs. The authors found that both hypnosis and play were associated with reduced self-report of pain and distress. There was no between groups difference. Oddby-Muhrbeck et al. [32] conducted a randomized clinical trial with 70 adult female oncology patients who were scheduled for elective breast surgery. Patients were randomized to either self-hypnosis (listening to a message with reassuring information focused on minimizing postoperative nausea and vomiting) or listening to a blank tape with low background music during surgery. There were no significant differences in the number of patients who experienced nausea and vomiting in the 24 h post-operative period. However, the patients exposed to positive suggestion less often recalled nausea and vomiting compared to the control group. While these findings suggest the power of hypnotic suggestions, researchers were not able to rule out some implicit processing during balanced anesthesia.

Hockenberry-Eaton and Cotanch [33] conducted a randomized clinical trial with 22 pediatric oncology patients examining impact on self-competence scores (utilizing the Harter Perceived Self-Competence Profile [34]. Patients were randomized into two different groups: (1) self-hypnosis and (2) standard care. Over four courses of chemotherapy, the self-hypnosis group showed increased self-competence scores, while the control group evidenced a decrease in this score. Limitations of this study include small sample size and lack of p-values reported.

Mechanism of Action. Two recent reviews of the use of hypnosis in management of chronic pain provide detailed discussion of the flourishing research over recent years adding significantly to our understanding of the mechanisms of action involved in clinical effects of hypnosis [7, 23]. In their review of hypnotic approaches for chronic pain management, Jensen and Patterson [23] emphasize that findings from controlled clinical trials show effectiveness in reducing chronic pain, but note that response to hypnosis treatment is variable by individual. They describe that recent advances in the literature show how hypnosis has a measurable impact on neurophysiological activity and functioning of pain. Specifically, "the cortical areas most activated during pain are the thalamus, anterior cingulate cortex (ACC), primary and secondary sensory cortices and prefrontal cortex" (p. 171), and they explain how there is a growing body of evidence that each of these areas respond to hypnosis in some fashion. Overall, hypnosis appears to be involved in the *processing* of pain in several regions of the brain, rather than a single, unilateral mechanism. Furthermore, they review studies that demonstrate how hypnosis can

be targeted to specific brain regions [35, 36], by decreasing beta activity while increasing alpha activity [37, 38]. Liossi et al. [7] expand the discussion to include supraspinal sites that have been implicated in responding to the analgesic effects of hypnosis. They also emphasize that these studies have been conducted primarily on adults, and making direct inferences to the pediatric population, due to differences between structural and functional neurodevelopment throughout childhood, may be a stretch. Rubia [39], reviewing functional magnetic resonance imaging (fMRI) studies on brain development, explains that as the brain matures, there is increased functional activation in several brain regions that mediate higher level control functions, including the lateral and medial frontal, striatal, and parieto-temporal areas. This developmental trajectory may help explain the tendency for increasing pain toleration and coping abilities in adolescence compared to children.

Level of Scientific Efficacy. *Strong evidence for benefits*. Challenges of applying blinding contributes to difficulty in examining the effectiveness of hypnotherapy. However, there is a growing literature of large, well-designed studies that provides firm evidence documenting positive effects of hypnosis in reducing both acute and chronic pain [7] and strong evidence of effectiveness specifically for use of hypnosis with cancer patients on reducing anticipatory nausea and vomiting, cancer-related pain, and anxiety [22].

Potential Risks/Adverse Effects. Hypnosis is generally considered a safe treatment modality, with few adverse effects when administered under the care of an appropriately trained therapist or health care professional. However, reported adverse effects include headache, dizziness, nausea, panic, and the "creation" of false memories. Additional risks may be present for individuals with dementia or severe mental illness such as schizophrenia; therefore, this may not be an appropriate modality for intervention with such patients.

Finding a Provider. Many hypnosis providers are licensed in another area of health care, such as psychology or nursing; or they may be a dentist or physician, or work under the supervision of a physician. Some hypnosis providers choose to become certified to demonstrate their training and expertise. A good starting place to find a qualified hypnosis provider is to contact an organization such as the American Society of Clinical Hypnosis (http://www.asch.net/).

28.2.2 Biofeedback

Background. Biofeedback is a process in which the individual receives "feedback" regarding physiological processes during relaxation training. Often this is accomplished through the use of a computer and various sensors, although there are additional ways to obtain data regarding the individual's reaction to training, such as measurement of skin temperature. Biofeedback has several uses, but it is commonly used to help reduce pain, anxiety, or other discomfort by helping the individual become more aware of their bodily reactions and then learning strategies to control physiological changes associated with the stress response. These monitored changes [40] may include muscle tension, peripheral skin temperature, sweat gland response, heart rate variability, brain wave activity, or breathing rate, with the goal of increasing the body's "relaxation response." Using biofeedback helps individuals learn about their body's responses to stress and become aware of their own abilities to alter those responses.

Potential Indications. Reduction of pain, anxiety, stress, procedural distress, and chemotherapy induced nausea and vomiting.

Clinical Studies. A small randomized control study with advanced cancer patients examined the effect of relaxation training supplemented with electromyographic (EMG) biofeedback on cancer-related pain [41]. The experimental group (n = 12) received six EMG biofeedback-assisted relaxation sessions over a 4-week period. The control group (n = 12) received conventional care. After intervention, the treatment group reported significantly lower pain levels compared to the control group. Study limitations include small

sample size and a study design in which EMG biofeedback was combined with relaxation training. Thus, it was not possible to determine whether relaxation alone would have produced the same benefits.

However, an earlier randomized clinical trial examined the effects of EMG biofeedback, skin-temperature (ST) biofeedback and relaxation training (RT) in reducing the adverse reactions associated with chemotherapy [42]. Eighty-one cancer patients were matched on multiple individual-difference variables and randomized to one of six groups formed by a 3 (EMG Biofeedback, ST Biofeedback) x2 (RT, No RT) factorial design. Outcomes included physiological data, and both patient- and nurse-reported measures assessed over five consecutive chemotherapy treatments. RT patients showed decreases in nausea and anxiety during chemotherapy and physiological arousal after chemotherapy. EMG and ST biofeedback reduced some indication of physiological arousal but had no other effects on chemotherapy side effects. Results suggest that relaxation training is better at reducing the aversive effects of chemotherapy when compared to biofeedback training. The authors concluded that the positive effects found for biofeedback in earlier research resulted from the RT that was provided during biofeedback, rather than to the biofeedback alone [42].

In another study, investigators assessed change in the immune system and psychological symptoms of 13 women with breast cancer over the course of 18 months who had recently undergone radical mastectomy [43]. Patients were randomized into either the immediate treatment group or the delayed treatment control group. In the immediate treatment group, patients were trained in relaxation, guided imagery, and biofeedback over a 24-week period. The delayed treatment (control) group was placed on a waiting list. Results indicated that relaxation, guided imagery, and biofeedback interventions were associated with immune system changes, including natural killer cell activity, mixed lymphocyte responsiveness, concanavalin A responsiveness, and the number of peripheral blood lymphocytes. No significant psychological changes were reported, though some reductions were seen in psychological inventory scales measuring anxiety. Small sample size and multi-modal intervention limit the conclusions that can be drawn [43].

Biofeedback has been extensively evaluated in its effectiveness for treating headaches, and there are several studies examining its efficacy in the pediatric population [44–50]. Additionally, biofeedback has been found to be effective in the treatment of abdominal pain in the pediatric population [51, 52].

Fentress et al. [44] randomized 18 children ranging in ages from 8 to 12 years, who had recurrent intermittent headaches to assess efficacy of EMG biofeedback, relaxation-response training, and pain behavior management. Six patients received all three treatment interventions, six received relaxation-response training and pain behavior management (without biofeedback), and the remaining six were assigned to a wait-list control group. Treatment groups completed nine 1-hour sessions in 11 weeks. Headache diaries were evaluated throughout the study and at a 1-year follow-up assessment. Outcome measures included frequency, intensity, and duration of headaches. Compared to the control group, both treatment groups had improvement documented in their headache diary compared to baseline and at the end of the 15-week study period. The headache reduction in the treatment groups was maintained 1 year after end of treatment. Results suggested that a combination of relaxation-response training together with pain behavior management (with or without biofeedback), was effective in treating pediatric migraine. This study was limited by small sample size, absence of data, and other design problems [44].

Bussone et al. [45] randomized 30 children ranging in age from 11 to 15 years with episodic tension-type headaches to either a biofeedback-relaxation (BFB-REL) intervention or a relaxation placebo (REL-PLAC) control condition for ten sessions occurring twice weekly. Both groups had a 55 % improvement in headache severity at the 1 month assessment, but only the BFB-REL group had improvement at the sixth and 12 month follow-ups, with an 85 % improvement in headache severity by the last assessment [45].

Kroner-Herwig et al. [46] randomized 40 children, ages 8–14 years, with tension-type or

combined headaches to an EMG-frontalis biofeedback or progressive relaxation (PR) condition with and without parental involvement (PI) or to a wait list control group. There were 12 biweekly sessions and the parent condition included three 1-hour parent sessions. All four intervention groups had significant main effects in all outcome domains post-intervention. Yet, at the 6 month assessment, the biofeedback group without PI showed the greatest changes, followed by biofeedback with PI, PR alone, PR with PI, and then the control group. The biofeedback group without PI had the highest mean effect size for headache outcomes, suggesting that parental involvement in this adolescent population was not a necessary component in achievement positive results [46].

Grazzi et al. [47] provided EMG biofeedback to ten children, ages 12–15 years, with tension headaches twice weekly for 6 weeks. The "Pain Total Index" was collected with a headache diary, and muscular tension scores decreased in all patients from baseline to treatment completion. In a later longitudinal study, Grazzi et al. [48] provided an EMG biofeedback-assisted relaxation program in 54 children, mean age of 12 years, with episodic tension-type headaches with two treatment sessions per week for 5 weeks. The Pain Total Index via daily diaries were significant at treatment termination but not at the 1 year follow-up. At the 3 year follow-up assessment, 84 % of the participants were symptom-free. Given the lack of a control condition, the percent of children who would have been headache free even without intervention at 3 years is unknown. Other study design weaknesses limit the generalizability of the findings [48].

Arndorfer and Allen [49] conducted a within subject, multiple baseline, time-lagged study to evaluate thermal biofeedback therapy in five children, aged 8–14 years, with tension-type headaches. Baseline data over 4–7 weeks were followed by six thermal biofeedback treatments. All participants showed clinical improvement via daily headache diaries and four of the five were headache-free at 6 months. While these findings are promising, the size of the treatment group limits the generalizability [49].

Scharff et al. [50] randomized children ages 7–17 years with migraines to one of three groups in order to examine benefits of thermal biofeedback (TB) on pain, anxiety, and depression. The groups included: (1) a treatment condition including stress management with thermal biofeedback (TB), (2) a control condition consisting of hand-cooling biofeedback (HCB) only, and (3) a wait-list control condition. At the 6 week post-treatment assessment, no one in the waitlist control condition had headache improvement with one child (10 %) in the HCB reporting decreased headache severity, while seven (54 %) in TB group had significant reduction in headache severity. In a combined analysis, both treatment groups had reduced headache severity and frequency, although no changes were appreciated in anxiety or depression measures. Upon 6 month follow-up, there were no measurable changes. While this study is often cited as evidence of thermal biofeedback for migraines in children and despite its promising title, caution is warranted because the confounding variables limit generalizability of the findings [50].

Biofeedback was successfully applied to middle school students who demonstrated significant anxiety [51]. In this study, 300 seventh and eighth grade students were given a self-report anxiety measure, the IPAT Anxiety Scale [52], and 150 students were identified as "highly anxious" on the basis of this measure. They were then randomly assigned to the biofeedback experimental treatment group or to the no-intervention group. The treatment group subjects (N = 72) received 12 sessions of biofeedback training (six session of thermal training and six session of EMG training). Results indicated that compared to the control group, the subjects in the treatment group experienced significantly lower state and trait anxiety scores. The authors concluded that these findings were very promising, but that future research was needed to determine the long-term stability of the reduced anxiety levels [51].

Heart rate variability (HRV) has also been shown to be promising in the treatment of cardiac vagal tone restoration, of which has been thought to be an indicator of overall parasympathetic nervous system status. Sowder et al. [53] provided six sessions of HRV biofeedback to restore vagal

tone in 20 children, ages 5–17 years, with functional abdominal pain (FAP) and compared outcomes to ten children without FAP. The significant decrease in low frequency/high frequency (LF/HF) ratio after intervention suggested an improvement in cardiac vagal tone, along with a decrease in pain frequency and a significant correlation between the decrease in LF/HF ratios and pain frequency. This novel study of heart rate variability biofeedback in FAP was limited by the study design (no randomized trial with a control condition), but demonstrates some indication that HRV may be beneficial in the treatment of FAP [53].

In another study examining FAP, Schurman et al. [54] randomized 20 children, ages 8–17 years, with FAP to an intervention group consisting of standardized medical care (SMC) plus ten sessions of biofeedback-assisted relaxation training (BART), or to a control group consisting of SMC only. Children in the intervention group demonstrated significantly improved pain intensity and duration of pain episodes, as reported via pain diary. The intervention group also showed greater clinical improvement in comparison to the control group on a physician-rated Global Response Assessment rating. Methodological limitations include the lack of a true attention control group. Specifically, although children in both groups returned to clinic to meet with physician staff on the same schedule, children receiving medication plus BART had six additional visits and greater contact time than children receiving medication only. As a result, the authors could not rule out the possibility that some of the effect of the combined treatment could be due to this attention factor [54].

A small, non-randomized feasibility study was completed with 12 children examining benefits of HRV biofeedback, a technique introduced above that measures the rhythms of the naturally occurring "beat-to-beat" changes, on reducing procedural distress [55]. Participants completed a 4-session intervention combining relaxation and biofeedback. Participants showed lower state and trait anxiety scores from session 1 to session 4. Participants also demonstrated an improvement in HRV coherence scores in sessions 3 and 4. Eleven of the 12 participants also completed a 5-item Likert-type scale satisfaction questionnaire. The majority of those 11 participants reported belly breathing alone helped them feel less scared (63 %), and that the combination of belly breathing and biofeedback techniques helped them to feel more "in charge" of their bodies before their procedures (81 %). Less than half reported that biofeedback alone helped them to feel less scared (45 %). Procedural fear scores did not change. This study is limited by small sample size and lack of control group, although it provides promising efficacy of HRV training [55].

Mechanism of Action. Shifts in heart rate variability in some studies of biofeedback suggest that changes are autonomically mediated [56]. But additional research is needed to examine the physiological and biochemical changes associated with biofeedback.

Level of Scientific Efficacy. As reviewed above, research support is suggestive of efficacy, but not strong. There is presently a lack of good quality, single-intervention trials. Some studies indicate an improvement in pain relief and chemotherapy-related nausea and anxiety. However, these studies have not been replicated and have considerable methodological limitations [57]. Also, biofeedback is often used together with relaxation procedures, so it is difficult to discern separate effects. In addition, due to the difficulty in creating appropriate and credible placebo conditions, double-blind studies are difficult to complete for this intervention.

That being said, some children report significant benefit from biofeedback and greater engagement when using it as an adjunct in learning relaxation strategies. Providing targeted biofeedback to children who need self-management tools to cope with pain, anxiety, or stress, long after treatment has been completed has appeared to be beneficial. For example, when muscle tension is a primary cause of pain, it may be useful to utilize EMG biofeedback to help learn to reduce muscle tension in those body areas where it is a primary cause or contributor to the pain. Alternately, skin temperature warming might be appropriate for children with migraines. HRV biofeedback may

be useful in teaching a general relaxation response to help reduce anxiety and stress.

Potential Risks/Adverse Effects. Biofeedback has a good safety record, with minimal risks, although some concerns have been raised about use with individuals with a severe psychiatric history. For example it is likely contraindicated for individuals with psychoses or severe cognitive impairment that renders it difficult for the individual to understand the purposes and procedures of this intervention.

Finding a Provider. Many biofeedback therapists are licensed in another area of health care, such as psychology, nursing, or physical therapy, and there are technicians who are able to work under a licensed provider. Some biofeedback therapists choose to become certified to demonstrate their training and expertise. A good starting place to find a qualified biofeedback provider is to contact an organization such as the Association for Applied Psychophysiology & Biofeedback (http://www.aapb.org) or the Biofeedback Certification International Alliance (http://www.bcia.org).

28.2.3 Aromatherapy

Background. Aromatherapy is another common type of CHA and refers to the therapeutic use of essential or aromatic oils [58]. The oils used in aromatherapy are extracted from the roots, flowers, leaves, and stalks of plants and certain trees using steam distillation or mechanical expression. These essential oils are also known as "volatile oils" [59]. Typically, the essential oils of aromatherapy are inhaled after being diffused in the air or administered topically in diluted form (e.g., via massage). They are not commonly administered orally. There are over 300 different essential oils available in today's market [60, 61]. Some essential oils are known to have antibiotic and antiviral properties. Aromatherapy is widely used in different cultures to calm, balance, and rejuvenate mind, body, and spirit [58, 62].

Potential Indications. Reduction of pain, depression, anxiety, insomnia, fatigue, stress-related disorders, procedural distress, and chemotherapy induced nausea and vomiting.

Clinical Studies. A survey study indicated that aromatherapy has been used by 31 % of newly diagnosed adult cancer patients in the U.K. [63]. In the U.S., aromatherapy is increasingly utilized as a complementary therapy among childhood cancer survivors who have completed treatment. In one study of 197 pediatric/young adult cancer survivors, approximately 14 % reported utilizing aromatherapy within the past 12 months [14].

Studies have indicated a positive effect of aromatherapy in promoting psychological well-being by reducing anxiety and depression [62, 64]. Specifically, with respect to clinical effects of aromatherapy among cancer patients and survivors, studies have suggested some positive effects of this intervention, such as alleviating pain, constipation, stress, depression, and anxiety [65–69].

In one study, 39 cancer patients were randomly assigned to receive either aromatherapy massage (n = 20) or cognitive behavioral therapy (n = 19) in addition to cancer treatment as usual for up to eight weekly sessions [68]. Cognitive Behavioral Therapy (CBT) is considered to be an efficacious psychotherapeutic intervention for many psychiatric conditions [70]. The authors found that the patients who received aromatherapy massage sought more sessions (mean = 7.2 sessions) than the patients who received cognitive behavioral therapy (mean = 5.4 sessions), suggesting patients' preference for the aromatherapy massage intervention. Additionally, results indicated that aromatherapy massage and CBT were both effective in reducing anxiety and depression over the course of treatment. Another study examined the effectiveness of aromatherapy in stress reduction (i.e., cortisol levels) among cancer patients. In this study, a total of 39 patients, ages 16 and older, who were actively in treatment (i.e., chemotherapy and/or bone marrow transplant) were randomly assigned to receive a 20-minute massage therapy with aromatherapy oil (treatment group 1), massage with regular oil (treatment group 2), or to rest only with no massage (control group). The results indicated that those who received massage with or without aromatherapy oil revealed a significant reduction in

cortisol, as measured through serum cortisol and prolactin levels compared with the group that engaged in resting only [69]. The lack of difference between treatment conditions (massage with and without aromatherapy) suggests that positive changes observed could be due to the massage intervention, rather than aromatherapy.

Other studies failed to show clinical benefits of aromatherapy. For instance, Graham and associates [71] investigated the effectiveness of aromatherapy in the form of inhalation among adult cancer patients in reducing anxiety. In this study, 313 adult cancer patients, ages 33–90 years, who underwent radiotherapy were randomly assigned to receive inhalation of either essential oil (a combination of bergamot, cedar wood, and lavender oil), carrier oil (sweet almond cold-pressed pure vegetable oil), or carrier oil with fractionated oils (low grade and low dosage essential oil) during radiation treatment. The authors found that there were no significant differences in the participants' anxiety level between the treatment (patients who received essential oil) and control (carrier oil and carrier oil with fractionated oils) groups and concluded that aromatherapy was not effective in reducing anxiety among this particular population. The authors indicated that patients may have negatively associated the aromas with radiotherapy, which was already anxiety-provoking for them [71].

Research studies examining the clinical effects of aromatherapy specifically among pediatric cancer patients or survivors are further limited. Ndao and colleagues [72] conducted the first double-blind, placebo-controlled randomized trial among 37 patients in a pediatric population. The patients were all between 5 and 21 years old and were undergoing stem cell infusion. The effects of the aromatherapy were evaluated with respect to anxiety, nausea, and pain reduction. Aromatherapy was administered in the treatment group (n = 17) via inhaling bergamot essential oil (a type of citrus oil believed to improve relaxation and/or anxiety and prevent nausea) during infusion. The control group (n = 20) was assigned to receive inhalation of placebo (a non-essential oil with shampoo scent). Results indicated that the bergamot essential oils were not found to reduce anxiety, nausea, and pain among children and adolescents who were going through stem cell infusion. Moreover, anxiety levels and nausea in the treatment group persisted following the infusion of stem cells, indicating that essential oils may have contributed to extended anxiety among this group. The authors also noted that this study was limited due to small sample size, and suggest further investigation with a larger sample size and additional administration of aromatherapy via massage in order to better understand aromatherapy's potential effectiveness among childhood cancer patients and survivors [72].

Mechanism of Action. Topical application of some aromatic oils may exert antibacterial, anti-inflammatory, and analgesic effects [73]. There are different theories about other mechanisms of action for aromatherapy and essential oils. Studies in animals show sedative and stimulant effects of specific essential oils [74] as well as positive effects on behavior and the immune system in response to painful or stressful stimuli [75, 76]. Supporters of aromatherapy often reference the connection between olfaction and the limbic system in the brain as the basis for the effects of aromatherapy on mood and emotions. The National Cancer Institute's Physician Data Query (NCI PDQ) cancer information summary about aromatherapy and essential oils notes that functional imaging studies in humans do support the influence of odors on the limbic system and its emotional pathways; and that most of the aromatherapy literature does not reference that literature or provide in-depth neurophysiological studies on the nature of that connection [73]. Researchers in animal studies have also found significant plasma levels of the fragrance compounds after inhalation, suggesting that the effects of aromatherapy may result from a direct pharmacological interaction rather than an indirect central nervous system relay [74].

Level of Scientific Efficacy. Suggestive, but not strong. Despite some promising beneficial effects of aromatherapy, the overall results do not provide firm indications for the clinical benefits of aromatherapy, especially when used alone or through inhalation [77]. There is presently a lack of good quality, single-intervention trials. Also, research is limited by lack of standardization in

specific treatments used for different illnesses/symptoms across different providers. Despite some conflicting results of trials, there is some weak evidence of short lasting positive effects from aromatherapy on psychological well-being, depression, anxiety, sleep, overall well-being, symptom relief, and pain control compared to standard care alone in cancer patients. In conclusion, weak evidence suggests that aromatherapy *could* reduce anxiety, depression, sleep problems and improve a patient's general well-being for periods of up to 2 weeks [78].

Potential Risks/Adverse Effects. Minimal adverse effects have been reported for use of essential oils, especially with administration topically and/or by inhalation in appropriate concentrations. However, allergic reactions can occur, especially after topical administration. There have been some reports of contact dermatitis, typically with aromatherapists who have had extended skin exposure to essential oils through massage [79]. There have also been reports of phototoxicity when essential oils are applied to the skin before exposure to the sun, especially citrus oils. In addition, a single case report indicated contact dermatitis was reported from inhaled aromatherapy [80]. Some essential oils (e.g., camphor oil) can cause local irritation; therefore, care should be taken when applying them. Care should be given to the possibility that an individual may have an adverse response as a result of a negative psychological association to particular odor(s). Lavender and tea tree oils may have weak estrogenic and antiandrogenic effects; and they were associated with reversible prepubertal gynecomastia in one study of repeated topical exposure boys [81]. Thus, NCI's PDQ cancer information summary of aromatherapy and essential oils recommends avoiding these two essential oils in patients with estrogen-dependent tumors [73].

Finding a Provider. Several schools throughout the United States offer aromatherapy training and certification, though no license is required to practice. As a result, there is limited consistency in specific treatments utilized across providers. The National Association for Holistic Aromatherapy (NAHA) (www.naha.org/) and the Alliance of International Aromatherapists (www.alliance-aromatherapists.org) are two governing bodies for national educational standards for aromatherapists. NAHA is taking steps toward standardizing aromatherapy certification in the United States. Many schools offer certificate programs approved by NAHA. A list of these schools can be found on the NAHA Web site (www.naha.org/schools_level_one_two.htm). A starting place to find a qualified aromatherapy provider may be to contact one of these organizations or certificate programs for referrals.

28.2.4 Massage Therapy

Background. Massage therapy is a method of manipulating the soft tissue of one's body with techniques such as applying pressure, stroking and rubbing [82], and is known as one of the oldest therapeutic interventions. Swedish massage is the most common type of Western traditional massage therapy and involves stroking and kneading on the superficial layers of muscles. Reflexology is one of the most common methods utilized among Eastern tradition massage therapy, and therapists use their fingers and thumb pressure to stimulate specific points on the feet, hands, or ears, which are believed to be associated with specific body zones, organs, or areas [83, 84]. And as mentioned earlier, massage therapists often use essential oil for medicinal value or as a lubricant [85], and historically, it has been utilized to improve circulation and lymph flow, which in turn induces relaxation and alleviates muscle stress and cramping [86]. Additionally, massage therapy has been used to improve mood while reducing anxiety and stress [87].

Massage therapy is one of the most popular CHA practices. Massage therapy has also been increasingly used as an intervention to relieve symptoms commonly experienced in cancer patients (e.g., stress, anxiety, depression, nausea, pain, fatigue, and/or sleep difficulties). For example, in a survey of 453 adult patients at M.D. Anderson Cancer Center, 26 % reported using massage therapy [88]. In another survey of over 4,139 adult cancer survivors, 10–24 months after diagnosis, 11.2 % percent of the cancer survivors reported utilizing massage therapy [89].

Potential Indications. Decreased pain, anxiety, depression, sleep difficulties, nausea, fatigue and stress; improved quality of life.

Clinical Studies. Overall, massage therapy is typically found to have few adverse effects when conducted by properly trained professionals and when appropriate precautions are utilized. Serious adverse effects are extremely rare. Minor side effects may include temporary pain or discomfort and sensitivity or allergic reaction to oils using during massage [90, 91]. Potential contraindications include burns, skin infections, open wounds, bone fractures, advanced osteoporosis and deep venous thrombosis. Pregnant women should also consult with their health care provider prior to receiving massage therapy. Corbin [90] conducted an academic topic review of safety and efficacy findings for massage therapy specifically with cancer patients. Her findings indicate that while massage is typically safe for cancer patients, this patient population may be at higher risk for rare adverse effects. Thus, oncology patients are advised to consult with their oncologist before massage therapy and to receive services from a massage professional experienced in working with an oncology population. Corbin [90] notes that intense pressure should be avoided by individuals with bleeding disorders, low blood platelet counts, or weakened bones. Direct pressure over a tumor should also generally be avoided.

Several researchers have assessed effectiveness of massage therapy, including reflexology, among cancer patients and survivors [82, 83, 92–97]. However, existing studies of massage therapy have small sample sizes and are not robustly designed, limiting conclusions that can be drawn about efficacy. For example, Listing and colleagues [94] investigated the effectiveness of massage therapy among breast cancer patients in decreasing various symptoms and improving mood. Eighty-six women were randomly assigned to two groups, either receiving massage therapy (n = 50) for 5 weeks, or receiving treatment as usual (n = 36). The results revealed that the intervention group reported significant reduction of their physical discomfort, fatigue, and mood disturbances compared with the control group. Differential sample sizes between the massage and control groups and lack of follow-up measures beyond 6 weeks post treatment limit psychometric value [94].

Another study investigated the effectiveness of reflexology among cancer patients who were going through chemotherapy [97]. Thirty patients were randomly assigned to a 30-minute therapeutic foot massage (n = 15) or no foot massage (n = 15). The authors found that the treatment group reported significant reductions in anxiety (measured by the Spielberger State-Trait Anxiety Inventory [98]) compared with the control group. Factors that may limit generalizability for this study include small sample size, randomization not accounting for patient diagnosis or illness severity, and the lack of long-term follow up measures [97].

Kutner et al. [99] conducted a study with 380 adults with advanced cancer, who were experiencing moderate to severe pain. Ninety-percent of these patients were enrolled in hospice care at the time of the study. The participants were randomized to receive either six 30-minute massage sessions (n = 188) or six simple touch sessions (n = 192) over a 2-week time period. Both groups showed immediate improvement in pain and mood. However, the massage group showed greater improvements in these symptoms. Nonetheless, there were no significant differences between the two groups over time, and both groups showed improvements in quality of life and symptom distress. Study limitations include subject attrition due to death and the lack of a "treatment as usual" control group [99].

In another study, Post-White et al. [100] randomized 230 cancer patients in a crossover design study to three different groups: standardized massage (n = 63), healing touch (n = 56), or presence of a staff member (n = 45) in the room. Each intervention was provided once a week for 45 min over a 4-week time period. All subjects also received 4 weekly sessions of a standard care/control; and the order of conditions (intervention or control) was randomized. All three groups showed physiologic effects (e.g., decreased heart rate and respirations). In the massage therapy group, use of pain and nonsteroidal anti-inflammatory medications decreased. Anxiety levels decreased

in both the massage therapy and healing touch groups. Study attrition was higher in the staff member presence group, as a greater number of subjects dropped out due to not wanting to be in that control group arm of the study. Although this study provides support for the short-term effects of massage therapy and healing touch, limitations include lack of blinding. Also, as the authors note, further study is needed to test the long-term effects and the longevity of specific effects on symptoms [100].

Cassileth and Vickers [101] conducted a large retrospective study of pre- and post-massage symptom scores with 1,290 patients at Memorial Sloan-Kettering Cancer Center. Patients rated symptoms including pain, fatigue, anxiety, nausea and depression on a 0–10 scale. An average 50 % reduction in symptoms was reported after massage, and follow up surveys 48 h later showed continued benefit. For the symptom rated highest pre-massage, improvement was 54 %. The authors note that the effects of massage were smaller and less persistent for inpatients; and that long-term follow up data would be important to determine persistence of benefits [101].

A survey of 191 parents of healthy children, conducted in a primary care medical setting indicated that massage therapy is one of the most popular types of CHA modalities, and was utilized to help promote children's relaxation, stress reduction, sleep, and headaches [102]. In the same survey, parents also reported that they utilized reflexology for their children to treat medical conditions, such as asthma and diarrhea [102]. In a study with preschool children, massage therapy was found to be effective in improving mood and cooperative behaviors in school and home settings [103].

Among children with cancer, massage therapy has shown increased use based on a recent survey, with utilization ranging from 7 to 66 % over the previous decade [104]. According to parents' report in this survey, massage therapy has been employed to reduce various symptoms, such as fatigue, pain, and nausea, as well as improving children's overall quality of life. Field et al. [105] examined the effects of massage on child and parent mood, as well as immune functioning in 20 children diagnosed with acute lymphoblastic leukemia. Children were randomly assigned to either daily 15-minute massage from their parent for 30 days or to a waitlist control group. Child and parent anxiety and mood were assessed before and after the first massage and on the last day of the trial. Massage was associated with reduced negative mood in children and parents, as well as increased white blood cell and neutrophil counts in children from first to last day of the study. This study is limited by the small sample size, which may limit its generalizability [105].

Post-White and colleagues [106] conducted a study with children with cancer, ages 1–18 years undergoing chemotherapy. Twenty-three children/parent dyads were enrolled in the 2-period crossover design study, in which 4 weekly massage sessions alternated with 4 weekly quiet-time control sessions. Massage was more effective than quiet time at reducing the following: heart rate in children, parent anxiety, and anxiety in children less than 14 years old. However, there were no significant reductions in blood pressure, cortisol levels, pain, nausea, or fatigue. Furthermore, a systematic literature review examined the feasibility of incorporating massage therapy for children with cancer, and found that massage is noninvasive and can be applied to cope with various treatment-induced side effects and emotional difficulties linked to cancer treatment [86].

Mechanism of Action. Many studies examining clinical effects of massage have demonstrated increased vagal activity, which has been shown to decrease cortisol and improve immune functioning [56].

Level of Scientific Efficacy. Positive, but weak findings for benefits of massage. In summary, there is a growing literature that massage therapy may provide a wide range of benefits, particularly in a cancer population, such as reduction in pain, nausea, anxiety, depression, stress, and/or fatigue and improving quality of life. However, methodological limitations of existing studies (e.g., small sample sizes, lack of blinded assessment) remain a barrier to definitive conclusions that massage therapy is indeed effective.

Therefore, further investigation with rigorous research methodology is needed. Also, with rising use of pediatric massage therapy, including reflexology among children with cancer, specific massage guidelines will be important, relating to type, location, duration, and pressure level, in order to provide appropriate treatment to this particular population [86].

Potential Risks/Adverse Effects. Classical/Swedish massage administered as a symptomatic treatment has benefits for cancer patients and is generally considered safe. Documentation indicates that contraindications include strong forceful massage in patients suffering from hemorrhagic disorders, low platelet counts, and those taking blood thinning medication.

Finding a Provider. Most states require licensure for massage therapists. Local massage therapy schools can be a source of referrals, as can the American Massage Therapy Association (http://www.amtamassage.org/).

28.2.5 Reiki

Background. Reiki, a Japanese term that signifies *universal life energy*, is a form of natural healing techniques and classified as part of "biofield energy therapy" [107]. Reiki is originally rooted in ancient Tibetan healing arts and was rediscovered and refined by a Japanese master in the early 1900s [108]. Reiki practitioners typically administer Reiki through a gentle laying of their hands on the recipient's body, and it is believed that people have natural ability to heal their body. Therefore, Reiki facilitates the process of "re-balancing" the body's life energy, which in turn enhances physical, emotional, and spiritual well-being [109]. In recent years, Reiki has been utilized to reduce stress while promoting relaxation [110] and generally does not require any particular facilities or equipment; thus, it can be applied in many settings, including the hospital environment. Of the studies conducted examining the efficacy of Reiki, some have demonstrated improved mood, alleviation of pain, and facilitating recovery following surgery [109, 111–113]. However, these studies have limited design methodology, and findings have overall been variable.

Potential Indications. Improving mood, pain, and emotional/spiritual well-being.

Clinical Studies. The effectiveness of Reiki has not been firmly established in use with cancer survivors due to serious methodological limitations, such as small sample size, inadequate study design, and a low quality of reporting [107, 114, 115]. Nevertheless, in a recent survey study among patients who utilized Reiki therapy at a cancer infusion center, over 90 % of the participants reported Reiki as a positive experience, and more than 70 % of them also reported improved mood and relaxation, as well as reduced anxiety [116]. Additionally, Birocco and associates [108] conducted a 3-year study to investigate the role of Reiki in managing anxiety, pain, and overall well-being among 118 cancer survivors. All 118 participants received at least one Reiki treatment, 61 participants received two Reiki treatments, 37 participants received three treatments, and 22 received four Reiki treatments. Results indicated that individuals who completed a total of four Reiki treatments reported significant reduction in their anxiety and pain post-treatment, as well as enhanced quality of life compared to their baseline scores. However, study design limitations prevent generalizability of findings [108].

In contrast, a pilot randomized control trial examined the effectiveness of two types of CHAs among 54 prostate cancer patients undergoing radiation treatment [117]. In this study, the patients were randomly assigned to receive either weekly relaxation response therapy (RRT) plus cognitive restructuring training (CR) (n = 18), twice weekly Reiki (n = 18), or control wait-list (n = 18). Participants completed anxiety, depression and quality of life questionnaires at multiple time points. While the results revealed no statistical significance between RRT plus CR, Reiki therapy, and control group on anxiety, depression, or overall quality of life, the RRT plus CR subjects showed improved scores on the

emotional well-being subscale of the quality of life measure [117].

Mechanism of Action. The basic concepts of Reiki are not consistent with scientific knowledge, and the exact mechanism of action is not well understood.

Level of Scientific Efficacy. There are few published studies of Reiki and most have significant methodological limitations and are not conclusive. Due to the lack of research studies conducted to examine the effectiveness of Reiki, well-designed clinical trials are needed to examine its potential benefits, particularly in the oncology and pediatric populations.

Potential Risks/Adverse Effects. Reiki is not believed to have the potential to cause serious direct harm.

Finding a Provider. The best way to find a qualified provider is to contact the Reiki Membership Association, a non-profit organization that offers training and resources. In addition to specific courses that need to be taken with a Certified Reiki Teacher, members also abide by a code of ethics and professional standards of practice. The directory can be accessed through their website at www.reikimembership.com.

28.2.6 Chiropractic

Background. *Chiropractic* is derived from the Greek words *praxis* and *cheir*, which means to *treat by hand*, and involves various techniques, such as joint adjustment and manipulation with a particular focus on joint subluxation [118]. Chiropractic is typically used to treat and prevent abnormalities of the neuromusculoskeletal system, reduce pain, and promote overall health [119].

Chiropractic is the most commonly sought treatment among CHAs, and estimates of 6-12 % of the U.S. population utilize chiropractic techniques, primarily for back and neck pain [120]. Among children, chiropractic is also the most common CHA modality [121, 122]. In addition to treating the traditional musculoskeletal conditions, parents seek chiropractic care for their children to treat feeding problems, sleep difficulty, ear infections, asthma, headaches, constipation, and a various symptoms of autism [123, 124].

Chiropractic is also popular among adult cancer patients [125], as well as childhood cancer survivors [126]. Montgomery and associates [126] surveyed over 9,000 childhood cancer survivors and found that this population was more likely to utilize chiropractic service (12.4 %) compared with physical therapy (9.2 %). The authors also found that greater severity of late effects (e.g., musculoskeletal, neurological, or cardiovascular conditions) were associated with higher chiropractic utilization.

Potential Indications. In addition to treating the traditional musculoskeletal conditions such as back and neck pain, parents seek chiropractic care for their children to treat a wide variety of concerns, including but not limited to: ear, nose and throat difficulties, digestive problems, headaches, attention problems, asthma, and allergies [127]. In their 2002 Position Statement regarding chiropractic care for children, the Canadian Pediatric Society notes that different philosophies have developed within the profession of chiropractic with regard to whether chiropractic should be considered a nonsurgical musculoskeletal discipline or a broadly based alternative to traditional medicine. They also reference a framework developed by Biggs et al. [128] to help clarify the different approaches to the practice of chiropractic. The conservative chiropractic philosophy emphasizes the scientific validation of chiropractic concepts and methods. In general, chiropractors who adhere to this philosophy have a narrow scope of practice restricted to treating musculoskeletal conditions. The liberal philosophy posits that chiropractic treatment encompasses a broad range of practices beyond the treatment of only musculoskeletal conditions. Results of a 1997 Canadian survey by Biggs et al. [128] found that 19 % of respondents held the conservative viewpoint, 22 % of respondents endorsed the liberal philosophy, and 59 % held "moderate" beliefs somewhere in between these two positions. However

74 % of the chiropractors in the study believed that they should not be limited to treatment of only musculoskeletal conditions. Similarly, a survey of chiropractors in the US showed that most respondents considered chiropractic to be a complete system of healing rather than therapeutic techniques [129].

Clinical Studies. Spinal manipulation therapy (SMT) is one technique practiced by health care professionals such as chiropractors, osteopathic physicians, naturopathic physicians, physical therapists, and some medical doctors. Practitioners perform spinal manipulation by using their hands or a device to apply a controlled force to a joint of the spine. The amount of force applied depends on the form of manipulation used. A 2011 review of 26 randomized controlled trials [130] examined the effectiveness of SMT in adults with chronic low back pain. Results indicated that SMT is as effective as other common interventions (e.g., exercise therapy, standard medical care or physiotherapy) for reducing pain and improving function in adult patients with chronic low-back pain. However, our literature review found few studies of effectiveness of pediatric chiropractic overall, and none with pediatric cancer survivors specifically.

Vaughn et al. [131] conducted a systematic review to evaluate the evidence for SMT interventions in pediatric patients presenting with headaches and/or mechanical spinal pain. In their literature search, they were only able to identify two randomized control trials and two studies with lower levels of evidence that met their search criteria. Furthermore, the authors report that the four studies reviewed were not of adequate quality to either support or refute the use of SMT interventions with the pediatric pain population that was a focus of their study. They emphasize that in order to establish efficacy, well powered studies with strong research design will be necessary [131].

Gleberzon and associates [132] conducted a search of the literature between 2007 and 2011, examining use of SMT for various pediatric health conditions. They identified 16 studies, none of which examined the effectiveness of SMT for spinal pain. Six studies investigated effectiveness of SMT for infantile colic. Two studies evaluated use of SMT on children with asthma. Two studies examined effectiveness of SMT on enuresis. One study each examined effectiveness of SMT for hip extension, otitis media, suboptimal breastfeeding, autism, idiopathic scoliosis, and jet lag. The authors reported that conclusions about efficacy of SMT for these pediatric conditions were not possible, given serious methodological flaws of many of these studies (including small sample sizes, lack of significant follow up periods, and failure to account for confounding variables). Overall, the authors concluded that further research will be necessary to support the use of pediatric SMT, given the poor methodological quality of many existing studies [132].

In their 2010 literature review, Ferrence and Miller [133] report that there is a large literature base describing the response (or lack of response) of various common pediatric conditions to chiropractic care. They also explain that most existing publications are case reports or case series, and thus of lower scientific value. They further note that the more scientifically rigorous studies indicate conflicting results for conditions of colic and crying infants and provide little support for benefits with conditions of otitis media, asthma, nocturnal enuresis, or attention deficit/hyperactivity disorder. They conclude that, "The efficacy of chiropractic care in the treatment of non-musculoskeletal disorders has yet to be definitely proven or disproven, with the burden of proof still resting upon the chiropractic profession." ([133], p. 1)

Mechanism of Action. A central belief of chiropractic care is that diseases are often caused by subluxations of the vertebrae, which lead to an interruption of nervous impulses; and that the correction of these subluxations allows the body to heal itself. In their 1996 consensus statement, The Association of Chiropractic Colleges stated that: "Chiropractic is concerned with the preservation and restoration of health, and focuses particular attention on the subluxation. A subluxation is a complex of functional and/or pathological articular changes that compromise neural integrity and may influence organ system function

and general health" [134]. However, research is still lacking with respect to the theory that musculoskeletal dysfunctions can be implicated and appropriately treated in children with nonmusculoskeletal conditions [135].

Level of Scientific Efficacy. SMT has shown effectiveness for reducing low-back pain in adults. However, to our knowledge, this has not been examined in a pediatric population, or specifically within a population of pediatric cancer survivors. Despite chiropractic popularity and high rate of utilization, the efficacy of chiropractic, especially with a pediatric population and for the range of problems treated with this modality, is not well studied, and existing research suffers from multiple methodological limitations [131–133]. Researchers argue that more rigorous research studies are warranted before drawing conclusions on the efficacy of chiropractic [136]. Furthermore, practitioners should have training in chiropractic with children and specifically pediatric cancer survivors before providing care to this population [137].

Potential Risks/Adverse Effects. Short-term side effects from spinal manipulation are relatively common and can include headaches, tiredness, or discomfort in the parts of the body that were treated. Serious complications such as stroke, cauda equina syndrome, and worsening of herniated discs have been rarely reported. Vohra and associates [138] conducted a comprehensive literature search to identify and summarize available data regarding adverse events that have been linked to pediatric SMT. Thirteen studies (2 randomized trials and 11 observational reports) were included in their review. Fourteen cases of direct adverse events involving neurologic or musculoskeletal events were identified. Of those 14 cases, nine involved serious adverse events such as subarachnoid hemorrhage or paraplegia. Two of the cases involved moderately adverse events that required medical attention (e.g., severe headache). Three cases involved minor adverse events (e.g., midback soreness). In addition to the 14 cases of direct adverse events, another 20 cases of indirect adverse events were indicated. These indirect adverse events involved issues such as delayed diagnosis (e.g., diabetes, neuroblastoma) and/or inappropriate use of SMT for serious medical conditions (i.e., meningitis, rhabdomyosarcoma). The authors conclude that serious adverse events may be associated with pediatric SMT and that multiple risk factors (e.g., immaturity of the spine) may cause children to be more vulnerable to adverse events from SMT [138]. Given the findings from these observational studies, they express particular concern that spontaneous reporting of adverse events (such as through the case studies typical in the current literature on pediatric SMT) is widely recognized to underestimate the risk. They caution that "neither causation nor incidence rates can be inferred from observational data (p. 1)," and emphasize that prospective population-based active surveillance studies will be necessary to appropriately examine the possibility of rare, yet serious, adverse events related to SMT with pediatric patients ([138], p. 1). Vaughn et al. [131] also emphasize that research regarding patient safety of SMT with a pediatric population is critical and cannot be inferred from existing studies. They explain that the current literature of observational data is not sufficient to determine causality and/or frequency of adverse events. Accordingly, there is wide consensus that patient safety should remain an important and ongoing focus of research in pediatric SMT [139, 140]. Of note, Marchand [141] recently developed a scaling model to help guide safety and clinical decisions for SMT with infants and children. This model is based on a literature review of tensile strength in adult compared to pediatric samples, in which the author found tensile strength differences in these groups. Based on these findings, the author has proposed a preliminary model of care that includes maximum loading forces by age group [141].

Finding a Provider. To find a provider, the American Chiropractic Association (ACA) is a resource to identify providers that meet minimum requirements for training and experience. Their website is www.acatoday.org.

28.2.7 Acupuncture/Acupressure

Background. Acupuncture, having originated in China over 2,000 years ago, includes various modalities, such as Japanese acupuncture, French auricular acupuncture, and trigger-point acupuncture [142]. Five-Element acupuncture, or Traditional Chinese Medicine (TCM) acupuncture, is an ancient type of acupuncture and the most well-known form. TCM acupuncture has been practiced as a form of healing by inserting thin needles on particular acupuncture points (*acupoints*) into the skin to provide proper energy (*Qi*) distribution via a complex network channel called "meridians" [143–145]. In traditional Chinese medicine, it has been believed that various issues, such as physical, psychological, spiritual, and emotional challenges, obstruct *Qi*; therefore, acupuncture has been utilized to assess and treat such issues by restoring altered *Qi* [146].

Acupressure is a technique derived from acupuncture, where physical pressure, instead of needles, is applied to *acupoints* by one's hand, elbow, or with various devices to treat disease [147]. Several advantages of acupressure over acupuncture include one's ability to self-administer with little effort and time, low cost, and minimal training [147]. Additionally, some people prefer to use acupressure intervention due to its non-invasive nature [148].

Among the CHAs, acupuncture is the most frequently referred type of intervention and is currently practiced in over 140 hospitals in the United States [149–151]. In general adult populations, various research studies indicate that acupuncture is effective in treating many conditions, including nausea and vomiting [152], anxiety [153, 154], and pain management [155]. Similarly, self-administered acupressure is shown to have positive effects on sleep quality and quantity [148, 156, 157] in chronically ill individuals.

Potential Indications. Reduction of pain, anxiety, insomnia, fatigue, depression, poor appetite, xerostomia, hot flashes, peripheral neuropathy, GI symptoms (constipation and diarrhea), and chemotherapy induced nausea and vomiting. It is also thought to enhance immune functions.

Clinical Studies. In reviewing acupuncture and acupressure treatment among cancer patients and survivors, researchers suggest that, although potential benefit is emerging, firm conclusions are yet to be drawn on its efficacy in treating various cancer-related symptoms [158–160]. That being said, many studies demonstrate promising efficacy of acupuncture on reducing nausea and vomiting, including those induced by chemotherapy and radiation treatment [159–162]. In addition, the effectiveness of acupuncture for treating cancer-related pain has been emerging. Some research, however, has not found discernable benefits of true acupuncture compared to sham acupuncture [163].

For example, Kasymjanova and colleagues [164] examined the effect of acupuncture as a potential intervention choice in 33 cancer patients who received 45-minute acupuncture sessions for at least four times. The study results indicated statistically significant improvement in pain, appetite, nausea, nervousness, and overall well-being. Study limitations of small sample size and lack of a control group limit generalizability. A meta-analysis conducted by Choi and associates [158] observed that the majority of acupuncture treatment, demonstrated positive effects for treating cancer pain. However, they concluded that acupuncture treatment *alone* did not result in improved relief from cancer pain compared with pharmaceutical therapy, although combined acupuncture and pharmaceutical interventions demonstrated improved outcomes [158].

Among pediatric populations, acupuncture has been utilized to treat a wide range of conditions, including nausea and vomiting [165], epilepsy [166], migraine [167], constipation [168], and allergies [169]. However, there are very few empirically supported pediatric studies available to confirm the efficacy of acupuncture for children [159].

In a multicenter, crossover study conducted by Reindl and associates [165], researchers analyzed the effectiveness of acupuncture on nausea and vomiting in nine children, ages 10–16 years, undergoing chemotherapy for solid tumors. The children were randomly assigned to undergo chemotherapy with either antiemetic medication plus acupuncture or antiemetic medication only.

Acupuncture was given on day one of chemotherapy and at subsequent days upon patients' request. Results demonstrated that those individuals who received acupuncture in addition to antiemetic medications, compared to those who receive antiemetic medications alone, experienced higher levels of alertness, as well as reduced nausea and vomiting as measured through their subjective experiences, while undergoing chemotherapy. While this study provides some efficacy of positive outcomes, the small sample size is a significant limitation. Further controlled studies are needed in order to establish the usefulness and effectiveness of acupuncture with children [159].

The effectiveness of *acupressure* with pediatric cancer survivors has not been extensively examined, and limited evidence suggests mixed findings in using acupressure to address nausea and vomiting among children in active treatment [170, 171]. Jones and associates [170] examined the effectiveness of acupressure to prevent chemotherapy-related nausea among 18 children who were also receiving standard antiemetic therapy. The study was a randomized crossover clinical trial in which participants were randomized into one of two treatment sequence groups. The first sequence group (n = 8) consisted of wearing acupressure wrist bands during the first chemotherapy, not wearing wrist bands during the second chemotherapy, and wearing placebo acupressure wrist bands during the third chemotherapy. The second sequence group (n = 10) consisted of wearing placebo wrist bands in the first chemotherapy, followed by not wearing wrist bands in the second chemotherapy, followed by true acupressure wrist bands in the third chemotherapy. Results indicated no significant differences in nausea between their three study conditions: acupressure wrist bands, placebo bands, and no bands. The authors concluded that while there were no adverse effects of wearing the acupressure bands, efficacy was not established. In contrast, Yeh and colleagues [171] studied the effectiveness of acupressure on chemotherapy-related nausea in a pediatric cancer population and found that acupressure significantly reduced the occurrence of nausea and vomiting among children who utilized an acupressure intervention. This study was a crossover randomized study design, and all participants received three courses of chemotherapy. All ten patients received standard care during the first course of chemotherapy. Prior to the second chemotherapy course, participants were randomized into two treatment groups: (1) auricular (outer ear) acupressure intervention (treatment condition), in addition to standard care and (2) auricular acupressure using sham points (control condition) in addition to standard care. For the third course of chemotherapy, the groups were crossed over to the other treatment condition. Results of the study indicated lower occurrence of both acute and delayed nausea and shorter duration of vomiting in the intervention condition compared to either the control condition or the standard of care condition across time. Though this study shows a strong study design, small sample size is a limitation [171].

Mechanism of Action. Traditional Chinese Medicine (TCM) theory posits that Qi can be unblocked by using acupuncture at certain places on the skin, called *acupoints*. These acupoints are places where meridians come to the surface of the body; with humans having more than 360 acupoints that correspond to conditions being treated. However, traditional TCM theory is not supported by scientific evidence, and it is challenged by research showing lack of differences between true and sham acupuncture. For example, Moffet [163] conducted a systematic review of 38 studies from 2005 to 2006 comparing acupuncture with needle insertion at clinical sites versus acupuncture with needle insertion at wrong points or at non-points, and comparing normal needle insertion and stimulation versus superficial insertion or minimal stimulation. The author found that most studies (22 out of 38) found no statistically significant differences in outcomes. Most (13 out of 22) found that sham acupuncture was as effective as true acupuncture, especially when superficial needling was applied to non-points [163].

Other theories being researched to explain acupuncture's mechanisms of action include neurophysiological theories such as a gate-control mechanism, and effects on neurotransmitters like endorphins [172]. Furthermore, an NIH

Consensus Panel concluded that acupuncture can cause multiple local and distal biological responses, acting on the sensory neurons within the central nervous system (CNS), and the autonomic nervous system, thereby balancing the sympathetic and parasympathetic systems. Acupuncture is also thought to regulate blood flow and activate the pituitary gland and hypothalamus, which can produce a cascade of systemic reactions, including changes in hormones, peptides, and neurotransmitters [173], and electrophysiological effects on cytokines and neuropeptides [174–176]. There may be an analgesic effect through the release of opioid peptides [177, 178]. Furthermore, animal studies have demonstrated increased immune functions by enhancing natural killer (NK) cell and lymphocyte activity [179–181], and may be beneficial in reducing chemotherapy-induced emesis [182].

Level of Scientific Efficacy. Suggestive, but not strong. The strongest efficacy for acupuncture has been shown with reducing chemotherapy-induced nausea and vomiting. Many of the studies examining this have been randomized and well-controlled. In contrast, while acupuncture is most commonly used for pain relief, there are few studies on cancer pain that are well-controlled or have adequate sample sizes. Further, there are many other clinical acupuncture studies in the literature supporting the benefits of acupuncture for treating a variety of symptoms. However, most have been case studies or limited by significant methodological flaws. Controversy about the most appropriate control for acupuncture limits the ability to draw conclusions from clinical trials.

Despite limited evidence available for both acupuncture and acupressure treatment with pediatric cancer survivors, the current surveys yield feasibility and acceptability data for pediatric for populations. For example, Kemper and colleagues [183] interviewed 47 children who were seeing a pediatric acupuncturist and found that the majority of children (67 %) rated acupuncture treatment positively in helping manage their pain. Clearly, more controlled study of the efficacy of acupuncture and acupressure is needed to determine the usefulness with pediatric cancer survivors, both during treatment for the cancer and for the medical late effects after treatment.

Potential Risks/Adverse Effects. Mild adverse effects (e.g., pain or bleeding at the site of acupuncture, tiredness or pain) have been reported in both adults and children, but can be minimized by appropriate management [184–187]. Serious complications, such as pneumothorax, are very rare. Also, there have been very few infection reports since 1988, when disposable needle use became widespread and national certification requirements were developed for clean-needle techniques [188]. However, given the immunocompromised condition of cancer patients undergoing chemotherapy or radiation therapy, it is important to take precautions and strictly adhere to sterile-needle techniques when acupuncture treatment is given [189]. Potential relative contraindications for acupuncture include bleeding abnormalities, infections, edema, epilepsy, pregnancy, and needle phobia [190].

One of the major concerns about utilizing acupuncture, particularly among cancer patients, has been the occurrence of thrombocytopenia, a side effect of chemotherapy, which is related to a heightened risk of prolonged bleeding. Ladas and associates [186] examined this risk in a study of thirty-two children who received acupuncture treatment for various reasons (e.g., gastrointestinal symptoms, neurologic symptoms, and pain management), with almost half of them (47 %) diagnosed with mild, moderate, or severe thrombocytopenia. During treatment, there were no reported acute side effects, and the researchers concluded that acupuncture can be safely administered to pediatric cancer patients, including children with thrombocytopenia, without an increased rate of bleeding or negative effects [186].

Finding a Provider. Most, but not all, states in the United States have laws regulating the practice of acupuncture. The National Certification Commission for Acupuncture and Oriental Medicine (NCCAOM) offers national certification examinations for practitioners of acupuncture and traditional Chinese medicine (www.nccaom.org). Most, but not all, states require this certification.

The NCCAOM website noted above has a resource to help identify appropriately trained providers. Some insurance companies provide coverage for acupuncture treatment. However, federal insurance programs (e.g., Medicare) generally do not.

28.2.8 Mindfulness and Meditation

Background. *Mindfulness* is an Eastern concept derived from a Buddhist spiritual tradition [191]. In particular, Kabat-Zinn [191] further defines mindfulness as a way of developing one's ability to pay attention and observe in the present moment without judgment. Wallace, Benson, and Wilson [192] define meditation as a state of being awake, yet relaxed, alert, and focused. According to Segen [193], mindfulness has been referred to as a "Zen-like" approach to meditation, in which one focuses on the activity or event occurring in the moment, which is different from traditional meditation, in which the purpose is to free the mind of all thought. Nonetheless, the words mindfulness and meditation are utilized interchangeably in research settings [194, 195].

Historically, within the Buddhist religion, mindfulness has been an essential component to achieve enlightenment and is attained through meditation practice [196]. In modern Western psychology and behavioral medicine settings, mindfulness meditation is taught and applied to potentially change one's perception and behavior patterns by deliberately observing and describing experiences nonjudgmentally in the present moment [197].

Over the past 30 years, various patient populations have utilized the Buddhist concept of mindfulness-based treatments [198]. Initially, patients with chronic physical and psychological conditions had begun utilizing such interventions, but later these treatments appealed to wider, non-clinical populations [199]. In clinical settings, mindfulness practice has been used to treat various physical and emotional conditions, such as chronic pain, depression, and anxiety [196].

Mindfulness is typically gained through formal meditation practices, including sitting meditation, walking meditation, and/or mindful movements [191]. Researchers have found several positive effects of mindfulness meditation on both physical and psychological well-being, including decreased heart rate [200], lowered blood pressure [201], improved sleep [202], reducing pain level [203], and decreasing mood disturbances, such as anxiety and depression [204–207]. Estimates of between 8.4 and 41 % of breast cancer survivors have utilized relaxation/meditation techniques [208].

Among several methods to cultivate mindfulness, the Mindfulness-Based Stress Reduction (MBSR) program is the most commonly utilized training model in clinical setting [209]. MBSR, originally developed by Kabat-Zinn and colleagues in 1979, is a structured, group formatted, psycho-educational, and skill-based experiential program that patients attend once a week for an average of 2½ h for 8–10 weeks. The program is comprised of mindfulness meditation, also known as *Vipassana*, which includes the body scan, mindfulness of breath and other sensory experiences. Additionally, the program includes Hatha yoga exercises, designed to develop mindfulness during movement, along with an additional full day intensive "silent meditation retreat" [191]. MBSR has been prevalent and has been one of the most common interventions used by cancer patients and survivors [210].

Potential Indications. Reduced anxiety, pain, depression, stress, and insomnia. Enhanced immune functioning and overall wellness.

Clinical Studies. MBSR may be a useful program for promoting physiological and psychological health and well-being for adult cancer patients and survivors [209, 211–214]. For example, Lengacher and associates [210] investigated the effects of MBSR program on symptom severity among 82 breast cancer survivors and found that, after the 6-week post-intervention, the women who received MBSR treatment (n = 41), compared to the wait-list control group (n = 43), showed statistically significant reduction in fatigue and disturbed sleep. Similarly, researchers examined the feasibility of an 8-week MBSR program on a group of 19 breast cancer

survivors' emotional well-being, physical health, and quality of life. Findings with the 17 women who completed the program indicated significant improvements on fear of recurrence, perceived stress, anxiety, depression, and overall quality of life upon completing MBSR participation [210]. However, study limitations include small sample size, lack of a control group, and lack of extended follow-up evaluation for participants. Likewise, Matchim and associates [215] examined the effects of an 8-week MBSR program on physiological and psychological well-being among 36 early-stage breast cancer survivors, and the intervention group (n = 19) exhibited statistically significant improvement in reduced blood pressure, heart rate, and respiratory rate as well as increased mindfulness state, compared to the control group (n = 17) who did not receive MBSR intervention. The authors also found that participants exhibited overall improvements in their psychological well-being with improved mood. Study limitations include small sample size and lack of randomization [215].

Despite the promising effectiveness of MBSR on adult cancer patients and survivors' physical and psychological health, little is known about its effect on pediatric cancer patients and survivors, and to our knowledge, there is no available literature on MBSR treatment in pediatric cancer patients or survivors [126]. Nonetheless, some researchers have examined the effects of *mindfulness* on children's overall well-being [217–219]. Huppert and Johnson [217] examined 155 adolescent male students' mindfulness, resilience, and emotional health through mindfulness training. They were randomly assigned to receive either four 40-minute mindfulness classes (once per week) or to receive regular religious studies lessons. Participants completed questionnaires before and after the 4-week intervention period, measuring mindful awareness, resilience, and well-being. While this study did not indicate a statistically significant difference between the mindfulness training group and the control group on any of these measures, the participants in the mindfulness training group demonstrated a positive association between frequency of practice outside the classroom and improvement in emotional well-being and mindfulness. The authors also found that improvement in the students' emotional well-being was mediated by personality variables, such as agreeableness and emotional stability. Another study evaluated the effects of a school-based program called Mindful Awareness Practices (MAPs) on executive function among children between the ages of 7 and 9 [218]. The MAPs program consisted of 30 min of mindfulness activities twice per week, for 8 weeks. Sixty-four children were randomized into either the MAPs intervention (n = 32) or a control group (n = 32) consisting of silent reading periods. Children who received the MAPs program exhibited greater improvement in executive functioning compared with the control group. In particular, those children demonstrated improvements in behavioral regulation, metacognition, and overall global executive control [218].

For children, Thompson and Gauntlett-Gilbert [195] suggest modifying mindfulness to correspond with different developmental stages and age ranges. For instance, compared to adult populations, adolescents require more explanation and rationale in order for them to fully engage, and benefit from shorter practice times compared to the typical 20–45 min typically utilized by adults. Finally, it is important to involve parents and caregivers when teaching mindfulness to children and youth. The overall impression of the MBSR studies is very promising for the powerful benefits among cancer survivors; therefore, researchers believe that the program may also be beneficial for childhood pediatric cancer survivors as well [216].

Mechanism of Action. Moenaert and Sieh [220] note that while research regarding the psycho-neuro-immunology effects of mindfulness-based interventions is still in its early stages, mindfulness meditation is believed to help regulate emotions, leading to a decreased sympathetic nervous system activity and reduced stress hormone levels. Field [56] describes how mindfulness research has shown that meditation practices are associated with changes in resting electroencephalography (EEG) patterns and suggests long-lasting changes in brain activity. Also, research utilizing MRI to

examine differences in physical brain structure has shown increased cortical thickness in subjects with extensive meditation practice compared to matched controls. These differences in cortical thickness were observed in brain regions associated with attention and sensory processing (prefrontal cortex and anterior insula) [221].

Level of Scientific Efficacy. Some evidence of efficacy. A 2007 NCCAM-funded review of the scientific literature found some evidence suggesting that meditation is associated with potentially beneficial health effects. However, the overall evidence was inconclusive. The reviewers concluded that future research needs to be more rigorous before firm conclusions can be drawn [222]. In a more recent systematic review and meta-analysis [203], mindfulness meditation programs with various adult clinical populations in improving stress-related outcomes, including anxiety, depression, stress/distress, positive mood, mental health-related quality of life, attention, substance use, eating habits, sleep, pain, and weight were evaluated. This review identified 47 randomized clinical trials with active controls. The authors found moderate evidence of improved anxiety (effect size, 0.38 at 8 weeks and 0.22 at 3–6 months), depression (0.30 at 8 weeks and 0.23 at 3–6 months), and pain (0.33). The authors found low evidence of improved stress/distress and mental health-related quality of life. Their findings did not suggest effects of meditation programs on positive mood, attention, substance use, eating habits, sleep and weight. Further, there was no evidence that the meditation programs were more effective than other interventions utilized in the various studies, including exercise, cognitive behavioral therapy, or medication [203].

Potential Risks/Adverse Effects. As noted in the CAM-Cancer Consortium review of Mindfulness interventions, mindfulness-based clinical interventions are generally considered to be safe. Adverse effects are rare, though there are some concerns that meditation could cause or worsen symptoms in people who have certain psychiatric problems, though this question has not been fully researched [222].

Finding a Provider. Training for mindfulness based interventions is not standardized. However, various training institutions have made recommendations for training hours and clinical experience with meditation. These recommendations vary widely. One easily accessible and helpful internet resource for both professionals and children and their families is www.InnerKids.org.

28.2.9 Yoga

Background. The word *Yoga*, a mind-body practice that originated in India, is derived from the Sanskrit root *Yuj*, which means to harness or yoke [223]. As such, the purpose of yoga was originally established to integrate body, mind, and spirit to lead to self-realization or the authentic self [223]. There are over 40 different styles of yoga based on different approaches and techniques of training, and common elements of yoga include postures (asanas), breathing (pranayama), and meditation [224]. In particular, breath plays an important role in yoga as it is intricately related with the mind. Therefore, it is believed that adjusting the breath to a slow pace would slow and calm the mind.

Historically, the *asanas* are aimed to help both physically and psychologically, with benefits such as improved endocrine system, gastrointestinal functioning, attention, and mood [223]. The modern practice of yoga is widely used for the benefit of fitness, stress management, and other mental health concerns [225]. Its growth has facilitated yoga's inclusion with alternative medicine in health care settings [224].

Utilization of yoga among cancer patients and survivors varies from 1.2 to 33.9 % [226]. For example, according to a nationally representative study in the United States, the National Health Interview Survey (NHIS) in 2007, 9.8 % of male and 9.9 % female cancer survivors reported having used yoga in the past year [227]. Moreover, an analysis of over 2,500 breast cancer survivors in the Women's Healthy Eating and Living Study revealed that 33.9 % of the women reported having used yoga in the past [228]. More specifically, Park and associates [226] examined the use of yoga

among 286 young adult cancer survivors. They found that 33 % of reported practicing yoga since their initial diagnosis, mostly to maintain physiological flexibility and promote relaxation, and they tended to practice yoga more than seven times per month and over 26 months of duration.

Potential Indications. Reduction of pain, anxiety, depression, stress, fatigue, hot flashes, insomnia (and need for sleep medications), PTSD. Improved flexibility, body balance, and feelings of both well-being and sense of control.

Clinical Studies. Yoga seems to help improve physical and psychological health among adult cancer patients and survivors [229–232]. For example, Vadiraja and associates [233] examined the effects of an integrated yoga program among 88 stage II and III breast cancer patients. Compared with the control group (n = 44) who received brief supportive therapy consisting of three to four 15-minute education sessions for 6 weeks, the yoga group (n = 44) received three yoga sessions per week for 6 weeks and yielded significant decreases in anxiety, depression, perceived stress, as well as salivary cortisol compared to those in the brief supportive therapy group. Similarly, Banasik and associates [234] conducted a study with 18 participants randomly assigned to two groups, one in which participants attended a 90-minute yoga practice session twice weekly for 8 weeks, and the remaining participants (n=10) were placed in a waitlist control group. The women in the treatment condition showed lower salivary cortisol levels and reported improved psychological health and fatigue scores compared to the waitlist control group. The researchers concluded that yoga may have a positive impact on psychological stress and circadian patterns of stress hormones in breast cancer patients. Limitations of small sample size and the relatively homogenous sample of Caucasian women with breast cancer limits generalizability. Additionally, Cohen and colleagues [235] explored the effects of a Tibetan yoga on sleep quality among 38 lymphoma survivors. The study result revealed that the yoga group (n = 19) reported significantly lower sleep disturbance upon completing the 7-week yoga sessions, such as better sleep quality, longer sleep duration, and less use of sleep medications compared with the waitlist control group (n = 19). Limitations include the small sample size, relying on only self-report, and potential for confounding variables (e.g., social support, attention, relaxation, or stretching).

Among pediatric populations, researchers have found that more than 1.5 million children in the United States used yoga in 2007 [4]. The focus of yoga among children is more on the cultivation of compassion, non-judgment, connection between breath and postures, and enhancing the foundations of a life-long practice [224]. Generally, the effects of yoga in healthy children and children with a cancer history remain inconclusive due to small sample sizes, inconsistent intervention description and outcomes, and low statistical power [224, 236]. Despite the lack of high quality studies of yoga in children, evidence suggests that yoga is linked to enhanced cardiovascular condition, physical functioning, and behavior [237]. A meta-analysis with 34 studies on the effects of yoga among children reports that children who participated in yoga treatment had improved cardiovascular fitness, increased lean body mass, lower blood pressure and heart rate, refined balance, fine motor skills, and hand grip strength [236]. Results of the meta-analysis further indicated a variety of emotional benefits in the groups of children that received yoga interventions, including improved mood, reduced stress, anxiety, and negative emotions, and decreased tension, anger, and fatigue. However, the authors caution that these findings should be considered preliminary, as many of the studies they reviewed were of low methodological quality (e.g., unclear description of randomized methods, withdrawal/dropouts, limited details of the yoga interventions utilized).

Specific to pediatric cancer survivors, Thygeson and colleagues [238] conducted a study examining the effects of yoga among children and adolescents with a cancer diagnosis and their parents. Eleven children (6–12 years of age), five adolescents (13–18 years of age), and 33 parents completed a yoga session. The researchers found that, upon completing the yoga session, the

adolescents and parent groups reported significantly decreased anxiety and improved sense of well-being. The child group did not report elevated anxiety at baseline; and this was maintained after the yoga intervention. Moreover, all participants reported positive feedback about the yoga experience. The authors concluded that yoga is a feasible adjunct treatment option for pediatric cancer patients and is beneficial particularly to adolescents and their parents. Limitations of this study include small sample size, lack of randomization and blinded study design, in addition to potential confounding variables [238].

Separately, Geyer and colleagues [239] conducted a feasibility study regarding the effects of yoga on quality of life in a sample of hospitalized pediatric oncology patients. Six children participated in five yoga sessions over a period of 2 months. A quality of life measure was administered to the children and their parents, both at baseline and after completing the yoga intervention. Results on this quality of life measure indicated statistically significant differences in children's perception of their gross motor function subsequent to the yoga intervention. The major limitation of this study was the small sample size.

Mechanism of Action. Research suggests that yoga increases vagal activity [240] and reduces cortisol levels [234]. In addition, postures of yoga are believed to improve body self-awareness, helping an individual to identify problematic symptoms and also to increase their knowledge about conditions in which they experience balance and calm [241]. Some studies have shown that the meditation component of yoga increases blood flow to the brain, releases endogenous dopamine, and reduces respiratory rate [242]. Neuroplastic mechanisms may be related to the therapeutic mechanisms of yoga in depression, including elevated serum brain-derived neurotropic factor (BDNF) levels [243]. Yoga may also be helpful in reducing depression and anxiety due to increase in brain GABA levels. Specifically, in one study, experienced yoga practitioners have shown increases in brain GABA levels after a 60-minute session of yoga, compared with control group of a 60-minutes reading condition [244]. It has been theorized that improvements in fatigue, sleep disturbance, anxiety, and quality of life may be related to increased parasympathetic and decreased sympathetic activities, stimulation of the vagus nerve, and reduction in allostatic load. These changes are believed to improve homeostasis in stress response systems [245], and replacing the flight-or-fight response with the relaxation response [246].

A recent study by Villemure and associates [247] demonstrated that regular and long-term practice of yoga may improve pain tolerance via practitioners utilizing specific cognitive tools to deal with sensory inputs and associated emotional reactions. Increased gray matter observed in the yoga practitioners (compared to matched controls) suggests that these differences in coping strategies may lead to structural changes in brain anatomy and connectivity [247].

Level of Scientific Efficacy. Suggestive, but not strong. Small clinical trial research with breast cancer survivors suggests small, short-term positive effects on quality of life and well-being. There are mixed and/or non-significant findings for effects on fatigue, physical function, psychological health, and sleep. Most yoga studies lack a manualized intervention where poses for the study are shown so the study could be replicated, even with individualized adjustments based on participant's needs during the sessions [248]. Additional studies should include mechanisms and outcomes [249].

However, for pediatric cancer survivors, regular yoga practice may be a low-risk, cost-effective method to enhance physical and psychosocial functioning. This may, in turn, serve as a foundation for the nurturing of inner resources and strengths to facilitate lifelong health and well-being after cancer treatment.

Potential Risks/Adverse Effects. Yoga has few adverse effects and is generally considered safe when practiced appropriately under the guidance of a well-trained instructor. Single case reports suggest serious adverse events are rare but possible, especially when certain yoga practices are used too aggressively. Some types of Yoga

require special safety consideration. For example, Bikram yoga's use of high temperatures may be contraindicated for some individuals; advanced Iyengar classes may have poses that are too difficult for beginners [56]. Caution, including avoidance of specific postures such as inverted postures, has been suggested in pregnancy and in individuals with hypertension or glaucoma. It has also been suggested that breathing exercises, particularly if vigorous, could potentially exacerbate asthma and other respiratory problems, and are contraindicated in pregnancy. Individuals with sciatica may need to modify or avoid certain yoga poses.

Finding a Provider. Cancer survivors interested in beginning yoga should first consult their physicians. In addition, it is recommended that this population learn proper yoga techniques from certified instructors who have experience working with cancer survivors, as they may require special precautions due to their individual health/treatment history.

Many yoga instructor training programs exist, with a wide range of training required—from days to years. The International Association of Yoga Therapists (www.iayt.org) is developing standards for yoga therapy training. The Yoga Alliance (www.yogaalliance.org) is one nonprofit group that represents the yoga community and provides a directory of trained professional teachers and teacher-training programs. While there are many different types of yoga, Hatha yoga and specifically Iyengar yoga require extensive training and certification processes for instructors and can be extremely helpful for stretching, relaxation, body balance, and feelings of increased control.

28.2.10 Music Therapy

Background. Music therapy is one of the most common types of creative CHAs. It is described as the clinical use of music to enhance an individual's physical, psychological, and social needs [250, 251]. Through music therapy, individuals are exposed to listening to music, playing musical instruments, and/or composing music, which are believed to help them address their emotional state, cognitive processing, pain management, communication, and socialization with others [252, 253].

Potential Indications. Decreased pain, anxiety, depression, and stress. Improved mood, sense of well-being, emotional expression, memory, communication, and physical rehabilitation

Clinical Studies. Among adult cancer patients, music therapy has been shown to have positive physical and psychological effects, particularly reducing pain, anxiety, and distress [253–258]. For instance, Shabanoei and colleagues [257] examined the effectiveness of music therapy in reducing pain and anxiety among 100 adult patients who were undergoing bone marrow biopsy. The participants were randomly assigned to a music therapy intervention group (n = 50) or a control group who did not receive music therapy. The authors found that after receiving 30 min of music therapy, 42 % of the treatment group reported 50 % relief from pain and anxiety compared with 8 % of the control group experiencing the same relief. Additionally, Li and associates [255] examined the effectiveness of music therapy on pain reduction among 120 adult patients with breast cancer upon the completion of mastectomy. The patients were randomly assigned to either the treatment group (n = 60), involving music therapy from the day after mastectomy to the third admission to hospital for chemotherapy, or the control group (n = 60), involving only routine nursing care. The study results indicated greater pain relief in the treatment group, compared to the control group, suggesting the benefit of music therapy to those patients. One major limitation for this study is that lack of randomization. Increased natural killer cell number activity has also been found in some studies following music therapy intervention [259, 260]. Other studies have shown reductions in heart rate, blood pressure, breathing rate, insomnia, depression, and anxiety with music therapy [261].

However, some researchers point out that research results are inconsistent [253, 258, 262]. A study compared the effectiveness of music

therapy and simple distractions (e.g., listening to a tape-recorded book) on pain and anxiety reduction among 58 adult cancer survivors. The results demonstrated that there was no significant difference in the level of pain and anxiety reduction among the patients who received music therapy (n = 24), simple distraction (n = 14), or treatment as usual (n = 20). The researchers concluded that the patients might have individual preferences to cope with their pain and anxiety; therefore, inquiring about the patients' preferred method for coping is warranted [262]. Limitations of the study include small sample size and potential confounding variables due to the frequency and timing of assessment. Specifically, the baseline assessment was taken 5–15 min before the physician arrived at the procedure room, and the follow up was measured after the procedure. Thus, baseline anxiety could have been due to anxiety related to anticipation of the physician visit, resolving after that visit was complete.

Within pediatric populations, findings regarding the effectiveness of music therapy have been similar to those of adult populations [263, 264]. For instance, exposure to live music has been shown to deliver positive outcomes among pediatric populations [265, 266]. Longhi and Pickett [265] explored the physiological effects of live music among children who had experienced a long-term hospitalization. In this study, 21 children, aged 3 months to 14 years, received music therapy for 30 min, while heart rate and oxygen saturation level were measured pre- and post-music therapy. The authors found that although heart rate remained unchanged, oxygen levels increased significantly post-therapy. Limitations include small sample size and lack of control group [265].

Among a pediatric cancer population, Barrera et al. [267] conducted an uncontrolled pilot study examining the effectiveness of a 15- to 45-minute therapy sessions with an accredited music therapist among 65 pediatric oncology inpatients. Outcome measure included the faces pain scale completed pre- and post-intervention sessions by children at least 3 years of age or by parents of younger children. Pain improved according to child and parent report. Barry and associates [263] examined the efficacy of utilizing music therapy to reduce distress among children with cancer. Eleven pediatric cancer patients, aged 6–13 years, were randomly assigned to either creating a music CD before their radiation therapy and listening to the CD during the treatment, or receiving standard care. Measures included both a questionnaire completed by the children and interviews with the patients. The authors found that 67 % of the standard care control group reported social withdrawal as their primary coping strategy, while none of the children in the music therapy treatment group reported engaging in social withdrawal. Rather, 80 % of the music therapy group utilized distraction or wishful thinking. The authors concluded that the music intervention provided both interpersonal benefits (e.g., psychosocial support between the children and others) and intrapersonal benefits (e.g., report of having fun and ability to distract themselves, greater sense of empowerment). Small sample size is a limitation for this study. Another study examined the effectiveness of music therapy in reducing pain and anxiety among pediatric patients who were undergoing lumbar punctures. Forty children, ages 7–12 years, were randomly assigned to either a music therapy group (n = 20) who listened to music or a control group (n = 20) who wore earphones without music before lumbar punctures. Data were collected through recording heart rate, blood pressure, and oxygen saturation, as well as self report from personal interviews and completion of an anxiety inventory. Study results revealed that the children in the music therapy treatment group reported significantly reduced pain and anxiety levels compared with the controls [264]. The limitation of the study includes lack of validation for the use of the anxiety inventory in children. Also, the authors note that the children found the earphones uncomfortable, which may have the outcome. Further, the control group was recruited with the knowledge that they may receive music therapy, but was randomized to the control group, which may have led to a sense of disappointment.

Mechanism of Action. Research on the effects of music therapy has shown reductions in heart rate, blood pressure, breathing rate, insomnia, depres-

sion, and anxiety [261]. Increased natural killer cell number activity has also been found in some studies following music therapy intervention [259, 260].

Level of Scientific Efficacy. Positive, but limited findings. Initial research suggests that music therapy may be helpful by way of supportive care to adult and pediatric patients, including cancer survivors. However, evidence is not strong, and there is much variability between trials with respect to the way in which music therapy is provided, limiting generalizability. More rigorous research methodology and larger sample sizes will be beneficial to clarify the effectiveness of music therapy.

Potential Risks/Adverse Effects. No safety issues have been reported. In general, music therapy done under the care of a professionally trained therapist may be beneficial in improving mood, comfort and sense of well-being. However, musical intervention by untrained providers could be ineffective or even cause increased stress and discomfort.

Finding a Provider. More than 70 colleges and universities in the U.S. have degree programs that are approved by the American Music Therapy Association (AMTA). A separate, independent organization, known as the Certification Board for Music Therapists (CBMT), certifies music therapists. Music therapists are required to have a bachelor's degree, 1,200 h of clinical training, and one or more internships to become certified. The AMTA website provides assistance in locating qualified music therapists (www.musictherapy.org).

28.2.11 Art Therapy

Background. Art therapy is another type of CHA and is referred to as an intervention to heal and promote one's physical and emotional well-being [268]. Art therapy involves creative processing, which is believed to facilitate one's awareness and expressions that may be difficult to do so otherwise [269]. For both adult and pediatric cancer patients, art therapy is believed to address emotional needs and improve coping with various symptoms [270–272]. As a result, utilization of art therapy is a growing component of cancer treatment and rehabilitation. Cancer patients often utilize creative art during individual sessions as well as support groups [268, 269, 273].

Potential Indications. General coping and emotional expression, anxiety, and depression.

Clinical Studies. Despite its growing popularity, the effectiveness of art therapy among cancer patients and survivors has not been widely studied. Among adult cancer patients, Nainis and associates [274] investigated whether art therapy is effective in reducing pain and other cancer related symptoms in a sample of 50 adult cancer patients. The participants' level of pain and anxiety, as well as subjective experiences, were assessed before and after art therapy. The authors found statistically significant symptom reduction among the participants, including pain, fatigue, depression, anxiety, and breathlessness, and found an overall increase in sense of well-being. Limitations include no control group or randomization, suggesting that other variables may have contributed to the outcome. In addition, there was no long term follow up with participants to evaluate sustainability of benefits from the intervention [274].

A more recent study examined the effectiveness of art therapy on quality of life among adult breast cancer patients [275]. In this study, 41 women with a breast cancer diagnosis were randomly assigned to either receiving a total of five art therapy sessions once per week (n = 20) or treatment as usual (n = 21). The participants were asked to complete questionnaires measuring coping, quality of life, and other symptoms prior to treatment, 2- and 6-months post treatment. Findings from this study indicated that the art therapy group reported significant improvement in their overall quality of life and general health by the third session compared with the controls, and the gains were maintained at 6 months post treatment. Limitations include small sample size, lack of blinding and lack of an active control group to account for potential confounding variables (e.g., social support, attention) [275].

Art therapy is believed to promote children's growth and development among pediatric populations [270, 272, 276, 277], and is widely used in therapeutic settings. However, studies examining the effectiveness of art therapy among pediatric cancer populations are limited. In a study examining the effectiveness of art therapy in reducing anxiety and fear among pediatric cancer patients, 32 children aged 2–14 years received art therapy before, during, and after painful procedures. Results indicated that children who received art therapy exhibited increased cooperative behavior and decreased anxiety, measured through behavioral observation, compared to a control group consisting of 17 children who did not receive art therapy [271]. Limitations include small sample size and design issues such as lack of standardized assessment or randomization and use of an historical sample for comparison group. Packman and associates [278] examined the effectiveness of art therapy on overall coping among siblings of children with cancer diagnosis. A total of 77 children aged 6–17 years along with their parents participated in the study, 18 of whom lost their siblings to cancer. These children were asked to complete several measures, such as the Human Figure Drawing (HFD) and the Kinetic Family Drawing—Revised (KFD-R). The study results indicated overall improvement in family environment upon receiving art therapy, although the results were significant only among children who had not lost their siblings to cancer. Limitations of this study include lack of a control group, objective assessment, and no long term follow up [278].

Potential Mechanism of Action. There is no current knowledge of the mechanisms of action in patients.

Level of Scientific Efficacy. Positive, but limited findings. The research findings thus far have been promising and demonstrate positive outcomes of art therapy among pediatric cancer patients, but more rigorous research methodology and large sample size will be necessary to more clearly determine its effectiveness.

Potential Risks/Adverse Effects. Art therapy is considered safe when provided by a skilled therapist. Although uncomfortable feelings may be raised through the course of art therapy, this is considered part of the healing process.

Finding a Provider. Providers can be found through the American Art Therapy Association (www.arttherapy.org). Many art therapists are licensed mental health professionals as well.

28.2.12 Animal Facilitated/ Pet Therapy

Background. Animal facilitated therapy (AFT), also known as *pet therapy*, is a type of CHA intervention and involves a trained animal and handler working with patients on specified therapeutic goals [279, 280]. AFT usually includes (1) animal-assisted activity, such as animal visitation to enhance rapport and communication, and (2) animal-assisted therapy, in which animals facilitate patients to achieve certain therapeutic goals such as balancing and/or throwing balls [281]. AFT has been widely accepted in hospitals in the U.S., and currently over 600 hospitals incorporate AFT into their practice [282].

Potential Indications. Reduction of distress, pain, depression, and anxiety; improving coping through distraction and positive focusing.

Clinical Studies. Among adult populations, including cancer patients, AFT has been shown to reduce distress, pain, depression, and anxiety while facilitating positive coping processes, such as distraction and focusing on the positive [283–285]; however, results have not been consistent. In a study examining the effects of brief dog visitation on pain management among adult outpatients, a total of 235 patients were introduced to spend time with the dog while they were in the waiting room over a 2-month period [286]. The researchers found that the patients who received dog visitations reported significant pain reduction as measured through a self-reported pain rating scale. The study limitation includes lack of control group. In another study, the effects of animal-assisted activity on cancer patients' mood and self-reported health were assessed, and

30 adult patients undergoing radiation therapy were randomly assigned to either 12 dog visitations (n = 10), 12 human visitations (n = 10), or 12 quiet reading sessions (n = 10) during a 4-week period [287]. While the authors found no statistical difference on participants' mood, the treatment group who received dog visitations reported an improvement in self-perception of positive health. Limitations of this study include small sample size and the lack of assessment of potentially confounding variables, including disease status and side effects from radiation treatment during the study.

Among pediatric populations, research studies have revealed physical and emotional benefits for AFT [279, 281, 282]. In a study examining the effect of animal-assisted therapy in decreasing pain among pediatric populations, 57 children, aged 3–17 years, received either animal-assisted therapy (n = 18) or treatment as usual without animal-assisted therapy (n = 39) [279]. The results indicated significant pain reduction, based on the FACES pain scale, among the treatment group compared with controls. Limitations include small sample size and lack of true randomization, lack of comparison to other AAT dogs (as only one dog was utilized for the study), and lack of follow up measurement of pain levels to assess whether treatment benefits were sustained. Another study investigated the effect of canine visitation therapy in managing pain among pediatric populations [282]. In this study, 25 children ages 5–18 years who went through surgery received canine visitation intervention once. Each child completed a survey pre- and post-intervention, as well as a post-operation interview. The results indicated that the children who had canine visitation reported significant pain reduction. Limitations include small sample size and lack of control group.

Level of Scientific Efficacy. While AFT has been shown to bring positive outcomes among adult and pediatric patients in general, its efficacy is difficult to establish due to limited controlled studies. However, anecdotal data and personal clinical experience of the authors indicate positive immediate outcomes. Long term benefits have not yet been established.

Potential Risks/Adverse Effects. Obstacles related to AFT implementation involve safety issues, such as dog biting, infections, and/or allergic reactions [281]. Therefore, infection control and proper dog and handler certification procedures are generally required prior to implementing AFT to reduce the risk for such concerns [284]. Additionally, prior to incorporating AFT among cancer patients, particularly in pediatric populations, it is important to examine the patient's allergy history, immune status, and past experience with animals to avoid potential adverse effects [281].

Finding a Provider. Many children's hospitals utilize trained animals as an adjunct therapy. Animals are also trained in special programs to be of eye, hearing, limb extender, and other services to children with specific disabilities. Many providers can be located through Pet Partners (www.petpartners.org). Equine therapy, can be found through the Professional Association of Therapeutic Horsemanship International (PATH Intl.) at www.pathintl.org.

28.2.13 Physical Exercise

Background. A large body of literature supports the association of exercise and physical activity with better quality of life and health outcomes [288], and reductions in symptoms of both depression [289] and anxiety [290]. We also know that in the general population, regular exercise helps to prevent many diseases and conditions, including hypertension, type-2 diabetes, cardiovascular disease, obesity, and osteoporosis, as well as others, and has shown many mental health and quality of life benefits [289, 291–293]. Among adult populations, several studies have shown the benefits of physical activity in alleviating physical and psychological symptoms, but the results are not consistent [294, 295]. For instance, several randomized controlled trials have demonstrated that physical activities focusing on strength training (e.g., push-ups and pull-ups) have positive effects in reducing pain, anxiety, depression, and fatigue, while improving sleep and self-esteem [294].

Additionally, a literature review revealed that when patients participated in physical activity prior to undergoing cardiac or abdominal surgery, patients reported reduced postoperative complications and length of hospital stay [295]. However, in the same study, the patients who underwent joint replacement surgery did not have significant change in their postoperative complications and length of hospital stay after engaging in physical activity.

For cancer patients, physical exercise may result in improved physical functioning and quality of life [296–298]; and physical activity *may* reduce the risk of recurrence and increase survival [299]. Other studies have found a positive link between exercise and levels of fatigue, depression, anxiety, self-esteem, happiness, and quality of life in cancer survivors [289, 300, 301].

Among pediatric cancer survivors, as discussed in this manuscript, researchers have indicated several late effects of cancer treatment, such as premature cardiovascular disease, osteoporosis, and obesity [302, 303]. Limited evidence suggests that physical activity may be associated with decreased risk of negative physical and psychological outcomes, as well as enhanced quality of life [292, 304]. White and associates [303] found several potential obstacles to engaging in physical activity among children undergoing treatment for ALL. They argue that children with ALL tend to avoid physical exercise because of side effects from chemotherapy and fear of contracting unwanted infections. Additionally, parents of children with ALL typically restrict their children from engaging in physical activity due to potential injuries or infections from such exercise.

In fact, Florin et al. [305], based upon results from the Childhood Cancer Survivor Study (CCSS), reported that childhood ALL survivors *failed to meet the CDC recommendations for physical activity* and were more likely to be inactive compared to the general population. Of those at particular risk were individuals who received cranial radiation. As this level of inactivity in the healthy population is known to increase risk of cardiovascular disease, osteoporosis, and diabetes, discussed elsewhere in this manuscript, this lack of exercise is especially important to childhood cancer survivors who are already at risk for these long-term late-effects.

Although there is increasing evidence of a positive association between physical activity and well-being among cancer patients and survivors, research on pediatric populations and childhood cancer survivors are very limited. Therefore, it will be beneficial for future research to include standardized research methodologies and larger sample sizes in order to further examine the impact of physical activity among this population of pediatric cancer survivors.

Potential Indications. Exercise is indicated in most individuals, and has been found to be beneficial in the following areas: weight control and management, obesity, improving insulin sensitivity and glycemic control; decreasing blood pressure and low-density lipoprotein; increasing high-density lipoprotein; decreasing prevalence of cancer; osteoarthritis; migraines and fibromyalgia; coronary artery disease; metabolic and inflammatory conditions; respiratory conditions; improvement of psychological functioning such as anxiety and depression; increasing self-confidence and self-esteem; and improvements in cognitive functioning.

Clinical Studies. There are few randomized controlled trials that *directly* address childhood cancer survivors and physical exercise. Azar and colleagues [306] at the Edmond and Lily Safra Children's Hospital in Israel placed ten young childhood cancer survivors in an exercise group and 13 in a control group (usual lifestyle). The exercise group performed 2–3 exercise sessions per week for 6 months. Twenty-two children completed the study. Results indicated changes in aerobic fitness, lean body mass, femoral neck bone mineral density, bone mineral content, and social quality of life. While this study had a small sample size which limits its generalizability, it does indicate that exercise among childhood cancer survivors may have a positive effect on physical and mental health and should be encouraged. This is especially important given survivors' risk for bone disorders, such as osteoporosis.

In a meta-analysis conducted by Braam and colleagues [307], four randomized controlled trials and one clinical controlled trial were evaluated. All of the studies implemented physical exercise during chemotherapy of children and young adults with ALL with a control group. Results did not produce statistically significant findings that demonstrated improved physical fitness among the treatment groups. However, trends in improved physical fitness among the intervention group compared to the control group were observed, with changes in body composition, flexibility, cardiorespiratory functions, and physical fitness. The authors stress that the evidence linking physical exercise and physical fitness is limited in this population; however, studies involving other cancers and larger sample size are warranted given the trends found in this analysis [307].

Mechanism of Action. Exercise creates a series of actions in the body. When muscles are activated, they need glucose and ATP for contraction and movement. As the body requires more oxygen, increased respiration ensues and the heart rate increases to supply more blood to the muscles. Lactic acid is then released in the muscles, which in turn causes tiny tears that heal and create new muscle growth. With regular exercise, the heart and lungs become more efficient, reducing blood pressure and increasing the amount of new blood vessels to form. Increased blood flow to the brain also occurs, which increases neurocognitive functions, and promotes the growth of new brain cells [308]. During exercise, a number of neurotransmitters are released, including endorphins, serotonin, glutamate, dopamine, and GABA [309]. Weight-bearing exercise helps to prevent and in some cases mitigate osteoporosis [310]. Animal studies have also provided strong evidence that exercise and regular physical activity positively impact the pathophysiological processes of anxiety through a variety of mechanisms [290].

Level of Scientific Efficacy. Moderate to strong. There appears to be ample evidence of the physical and mental health benefits of regular exercise among healthy individuals, and growing evidence among cancer survivors.

Potential Risks/Adverse Effects. Hoffman and colleagues [311], in a prospective study examining the health of childhood cancer survivors found that survivors may require specialized exercise interventions, as there may be underlying physiological deficits that may affect exercise outcomes. Therefore, prior to implementing any exercise regimen for cancer survivors, a physical examination should be given to determine if there are any types of exercise that should be avoided (i.e., weight bearing exercises, weight lifting, etc.). For those individuals with a history of cardiovascular disease, cardiac monitoring during exercise within a rehabilitation setting may be indicated until such time they are free from any acute cardiac events related to physical exercise.

Finding a Provider. Due to the complexities of the childhood cancer survivor, finding a qualified trainer is essential. One excellent resource is the American College of Sports Medicine in collaboration with the American Cancer Society (ACSM/ACS). They have developed a Certified Cancer Exercise Trainers (CET) certification that requires the trainers to tailor their fitness assessments and exercise programs specific to the cancer survivor based upon their specific cancer diagnosis, treatment and recovery status. They can be contacted at http://certification.acsm.org/acsm-cancer-exercise-trainer.

Additional organizations providing certification for personal trainers include: the National Association of Sports Medicine (NASM), http://www.nasm.org, and the American Council on Exercise (ACE), http://www.acefitness.org.

28.2.14 Other Complementary Methods

Other methods available to cancer survivors, such as modifications to diet and dietary supplements, have been researched in varying degrees. However, these strategies are beyond the scope of this chapter and will be briefly reviewed below.

Natural Products: Herbal and Dietary Supplements. An herb is botanical extract of various plants that comes in tablets, capsules,

powders, teas, liquid extracts, fresh, or dried form [312]. Studies suggest that herbal medicines are commonly used, as 12.1 % of adult cancer patients and survivors utilize herbal medicines in European countries and 19.7–68.2 % in the U.S. [313–316]. Among childhood cancer survivors, a recent survey study suggests that 72 % of the children and adolescent cancer survivors have used dietary supplements, including herbs, botanicals, and minerals. This particular population reported initiating the supplement intake upon completion of the cancer treatment [10].

While herbal medicines continuously attract more people in treating their various symptoms with some positive effect, researchers caution about the potential negative side effects of herbal medicines [315, 317–319]. For example, Olaku and White [318] reviewed literature on herbal medicines among adult cancer patients and determined that while some patients experienced antitumor effects through herbal therapy, other cases were reported as having toxic effects, such as delayed hypersensitivity, renal failure, or bone metastasis.

With regard to natural products or herbal and dietary supplements, the National Center for Complementary and Alternative Medicine (NCCAM) at the National Institutes of Health states that:

> "Some of these products have been studied in large, placebo-controlled trials, many of which have failed to show anticipated effects. Research on others to determine whether they are effective and safe is ongoing. While there are indications that some may be helpful, more needs to be learned about the effects of these products in the human body and about their safety and potential interactions with medicines and with other natural products." [320]

While a complete description of the many herbal medicines are beyond the scope of this chapter, there are several excellent resources for more information on this topic. The websites listed below provide detailed reviews of specific herbal/dietary supplements and may provide a useful starting point in this regard.
http://www.nlm.nih.gov/medlineplus/druginfo/herb
http://www.nccam.nih.gov
http://www.mskcc.org/mskcc/html/11570.cfm
http://www.cam-cancer-org

Nutrition and Dietary Therapy. Numerous researchers have examined a relationship between healthy diet and cancer survival [321], and it is well known that a healthy diet rich in fiber, fruits, vegetables, and "good" fat (i.e., olive oil), has many health benefits. Some studies have focused on particular food intake, such as fruit and vegetable consumption, low-fat diet, and whole grain intake, while others have focused on overall quality of food consumption in relation to cancer recurrence and mortality [322–324]. Overall, the results from those studies have been inconsistent due to various issues, such as poor methodological quality and small sample size. For example, a study explored the relationship between dietary intake and survival rate among 103 adult breast cancer survivors [322]. The results of the study revealed that the patients who consumed high level of vitamins, particularly beta-carotene and vitamin C based on self-reported food record, had the lowest risk for breast cancer recurrence compared with those who had intermediate or low consumption level of beta-carotene and vitamin C. Limitations include lack of randomization and potential for confounding variables. In contrast, Pierce and associates [323] found no effect of particular nutrition intake on future cancer prevention. In this study, the authors randomly assigned 1,537 adult breast cancer survivors to the intervention group who received cooking classes, promotion newsletters containing information regarding fruit, vegetable, and fiber consumption, and counseling calls. The control group consisted of 1,551 breast cancer survivors who received only a paper description of dietary guidelines. After following the participants over 7 years, there was no significant relationship between the treatment and control groups on cancer recurrence and mortality. The authors concluded that adhering to a high fruit, vegetable, and fiber diet did not significantly reduce cancer recurrence or death. Potential limitations of this study include evaluation with a homogeneous population (predominantly Caucasian, age under 70, in which stage 1 cancer patients were excluded from the study) and significant between group difference on fat intake, which could have comprised the outcome [323].

A more recent study has demonstrated similar results, as 4,103 adult cancer survivors from 11 states were asked to complete a questionnaire regarding medical and lifestyle factors and the Food Frequency Questionnaire (FFQ) biannually for 26 years. The study results indicated that diet quality was not associated with reduced risk of cancer recurrence and death among adult cancer survivors [324]. Limitations include no measure on other factors such as physical activity and treatment and recurrence, use of self-reported food intake information may have interfered with the accuracy of food intake, and the exclusion of participants with severe disease (who recurred or died less than a year after breast cancer diagnosis).

Among pediatric cancer survivors, research has established the long-term late-effects associated with cancer treatment and survival, such as cardiovascular disease, obesity, diabetes, osteoporosis, gastrointestinal side effects, and low bone mineral density [325–328]. These are discussed elsewhere in this manuscript. Briefly, a recent study found that 20 % of pediatric cancer survivors are either overweight or obese, and 54 % of them were eating well beyond their recommended daily caloric intake [325]. Moreover, Tylacvsky and colleagues [328] explored the relationship between cancer survival and bone mineral density. A total of 164 childhood Acute Lymphoblastic Leukemia (ALL) survivors participated in this study, and more than 70 % of the participants did not meet daily consumption of several nutrients, including vitamin D, calcium, potassium, or magnesium, which are linked to bone density. Additionally, a high percentage of "sweets" consumption (70 % higher than recommended amount) was observed among this population. Limitations for this study include a modest sample size, the cross-sectional nature of the study design that did not include long term follow up, and a homogeneous population (Predominantly Caucasian in the Midsouth region) [328].

Despite a high risk of complex side effects among childhood cancer survivors, nutrition intake has not been well studied thus far. A recent study by Landy and associates [329] compared cancer survivors and their siblings on the quality of food intake and overall health status. A total of 90 childhood cancer survivors and 30 siblings were compared on their daily food intake, physical activity, and body fat. The results indicated that cancer survivors who reported having low consumption of dark green vegetables and whole grains were more likely to score high in body fat, while those who adhered to a high quality diet were low in body fat. Future studies should determine how to improve the quality of food consumption among cancer survivors and assess the effect of such improvements on various health indicators.

A review of specific dietary approaches is beyond the scope of this chapter. Therefore, the reader is directed to the CAM-Cancer website for more information. This resource provides details of various dietary approaches and information regarding safety and efficacy of individual dietary practices, and can be found at http://www.cam-cancer.org/CAM-Summaries/Dietary-approaches.

28.3 Conclusions

There is increasing use of complementary health approaches (CHAs), especially for pediatric cancer survivors. This chapter reviewed the key literature on studies that pertain to CHAs that have been utilized in this population. Importantly, research for CHAs is still developing; as a result, many studies lack robust methodological design and limit the conclusions that can be drawn regarding efficacy. However, some CHAs have established stronger research support, such as hypnotherapy for pain and exercise for physical and mental health. In addition, acupuncture research is growing but there are few well-designed studies in children compared to those in adults. The risks of CHAs vary by type of intervention; and many CHAs have limited adverse effects associated with their use. Most risks are related to the background and training of the practitioner and good clinical judgment (e.g., avoiding massage in children aversive to touch). However other CHAs require more complete investigation to determine safety (e.g., chiropractic care and certain natural

products or herbal and dietary supplements). Integration of most CHAs is considered safe when used as part of collaborative care while taking the entire individual's background, experiences, and current medical state into developing the most beneficial therapies.

28.4 Resources

The CAM-Cancer website is a helpful resource for learning more about CHAs with oncology survivors. "CAM-Cancer" is the name of a project entitled "Concerted Action for Complementary and Alternative Medicine Assessment in the Cancer Field" (CAM-Cancer). It was originally funded by the European Commission (EC) within the Framework 5 Programme, and is now hosted by the National Information Center for Complementary and Alternative Medicine (NIFAB) at the University of Tromsø, Norway. One of the primary goals of the CAM-Cancer project is to prepare and disseminate suitable evidence-based information for health professionals in order to assist them in informing their patients. Their website provides CAM Summaries for specific interventions utilized with cancer patients/survivors. These summaries are up-to-date, peer-reviewed summaries of the existing scientific information on CHAs in cancer. http://www.cam-cancer.org/CAM-Summaries.

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29 Barriers and Disparities in Accessing Quality Care Amongst Childhood Cancer Survivors

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29.1 Introduction

Despite decades of improvement in the treatment of childhood cancer and the knowledge accumulated about the appropriate follow-up of survivors for late effects, such advances cannot have ultimate impact if survivors do not or cannot access care guided by this knowledge. There are over 353,500 survivors of childhood cancer (diagnosed between 0 and 19 years of age) living in the United States [1]. Although 88.8 % of childhood cancer survivors report receiving some form of medical care, only 31.5 % reported care that focused on their prior cancer (survivor-focused care), and only 17.8 % reported survivor-focused care that included advice or discussion about health risk reduction [2]. Of even greater concern is that among patients at increased risk for cardiomyopathy or breast cancer, only 28 % and 41 % had undergone a recommended echocardiogram or mammogram, respectively. Of note, these results were from the Childhood Cancer Survivor Study (CCSS), a large cohort study of over 14,000 cancer survivors in the USA treated between 1970 and 1986 [3]. Since this group of survivors have been under longitudinal follow-up, their rates of follow-up are potentially better than in the childhood cancer survivorship population as a whole. Therefore, identifying barriers to appropriate survivorship care and developing successful strategies to overcome these barriers is of paramount importance. In this chapter, we review the current knowledge regarding barriers and disparities in accessing quality care among childhood cancer survivors.

Disparities in access to quality care have been attributed to the interplay of several factors which impact behavior as well as policy and health-care delivery. The Institute of Medicine's (IOM) model of access to personal health services [4] has been used as a framework to guide understanding of access to quality care and its impact on health outcomes (Sect. 29.1). The IOM model

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includes a combination of factors based on equity, including barriers to access, use of services, and mediators that have a unidirectional linear relationship with each other. More specifically, Oeffinger suggests a theoretical framework for optimal healthcare for pediatric cancer survivors (Sect. 29.2) [5]. The proposed framework builds off of concepts from the Health Belief Model [6], the multidimensional health locus of control model [7, 8], and the behavioral model of utilization [9, 10]. The framework identifies survivor-related, physician-related and health systems-related factors that work to facilitate or impede optimal access to long-term care.

Briefly, survivor-related factors include emotional and physical aspects of the cancer experience, as well as survivors' knowledge of their diagnosis and treatment. Internal modifiers including sociodemographic (e.g., age, gender) and cultural factors also influence access to care. Survivor-related factors also include an individual's core health beliefs, including perceived vulnerability to and the severity of late effects, as well as one's self-efficacy or health locus of control. External modifying factors, such as the influence of family and peers, are also included as survivor-related factors in obtaining quality care. Provider-related factors include practitioners' attitudes towards cancer survivors, knowledge regarding the specific needs of cancer survivors, experience with cancer survivors, attitudes towards prevention, and the structure of practice. Finally, health system-related factors include broader issues of the health care system, such as organization and health care policies. Medical insurance status also fits into this category. In this paper, we utilize the IOM's model and Oeffinger's model as a basis for examining aspects of barriers to access at the survivor level (personal), physician level (services/structural), and health-systems level (structural/financial) that may inhibit use of service among childhood cancer survivors and lead to disparities. Given the broad diversity of childhood and adolescent malignancies and their treatments, we will focus on issues which apply to childhood cancer survivors in general, highlighting some, but not all, factors which may be specific barriers to access in survivors of particular cancers or treated with particular therapies.

29.2 Personal Factors

Personal factors which play a role in accessing quality health care for childhood cancer survivors have some similarities with those of other chronic diseases [11]. They include both internal (sociodemographic factors, mistrust of the system, lack of adherence to post-cancer health needs) and external factors (lack of or insufficient insurance, inability to cover costs of care), as well as survivors' cancer experience and health beliefs. These personal factors are often a combination of internal characteristics and how they interact with society's response to that characteristic such as race, culture, gender and socio-economic status, which may hinder childhood cancer survivors, acceptability of the need for follow-up care as well as the ability to access it. However, because little research has been performed regarding personal factors that act as barriers associated with accessing quality health care specifically in childhood cancer survivors, most of this section cites the larger adult literature on barriers to care, only some of which is specific to cancer screening, active treatment, or survivorship in adults.

29.2.1 Race and Ethnicity

Within the personal or individual domain, disparities in cancer survivorship exist by race, with African Americans having lower survival rates than other racial groups in the United States [11–13]. This trend has also been shown to exist specifically within childhood cancer. Despite slightly lower incidence rates, African American children have worse survival after diagnosis than Caucasian children, ranging between 5 and 10 absolute percentage points lower, depending upon cancer type [1, 14]. Overall, Caucasian children had a 5-year relative survival rate of 83.7 % compared to 76.4 % in African Americans [1, 14]. Given that such disparities based on race/ethnicity occur during active treatment for childhood cancer treatment, it is likely that such disparities exist or are worse with survivorship care.

Little is known regarding racial disparities in access to quality care for childhood cancer

survivors. Inferences could be made that, since disparities in survivorship care are similar across types of cancer among adults [15], personal barriers to access to quality care observed might apply to childhood cancer survivors. Many contributing factors have been identified to attempt to explain disparities in cancer survival, including lower socio-economic status, lower education levels, and racial discrimination [12, 16, 17]. In addition to disparities in adherence to cancer prevention behaviors (e.g., diet, exercise, smoking habits) and to recommended cancer screenings, African Americans have been observed to have less access to the best cancer treatments [12, 15, 18]. This has been associated primarily with lower-socioeconomic status [15, 19]. However, researchers have identified discriminatory practices on the part of physicians towards African Americans patients compared with their Caucasian counterparts [11, 20] as well as perceived racially-motivated inequality in treatment standards [20–22]. Studies have found that African Americans are often provided with lower quality care and treatment than Caucasians [11, 23]. In the case of access to follow-up care, childhood cancer survivors of African American or Hispanic descent might continue to face similar barriers related to their sociocultural backgrounds.

29.2.1.1 Culture

Cultural variations can also affect the individual's decision to seek and or sustain health care [23], since culture is defined as the "integrated pattern of human behavior that includes thoughts, communications, actions, customs, beliefs, values and institutions of a racial, ethnic, religious or social group" [24]. As childhood cancer survivors require lifelong commitments to risk-based health care management, sustained cultural beliefs and practices can have a particularly significant role in health seeking behaviors. Although it is unknown whether they are more or less likely to do so, childhood cancer survivors that embrace the belief of fatalism, which dictates that there is little an individual can do to change the course of their fate [25], may be less likely to seek treatment over the course of time as it may be seen as futile. Failure of health care providers to ascribe to the cultural practices of childhood cancer survivors can result in missed opportunities for screening due to multiple reasons. These reasons include, but are not limited to, inadequate knowledge of prevalence of conditions among certain minority groups (such as the long term adverse health outcomes for childhood cancer survivors), inaccurate diagnoses based on miscommunications, harmful drug interactions with traditional remedies, and an inability to properly treat their patients because of differences in treatment adherence [23]. It has also been indicated that in illnesses where health decisions are literally life or death, as may be case in the subsequent conditions for some childhood cancer survivors patients, health decisions are more heavily influenced by cultural beliefs [26]. Within this concept, Surbone asserts that the communication between physicians and cancer patients/survivors is particularly complex because of the overarching issues of physical and psychological distress, uncertainty in prognosis and social stigmatization, and discrimination [27]. This makes cultural sensitivity and competence a must for clinicians in this field. Differences in belief and value systems between the patient and the clinician consequently play a tremendous role in the underlying communicative value of health discussions as one may not fully comprehend the perspective of the other [26]. An example of cultural nuances that may influence childhood cancer survivors' treatment seeking and adherence behaviors is the concept of disease attribution [27]. In many religious or faith-based cultures, cancer is seen as caused by or permitted by a higher being for various reasons [28, 29]. By not being aware of the sociocultural context [30], a physician may not understand treatment seeking behaviors of childhood cancer survivors who may associate not only their cancer, but also their survival to mystical beings or spirituality. Thus it may be extrapolated from the literature [22, 23, 31, 32] that in order to reduce the cultural barriers for childhood cancer survivors to access health care, cultural competency on the part of health care providers may be of great importance, especially for minority (e.g., Hispanics, African Americans, Asians) groups where the cultural divide is more pronounced [23, 32].

29.2.2 Communication/Language

Communication between health providers and their patients may also be a barrier to better knowledge about health issues and health behaviors, especially for childhood cancer survivors who must proactively monitor their preventive health behaviors. The efficacy of this clinician-patient communication can be severely hampered if there is discordance in patient-physician culture since in these cases, minorities (African Americans, Hispanics) may perceive bias in medical treatment and have been shown to experience less satisfaction with care [33]. Additionally, individuals from vulnerable populations, such as those of lower socio-economic status or different cultural background, often receive communication of health messages not tailored to their socio-cultural realities and/or languages [12, 34, 35]. This breakdown in communication may result not only in poor knowledge of health risks and long term prevention in childhood cancer survivors but also lead to a general lack of acceptability of the follow-up care and a mistrust of their physicians.

Language is an inherent part of one's cultural definition and has been identified as a barrier to access to health care in general [36]. It has been demonstrated that limitations of English fluency contribute greatly to the ethnic disparities in healthcare [37]. Minority childhood cancer survivors would be no exception and it can be easily inferred that language barriers also pose a real threat to their access to follow-up care.

29.2.3 Gender

Among childhood cancer survivors, gender disparities in access to follow-up care have not been well documented. There is some evidence that there are differences in gender vulnerability to various types of late effects—both malignant and non-malignant conditions such as anthracycline cardiomyopathy [38]; however this is largely due to biological differences and socioeconomic factors rather than differential access to care. Male childhood cancer survivors have also been shown to be 2.5 times more likely to go without any care compared to women and 1.1 times more likely to have general care vs. risk-based care [2]. Male childhood cancer survivors are also more likely to be uninsured, demonstrate lack of concern with future health, and to be less likely to report a visit. Conversely, women are more likely to utilize Medicaid (especially if older) [15].

Among childhood cancer survivors, females were more likely to have adverse health outcomes, however, this was correlated with lower levels of educational attainment [39]. Differences in access to care by gender have not been established but the little research available indicates some differences in utilization of services exist between the genders. While apparently independent of other factors, these differences should be considered by the care provider in conjunction with individual patients' other characteristics such as ethnicity, race and SES.

29.2.4 Cancer Experience

Aspects of the cancer experience that influence access to quality care include the psychosocial functioning of the cancer survivor and the survivor's knowledge of his or her cancer treatment and risk for late effects. A recent review summarizing reports from the Childhood Cancer Survivor Study (CCSS) demonstrated that the majority of childhood cancer survivors are psychologically healthy and generally satisfied with their quality of life, but certain groups are at risk for psychological distress and poorer physical health-related quality of life (HRQOL) [40]. Specifically, risk factors included female gender, lower educational attainment, low income, unmarried status, unemployment status, lack of health insurance, presence of a major medical condition, and previous cranial radiation and/or surgery. Higher levels of psychological distress have been associated with poorer health behaviors, such as smoking [41] and alcohol use [42], and reduced health-promoting lifestyle activities, such as nutrition and exercise [13].

Given that psychological distress influences health behaviors, it is likely that psychological

distress would also interfere with receiving risk-based survivor-focused long-term care. A modified Delphi panel of young adult survivors of childhood cancers reported several psychological barriers to obtaining risk-based care, including anxiety or fear of being diagnosed with cancer again, desire to "move on" from the cancer experience, and anxiety or fear of being diagnosed with a secondary illness caused by previous cancer treatment [43]. A report from the CCSS indicated that survivors were at four times greater risk of symptoms consistent with post-traumatic stress disorder (PTSD) compared to siblings, with an overall prevalence rate of 9 % [44]. Furthermore, other studies have suggested that young adult survivors may be particularly vulnerable to symptoms of PTSD [45–47]. One hallmark of PTSD symptoms is avoidance of people and places that might trigger memories of the traumatic event, which could include the cancer center or treatment team. Increased arousal or anxiety associated with PTSD might also interfere with survivors' ability to obtain appropriate care and health information [48, 49]. Thus, survivors who experience PTSD might have more difficulty in obtaining care when the environment is the same setting as their previous treatment. Attending to the psychological distress associated with cancer screening and late effects follow-up might also reduce psychological barriers to receiving appropriate long-term follow-up care.

Another psychological aspect to consider is survivors' ongoing relationships with their pediatric oncology treatment team. Most children's hospitals require a transition from the pediatric team to an adult-focused team due to age restrictions, though some programs are able to see survivors indefinitely. Strong positive relationships between survivors and their treating pediatric oncology team might make the transition to adult-focused survivorship or primary care more challenging [49].

The modified Delphi panel of young adult survivors of childhood cancers mentioned above also identified survivors' lack of knowledge regarding long-term health risks as a major barrier to receiving optimal treatment [43]. Many survivors of childhood cancers are very young at the time of treatment, with their parents being responsible for treatment decisions; therefore, survivors may be unaware of the specific treatments received. Even if older at the time of treatment, parents are typically responsible for medical decision-making, and medical terms and procedures may be difficult for a child or adolescent to understand and remember. A cross-sectional phone survey of a subsample of 635 survivors from the CCSS indicated that many survivors lack accurate knowledge of their cancer treatment [50]. Only 72 % of survivors were able to accurately report their diagnosis, and while the majority of survivors accurately reported whether or not they received chemotherapy and/or radiation, there were low rates of accuracy regarding the details of the treatment. For example, only 30 % recalled receiving daunorubicin and only 52 % recalled receiving doxorubicin, even after prompting with the drugs' names, and only 70 % could correctly recall the site of radiation therapy. Further, only 35 % of survivors reported that their cancer therapies could cause a serious health problem and only 15 % reported receiving a written summary of their cancer treatment.

The lack of knowledge regarding their cancer therapy and the potential impact of their cancer and its treatment on their future health presents an important barrier to childhood cancer survivors seeking and accessing appropriate follow-up care, and the transition to adulthood may lead to health decision-making without a comprehensive knowledge of their cancer experience. This places an additional responsibility on adult primary care providers to be informed of the particular health issues tied to a childhood experience. Unfortunately, studies have highlighted that neither childhood cancer survivors nor their providers are adequately informed as to the potential long term health complications of surviving childhood cancer [43]. Results such as these highlight the need for interventions to enhance survivors' knowledge of their previous treatment and current/future health risks, as well as providers' knowledge and awareness of the needs of childhood cancer survivors. For example, many

centers provide the survivor with a treatment summary that indicates the treatment regimen they received so that they can impart that knowledge to their adult care providers.

A brief mailed survivorship care plan showed improved uptake of mammogram and echocardiogram in survivors of Hodgkin lymphoma at-risk for breast cancer and cardiovascular disease [51]. This intervention also offered survivors and primary care physicians access to a website with information regarding risks for late effects and various resources, but only a small percentage of survivors visited the website and none of the primary care physicians used the online resources to improve their knowledge of late effects. Overall, this study demonstrated that mailing a brief, survivorship care plan is feasible and effective in communicating risk and recommending follow-up care to survivors, but different strategies are needed for communication with primary care physicians.

29.3 Provider-Related Factors

Provider-related factors that influence survivors' access to quality health care include providers' beliefs regarding prevention, knowledge of late effects for survivors of childhood cancers, attitudes towards cancer survivors, and the organizational structure of practice, such as time constraints [5]. The IOM indicates that the essential components of survivorship care are prevention and detection of new cancers and recurrent cancers, surveillance for recurrence or secondary cancers, interventions for consequences of cancer and late effects of treatment, and coordination of multiple providers to meet survivors' health care needs [52]. Survivorship care can be provided by oncologists, other specialists, or primary care physicians (PCPs) [52]. Currently, there are multiple models of survivorship care and debate regarding which model would provide optimal care for survivors, with the suggestion that different models of care might be better for different individuals [53, 54]. Models of care in the US can be broadly grouped into cancer center-based care, community-based care, or a hybrid of the two [55, 56]. Recently, Oeffinger and colleagues described the strategy of incorporating PCPs into a risk-stratified shared-care model [48, 54, 57, 58].

One of the barriers to community-based care and shared-care is PCPs' lack of training in the specialized care of childhood cancer survivors [54, 59]. In 2000, it was estimated that a typical PCP would see 2 to 3 survivors of childhood cancers in their practice, with a projected increase to 6–9 per year by 2010 [60]. Given that PCPs receive little training in survivorship care and are unlikely to see a large number of patients in practice, there is a gap in knowledge regarding how to provide optimal care [5]. Studies of PCPs' views of providing follow-up care for survivors of adult cancers indicate a willingness to provide care but low levels of comfort and confidence in providing appropriate, guideline-based care [61, 62]. One study found that 38 % of PCPs and only 16 % of oncologists preferred a shared model of care, while 35 % of PCPs and 57 % of oncologists preferred an oncologist-led model [63]. Further, a lower percentage of PCPs felt confident in their ability to detect recurrent disease and manage late effects of cancer, and PCPs were more likely than oncologists to endorse routine use of non-recommended tests for detecting recurrence [63].

Together, these studies highlight the need for greater communication between oncologists and PCPs, including transfer of knowledge regarding how to appropriately care for cancer survivors. To facilitate sharing of knowledge, PCPs endorsed the following as the most helpful strategies: (1) patient-specific letter with details regarding follow-up recommendations; (2) printed guidelines; (3) expedited routes of referral to cancer specialists; and (4) expedited access to examination for recurrence [62]. Further, a Delphi panel of health care experts identified initiatives to promote communication between PCPs and cancer specialists as a top priority for enhancing the health care of adults survivors of childhood cancers [59].

In discussing models of care, a few advantages and disadvantages of different approaches should be noted. For example, while survivors are less likely to receive risk-based survivor-

focused care from PCPs in the community [2], PCPs may be more likely to attend to general preventive health care given their specialty and training. A recent survey of pediatric oncologists indicated that oncologists were less comfortable treating childhood cancer survivors as they aged, particularly with survivors who were 30 years of age or older [64]. Similar to the knowledge gap for primary care physicians, pediatric oncologists typically do not receive training in general adult medical care, and may be unfamiliar with healthcare issues that arise as the survivor ages [65]. Further, many pediatric oncologists are primarily involved in treating children with active cancer, rather than survivors. Therefore, an advantage of a primary care physician/oncologist shared care models is that it combines the expertise of both physicians [54, 59, 65]. In the Netherlands, a pilot study of a shared care model demonstrated the feasibility of this approach [66]. In this study, patients initially visited a specialized LTFU clinic, information was sent to a local family doctor who saw the patient 1 year later, and patients returned to the LTFU clinic 1 year later to discuss a plan for future follow-up. Overall, 88 % of survivors were satisfied with the treatment received and 82 % of family doctors were satisfied with the information received and the shared care approach. Several large institutions in the United States utilize this model, especially those that rely on satellite clinics to provide care for survivors.

As noted above, availability of health care providers who are knowledgeable of the risks faced by survivors of childhood cancers is a major barrier to obtaining quality care for many survivors. For those who live close to their treating institution, a specialized long-term follow-up clinic may be available (for a list of follow-up clinics by state, see http://www.ped-onc.org/treatment/surclinics.html or http://www.cbtf.org/learn/brain-tumor-survivor-late-effe). These programs are often housed within a pediatric institution, may not have dedicated space for survivorship, and frequently have age restrictions that limit how long patients are eligible to be seen. Many adult survivors do not want to return to their treating institution for care, feeling out-of-place in a pediatric center [55]. Even if a specialized clinic is available, it may not be geographically feasible to routinely access the clinic for follow-up care. Access might be particularly difficult for young adults given that young adulthood is a developmental period characterized by changes in geographic location, type of residence, job, education, marital status, and health care provider [56].

In a recent report describing comprehensive long-term follow-up programs, program directors identified several barriers to sustaining a comprehensive clinic, including financial issues, lack of institutional support and value, limited capacity for caring for survivors, communication barriers with community physicians, and survivor-related barriers such as competing commitments, unwillingness to return, and geographic limitations [67].

29.4 Financial Factors

29.4.1 Insurance

In the United States, lack of or inadequate health care insurance has repeatedly been shown to be a barrier to accessing health care services in many populations [68, 69]. For childhood cancer survivors, health insurance is a particularly salient issue given the special services potentially required for the appropriate, life-long, follow-up care. Evidence that childhood cancer survivors specifically had difficulty obtaining insurance was reported as early as 1986. In a small case–control study of 100 childhood cancer survivor/gender-matched sibling control pairs, only 83 % of these survivors treated between 1945 and 1975 currently had health insurance, while 92 % of their siblings did ($p<0.04$) [70]. Further, 24 % of survivors reported having difficulty obtaining insurance while none of their siblings did. Another study performed about the same time found that 14 % of male survivors and 9 % of female survivors were rejected for health insurance compared to <1 % of controls [71, 72]. However, these studies were performed prior to legislation that should have

increased survivors' access to health insurance: the Comprehensive Omnibus Budget Reconciliation ACT of 1986 (COBRA), the American with Disabilities Act of 1990 (ADA), the Health Insurance Portability and Accountability Act of 1996 (HIPAA), and more recently, the Patient Protection and Affordable Care Act (PPACA), discussed later in this chapter.

The CCSS has also evaluated the issue of health insurance coverage in childhood cancer survivors and its association with access to different types of health care. At baseline survey, 84.9 % of adult survivors (≥18 y.o.) had health insurance compared with 88.3 % of siblings ($p<0.001$) [73]. Significant differences remained (88 % vs. 91 %, $p<0.01$) 6 years later. In multivariate analysis of these survivors, factors associated with being uninsured included younger age at diagnosis (<15 year of age), male gender, lower level of attained education (all levels less than college graduate), income (< $60,000), marital status (widowed/divorced/separated and living as married categories compared to never married), smoking status, treatments that included cranial radiation, and an original diagnosis of a CNS tumor compared to leukemia. On the other hand, survivors who developed a recurrence or developed a second cancer were more likely to be insured. A total of 29 % of survivors had some difficulty obtaining insurance even if successful in eventually obtaining insurance compared to only 3 % of siblings. Interestingly, factors associated with difficulty in obtaining insurance in those 18 years or older, after multivariate adjustment, were largely the reverse of those which predicted a lack of health insurance coverage. These factors were age >15 years at diagnosis, diagnosis of leukemia, recurrence, occurrence of second malignancy and female gender. In the same model attained age of 18 to 21 at baseline, black or other race, college graduate, and annual household income of ≥$60,000 were associated with less difficulty in obtaining health insurance.

These investigators also studied survivors who were less than 18 years of age at baseline in the CCSS cohort. Given that children mostly get health insurance through their parents, it was not surprising that rates of health insurance in survivors were not statistically different than their siblings, 93.3 vs. 94.2 % [73]. Only lack of recurrence and household income of <60,000 were associated with being uninsured in the multivariate model. However, having another benign tumor or a recurrence was associated with having difficulty obtaining insurance as was Caucasian race (compared to black or other) and income less than $40,000.

Additionally, Park and colleagues found that the source of health insurance and quality of health insurance was significantly different between survivors and their siblings, regardless of age at baseline survey [73]. Coverage through work was 56 % in survivors and 60 % in siblings ($p<0.001$), and through a parent or spouse in 27 % vs. 31 %, ($p<0.001$) respectively. Significantly more survivors than siblings (12 % vs. 3 %; $p<0.001$) received health insurance through Medicaid or other public assistance. Interestingly, employed male survivors were 30 % more likely to lack insurance compared with their employed males siblings. Survivors in both age groups were significantly more likely to report exclusions on their policies than their siblings. In adult survivors, 4.4 % reported exclusions while 22.5 % did not know if their policy had exclusions compared with 1.0 % and 8.0 %, respectively, in siblings. In addition, 2 % of survivors reported extra premium charges because of their health history compared with 0.2 % of siblings ($p<0.001$). These results confirm an earlier, smaller study that demonstrated that not only were survivors less likely to have health insurance but even when they had coverage they were more likely to have policies that excluded care for pre-existing conditions [74].

CCSS investigators have also been able to demonstrate that lack of insurance and type of insurance affects usage of medical care in childhood cancer survivors of all ages [2, 59] and specifically in adult survivors [75, 76]. Using follow-up data from the 2002–2003 questionnaire, Nathan and colleagues demonstrated that almost 30 % of uninsured survivors had not received medical care in the previous 2 years, compared with 10 % of insured survivors [2].

Furthermore, even when uninsured survivors received medical care, they were 41 % less likely to have received risk-based survivorship care than insured survivors. In particular, amongst those in which echocardiogram was indicated by COG late effects guidelines, survivors who were uninsured were 2 times more likely to have not received this recommended screening. As the authors note, these results were comparable to the results from a study of 1,718 survivors of adult cancers using data from the National Health Interview Survey (1998 and 2000 surveys). This study found that 45.1 % of uninsured survivors reported missing needed medical care within the preceding year because of concerns about the cost of that care. In contrast, only 16.7 % of publicly insured and 4.4 % of privately insured survivors reported missing needed care [77].

Both publically- and privately-insured adult survivors (≥18 years old) in the CCSS living in the United Sates had greater healthcare utilization than uninsured survivors [76]. Interestingly, those with publicly-provided insurance reported having a higher rate of receiving cancer-specific follow-up care and of visits to a cancer center than those with private insurance, but they were significantly less likely to have received some general preventive services such as a dental exam and in women cervical cancer screening. This may be due to the fact that individuals who had public health insurance were more likely to have chronic health problems, have had recurrence or second cancers, and have an original diagnosis of brain cancer—affecting ability to be employed—all of which may increase the need for follow-up. However, this analysis adjusted for race/ethnicity, age at survey follow-up, gender, household income, level of education, and presence of a serious health condition. It is possible that public insurance provides more freedom to access services from different providers as private-insurance plans, such as PPOs and HMOs, often restricts or favors certain providers whereas public insurance is less likely to do this [78]. Tertiary care centers, such as comprehensive cancer centers, also tend to be part of larger institutions which generally accept Medicaid and Medicare, whereas private-insurers may choose not to contract with them restricting access of their covered individuals to cancer center services. In any case, these results generally held up in stratified analysis by race/ethnicity, though small sample sizes often precluded statistical significance.

29.4.2 Employment

Part of the reason survivors are less likely to have insurance is that they are less likely to be employed or be employed in jobs with benefits due to true disability and discrimination. Prior to the passage of the American with Disabilities Act in 1990 (ADA), studies showed that survivors had more difficulty obtaining jobs compared to siblings and the general population [70, 71]. Since the ADA explicitly refers to cancer as a condition that is covered as a disability and likely decreased the amount of discrimination, we review only studies performed since then. In a study of survivors treated at St. Jude's Children's Research Hospital between 1962 and 1992 who were at least 10 years past diagnosis and at least 18 years old at the time of the survey, survivors had a higher unemployment rate (25 %) than the population at large [79]. This held true for all diagnostic groups, including hematologic malignancy, solid tumor, or CNS tumor, regardless of treatment with irradiation. Survivors diagnosed with CNS tumors had the highest unemployment rate of 50 % compared to the age and gender matched rate of 5.6 %. In all groups, except hematological malignancies treated without irradiation, lower rates of employment were due to both lower full-time and part-time employment. In survivors of hematological malignancies treated without irradiation, full-time employment was reduced but not significantly. However, the level of employment was slightly higher than that seen in other published data [76] up to that point and may reflect the fact that children treated at St. Jude's likely have access to better follow-up care. Treatment and follow-up are free and neuoropsychological services that include addressing issues affecting employability are quite advanced at this hospital.

In a meta-analysis of 40 studies of adult survivors of childhood cancer from the U.S.A., Europe, and Israel, the average rate of unemployment was 20 % in studies with comparison groups and 40 % in those without comparison groups [80]. Overall, survivors were twice as likely to be unemployed compared to healthy controls, with survivors of brain tumors having the greatest gap compared to their controls with a 5 times higher risk of unemployment. American survivors had a greater risk of being unemployed compared to European childhood cancer survivors, potentially reflecting differences in societal support and attitudes toward potential disabilities.

Baseline data from the CCSS also demonstrates that adult survivors of childhood cancer are at higher risk of unemployment compared to siblings and this was true for all cancer-specific diagnoses groups except Wilms tumor survivors [81]. Interestingly, the overall lifetime unemployment of 5.7 % was actually lower than in both the De Boer meta-analysis and the St. Jude's study. The greatest risk of unemployment in the CCSS as well as in the meta-analysis was amongst survivors of CNS tumors and for any survivor who received ≥30 Gy of cranial irradiation, confirming earlier findings in survivors of ALL by Pui (2003) [82]. Not surprisingly, multiple studies from both United States and Europe have demonstrated that risks for unemployment in childhood cancer survivors include lower education level and diminished cognitive function, including deficits in memory, attention, concentration, quantitative skills, abstract reasoning and fatigue [79, 83–90]. And of course deficits in these skills are most common in survivors of ALL who received ≥18 Gy of CNS irradiation and brain tumor survivors. In fact, analysis of data from survivors older than 24 years of age at the 2002–3 CCSS follow-up questionnaire demonstrated that those who received cranial irradiation between 18 and 25 Gy, as well as those receiving ≥25 Gy, were at increased risk of health-related unemployment compared to other survivors after adjusting for other treatment and socioeconomic factors. Other risk factors predicting unemployment in this multivariate model included age between 35 and 44, gender, black, Hispanic or other race, female gender, more than 20 years since diagnosis, cancer recurrence, second cancer or any type of bone cancer surgery—including limb-sparing surgery. Limb-sparing surgery and cranial irradiation of ≥25 Gy had the greatest relative risks of 4.23 and 3.47, respectively for unemployment [91]. Of note, unemployed survivors were more likely to be publicly insured than unemployed siblings [91]. This suggests that survivors may better realize the need for health insurance, may have more disabilities that qualify them for public health insurance, or both.

Employment, or its surrogate, income, is associated with health insurance status and use of medical care in adults who are survivors of childhood cancer, but not always in the direction one would expect. Although employment status is related to insurance status in univariate analyses, most studies also include household income in the multivariate models, and income is more strongly related to insurance status, eliminating employment as a risk factor [73]. Clearly this is because income is causally related to employment but has more graduations, and not because it is a confounder. Indeed the single-center study from St. Jude's did not include income in its multivariate model and found that current employment decreased the rate risk of insurance denial by 29 % [79]. While employment status was not significantly associated with whether a survivor had any medical follow-up in the prior 2 years, somewhat surprisingly those who were unemployed were 43 % more likely to had risk-based, survivor-focused care as opposed to non-specific care compared to survivors who were employed [2]. One possible explanation was that people who were unemployed were more likely to qualify for public health insurance [92], and as mentioned above, a separate report from the CCSS indicated that those who were publically insured had higher rates of survivor-focused care compared with non-specific care [76]. However it was not possible to distinguish between preventive care and care for ongoing late effects. On the other hand, in the St. Jude's study, current employment and current insurance each independently dramatically decreased the difficulty in obtaining care in the prior 12 months as well as

increasing the likelihood of obtaining needed care [79].

Independent of insurance, income still appears to have an effect on ability to access health care. After adjusting for insurance coverage and other sociodemographic variables, survivors with an income <$40,000 were 40 % more likely to go without any medical care, but if they received medical care they were not significantly more or less likely to receive risk-based care than those with higher or unknown incomes [2]. Amongst those survivors whose history suggested they needed one of the following screening exams, an annual household income of <$40,000 decreased the likelihood of receiving a needed echocardiogram but had no appreciable effect on needed mammography, though for the latter analysis the sample size was only 414 compared to 1,810 for the echocardiography analysis.

29.4.3 Public Policy

The passage of the Patient Protection and Affordable Care Act (PPACA) in 2010 should help to address many of the barriers to appropriate survivorship care related to insurance, but not all of them [93, 94]. Although the Comprehensive Omnibus Budget Reconciliation Act of 1986 (COBRA) and the Americans with Disabilities Act of 1990 (ADA) provided some protection of health insurance coverage maintenance related to loss of employment, discrimination, or change of position or status, these protection only applied to group health insurance plans. The Health Insurance Portability and Accountability Act of 1996, which applies to both individual and group health insurance plans, requires that insurers do not impose pre-existing condition clauses on those who have been previously covered. However, medical underwriting in the individual or small group market can make such coverage very expensive. For individuals without employer or government coverage, private insurance has often been expensive, restrictive and/or simply unavailable [93].

PPACA should positively impact childhood cancer survivors' access to care both as children but even more so as adults. Prior to PPACA, private insurance plans usually ended dependent coverage at age 21 or upon the completion of a college education. Those survivors on publicly funded insurance usually aged out at the age of 18 as they were no longer protected by Title V, and the criteria for Medicaid eligibility for adults is much stricter. Childless adults were ineligible and individual with disabilities could have a maximum income of 74 % of the federal poverty level to be eligible [95]. In the pre-PPACA marketplace, individuals not fortunate enough to be offered an affordable group plan by their employer could be charged extra for a pre-existing condition, including childhood cancer, covered except for conditions arising from their pre-existing condition or denied coverage outright. Plans also could compete in the marketplace by minimizing their coverage, by not paying for preventive care, imposing lifetime or annual limits on coverage, and/or limiting coverage to certain providers, which did not have to include survivorship specialists. However, these limitations were often hidden. For example, most survivors of childhood brain cancer who had health insurance had plans that did not cover neurocognitive and psychological services which were clinically indicated [96].

Table 29.1 lists the potential benefits of PPACA for survivors by their implementation dates [93]. Regardless of implementation date, reforms benefiting survivors relate to three primary areas: access to, affordability of, and quality of health insurance plans. Changes required by this law which took effect prior to 2011 largely affect private insurance and included expansion of dependent coverage until 26 years of age, prevention of coverage denial, coverage due to pre-existing conditions or cancelation of coverage due to onset of serious illness or injury, outlawing lifetime caps, and requiring 100 % coverage of needed preventive care without out-of-pocket costs. Requiring that family plans expand coverage up to age 26 is particularly important, as this age period corresponds to survivors' time of transition into the adult health care system and increased responsibility for their own health care. Childhood cancer survivors are more likely to be

Table 29.1 Potential benefits of the patient protection and affordable care act (PPACA)

Started in 2010	Further explanation
Children cannot be denied coverage for a preexisting condition or no one (adults and children) can be dropped from coverage if they or their guardians become sick	Children with pre-existing conditions can no longer be denied coverage. Individuals of all ages denied a policy because of health conditions, and who have been uninsured for 6 months, can immediately get coverage through high-risk insurance pools, an option that was not previously available in all 50 states. Insurers cannot drop an individual's health coverage if he/she gets seriously ill or hurt
Needed care must be covered if survivor becomes ill	Insurers are banned from putting a lifetime cap on the amount they will pay for an individuals care and any annual caps must be approved by the Secretary of Health and Human Services. Annual caps will be prohibited by 2014
Children can stay on parent's policy until they turn 26 years old	Insurers must allow dependent children to remain on their parent's health care policy (if a family plan) until they turn 26 years of age, whether they are in school or not
Preventive care must be covered at 100 % without out-of-pocket cost to the insured	Health care plans must cover preventive services recommended by the U.S. Preventive Services Task Force or mandated by the Secretary of Health and Human Services, without co-pay or out-of-pocket costs
Insurance companies must justify rate increases	All insurance companies are required to go through a review process to justify rate increases. Beginning in 2014, if a rate is found to be unjustified, the company can be prevented from selling coverage in the insurance exchange
Incentives to increase number of primary care doctors and practitioners	The Federal government is authorized to make new investments to help increase the number of primary care and preventive care providers, including doctors, nurses, nurse practitioners and physician assistants. However, these funds need to appropriated (provided) by Congress every year
Insurance companies must spend most of your premiums on health care services	All insurers that offer large group policies (businesses with more than 50 employees) have to spend at least 85 % of the premiums they collect on health care. For individual and small group policies, they must spend at least 80 % of premiums on care. If these conditions are not met, the insurers must rebate the difference to those they covered the next year. This is one of the tools to help keep premiums from rising
Additional benefits added until full enforcement in 2014	
Adults as well as children cannot be denied coverage for a preexisting condition or dropped from coverage if they or their guardians become sick	Individuals of all ages with pre-existing conditions can no longer be denied coverage
Incentives for employers to maintain health coverage of employees	Companies with more than 50 full-time employees will pay a $2,000 fee for each full-time employee not offered health coverage (businesses do not have to pay the fee on the first 30 employees not covered). The fee would then help employees to buy their own individual policy in the insurance 'shopping mall,' or exchange
Enhanced options for employed individuals to obtain health coverage	Employees whose employer's based health care policy costs 8 % or more of their salary, will have the option of buying their own coverage and the employer must provide a voucher to use for this, that is equal to the amount they would have spent on the individual's health insurance premium. If the cost of the insurance is 9.5 % of your salary or more and your income is below a certain level, you will also get a tax credit to help you purchase insurance in the exchange. (These rules apply only to employees of firms with 50 or more employees

(continued)

Table 29.1 (continued)

Started in 2010	Further explanation
Increased options for health coverage for those unemployed	Beginning in 2014, if you are laid off from your job, you may buy a good policy for you or your family through their state's insurance exchange (earlier if your state creates an exchange sooner). If you have very low income, you can get coverage from Medicaid
Increased pay to primary care providers seeing Medicaid patients in order to ensure that enough doctors are available to see this population	The federal government will pick up 100 % of the new costs of the incentives for 2 years starting in 2013
Requires all Americans to have health care coverage ensuring that prices are kept down	This will spread the cost of health care amongst those among the entire population and prevents people from purchasing health coverage only when they are sick or believe they are at higher risk of being sick. Having insurance will also discourage use of the highest cost providers or delaying care until the most expensive treatments are needed
Requires companies to compete for your business using uniform criteria	Allows consumers to more easily compare different health care plans

Adapted from Consumer Reports Health, Prescription for Change. https://secure.consumersunion.org/site/SPageServer?&pagename=Rx_coverage_andemail_signup. Accessed October 10, 2011

unemployed or employed in lower paying jobs due to disabilities, making it harder to afford independent coverage. Yet, they may make too much to qualify for public insurance programs. Increased subsidies for low income working people authorized under PPACA would also help survivors in this gap if funding is actually appropriated. Expanding the age limit of coverage also helps survivors with the capacity to attend college, because college sponsored plans usually provide only catastrophic coverage, and survivors with mild cognitive impairment, though able to attend college, may not be able to carry a full academic load, disqualifying them from many college plans [93].

Other benefits of PPACA already in effect include provisions for obtaining appropriate preventive survivorship care [93]. Although not specifically addressing the Children's Oncology Group late-effects guidelines, insurance plans must provide coverage for all preventive services recommended by the United States Preventive Services Task Force, without out-of-pocket costs. Insurance coverage or payment for a particular service can no longer be denied due to a preexisting condition. Prior to health care reform, insurers could have denied coverage for services to treat conditions that might have been a late effect of a survivor's childhood cancer treatment or in fact completely dropped the survivor's insurance once such an event occurred, whether or not the condition was in fact related to the history of cancer. Additionally, PPACA banned lifetime caps on reimbursement of needed care in 2010 and currently any yearly caps must be approved by the Secretary of Health and Human Services. By 2014, yearly limits will be prohibited.

In terms of publically supported health insurance, PPACA reforms included expanding eligibility and improving services provided, with more changes to come with full implementation of the act. For those denied a policy because of health and who had been uninsured for at least 6 months, expanded high risk pools were initiated in June 2010. In terms of quality of care provided, beginning in 2011, federal payments to states were increased for low-income patients with more than one chronic condition in which care is coordinated through medical homes. A routine source of care has repeatedly been shown to increase the likelihood of preventive services and physician visits [97, 98]. A medical home, however, is not just a routine source of care but expands it to the ideal that the care provided is continuous, comprehensive, family-centered, coordinated, and culturally-effective [93]. Despite this fact and that the American Academy of Pediatrics and the U.S. Maternal and Child Health Bureau recommends that all children with special health care needs (CSHCNs) receive care

through a medical home, only 50 % of them did so in 2007 [99]. Of particular importance to survivors and other CSCHNs is that medical homes can reside in subspecialty practices as well as primary care practices [93, 100].

Full implementation of PPACA is scheduled for 2014 and will include additional benefits. Employers with more than 50 full time employees, which do not offer health insurance will have to pay a fee of $2,000 to subsidize the cost of their employees obtaining their own policies. If such an employer offers a plan but it is greater than 8 % of an employee's salary, the company will have to provide a voucher to the employee for the same amount the company would have spent and allow the employee to look for their own insurance. Additionally, individuals who make under a certain amount to be determined and whose cost of employer health insurance is greater than 9.5 % of their salary will also be eligible for tax credits to help them purchase health coverage. However, those employed by companies with 50 or less employees will be covered by different rules, and small businesses will be offered assistance to provide their workers with health insurance.

Even with the passage of PPACA, there will still be barriers for survivors to accessing quality follow-up care, including some which may be exacerbated by PPACA. The first is that PPACA is not yet fully implemented or funded and there are already serious efforts to overturn, repeal, or limit the funding to implement PPACA. Funding for implementing and maintaining PPACA is likely to be a contentious annual issue at least in the near future. Even if fully implemented it is estimated that about 8 % of the population will remain uninsured [101]. Lack of funding will also worsen the issue of a lack of sufficient primary care physicians, because even without the expansion of health insurance coverage through PPACA, a shortage of such providers already exists. Not only might this make it more difficult for survivors to find a PCP who has an opening in their practice, but such providers will be even more challenged to devote the time necessary to learn about and address the special health care issues relevant to the survivors specific history of cancer and its therapy. PPACA does not guarantee access to the Children's Oncology late effects nor other specialty recommended screening tests. Nor does it guarantee access to academic health centers, where most of the few adult survivorship programs exist, let alone the national experts on a particular topic, which may be necessary considering the rarity and lack of knowledge of some serious late effects of childhood cancer therapy. Nevertheless, the improved access to health care provided by PPACA, and in particular access to generally recommended age- and gender-based screening tests without out-of-pocket costs, represent progress. This piece of legislation also provides a base from which survivors and other populations with special health care needs can use to advocate for specific policies to better address their particular challenges regarding obtaining optimal health care. For example, survivors and their providers could join together to lobby for changes in PPACA to support the adequate reimbursement for the development of individualized cancer care plans and treatment summaries, which allow oncologists to facilitate the coordination of care in a manner described and endorsed by the Institute of Medicine's National Cancer Policy Board [48].

29.5 Conclusions

The last 40 years has not only seen a dramatic increase in the survival of most childhood cancers but a great amount has been learned about the potential adverse late effects of the powerful therapies that have lead to cures for so many children. Although much work remains to be done to better apply the knowledge-as extensively reviewed in this book—gained about late effects to specific childhood cancer survivors, an additional and just as critical element of ensuring that childhood cancer survivors receive ideal follow-up care is learning and overcoming the disparities and barriers to accessing quality late effects care. In this chapter we have reviewed these disparities and barriers using the IOM model of barriers to quality care in the general population (Sect. 29.1) and Oeffinger's model of optimal healthcare for

pediatric cancer survivors (Sect. 29.2) [5]. Both models divide factors that either facilitate or impede optimum access into long-term care into survivor-related, physician-related and health systems-related categories.

Survivor related factors include issues specific to an individual's cancer experience but also factors independent of having cancer, such as gender, culture, and education, though in some cases they could be influenced by the cancer experience. In terms of general individual barriers to accessing quality care, little work has been done to investigate these specifically in the childhood cancer survivor population; therefore, the majority of data related to race/ethnicity, culture, and language comes from the general adult literature on barriers and disparities in access to care, including research on primary and secondary cancer screening. This is in contrast to survivor-specific and provider-related domains where the literature in children on survivorship is more advanced than in adults. Nevertheless, even in these areas, there exists the limitation that much of the work on barriers to care is derived from single, albeit high-quality cohort study, the CCSS, which was not designed to look at barriers per se, but this is the study which helped solidify the argument that childhood cancer survivors need specific risk-based follow-up.

Given that one large study dominates our understanding of barriers and disparities in accessing quality childhood cancer survivorship care, evaluating these barriers in independent samples would be helpful. Nevertheless, we believe enough is known about disparities and barriers to accessing appropriate health care through a combination of the general literature, the children with special health care needs literature, and, the childhood cancer survivor literature. Therefore it is not too early to begin investigating possible interventions to improve access to appropriate survivorship care, ideally through randomized trials. Potential interventions could be targeted at individual related factors, such as providing culturally sensitive information, or physician-related issues, such as which type of providers are best at delivering risk-based care or tradeoffs that exist between providing short versus more comprehensive treatment summaries and late effects care plans. Interventions could also target health-systems related questions, such as whether eliminating co-pays for certain tests improves the rate at which survivors receive the test. The rates at which current, expert consensus-based guidelines are adhered to could be used as outcomes for such intervention studies, as these represent current best practice recommendations. Finally, survivors, their families, and health care workers should advocate for policies, laws, and funding that help ensure that all survivors have access to appropriate follow-up care. Advocacy should include lobbying lawmakers at all levels, insisting that health insurance providers cover appropriate follow-up with trained professionals. While the Patient Protection and Affordable Care Act (PPACA) holds great promise in reducing barriers to accessing appropriate health care for all and particularly childhood cancer survivors, pressure must be kept up to ensure that it is fully enforced and fully funded. Furthermore, even if fully implemented, PPACA will not eliminate all barriers as it does not necessarily address issues specific to childhood cancer survivors. Survivors must therefore remain alert and proactive about how health care reform can be expanded to improve their access to appropriate care. Advocacy groups such as the American Childhood Cancer Organization and the National Coalition for Cancer Survivors can assist individuals with specific issues and by bringing together survivors into groups that can provide a more effective voice than one individual alone.

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30 Educating and Preparing the Childhood Cancer Survivor for Long-Term Care: A Curriculum Model for Cancer Centers

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30.1 Introduction

The growing need to provide an infrastructure for cancer survivor care has been well recognized [1]. Several treating institutions have bridged the gaps in healthcare by implementing various transition models to facilitate transfer of care from a pediatric cancer center to adult-oriented care [2]. While these models may provide the necessary avenues for continued follow-up, the process is still far from complete. Several factors such as lack of health insurance, distance to the new facility, lack of trained professionals who can address the survivors' needs, conflicting work schedules, and many other reasons deter survivors from pursuing follow-up care. Furthermore, yearly visits done at the treating institution may not be enough to educate and prepare the survivor for mature, independent efforts to advocate for his or her own healthcare. Because of this, grassroots efforts have arisen in many different settings to impart health literacy to the childhood cancer survivors.

The Hyundai Cancer Institute at CHOC Children's Hospital "After Cancer Treatment Survivorship" (ACTS) Program has developed a series of workshops that were initially put together to constitute an educational curriculum to be taught to survivors in an effort to address basic health-related issues. The core team is composed of an oncologist, nurse practitioner, nurse coordinator, social workers, child life specialist, psychologist, and neuropsychologist. Other subspecialists, including endocrinologists, cardiologists, dietitian, and physical and occupational therapists, support the team, and provide services based on each survivor's needs. Each member of the core team has chosen to develop a module that is presented on a quarterly basis. This chapter will outline the various modules that have been compiled thus far and

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address the participants' increased awareness following their participation. This curriculum continues to evolve in line with changing needs and emerging research. Not only does this project empower cancer survivors to understand their health needs, but facilitates opportunities for increasing involvement in their health care decisions. The program familiarizes pediatric cancer survivors with the key issues in cancer survivorship, particularly as the survivor transitions to adult-focused care. It also highlights the responsibilities associated with being a cancer survivor, as well as its exclusivity, and, it aims to promote leadership skill building, networking, friendships, and provide survivorship resources. Furthermore, this project grants the added inclusions of increased options, full power of choice, and comprehension. In utilizing the modules in this program, cancer survivors themselves are made aware of the risks from cancer treatments, and the appropriate surveillance for each, as well as increasing awareness of available resources, health insurance and employment challenges, and address issues that are outside of the scope of their annual clinic visit, ultimately enabling patients to take control of their own lives. This program is one that tackles the responsibility we have as clinicians, that of empowering pediatric survivors to become proactive for their healthcare.

30.2 Modules

The following topics are addressed in the current curriculum:

1. Personalizing Your Risk Profile: Understanding Your Treatment Summary
2. Psychosocial Advocacy
3. The Cancer Survivor and His/Her Loved Ones
4. Nutrition
5. Wellness
6. Insurance, Education, and Employment
7. Oncofertility
8. Neuropsychological Evaluation and Cognitive Rehabilitation

Each module will be discussed below.

30.2.1 Personalizing Your Risk Profile: Understanding Your Treatment Summary

As mentioned in previous chapters, pediatric cancer survivors are enjoying longer lives post-therapy well into adulthood, making it all the more important for them to be educated of their previous medical diagnoses and treatment. However, for many patients, regardless of the treatment team's efforts to educate them during their treatment, maintenance and follow up phases, understanding the cancer diagnosis or the type of therapy they received has become a daunting task. Some survivors continue to rely upon their parents or primary caregivers to navigate their healthcare pathway, and thus may not take the effort to understand it for themselves. Others may have other challenges, such as changes in residency causing changes in healthcare providers during and after treatment. Yet, as survivors mature, it becomes even more essential for them to take ownership of their health needs as much as they are able to, especially as they transition from an intensive pediatric-based model of care that tends to be more inclusive of support systems to an adult-model of care which emphasizes independence and self-reliance. It is, therefore, crucial for them to know the details of their cancer diagnosis, treatment, and potential late effects.

One of the main purposes of the childhood cancer survivor workshops is to equip young survivors with awareness of their personal risk profiles based on their cancer diagnosis and subsequent treatment. This provides a framework for the survivor to take responsibility for surveillance of emerging symptoms in order to allow for prompt medical attention of possible late effects.

With the current methods of stratification for cancer treatment and frequent protocol modifications, survivors are likely to have varying risks of late effects contingent upon treatment methods, dosing, age at treatment, and the like. Therefore, individualizing each survivor's profile is critical. In this session, survivors are given individualized copies of their Treatment Summary (Fig. 30.1a) and list of potential late effects (Fig. 30.1b). They are then asked to complete a Risk Assessment

a

1. Name of disease you had: _____
2. Date of diagnosis: _____
3. Date that all treatment was complete: _____
4. Date of any relapse: _____
5. Place of treatment: _____
6. Doctor or Nurse Practitioner most responsible for your care:

_____

Treatment Information

Chemotherapy

Name	Total dose	How given (by mouth, Intravenous (IV), Intrathecal	Name	Total dose	How given (by mouth, IV, Intrathecal
Vincristine		IV	Cytoxan		IV
Doxorubicin		IV	Prednisone		Oral
Ara-C		IV, Intrathecal	6-MP (Mercaptopurine)		Oral
Methotrexate		IV, Intrathecal	6-TG (Thioguanine)		Oral

Surgery

Date	Type of Surgery	Surgeon

Radiation Therapy

Date	Area Treated	Total Dose

Bone Marrow Transplantation

Date	Type of Transplant

Disease/Treatment Complications

Date	Complications

Fig. 30.1 (**a**) Treatment summary. (**b**) Potential late effects [3]

b

Medical Follow-Up

(*Special health monitoring needs based on treatment you received*)

Treatment	Potential late effect	Medical tests
Chemotherapy		
Any chemotherapy	• Dental abnormalities: Tooth/root agenesis. Root thinning/shortening. Enamel dysplasia.	• Dental exam and cleaning every 6 months.
Vincristine	• Peripheral sensory or motor neuropathy – Areflexia, weakness,foot drop, paresthesias.	• Annual physical
Cytoxan	• Gonadal dysfunction (ovarian): Delayed puberty, premature menopause, infertility.	• Annual physical. Check FSH, LH, Estradiol – baseline at age 13 and as clinically indicated.
	• Gonadal dysfunction (testicular): Delayed puberty, hypogonadism, infertility.	• Annual physical. Check FSH, LH, Testosterone – baseline at age 14 and as clinically indicated.
	• Acute myeloid leukemia	• Annual physical. Check CBC with differential.
	• Urinary tract toxicity: Hemorrhagic cystitis, bladder fibrosis, dysfunctional voiding, hydronephrosis, bladder malignancy.	• Annual physical. Check urine analysis
Doxorubicin	• Acute myeloid leukemia	• Annual physical. CBC with differential
	• Cardiac toxicity: Cardiomyopathy, arrhythmias, subclinical left ventricular dysfunction	• Annual physical. EKG/ECHO every __ years (depending on total cumulative dose)
Methotrexate	• Osteopenia, osteopetrosis	• Bone density evaluation (DEXA), baseline with follow-up as clinically indicated.
	• Neurocognitive deficits: Functional deficits in executive function (planning/organizing), attention, memory, processing speed, learning deficits in math and reading.	• Annual evaluation of educational/ vocational progress. Neuropsychological evaluation, baseline with follow-up as clinically indicated.
	• Hepatic dysfunction	• Annual physical. Baseline liver function test
	• Renal toxicity	• Annual physical. Check BP and urine analysis.
Prednisone	• Osteopenia, osteoporosis	• Bone density evaluation (DEXA), baseline with follow-up as clinically indicated.
	• Cataracts	• Annual eye exam.
6-MP, 6-TG	• Hepatic dysfunction	• Annual physical. Baseline liver function test
Radiation Therapy		
Radiation: All fields, including TBI	• Secondary benign or malignant neoplasm (occurring in or near radiation field).	• Annual physical. Inspection and palpation of skin and soft tissues in irradiated fields.
	• Dysplastic nevi. Skin cancer	• Annual dermatologic exam of irradiated fields.
Cranial radiation	• Brain tumor	• Annual neurologic exam.
	• Neurocognitive deficits: Functional deficits in executive function (planning/organizing), attention, memory, processing speed, learning deficits in math and reading. Diminished IQ, behavioral change.	• Annual evaluation of educational/ vocational progress. Neuropsychological evaluation, baseline with follow-up as clinically indicated.
	• Clinical leukoencephalopathy: Spasticity, ataxia, dysarthria, dysphagia, hemiparesis, seizures.	• Annual neurologic exam.

Fig. 30.1 (continued)

a

Cancer Survivorship
Risk Assessment Worksheet

Name: _____

1. What is my cancer diagnosis? _____
2. Age at diagnosis? _____
3. Date of treatment completion? _____
4. Did I receive Bone Marrow Transplant? □ Yes □ No

   If Yes, when? _____ □ Allogeneic (from donor) □ Autologous (from self)
5. Did I receive Radiation Therapy? □ Yes □ No

   If Yes, check all locations: □ Head □ Neck/Chest □ Abdomen/Pelvis □ Total body □ Extremities

   If Yes, what was the total dose of radiation received? _____
6. Which chemotherapy did I receive? (*circle all that applies*)

Alkylating Agents	**Antimetabolites**	**Anthracycline**	**Others**
Busulfan	Cytarabine	Daunorubicin**	Bleomycin
Carmustine (BCNU)	Mercaptopurine	Doxorubicin**	Dactinomycin
Cisplatin	Thioguanine	Mitoxantrone	Etoposide
Cyclophosphamide*	Methotrexate	Idarubicin	Dexamethasone
Ifosfamide			Prednisone
Lomustine (CCNU)			Vinblastine
Carboplatin			Vincristine
Melphalan			
Procarbazine			
Thiotepa			

* If I received **Cyclophosphamide**, was the dose > 7.5gm/m^2? _____

** If I received **Doxorubicin** or **Daunorubicin**, was the dose > 300mg/m^2? _____

***If I received **Methotrexate**, was the dose > 1gm/ m^2? _____

Fig. 30.2 (**a**) Risk assessment worksheet 1. (**b**) Risk assessment worksheet 2

b

Cancer Survivorship
Risk Assessment Worksheet

Bone Marrow Transplant:

* Gonadal Failure

* Requires increased doses of chemotherapy → Higher overall risks

Radiation:

Head	*Neck/Chest*	*Abdomen/Pelvis*
□ Cognitive delays	□ Thyroid dysfunction	□ Infertility
□ Secondary cancers	□ Breast cancer	□ Colon cancer
□ Hormone dysfunction	□ Heart dysfunction	□ Vascular complications
□ Stroke	□ Pulmonary fibrosis	□ Dyslipidemia
□ Cataracts		□ Hypertension

Chemotherapy: Problems to organ systems (*check all chemotherapy used*)

Heart	*Kidney*	*Liver*	*Lung*
□ Anthracycline	□ Cyclophosphamide	□ Antimetabolites	□ Bleomycin
□ Cisplatin	□ Ifosfamide	□ Dactinomycin	□ Busulfan
□ Cyclophosphamide	□ Carboplatin		
	□ Cisplatin		

Bone	*Secondary cancers*	*Infertility*
□ Prednisone	□ Etoposide	□ Procarbazine
□ Methotrexate	□ Cyclophosphamide	□ Cyclophosphamide
□ Dexamethasone	□ Ifosfamide	
	□ Doxorubicin	

Fig. 30.2 (continued)

Worksheet, a tool that breaks down the key components of their treatment summary to aid survivors in understanding what the possible late effects might be (Fig. 30.2a, b). The individualized treatment summary is designed to be utilized in conjunction with the worksheet in order to answer the required fields in Fig. 30.2a, b. The complete guidelines are available through the Children's Oncology Group website (www.survivorshipguidelines.org) [3].

Instead of lecture format, the team engages the survivors through an active question and answer session, as well as through various visual and hands-on activities. Survivors are instructed how to build the skills necessary to understand their treatment summary, and be able to identify risks for late

effects. The primary goal for these activities are to spark survivor interest and willingness to take charge of their healthcare, as well as empowerment to make informed and responsible decisions. At the end of this session, a short survey is handed out to evaluate the effectiveness of the activities.

30.2.2 Psychosocial Advocacy

While numerous survivors are able to manage their daily routines, there is a subset of survivors who experience long-term challenges in several areas of their lives. Research shows that the cancer experience complicates the challenges faced by adolescents in areas involving increasing autonomy, relationships, and the need to make decisions about education and career paths, which exert their effects in different ways at varying time points in an adolescent survivor's life [4].

The Hyundai Cancer Institute at CHOC Children's ACTS program recognized these psychosocial issues within our patient population. Survivors acknowledge that their childhood cancer experience has impacted social interactions, as well as communication and coping skills, among others. Recent literature alludes to the fact that a cancer diagnosis initiates a new life path and social role for a cancer survivor that extends over the remainder of his or her life, regardless of life expectancy [5].

The CHOC ACTS Psychosocial Advocacy curriculum was developed to educate survivors on the social impact of cancer on peers, family and sibling relationships. The goal of the module is to increase the survivors' interest in managing their own psychosocial issues, improve family/sibling communication, and encourage emotional expression through healthy coping strategies. The curriculum highlights the contrasts between healthy and unhealthy ways of expressing emotion in relation to family and sibling dynamics. In addition, we encourage increased awareness in recognizing depression and/or anxiety, as well as seeking appropriate help if such signs are exhibited. The module consists of lectures, discussions, PowerPoint presentations, handouts, and interventions that specifically target the previously mentioned areas. The team provides skill-building strategies to identify the symptoms of depression and anxiety, as well as the listing of resources available to survivors in the community. Information about contacting local mental health services for insured versus uninsured patients, and identification and ability to contact religious/spiritual support services, as well as general support groups (Livestrong, Stupidcancer.org, and Cure Search) are provided. Lastly, survivors are taught how to utilize specific techniques like journaling, positive affirmations, relaxation and guided imagery, and meditation strategies to improve coping.

The following activities are included:

1. **Ice Breaker Game**- "**Who Am I**?": Each person is assigned a celebrity name that is posted on his or her back. Participants are encouraged to ask questions that could be answered by a yes or no, until they have enough clues to guess each other's identity. Young adult survivors often feel uncomfortable even in the presence of other survivors; icebreakers often ease them towards familiarity and provide a less threatening environment.
2. **Panel of Survivors**: In an effort to offer participants the opportunity to hear about other survivors' experiences, a panel of former patients share their journeys from diagnosis through long-term survivorship. We utilize five panelists, with histories of leukemia, lymphoma, and brain tumor, who are all young adults in different stages of psychosocial development, with some enrolled in college and some employed. The panelists discuss a variety of topics, including: body image, relationships, losses, education, and employment, as well as psychosocial struggles. Participants are given the opportunity to interact with the panel through shared experiences. All participants, including panel members, are then divided into two smaller groups to process their struggles, challenges, and the coping strategies they use. Social workers, child life specialists, and a psychologist (the Psychosocial Team) facilitate these group discussions and provide teaching regarding awareness of their personal and psychosocial needs. The team also provides mental health resources and academic scholarship information.

3. **Self-Care**: The symposium ends with a meditation session guided by one of the Psychosocial Team members. Instrumental music is incorporated while a guided imagery script is read to the participants focusing on whatever theme is derived, such as acceptance, healing, connectedness, etc. Each participant is provided with a relaxation kit that includes a guided imagery script, an instrumental music CD, and a list of mental health resources.

30.2.3 The Cancer Survivor and His/Her Loved Ones

As demonstrated throughout this manuscript, cancer not only affects the patient physically, spiritually and emotionally, but the entire family as well. Family and other interpersonal relationships may become stressed and strained due to the loved one's illness. In this difficult time, relationships are often challenged by a need for improved communication, acknowledgement, and expression of feelings, and desire for normal routine. When cancer finds its way into a family, the relationships between all members are affected. Studies have shown that among family members, siblings are most affected [6]. Siblings typically experience intermittent and sometimes lengthy family separation and disruptions of their daily routine [6], which often results in decreased social contact with important sources of emotional and social support, such as parents and peers [7].

The ultimate goal of this module is to enable survivors and siblings to understand the social effects and implications of cancer on peers, family, and specifically, relationships between brothers and sisters. It is important for survivors and their siblings to understand the common reactions to cancer and to gain insight about the experiences of the other members of their family. We also aim to highlight the following goals: enhancing positive coping skills, utilizing effective ways of communicating with loved ones, practicing self-care, and learning how to access mental health resources if needed. Survivors may not recognize the repercussions of their cancer experience on their relationships with their loved ones. But by helping the survivor and siblings become aware of these psychosocial issues, and by providing them with the appropriate tools, both parties can work towards building a closer and more meaningful relationship with one another.

For this workshop, cancer survivors are encouraged to invite their siblings. We began with an ice breaker in which participants are asked to describe a favorite memory regarding their sibling(s). Oftentimes siblings choose memories that precede the illness, while others choose newer memories. Of note, it is our experience that some siblings recall few pleasant memories after their sibling was diagnosed with cancer. Others share more recent memories, stating that the diagnosis has brought them closer to their brother or sister.

After sharing these memories, the psychologist presents on "Life after Cancer: Childhood Cancer Survivors and their Siblings." This presentation serves as a catalyst for the upcoming group discussions. The following discussion topics are included: common emotions felt between survivors and siblings during and after treatment, adjustment post-cancer, changes that have occurred within their family relationships, coping with those very changes, caring for oneself, and planning for one's future and knowing ways to find help and support.

Participants are then divided into two groups, one group consisting of the siblings, and the other consisting of survivors. A child life specialist and psychologist address the siblings and asked them a series of questions to help facilitate conversation, and to discuss the emotional impact felt during their sibling's treatment. Both negative and positive emotions are recorded on an easel so they could be later shared with the larger group. Themes that siblings have discussed in previous workshops include feelings of neglect, anger, anxiety, and isolation, with some siblings confiding that they believed themselves to have grown up too quickly because their parents were not around most of the time. According to Breyer et al., a disruption occurs in the routine of family life and in the allocation of parents' time, atten-

tion and resources [8]. Siblings often speak of missing activities and events with their own friends. They express being fearful at the time of diagnosis, often not being given much information. They indicate that they typically keep their fears to themselves, refraining from asking too many questions, because they do not want to be a burden to their parents.

Children, as compared to adults, are more likely to report communication difficulties and declining of family relationships [8]. Siblings express feelings of guilt because of the jealousy felt toward their sibling at the time of diagnosis due to all the attention and gifts that were showered upon the patient. Many siblings admit that some of those feelings still exist and remain unresolved. Even though anger and sadness often accompany family trauma and upheaval, some siblings may develop a new understanding of illness, a closer relationship with their ill sibling or an increased maturity and understanding about others' misfortunes [8]. Siblings also share positive experiences, such as becoming closer as a family by overcoming obstacles, celebrating milestones and becoming more compassionate toward others in their own lives.

The social worker and the oncologist leads the second group. Survivors vary in diagnoses and each share different challenges they each had to overcome, and express both positive and negative emotions concerning their sibling and other loved ones. Survivors often mention a loss of control, an inability to socialize with friends or to participate in "normal" activities and feeling less connected to their families while undergoing treatment. The survivors express how guilty and burdensome they felt about the sacrifices their family and siblings had to make during their cancer journey. They also express not wanting their family to suffer if a relapse were to occur. Concern about disease recurrence is universal among adolescent survivors, and its presence may adversely affect the way adolescents perceive themselves [9]. Survivors talk about feeling vulnerable—a simple fall, cold, or bump they felt on their body remind them anew of the possibility of relapse. They state that this kind of feeling never really leaves them.

Survivors are asked what positive attributes they could identify within themselves, having accomplished and endured so much during and after treatment. Common characteristics often mentioned include strength and resilience, and survivors are often shocked to see that strength and resilience within themselves. Investigators sometimes report certain beneficial outcomes in individuals as a result of diagnosis and treatment, such as gaining insights and supportive experiences they would not have anticipated before diagnosis [10]. Previous classes have revealed that the emotional support from family, friends, and individual's communities not only helped them, but also their parents and siblings as well. Survivors speak of the difficulty of finding out that many friends had left them due to an inability to handle the situation. Some mentioned that they grew closer to siblings during this period because they did not always have peer support. Others state that they felt angry because of their illness, and as a result pushed siblings and loved ones away.

This often leads into a discussion about difficulties of life after cancer. Survivors have expressed that integrating and adjusting back to normal life was challenging. The issue of fatigue is a frequent theme. An illness frequently disrupts peer interaction because of observed physical differences and limitations [11]. Survivors have reported feelings that they were still treated like "the sick one" by friends and family. Feelings of anxiety and concern are expressed about their quality of life, especially when it comes to friends, dating, body image, and having a family of their own someday. Many survivors said that they felt they were no longer the same person they were before their illness, sometimes having trouble relating to others, including their siblings. All survivors, even those apparently doing quite well, continue to be concerned about their physical, psychological and social qualities of their current and future relationships [12].

The two groups are then joined together to discuss what had transpired in the separate sessions. Child life and social work lead the discussion to help lessen the pressure of starting these conversations themselves, and the feelings and

concerns written on the easels are shared. It is our experience that after some discussion, siblings often express that they did not realize the survivors felt a sense of guilt and burden that the family was suffering at the time of diagnosis, and express having a new understanding of what the survivor went through at the time. Siblings report a greater understanding of survivorship concerns such as anxiety and continued fatigue. On the other hand, survivors often state that they did not realize that their siblings held feelings of continued guilt, as well as jealousy. Both groups have expressed feelings of resentment toward one other, which neither of the parties realized. For many, this is the first time they hear of the feelings and pains the other feels. They also express feelings of love and appreciation for each other, stating that their sibling had often been there during the worst of times. Past groups have given positive feedback about the discussion, feeling they had found a greater appreciation for their siblings, and expressed wanting to have a closer relationship with the other.

We end with a group activity and handouts. Handouts are centered on communication skills, how to take care of oneself, and how to access mental health resources. The group activity is meant to affirm and acknowledge each person's journey. Bins of different colorful textured beads are laid out around the room, and each is able to pick a bead that they feel represents their sibling in some way. They are asked to describe on paper how the beads remind them of their siblings. The beads and notes are then put into envelopes and given to the siblings so that they could be opened at home. The purpose of this exercise is for every participant to know how much they mean to those around them and to encourage the use of the beads during difficult times to help reflect on the support of their sibling.

30.2.4 General Nutrition

Healthy eating is one clear pathway that leads to healthy lifestyle. For example, knowing that food high in fat and sugar can lead to undesirable weight gain and potential health problems allows survivors to make choices for the benefit of their bodies. The objectives of this module include educating survivors about up-to-date nutritious needs based on USDA recommendations, as well as developing beneficial lifestyles. Preventative options to lessen health risks will also be discussed in great detail. The module incorporates appealing, hands-on exercises with meal options and proportion size, as well as ways to care for both body and mind through exercise and meditation.

There are various resources available, including websites such as: *ChooseMyPlate.gov* [13], a website which contains the tools and information to tell us what and specifically how much we should eat. This site provides recommendations based on the 2010 Dietary Guidelines for Americans (*Dietaryguidelines.gov*) [14], which cites portion sizes for different food groups as they relate to the individual's caloric and nutrient needs. The website outlines individual eating patterns that fit into different lifestyles and food preferences.

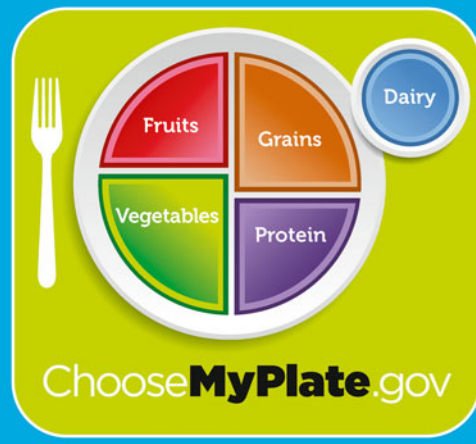
The 'MyPlate' Icon is the United States Drug Agency's (USDA) primary food group symbol, a reminder to select healthy food choices and to build a healthy plate at mealtimes. It is a visual cue which identifies the five basic food groups necessary for healthy living. Half of the plate must be filled with fruits and vegetables, and the remainder should consist of whole grains and lean proteins.

Other important tips also emphasized in the MyPlate Plan:

1. Drink water instead of sweetened drinks
2. Choose low-fat milk
3. Choose foods that are lower in sodium
4. Use moderation in foods that are high in fat or sugar such as cookies, cakes, pizza, or hot dogs
5. Be physically active everyday (Fig. 30.3).

Reading the *food label* on the product itself can help us make wise choices in consuming. Knowing how to read labels, and what to look for, helps us select provisions that are low in fat, calories, and sugar. Lastly, labels can help us determine how much of a food item is considered a healthy portion in serving size, influencing the number of servings for that particular food item a person should have.

What's on your plate?



Before you eat, think about what and how much food goes on your plate or in your cup or bowl. Over the day, include foods from all food groups: vegetables, fruits, whole grains, low-fat dairy products, and lean protein foods.

Make half your plate fruits and vegetables.

Make at least half your grains whole.

Switch to skim or 1% milk.

Vary your protein food choices.

Vegetables	Fruits	Grains	Dairy	Protein Foods
Eat more red, orange, and dark-green vegies like tomatoes, sweet potatoes, and broccoli in main dishes. Add beans or peas to salads (kidney or chickpeas), soups (split peas or lentils), and side dishes (pinto or baked beans), or serve as a main dish. Fresh, frozen, and canned vegetables all count. Choose "reduced sodium" or "no-salt-added" canned veggies.	Use fruits as snacks, salads, and desserts. At breakfast, top your cereal with bananas or strawberries; add blueberries to pancakes. Buy fruits that are dried, frozen, and canned (in water or 100% juice), as well as fresh fruits. Select 100% fruit juice when choosing juices.	Substitute whole-grain choices for refined-grain breads, bagels, rolls, breakfast cereals, crackers, rice, and pasta. Check the ingredients list on product labels for the words "whole" or "whole grain" before the grain ingredient name. Choose products that name a whole grain first on the ingredients list.	Choose skim (fat-free) or 1% (low-fat) milk. They have the same amount of calcium and other essential nutrients as whole milk, but less fat and calories. Top fruit salads and baked potatoes with low-fat yogurt. If you are lactose intolerant, try lactose-free milk or fortified soymilk (soy beverage).	Eat a variety of foods from the protein food group each week, such as seafood, beans and peas, and nuts as well as lean meats, poultry, and eggs. Twice a week, make seafood the protein on your plate. Choose lean meats and ground beef that are at least 90% lean. Trim or drain fat from meat and remove skin from poultry to cut fat and calories.
Eat 2½ cups every day **What counts as a cup?** 1 cup of raw or cooked vegetables or vegetable juice; 2 cups of leafy salad greens	**Eat 2 cups every day** **What counts as a cup?** 1 cup of raw or cooked fruit or 100% fruit juice; ½ cup dried fruit	**Eat 6 ounces every day** **What counts as an ounce?** 1 slice of bread; ½ cup of cooked rice, cereal, or pasta; 1 ounce of ready-to-eat cereal	**Get 3 cups every day** **What counts as a cup?** 1 cup of milk, yogurt, or fortified soymilk; 1½ ounces natural or 2 ounces processed cheese	**Eat 5½ ounces every day** **What counts as an ounce?** 1 ounce of lean meat, poultry, or fish; 1 egg; 1 Tbsp peanut butter; ½ ounce nuts or seeds; ¼ cup beans or peas

For a 2,000-calorie daily food plan, you need the amounts below from each food group.
To find amounts personalized for you, go to Choose**MyPlate**.gov.

USDA U.S. Department of Agriculture • Center for Nutrition Policy and Promotion
August 2011
CNPP-25
USDA is an equal opportunity provider and employer

Cut back on sodium and empty calories from solid fats and added sugars

Look out for salt (sodium) in foods you buy. Compare sodium in foods and choose those with a lower number.

Drink water instead of sugary drinks. Eat sugary desserts less often.

Make foods that are high in solid fats—such as cakes, cookies, ice cream, pizza, cheese, sausages, and hot dogs—occasional choices, not every day foods.

Limit empty calories to less than 260 per day, based on a 2,000 calorie diet.

Be physically active your way

Pick activities you like and do each for at least 10 minutes at a time. Every bit adds up, and health benefits increase as you spend more time being active.

Children and adolescents: get 60 minutes or more a day.

Adults: get 2 hours and 30 minutes or more a week of activity that requires moderate effort, such as brisk walking.

Fig. 30.3 What's on your plate?

The healing effects of alternative treatments, such as aromatherapy and acupuncture, are also discussed. A licensed acupuncturist is invited to facilitate this session. Finally, recreation time for art, music, and physical activities is provided.

30.2.5 Insurance, Education, and Employment

Survivors of childhood cancer may well face a variety of challenges related to insurance, education, and employment. These issues may have a profound effect on quality of life, encompassing both the physical and psychosocial well-being. While these issues are addressed elsewhere in this manuscript, a brief review is provided for purposes of highlighting how it is addressed in the curriculum.

Health insurance coverage is a weighty topic of concern for all Americans but especially so for cancer survivors. Such individuals require lifelong surveillance for and management of the late effects of their disease or treatment. Insurance policies, qualifications, and legal issues are confusing, complex, and ever changing. During the transition from adolescence to adulthood, survivors have a need to become more involved in the process of how their healthcare is acquired, funded, and managed. Understanding the variety of different types of options and laws regarding health care insurance is invaluable for the young adult cancer survivor, so that he or she may become an informed and responsible consumer of health care.

Many childhood cancer survivors experience educational challenges related to neurocognitive deficits resulting from their disease or therapy. The types of intellectual functions affected may result in deficits in memory, attention, and executive function, as well as processing speed and language skills. The level of disability may range from mild to severe. Multiple factors influence the ultimate neurocognitive outcome of survivors. These factors include: diagnosis, age at diagnosis, type of treatment (surgery, chemotherapy, intrathecal chemotherapy, radiation therapy, etc.), pre-treatment factors, length of time since treatment, and gender [15].

In the United States, there are certain Federal laws in place to protect the rights of students with educational problems ensuing from cancer treatment. These are discussed in more detail elsewhere in this manuscript, but a brief summary is provided herein:

1. *The Rehabilitation Act of 1973—Section 504*. The law provides accommodations for students with a "physical or mental impairment that substantially limits one or more major life activities." Each childhood cancer survivor in the United States is eligible for accommodations under this law, and all schools, colleges and universities which receive federal funding are required to comply [16].
2. *Individuals with Disabilities Education Act* (*IDEA*). This law ensures services to children and youth with disabilities throughout the nation. IDEA governs how states and public agencies provide early intervention, special education and related services [17]. It is necessary for survivors to have a well-rounded understanding of the potential educational issues related to their disease and treatment, as well as their rights as related to ongoing education. For childhood cancer survivors who do not plan to or are unable to attend college, additional resources may be available for vocational training or rehabilitation. These resources are managed individually by each state. To contact your state's vocational rehabilitation, visit your state's governmental website at www.<your state's abbreviation>.gov [18].

Childhood cancer survivors may possibly combat a variety of challenges related to employment. Impairments related to employment may be highly visible, as is the case with an amputation, or may frequently be less externally obvious, such as issues of chronic fatigue, neurocognitive deficits or neuropathic pain.

Both federal and state laws are in place to protect cancer survivors from discrimination in the workplace. The *Americans with Disabilities Act* (*ADA*) is a federal civil rights law that prohibits discrimination in all employment practices, and applies to every company with 15 or more employees. This act covers all aspects of employ-

ment, including job application, hiring, firing, advancement, compensation, training and other such employment privileges [19].

Many organizations such as the National Cancer Institute (www.cancer.gov), the American Cancer Society (www.cancer.org), the Lance Armstrong Foundation (www.laf.org) and the National Coalition for Cancer Survivorship (www.canceradvocacy.org) have developed educational materials and programs related to employment post cancer diagnosis and treatment. There are also many federally funded state vocational rehabilitation agencies in place to assist cancer survivors with employment issues.

It is important for childhood cancer survivors to be familiar with rights and available resources related to employment so that job opportunities, satisfaction and productivity can be maximized.

This module aims to educate the cancer survivors on unique types of insurance plans, qualifications and resources—the *how*/*what*/*when*/*where*/*why* issues which occur behind the scenes. The challenges in obtaining appropriate medical insurance coverage and available resources are discussed. Additionally, this module reviews laws and resources available to cancer survivors relating to educational and employment issues. Those who need it often underutilize these resources.

These topics are often glossed over during survivorship education, and many survivors and their families may not know where or how to seek this information. The information presented in this module will allow survivors to pursue options for comparable problems and seek help accordingly.

30.2.6 Oncofertility

Fertility after cancer treatment is an important area of concern for many cancer survivors. In the chaos surrounding the days of initial diagnosis, it is difficult for patients and families to understand and think about the impact of treatment on their future fertility. Most are still reeling from the shock of the cancer diagnosis, attempting to understand a complex treatment regimen, or struggling, perhaps, with questions of their own survival. In the past, oncologists have not emphasized the possibility of infertility as a long-term complication of treatment. Consequently, fertility preservation is often one of the most under prescribed and least implemented services, especially among adolescent and young adult patients [20]. However, from the patient's perspective, diagnosis of infertility may be just as devastating as the diagnosis of cancer [21]. The National Comprehensive Cancer Network (NCCN) Guidelines recommend that the risks of infertility and options for fertility preservation be discussed with all patients as early as possible after diagnosis [20].

The purpose of this workshop is to educate survivors concerning the risks of infertility based on their individual treatment exposure, and the pros and cons of current available treatment options. This module hinges on the survivor's understanding of their treatment summary and corresponding risk for infertility. A basic review of the dose-dependent effects of chemotherapy and radiation is conducted in an interactive learning environment. Following this, alternative options and their advantages, as well as disadvantages, are discussed. An informative presentation on fertility preservation is then given by one of the team members. With the current move towards use of lower doses of radiation and chemotherapy without compromising survival, as well as the use of targeted therapy and ongoing oncofertility research, the future for survivors is hopeful yet.

While discussed at greater length elsewhere in this manuscript, the risk of infertility after cancer treatment will be briefly reviewed as it is presented in the workshop. Fertility after cancer is impacted by multiple factors, including: treatment regimen, radiation and/or chemotherapy dose intensity, treatment duration, and the patient's age at the time of treatment. Alkylating agents, such as cyclophosphamide, ifosfamide, procarbazine, nitrosoureas, chlorambucil, melphalan, and busulfan, are up to four times more toxic to gonadal tissue than other chemotherapy agents [20, 22, 23]. Alkylating chemotherapy not only qualitatively affects ovarian function, but

also quantitatively shortens the reproductive life span. Determination of ovarian dysfunction may not be immediately apparent. Only 10 % of the ovary is needed to sustain menses, making the presence of menses after treatment a poor indicator of ovarian damage [23]. Because ovarian function declines with age, older female patients are more susceptible to the reproductive toxicities of chemotherapy.

Testicular tissue is very sensitive to the effects of cancer treatment, regardless of the patient's age at diagnosis. As little as 0.1 Gy can impair spermatogenesis, and only 4 Gy can cause permanent azoospermia. The Leydig cells are slightly more resistant to radiation but still become dysfunctional after 20–30 Gy [24]. These doses of radiation to the testes may be used in treatment of testicular involvement in leukemia or lymphoma, or as part of total body irradiation prior to stem cell transplant. Chemotherapy affects the testes in a similar manner, with the germ cells being much more sensitive to destruction than the Leydig cells. Because the Leydig cells continue to produce testosterone, secondary sex characteristics develop normally, although the patient may have no actual sperm production [24]. Semen evaluation is needed to further evaluate male fertility, even in the presence of normal sexual development.

Improved survival for childhood cancer survivors in the last 30 years has led to a paradigm shift among oncologists to design therapeutic approaches that reduce late effects and toxicities yet still maintain successful treatment outcomes. Much of the available evidence regarding fertility data after cancer treatment is drawn from retrospective cooperative group studies such as the Childhood Cancer Survivor Study (CCCS), a large cohort group which studies cancer survivors under the age of 21 at diagnosis [20]. The knowledge that we have derived from studying survivors has led to developments in many aspects of cancer care, including the development of fertility preservation. However, for survivors, options have remained very limited. Risk assessment tools, such as those available through *Fertile Hope* (www.fertilehope.org) have been developed and are available online to assess the individual's infertility risk based on treatment regimen and disease. More fertility preservation options continue to be developed for adolescent and adult patients. Unfortunately however, options for prepubertal patients remain limited for females, and effectively nonexistent for males.

Fertility Preservation Options for Males. Sperm cryopreservation is the most established technique for fertility preservation for post-pubertal male cancer patients. Collection of sperm should occur prior to any cancer treatment in order to optimize the quality of both the sample, and the sperm DNA. The sperm DNA quality may be compromised and the sample may be small after a single treatment, or with malignancies that involve the testicles, such as Hodgkin lymphoma or testicular cancer [22]. However, with improvements in reproductive technology, a successful fertilization may still be possible, despite poor sample quality. Sperm banking may be done locally or through a number of online companies (i.e. *Live*: *On*, a collaboration between the Livestrong Alliance and Fertile Hope), allowing the patients to collect in the privacy of their homes and mail-in the samples. In addition to the initial collection fees, the sperm banks also require yearly storage fees. Very few men, only 10–30 %, eventually return to utilize their stored sperm samples. The reasons are unclear, but do not appear to be financial [22, 25, 26].

For pubertal males with rare sperm in the ejaculate, other sperm retrieval methods may be considered. Using micro dissection testicular sperm extraction (TESE), sperm are obtained in over 50 % of cases, even in oligospermic men. The procedure involves dissection of the seminiferous tubules using an operating microscope, with biopsy and extraction of sperm. Sperm retrieved via testicular sperm extraction resulted in more pregnancies than ejaculated sperm from patients with severe oligospermia [27, 28]. Methods for TESE have been studied for pubertal and adult men, but still remain investigational.

The other methods for male fertility preservation are also largely experimental. Gonadal shielding from radiation may be attempted if the testes are in danger due to proximity to the radiation field. However, accurate care must be taken

to ensure that the appropriate doses of radiation reach the intended treatment area so that oncology care is not compromised. Hormonal suppression with gonadotropin releasing hormone (GnRH) analogs has been attempted during cancer treatment, though it has not been successful in either preserving fertility or enhancing recovery of spermatogenesis in previous smaller studies [22]. Investigations into animal models are currently underway to study testicular cryopreservation and reimplantation, and may offer fertility options in the future for pre-pubertal male cancer patients [29–31]. Currently, there are no fertility preservation options for pre-pubertal male patients.

Fertility Preservation Options for Females. Contrary to males, fertility preservation options for females are of greater complexity. The decision is influenced by a myriad of factors, including the patient's age, the availability of a sperm donor, the type of treatment, whether or not the cancer is involving the ovaries, the patient's ovarian reserve, and whether or not adequate time is available prior to starting cancer treatment [22, 23]. Methods that involve embryo or oocyte retrieval and preservation can be time-consuming and delay the initiation of cancer therapy by 2–6 weeks or more.

Embryo cryopreservation has been an established method of fertility preservation and treatment for many years [22, 23]. The process requires a sperm donor or partner, as the embryos, by definition, must be fertilized and cryopreserved at cleavage-stage. The success of embryo retrieval and cryopreservation depends on the number of embryos obtained, and consequently increases with more cycles completed. Each cycle of ovarian stimulation requires daily injections of follicle-stimulating hormone for 2 weeks from the start of the menstrual cycle, with blood tests and serial transvaginal ultrasounds needed to monitor follicle development. Oocytes are collected via ultrasound-guided transvaginal needle aspiration under intravenous sedation [22]. The entire process can be quite costly: financially, as most insurance companies do not offer fertility services, and logistically, since every cycle will delay the start of cancer treatment by 2–6 weeks. Similar to men, epidemiological studies indicate that few women actually return to utilize their embryos [22]. Time frame availability depends on the diagnosis and cancer treatment plan. Diagnoses that are treated initially with surgery and delay the start of chemotherapy or radiation for several weeks or months may allow for oocyte collection. However, for most patients starting treatment with upfront chemotherapy or radiation, such a significant time delay could be fatal.

Oocyte preservation is an acceptable alternative for females without a sperm donor (i.e. children, adolescents, females without a partner, or those wishing to delay fertilization) [22, 23]. However, oocyte preservation is problematic because of technical limitations and the inherent fragility of mature oocytes, leading to low pregnancy rates (less than 20 %), and limited availability of the procedure [23]. The process involves the same time delays as embryo cryopreservation, which, as well, limits its utility in patients requiring urgent initiation of chemotherapy.

Ovarian tissue cryopreservation and transplantation is another promising, though still experimental, option for children and adolescents, or other female patients without a donor or partner. It does not require a sperm donor, and collection may occur at any time during the cycle. Any patient who will receive chemotherapy or radiation targeting the ovaries is eligible, so long as there is little risk of the malignant involvement of ovarian tissue [23]. Tissue collection can be coordinated with initial surgery for biopsy or central line placement. The ovarian tissue is cut into thin strips, reviewed thoroughly for evidence of malignancy, and then cryopreserved. After the patient completes therapy, the tissue is thawed and implanted into the pelvis or subcutaneous tissue. Subsequent revascularization of the graft can lead to fibrosis and loss of up to 60 % of the graft tissue. FSH stimulation is used both to preserve the graft and to stimulate oocyte development once the graft becomes hormonally active in three-to-four months [23]. Several case reports of successful pregnancies have been reported but further investigation is needed to determine actual pregnancy rates [22, 32–34]. One potential concern in reimplantation of ovarian tissue is the

risk of reintroduction of malignant cells. No cases of cancer recurrence have been reported, although the procedure is new and experience is limited. Thorough investigation of the ovarian tissue for evidence of occult malignant cells should limit this risk [22].

Ovarian transposition may be an option for those patients who may undergo radiation to the pelvis. This involves surgical repositioning of the ovaries out of the radiation field and should be done prior to radiation to limit the remigration of the ovary back into the radiation field. Repositioning of the ovaries may still not, however, prevent damage to the ovaries from scatter radiation. If future infertility treatment is needed, oocyte retrieval may be complicated due to the fact that the exact location of the ovaries may not be known [22].

Ovarian suppression with GnRH agonist or antagonists has been investigated, though with conflicting results. Small observational studies employing GnRH analogs during chemotherapy suggest that these agents may preserve menstrual function [35]. However, menstrual function does not always equate with fertility. The interaction of drugs in hormone sensitive tumors, such as breast cancer, may worsen the effectiveness of chemotherapy overall [22, 23]. Further research is needed in this area to determine the impact of these agents on fertility preservation.

Despite the advent of in vitro fertilization, adoption, and surrogacy, the options are far from perfect, and often very costly. However, as techniques are perfected, the likelihood of higher success rates may still be achievable in the near future.

30.2.7 Neuropsychology Interventions/Cognitive Rehabilitation

Several risk factors have been identified which increase the risk of adverse neurocognitive side effects, including: younger age, treatment complications, use of intrathecal methotrexate, female gender, and use of radiation [36, 37]. Given that many pediatric cancers are diagnosed at a young age in children, the emerging skills tend to be the ones at greatest risk, and can include, but are not limited to: language development, reading, memory, fine motor skills, processing speed, and attention and planning and organization skills [38, 39]. Therefore, based on these risk factors, continued education for pediatric cancer and ongoing oncofertility research, the future for survivors and their families will aid in providing the critical psychoeducation and awareness of their personal, individual need for follow-up.

A model that is used to help identify children at greatest risk for adverse neurocognitive side effects could help improve quality of life by providing earlier access to services that would reduce the impact of these adverse effects. This model implements active screening programs to identify these children at greatest risk, and subsequently, forms comprehensive follow-up diagnostic testing and ultimate development of a treatment plan involving specific support services and interventions for the areas of identified need. This furthermore includes recommendations for important wrap-around services through tertiary care centers (e.g., outpatient clinics as well as intervention through the school district). A thorough assessment to help develop such a plan includes measurement of the domains of attention, memory, language, sensory and motor skills, as well the customary skills evaluation of intellectual and academic achievement. Furthermore, a proper and thorough evaluation of the family's available resources as well as the child's behavioral, adaptive, and psychosocial needs is also a critical process of the more comprehensive evaluation. It should be noted that, given the recent advances in treatment of pediatric cancer patients, such as the use of conformal radiation therapy, these have notably helped reduce some of the more overt global cognitive declines noted in patients who were previously treated with conventional radiation therapy [38]. Therefore, the standardized use of baseline and serial assessment has held a critical component in ascertaining the necessary sensitivity and specificity for the detection of more modest adverse neurocognitive side effects typically found in patients undergoing current treatment protocols [38, 39].

In reality, adverse neurocognitive side effects may not emerge until years after completion of treatment [40]. Therefore, pediatric cancer survivors may not show overt deficits on initial screenings assessing IQ and academic aptitude. As a result, these findings may mislead, and often are not an accurate portrayal of the learning risks based on the delayed emergence of late effects, which surface over time and would be detected through regular follow-up serial assessment [38]. Children tending to fall into the category of high risk for neurocognitive late effects include children with brain tumors and acute lymphoblastic leukemia. Therefore, such children are screened more aggressively in our clinics, and undergo routine follow-up neuropsychological testing. We also provide psychoeducation to the families early on in the treatment process. Young patients at risk are screened in follow-up clinic, and are then scheduled for comprehensive neuropsychological testing prior to their transition back to school. They also continue to undergo regular evaluations for several years after completion of treatment. While pediatric cancer patients may be informed of the possibility of cognitive late effects early in their treatment, this information is often overshadowed by the acute medical crises and imminent treatment decisions which families need to make shortly after their child is diagnosed. The fact that children may present with acute life-threatening conditions or complications immediately following diagnosis (e.g., acute hydrocephalus and increased intracranial pressure, severe sepsis, etc.) further lessens the likelihood that they will remember and absorb information given about possible adverse neurocognitive side effects. In addition, survivors and their families are also reminded about late effects at their yearly follow-up appointments, although survivors sometimes minimize their academic difficulties for a variety of reasons, which include the desire to not be treated differently from their peers. One center has proposed a neurocognitive screen to help identify those children who would benefit from a more thorough neuropsychological evaluation [41].

As part of a comprehensive multisystem level of care, we provide educational symposiums, workshops and seminars for the cancer survivors and their families. Many of our workshops involve a half-day block of presentations with question and answer sessions. A panel of experts from different disciplines gives presentations on distinct topics. The panel also openly engages in answering questions with patients and their families. The workshops are directly constructed for survivors, and almost always include a speaker who has expertise in neurocognitive late effects, an inclusion which provides important psychoeducation on resources and accommodations to address their neurocognitive late effects. Long-term survivors have already overcome the acute and life-threatening aspects of their illness. It is at this time that they must become aware of subtle neurocognitive side effects, which are more likely to emerge after completion of treatment [38, 40]. Families in this stage often have more emotional reserve to address these long-term issues, since the patient is no longer in acute medical crisis. We have found that the timing of the symposiums addressing neurocognitive late effects is often best received in patients nearing completion of treatment and transitioning back into their schools, but it can also be very beneficial to long-term survivors that have been in remission for several years. As mentioned in other sections, the integration of education about neurocognitive late effects into the symposium schedule was directly in response to the feedback provided by the CHOC Children's ACTS program. CHOC Children's interest in obtaining feedback from survivors and their families was based on the value this organization places on family-centered care.

30.3 Conclusions

Educating childhood cancer survivors cannot be accomplished solely through annual clinic visits. Developing a curriculum model that can be cyclically offered outside of the clinic will help inculcate health literacy and personal advocacy as part of ongoing education for the cancer survivor. By utilizing engaging and informative activities, we are hoping to employ the survivor as they journey through the complex maze of survivorship.

As research continues, the topics and recommendations will likewise evolve, though we have found our program to provide an excellent foundation for the childhood cancer survivor.

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Part VI

Appendix

Appendix: Resources

31

Beth Earhart

1. General Information
   a. Children's Oncology Group: Online information regarding diagnosis, treatment, coping, clinical trials, and follow-up care of the individuals with cancer. COG is a network of more than 200 hospitals, forming the world's largest pediatric cancer research consortium.
      i. www.childrensoncologygroup.org
   b. Hope Portal: Developed by Children's Hospital Los Angeles, this resource provides a wealth of information and links.
      i. www.searchhope.org
   c. National Cancer Institute: Federal governmental agency with a primary focus of providing research and training resources. In addition to supporting research, it collects and disseminates information regarding cancer treatment and outcomes.
      i. www.cancer.gov
   d. Pediatric Blood and Marrow Transplant Consortium: Provides information for parents of children undergoing blood and marrow transplants.
      i. www.pbmtc.org
   e. American Cancer Society: Provides general information, support and resources.
      i. www.cancer.org
   f. Canadian Cancer Society: Provides general information, support and resources for Canadians.
      i. www.bc.cancer.ca/ccc/
   g. Cancer Care: A nonprofit organization providing a variety of services and resources for cancer patients and their families
      i. www.cancercare.org
   h. American Childhood Cancer Organization: Nonprofit organization that provides information and support for children and adolescents with cancer and their families.
      i. www.acco.org
2. Medical and Health Insurance
   a. The National Children's Cancer Society
      i. http://www.beyondthecure.org/medical
         1. Late-effects assessment to develop a personalized list of potential medical and educational late effects specific to one's diagnosis and treatment.
            a. http://lea.beyondthecure.org
         2. Health Insurance
            a. http://www.beyondthecure.org/insurance
         3. Knowing and understanding one's insurance policy, rights, and the current health care reform.
            a. http://www.healthcare.gov/index.html

The authors assume no authorship of or responsibility for the use of the websites and resources contained therein.

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b. Foundation for Health Coverage Education: Works to simplify public health insurance eligibility information in order to help more people access coverage. Also available are downloadable resources detailing the public and private health coverage programs available in each state.
   i. http://coverageforall.org/
c. Health and You: Coalition made up of some of the country's leading organizations that represent consumers, patients, physicians, nurses, hospitals and pharmacists. Provides the public with easy-to-understand information about the health care law.
   i. http://www.healthcareandyou.org/
d. American Cancer Society: Covers financial and insurance issues in regards to children diagnosed with cancer.
   i. http://www.cancer.org/treatment/childrenandcancer/whenyourchildhascancer/childrendiagnosedwithcancerfinancial-andinsuranceissues/index
e. The Patient Access Network Foundation: Provides help to underinsured patients for out-of-pocket expenses for life-saving medications.
   i. http://www.panfoundation.org/
f. Long-term follow-up guidelines for survivors of childhood, adolescent, and young adult cancers. Website includes a list of individual health links (English and Spanish)
   i. http://www.survivorshipguidelines.org/
      1. Long-term follow-up program resource guide
         a. http://www.survivorshipguidelines.org/pdf/LTFUResourceGuide.pdf
      2. Risk-based, exposure-related clinical practice guidelines that provide recommendations for screening and management of late effects in survivors of pediatric malignancies.
         a. http://www.survivorshipguidelines.org/pdf/LTFUGuidelines.pdf
      3. Instructions, guidance, and template to create a comprehensive treatment summary.
         a. http://www.survivorshipguidelines. org/pdf/GuidelinesAppendixI.pdf
      4. Appendix of health links (English and Spanish).
         a. http://www.survivorshipguidelines.org/pdf/GuidelinesAppendixII.pdf
      5. Finding and paying for healthcare after treatment for childhood cancer (English and Spanish).
         a. http://www.survivorshipguidelines.org/pdf/FindingPayingforHealthcare.pdf
      6. Reducing the risk of second cancers (English and Spanish).
         a. http://www.survivorshipguidelines.org/pdf/ReducingSecondCancerRisk.pdf
g. Fertility
   i. http://www.beyondthecure.org/medical_fertility
      1. American Society for Reproductive Medicine
         a. http://www.asrm.org/
      2. Fertile Hope
         a. http://www.uicivf.org/uploads/08_FH_Onc_FastFacts.pdf
      3. Resolve: The National Infertility Association
         a. http://www.resolve.org/
   ii. Angels of Hope, Creating Miracles: Awards monetary grants to financially burdened married couples facing the cost of fertility assistance necessary to bring a child into their lives.
      1. http://www.angelsofhopeinc.org/creatingMiraclesGrant.htm
   iii. Attain Fertility: Provides education and answers questions surrounding cancer and fertility.
      1. http://attainfertility.com
   iv. Bonei Olam: Mission is to help every couple trying to build a family,

regardless of prior illness or post treatment.
1. http://www.boneiolam.org/services_detail.php?service=prepostcan

v. B.U.M.P.S., Inc.: Goal is to help create or expand families by in vitro fertilization.
1. http://www.yourbump.org/about.html

vi. The InterNational Council for Infertility Information Dissemination (INCIID): Helps individuals and couples by providing an In Vitro Fertilization (IVF) Scholarship to those in need.
1. http://www.inciid.org/

vii. Lotus Blossom Consulting: Provides consulting on infertility issues, planning, financial actions, and an in-depth understanding of cancer survivor issues.
1. http://lotusblossomconsulting.com/

viii. National Adoption Foundation: Offers financial aid to families to help offset expenses directly associated with the adoption process and the formation of families.
1. https://fundyouradoption.org/fund-your-adoption/our-programs/naf-grants/

ix. The Oncofertility Consortium at Northwestern University: Helps to navigate the complex fertility issues facing patients with cancer.
1. http://oncofertility.northwestern.edu/

x. ReproTech, Ltd. (RTL): Focuses exclusively on the long-term storage of reproductive tissue. Offers services at rates that are affordable and cost-effective. Also, offers programs that can help with fertility preservation costs.
1. http://reprotech.com/cryostorage/fertility-preservation-101/fertility-preservation-101-brochure-intro.html

h. State and Federal Programs/Insurance

i. Medicaid: Provides health coverage to children, families, pregnant women, the elderly, and people with disabilities.
1. http://www.medicaid.gov/

ii. State Children's Health Insurance Program (S-CHIP): Provides free or low-cost health coverage to children up to age 19. Covers U.S. citizens and eligible immigrants.
1. http://www.healthcare.gov/using-insurance/low-cost-care/childrens-insurance-program/

iii. Affordable Care Act: Lists a variety of alternatives to the individual private insurance market
1. http://medicaid.gov/affordablecareact/affordable-care-act.html

iv. Fair Health: Brings transparency to healthcare costs and health insurance information through comprehensive data products and consumer resources.
1. http://www.fairhealthconsumer.org/

v. Patient Services, Inc.: Helps people who live with certain chronic illnesses or conditions locate suitable health insurance coverage and access ways to satisfy expensive co-payments.
1. https://www.patientservicesinc.org

vi. Consolidated Omnibus Budget Reconciliation Act (COBRA): Gives employees the right to pay premiums for and keep the group health insurance that they would otherwise lose after reducing their work hours, quitting their jobs, or losing their jobs.
1. http://www.dol.gov/ebsa/COBRA.html

i. Drug-Coverage Programs

i. Medicare Prescription Drug Discount Card: Can help save money on prescription drugs for people with Medicare.Contact:1-800-MEDICARE (1-800-633-4227)
1. http://www.medicare.gov/Pubs/pdf/11109.pdf

ii. Together RX Access Card: Individuals and families without prescription drug coverage can gain access to immediate savings on hundreds of brand-name and generic products.
1. http://www.togetherrxaccess.com/

iii. Needy Meds: Devoted to helping people in need find assistance programs to help them afford their medications and costs related to health care.
1. http://www.needymeds.org/index.htm

iv. The National Children's Cancer Society (NCCS): Offers a free prescription drug card that provides significant savings on generic and branded drugs.
1. theNCCS.agelity.com

v. Medscape: A source of exhaustive information on prescription drugs and medical articles.
1. www.medscape.com

j. Advocacy

i. National Coalition for Cancer Survivorship: Understanding your health insurance
1. http://www.canceradvocacy.org/cancer-advocacy/advocacy-in-action/
a. Informational book on what cancer survivors need to know about health insurance
i. http://www.canceradvocacy.org/shop/health-insurance-publication/

ii. Patient Advocate Foundation: Provides patients with arbitration, mediation, and negotiation to settle issues with access to care, medical debt, and job retention related to their illness. (English and Spanish). Contact: 800-532-5274
1. http://www.patientadvocate.org/

iii. State Insurance Commissioner: Insures that consumers are protected. Contact: 816-783-8500
1. http://www.naic.org/state_web_map.htm

iv. Employee Benefits Security Administration (EBSA): Provides health benefits education focusing on life and work events and the benefit decisions they impact along with information on federal health benefits laws.
1. http://www.dol.gov/ebsa/consumer_info_health.html#.UOODP2hws20

v. Alliance for Childhood Cancer: Established to advocate on behalf of cancer patients. The alliances focuses on the advancement of research and policies to prevent cancer, and improve public education, and the diagnosis, treatment, supportive care and survivorship of children and adolescents with cancer.
1. http://www.allianceforchildhoodcancer.org/

vi. Cancer Legal Resource Center: Provides free information and resources on cancer-related issues to cancer survivors, caregivers, health care professionals, employers, and others coping with cancer.
1. http://www.disabilityrightslegalcenter.org/cancer-legal-resource-center

vii. Children's Cause for Cancer Advocacy: Empowers survivors and families through educational conferences, materials, and tools to become effective advocates and improve their quality of life.
1. http://www.childrenscause.org/

viii. LIVESTRONG: Works to raise awareness, increase outreach and facilitate collaboration in an effort to improve the cancer experience. (English and Spanish)
1. http://www.livestrong.org/

ix. PCRM The Cancer Project: Promotes cancer prevention and survival through a better understanding

through research, education, and advocacy.
1. http://pcrm.org/health/cancer-resources/

x. Association of Cancer Online Resources: A unique collection of online communities designed to provide timely and accurate information in a supportive environment.
1. http://www.acor.org/

xi. National Cancer Legal Services Network: Promotes increased availability of free legal services programs so that people affected by cancer may focus on medical care and their quality of life.
1. http://www.nclsn.org/

k. Long Term Follow Up Clinics
i. The National Children's Cancer Society offers a list of clinics by state.
1. http://www.beyondthecure.org/clinics

3. Employment, Disability and Social Security
a. The National Children's Cancer Society
i. Addresses entering the workforce and vocational rehab
1. The Americans with Disabilities Act (ADA) (English and Spanish). Contact: 1-800-514-0301
a. http://www.ada.gov/
2. The Equal Employment Opportunity Commission (EEOC). Enforces the employment section of the ADA. Contact: 1-800-669-4000
a. http://www.eeoc.gov/
3. Department of Rehabilitation (DOR). Assists those with disabilities obtain and retain employment and maximize their equality and ability to live independently in their communities.
a. www.your state's abbreviation.gov
4. CancerCare: Offers limited assistance for cancer-related costs and resources. Also addresses cancer and the workplace.
a. http://www.cancercare.org/financial
b. http://www.cancercare.org/connect_workshops/237legal_protections_workplace_062911_2011-06-29

b. Cancer and Careers: Dedicated to empowering and educating people with cancer to thrive in their workplace by providing expert advice, interactive tools and educational events. Also includes manuals and presentations for healthcare professionals.
i. http://www.cancerandcareers.org/en

c. Job Accommodation Network: Helps people with disabilities enhance their employability and show employers how to capitalize on the value and talent that people with disabilities add to the workplace.
i. http://askjan.org/index.html

d. Family Medical Leave Act
i. http://www.dol.gov/whd/fmla/

e. U.S. Department of Labor One-Stop Career Centers: Learn about careers, find career information, and locate career resources and advice.
i. http://www.dol.gov

f. National Coalition for Cancer Survivorship
i. Explains how employment discrimination laws protect cancer survivors, what one can do to avoid discrimination, and what one can do to enforce his/her legal rights. Includes a handbook on employment rights as a cancer survivor.
1. http://www.canceradvocacy.org/shop/working-it-out-cancer-survivor-employment-rights-eng/

g. Disability.Gov: The federal government website for comprehensive information on disability programs and services in communities nationwide. Provides answers to questions about everything from Social Security benefits to employment to affordable and accessible housing.
i. https://www.disability.gov/

h. Social Security: Program that pays benefits to disabled adults and children who have limited income and resources.
i. http://www.ssa.gov/pgm/ssi.htm

i. Bear Necessities Pediatric Cancer Foundation: A Bear Hug is a customized experience that brightens the life of a child going through cancer and provides immediate family support for financial burdens and essential needs.
   i. http://www.bearnecessities.org/HomePage.aspx
j. Children's Cancer Association: Engages a community network of caring people and organizations uniting families with resources and support during a difficult and financially depleting journey. Helps families with specific essential needs, provide connections to local and national resources, and often responds "yes" to a child's special wish not met by other organizations.
   i. http://joyrx.org/
k. Working Against Cancer: Support for young adult cancer patients through age-appropriate mentoring, self-evaluation tools, and career opportunity referrals.
   i. http://www.workingagainstcancer.org/

4. Education
   a. Educational issues following treatment of childhood cancer (English and Spanish)
      i. http://www.survivorshipguidelines.org/pdf/EmotionalIssues.pdf
   b. American Childhood Cancer Organization: Non-profit organization that provides a wealth of information regarding educational issues facing the childhood cancer survivor and how parents and teachers can meet their needs most effectively.
      i. www.acco.org
   c. The Association of Pediatric Hematology Oncology Educational Specialists (APHOES): Organization primarily devoted to disseminating information in addressing the educational needs of cancer and hematology patients.
      i. www.aphoes.wildapricot.org
   d. Cancervive teacher's guide for kids with cancer.
      i. http://www.cancersourcekids.com/parents/schoolintro.cfm?usertypeid=3
   e. United States Department of Education/Office of Civil Rights: Serves student populations facing discrimination and enforces several federal civil rights laws that prohibit discrimination in programs or activities including the Americans with Disabilities Act and the Rehabilitation Act.
      i. http://www2.ed.gov/about/offices/list/ocr/know.html
   f. American Cancer Society: Discusses returning to school, physical changes, schoolwork, learning problems, IEP's and 504 Plans, and educating others.
      i. http://www.cancer.org/treatment/childrenandcancer/whenyourchild-hascancer/children-diagnosed-with-cancer-returning-to-school
   g. Center for Parent Education and Resources: Excellent resource that includes information regarding educational issues and strategies, as well as information regarding student rights.
      i. http://www.parentcenterhub.org/
   h. Learning Disabilities Association: Non-profit organization providing education and resources for children and adults with learning disabilities.
      i. www.ldanatl.org
   i. Educational financial assistance and scholarships
      i. The National Children's Cancer Society: Provides financial assistance for families during treatment and college scholarships for childhood cancer survivors.
         1. http://www.beyondthecure.org/assist
      ii. Cancer Survivors' Fund: Provides scholarships for young cancer survivors to give them a new purpose and meaning in life and enable them to continue their college education.
         1. http://www.cancersurvivors-fund.org/
      iii. Ped-Onc Resource Center: Lists college scholarships for children with cancer.
         1. http://www.ped-onc.org/scholarships/

iv. National Grace Foundation: Provides free college admissions and financial aid counseling to pediatric cancer patients and survivors.
   1. http://www.graceamerica.org/
v. The SAMFUND for Young Adult Survivors of Cancer: Gives young adult survivors the tools and resources to overcome financial challenges and move forward with their lives.
   1. http://www.thesamfund.org/
vi. College Scholarship.org: Offers many varieties of funding (scholarships, grants, student loans).
   1. http://www.collegescholarships.org/
vii. Cancer for College: Provides scholarships to assist cancer survivors in reaching their goal of a college education.
   1. http://www.cancerforcollege.org
viii. The National Collegiate Cancer Foundation: Provides need-based financial support to young adult survivors who are pursuing higher education throughout treatment and beyond.
   1. http://www.collegiatecancer.org/
ix. FinAid: Contains information about scholarships for cancer patients, cancer survivors, and children of a cancer patient or survivor.
   1. http://www.finaid.org/scholarships/cancer.phtml
x. Stephen T. Marchello Scholarship Foundation: Allocating post secondary scholarship monies to survivors of childhood cancer, specifically current-year high school graduates.
   1. www.stmfoundation.org
xi. Rise Above It: Provides consultation and financial grants to individuals and families with immediate needs in their fight against cancer.
   1. http://www.raibenefit.org/
xii. Ryan Mullaly Second Chance Scholarship: Available to students who were diagnosed with cancer or had a recurrence of cancer between the ages of 13 and graduation from high school and who underwent treatment with chemotherapy and/or radiation.
   1. http://www.scholarships4students.com/ryan_mullaly_second_chance_scholarship.htm

j. Individuals with Disabilities Education Act (20 U.S.C. §1400 et seq.)
   i. http://uscode.house.gov/view.xhtml?req=(title:20%20section:1400%20edition:prelim)%20OR%20(granuleid:USC-prelim-title20-section1400)&f=treesort&edition=prelim&num=0&jumpTo=true
k. No Child Left Behind:
   i. http://www2.ed.gov/nclb/landing.jhtml
l. Family Educational Rights and Privacy Act
   i. http://www2.ed.gov/policy/gen/guid/fpco/ferpa/index.html
m. Electronic Code of Federal Regulations, *Nondiscrimination on the Basis of Handicap in Programs or Activities Receiving Federal Financial Assistance* (34 C.F.R. §104.1 et seq.):
   i. http://www.ecfr.gov/cgi-bin/text-idx?c=ecfr&tpl=/ecfrbrowse/Title34/34cfr104_main_02.tpl
n. Electronic Code of Federal Regulations, *Assistance to States for the Education of Children with Disabilities*. (34 C.F.R. §300.300 et seq.):
   i. http://www.ecfr.gov/cgi-bin/text-idx?c=ecfr&tpl=/ecfrbrowse/Title34/34cfr300_main_02.tpl
o. U.S. Department of Education links to state departments of education:
   i. https://www2.ed.gov/about/contacts/state/index.html?exp=3
p. U.S. Department of Education Office for Civil Rights:
   i. http://www.ed.gov/about/offices/list/ocr/index.html

q. Examples of Accommodations
   i. http://www.slane.k12.or.us/files/2010_Examples_of_Program_Accomodations.pdf
   ii. http://www.chadd.org/Portals/0/AM/Images/Understading/504accommodations.pdf

5. Family and Individual Psychological support
   a. Emotional issues following treatment of childhood cancer (English and Spanish).
      i. http://www.survivorshipguidelines.org/pdf/EmotionalIssues.pdf
   b. The National Children's Cancer Society
      i. Explains your emotions, dealing with stress and anxiety, post-traumatic stress disorder, depression, and attending a support group.
         1. http://www.beyondthecure.org/emotional
   c. American Cancer Society: Explains making treating decisions, coping with side effects, handling financial matters, caregiving, and living well after cancer. Also, has programs and services to help manage cancer treatments and recovery and finding emotional support.
      i. http://www.cancer.org/treatment/index
   d. The Cancer Support Community: Dedicated to providing support, education, and hope to people affected by cancer.
      i. http://www.cancersupportcommunity.org/Default.aspx
   e. Group Loop: A safe place for teens touched by cancer to connect to find support, education, and hope while dealing with cancer.
      i. http://www.grouploop.org/
   f. The Wellness Community: Offers a Virtual Wellness Community and emotional support for those dealing with cancer and their caregivers.
      i. www.thewellnesscommunity.org
   g. Imerman Angels: Carefully matches a person touched by cancer (cancer fighter or survivor) with someone who has fought and survived the same type of cancer.
      i. http://www.imermanangels.org/
   h. Stupid Cancer: Empowers young adults affected by cancer through innovative and award-winning programs and services.
      i. http://stupidcancer.org/index.shtml
   i. Leukemia and Lymphoma Society: Provides guidance and support to patients touched by blood cancers and the health care professionals who care for them.
      i. http://www.lls.org/#/
   j. Planet Cancer: Largest online community of young adults who have been affected by cancer. It's a place where members find and communicate with other young adults around the world about what's on their minds.
      i. http://myplanet.planetcancer.org
   k. I'm too young for this! Cancer Foundation: Social network for young adult cancer survivors and care providers that offers support to help improve quality of life for young adults (ages 15–39) affected by cancer.
      i. http://i2y.com
   l. MyLifeLine.org: Encourages cancer patients and caregivers to create free, customized websites to build an online support community of family and friends.
      i. https://www.mylifeline.org
   m. SeventyK: Mission is to change cancer care by educating patients, families, and their healthcare providers about age appropriate treatment and the unique needs of the adolescent and young adult (AYA) cancer patient.
      i. http://seventyk.org/
   n. Locks of Love: Nonprofit organization that provides hairpieces to financially disadvantaged children under the age of 18 suffering from long-term hair loss.
      i. www.locksoflove.org
   o. Starbright World: A virtual hangout where one can build on existing friendships or create new ones. Starbright is an online social network where teens (ages 13–20) who have serious medical conditions, and siblings of seriously ill teens,

can connect via moderated chat rooms, games, bulletin boards, videos, and more.
    i. https://www.starbrightworld.org
p. The Ulman Cancer Fund for Young Adults: Works to support, educate, connect, and empower young adult cancer survivors.
    i. http://www.ulmanfund.org/
q. Vital Options International: Began as the first psychosocial and advocacy organization specifically targeted to address the unique needs of young adults with cancer. Includes The Group Room (videos) clinical programs, featuring discussions with the world's leading medical professionals.
    i. http://www.vitaloptions.org/
r. 2-1-1: Telephone number that connects callers to information about critical health and human services available in their community.
    i. http://www.211us.org/
s. Caring Bridge: An online space where one can connect, share news, and receive support.
    i. http://www.caringbridge.org/
t. American Childhood Cancer Organization: Mission is to provide information and support for children and adolescents with cancer and their families.
    i. Offers Childhood Cancer Guides Publication and other free books (topics include: educating parents and teachers, siblings, animated cartoon DVD for children with cancer, and several journals).
        1. http://www.acco.org/we-can-help/
u. Now What: Educates, supports, connects, and empowers young people throughout their cancer experience.
    i. http://www.nowwhat.org.au/
v. American Psychological Oncology Society: Has a toll-free Helpline for people with cancer and their caregivers to obtain a local referral for counseling and other support services to manage cancer-related distress.
    i. www.apos-society.org
w. CureSearch for Children's Cancer: Supports patients and families by providing tools designed to help them through the cancer experience.
    i. http://www.curesearch.org/
    ii. Look Good, Feel Better for Teens: A free public service program that provides useful information and tips for adolescents dealing with the appearance and sociological side-effects related to cancer and its treatment.
        1. www.lookgoodfeelbetter.org
x. Support Groups
    i. National Association of Social Workers: Addresses topics such as living with an illness, anxiety, depression, and grief and loss.
        1. http://www.naswdc.org/
    ii. American Counseling Association: Offers a counselor directory to find a local professional counselor.
        1. http://www.counseling.org/aca-community/learn-about-counseling/what-is-counseling
    iii. CancerCare: Offers online, telephone, and face-to-face support groups.
        1. http://www.cancercare.org/support_groups
    iv. Teens Living with Cancer: Provides online resources dedicated to helping teens deal with the late affects of cancer with an online support group. (English and Spanish)
        1. http://www.teenslivingwithcancer.org/
    v. Teen Impact: Provides free social networking, camping trips, survivor retreats and peer-to-peer counseling for young adults affected by cancer.
        1. www.teenimpactprogram.com
y. Activities
    i. First Descendents: Offers young adult cancer fighters and survivors a free outdoor adventure experience designed to empower them to climb, paddle and surf beyond their diagnosis, defy their cancer, reclaim

their lives, and connect with others doing the same.
1. http://firstdescents.org/

ii. True North Treks: A non-profit organization dedicated to supporting young adult cancer survivors by connecting them with nature, other survivors, and oneself.
1. www.truenorthtreks.org

iii. River Discovery: Adventure programs for teenage cancer survivors on the Salmon River: 6 days of rafting, camping, hiking, and exploring.
1. www.riverdiscovery.org

iv. Prepare to Live: Uses the power of the web and documentary-style filmmaking to provide help, hope, information and inspiration specifically to young adults coping with cancer worldwide.
1. www.preparetolive.org

v. Next Step: Provides retreats and workshops that help young adults with cancer by providing a place to feel safe enough to laugh, share experiences, and create a sense of community with peers.
1. www.nextstepnet.org

vi. Cancer Climbers: Offers experiential and motivational adventures and excursions such as extreme climbing and summit tours.
1. http://cancerclimber.org/home.php

z. Camps

i. Ped-Onc Resource Center: List of camps for children by state.
1. http://www.ped-onc.org/cfissues/camps.html

ii. Children's Oncology Camping International Association: Strengthens the international community of camps for children with cancer and their families through networking, advocacy, and education.
1. http://www.cocai.org/

iii. Camp Make-A-Dream: A camp in Montana that provides a medically-supervised, cost-free experience for children, young adults and families affected by cancer.
1. www.campdream.org

iv. Camp Ronald McDonald for Good Times: Offers a variety of residential camping opportunities for cancer patients, their siblings and parents all year long.
1. http://www.campronaldmcdonald.org/

aa. Siblings

i. Supersibs!: Ensuring that siblings of children with cancer are honored, supported and recognized so they may face the future with strength, courage and hope.
1. http://www.supersibs.org/
   a. List of camps for siblings of children with cancer
      i. http://www.supersibs.org/get-help/sibcamp-connect/find-a-sibling-camp/

ii. Sibling Support Project: A national effort dedicated to the life-long concerns of brothers and sisters of people who have special health, developmental, or mental health concerns.
1. http://www.siblingsupport.org/

iii. Rainbows International Grief support Organization for Children: Dedicated solely to helping youth successfully navigate the very difficult grief process.
1. http://www.rainbows.org/

iv. Cancer.Net: Discusses key issues siblings of a child with cancer face.
1. http://www.cancer.net/coping/relationships-and-cancer/siblings-and-cancer

v. Cancer Care: Provides educational workshops, podcasts, publications and common questions regarding siblings of a child with cancer.
1. http://www.cancercare.org/tagged/siblings

vi. Books
1. American Cancer Society. (2002). *Because someone I love has cancer*: *Kids*' *activity book*. American Cancer Society.
   a. Designed to address the basic goals and therapeutic support for children who have a loved one with cancer.
2. Beall-Sullivan, C. (2000). *Hi*, *my name is Jack*: *A book for the healthy siblings of chronically ill children*. Bopar Books.
   a. Addresses the issues encountered by the healthy siblings of chronically ill, disabled or dying children.
3. Dodd, M. (2004). *Oliver's story*, *for* '*sibs*' *of kids with cancer*. Candlelighters Childhood Cancer Foundation (Also in Spanish).
   a. This books tells a story about one child. But there is an important story to be told for every brother and sister of a child with cancer.
4. Heegaard, M. (1992). *When someone has a very serious illness*: *Children can learn to cope with loss and change*. Woodland Press.
   a. A resource for helping children learn the basic concepts of illness and various age-appropriate ways of coping with it
5. Peterkin, A. (1992). *What about me*? *When brothers and sisters get sick*. Magination Press.
   a. This story deals with the many complicated feelings the well child experiences in such a situation.

6. Cognitive Rehabilitation
   a. The Society for Cognitive Rehabilitation: Provides education about cognitive rehabilitation and helps to find a therapist by name, location, or specialty.
      i. http://www.societyforcognitiverehab.org/index.php
   b. Neuropsychonline Cognitive Rehabilitation Therapy (NCRT): A cognitive skills enhancement system designed for the rehabilitation of those who have experienced cognitive impairment. NCRT is designed to develop and enhance cognitive functions across the following domains: attention skills, executive skills, memory skills, visuospatial skills, problem solving skills, and communication skills.
      i. http://www.neuropsychonline.com/ncrt.pdf
   c. National Academies Press (NAP): Released a prepublication PDF version of a book relevant to the practice.
      i. Cognitive rehabilitation therapy for traumatic brain injury: Evaluating the evidence
         1. http://www.nap.edu/catalog.php?record_id=13220
   d. Books
      i. Gillen, G. (2008). *Cognitive and perceptual rehabilitation*: *Optimizing function*. St. Louis, MI: Mosby Inc.
         1. Summarizes, highlights, and constructively critiques the state of cognitive and perceptual rehabilitation. Helps improve patients' quality of life by promoting improved performance of necessary and meaningful activities, and decreasing participation restrictions.
      ii. Halligan, P. W. & Wade, D. T. (2005). *The effectiveness of rehabilitation for cognitive deficits*. Oxford, New York: Oxford University Press.
         1. Critical review and discussion of the effectiveness of rehabilitation methods currently used to treat patients with cognitive impairments following brain injury. Provides a critique and consensus about what should constitute best practices.
      iii. Haskins, E. C., Trexler, L. E., Shapiro-Rosenbaum, A., Dams-O'Connor, K., Eberle, R., Cicerone, K., & Langenbahn, D. (2012). *Cognitive rehabilitation manual*:

Translating evidence-based recommendations into practice. Reston, VA: ACRM Publishing.
1. A guide for clinicians to effectively deliver evidence-based rehabilitation interventions in everyday clinical practice.

iv. Powell, T. & Malia, K. B (2003). *Brain injury workbook*: *Exercises for cognitive rehabilitation*. Bicester, UK: SpeechMark Publishing Ltd.
1. Contains over 140 cognitive rehabilitation exercises—tailored for memory, thinking skills, executive functions, awareness and insight, and emotional adjustment.

v. Sohlberg, M. M. & Mateer, C. (2001). *Introduction to cognitive rehabilitation*: *Theory and practice*. New York, NY: Guilford Press.
1. Described are clinical interventions for assisting persons with acquired cognitive impairments and for managing associated emotional and behavioral issues.

vi. Sohlberg, M. M. & Turkstra, L. S. (2011). *Optimizing cognitive rehabilitation*: *Effective instructional methods*. New York, NY: Guilford Press.
1. Presents evidence-based instructional methods specifically designed to help individuals learn more efficiently. The authors provide practical guidelines for teaching multistep procedures, cognitive strategies, the use of external aids, and more.

vii. Struss, D. T., Winocur, G., & Robertson, I. H. (2010). *Cognitive neurorehabilitation*: *Evidence and application*. Cambridge, UK: Cambridge University Press.
1. Summarizes the latest developments in cognitive neuroscience related to rehabilitation, reviews the principles of successful interventions and synthesizes new findings about rehabilitation of cognitive changes in a variety of populations.

e. Computer-Based Cognitive Remediation Programs
   i. www.lumosity.com
   ii. www.cogmed.com
   iii. www.braintrain.com

7. Complementary Medicine and Nutrition
   a. National Center for Complementary and Integrative Health (NCCIH): Comprehensive website that provides information for consumers, researchers, and practitioners. They conduct and support research and provide information-about complementary health products and practices.
      i. https://nccih.nih.gov
   b. Office of Cancer Complementary and Alternative Medicine: Website that coordinates the activities of the National Cancer Institute and Complementary/Alternative Medicine (CAM).
      i. http://cam.cancer.gov
   c. CAM-Cancer: Project entitled, "Concerted Action for Complementary and Alternative medicine Assessment for the Cancer Field." Website provides information regarding evidence-based data for health professionals.
      i. http://cam-cancer.org
   d. American Society of Clinical Hypnosis: Provides contact information for qualified hypnosis providers
      i. www.asch.net
   e. Association for Applied Psychophysiology & Biofeedback: Provides contact information for qualified biofeedback providers
      i. www.aapb.org
   f. Biofeedback Certification International Alliance: Additional resource for finding qualified biofeedback providers
      i. www.bcia.org
   g. The National Association for Holistic Aromatherapy (NAHA): Provides

resources to the public to promote and disseminate aromatherapy education.
   i. www.naha.org
h. Alliance of International Aromatherapists: Organization that aims to increase awareness of and expand access to aromatherapists.
   i. https://www.alliancearomatherapists.org
i. American Massage Therapy Association: Organization that provides education and resources, including finding a trained massage therapist.
   i. www.amtamassage.org
j. Reiki Membership Association: Organization that offers training, resources, and directory of providers.
   i. www.reikimembership.com.
k. American Chiropractic Association (ACA): Information and directory of providers that meet minimum requirements for training and experience.
   i. www.acatoday.org.
l. Inner Kids: Wonderful resource for those seeking more information as to how to help children learn mindfulness and awareness in everyday lives.
   i. www.InnerKids.org
m. The International Association of Yoga Therapists: Association that is developing standards for yoga therapy training.
   i. www.iayt.org
n. The Yoga Alliance: Nonprofit group that represents the yoga community and provides a directory of trained professional teachers and teacher-training programs.
   i. www.yogaalliance.org
o. American Music Therapy Association (AMTA): Certifies music therapists and provides assistance in locating qualified music therapists
   i. www.musictherapy.org
p. American Art Therapy Association: Resource to find information regarding art therapy, qualifications of membership and provider directory.
   i. www.arttherapy.org
q. Pet Partners: Non-profit organization that aims to demonstrate and promote positive human-animal interactions to improve the physical, emotional and psychological lives of individuals.
   i. www.petpartners.org
r. Professional Association of Therapeutic Horsemanship International (PATH Intl.): Non-profit organization that promotes safety and optimal outcomes in equine-assisted activities and therapies for individuals with special needs, and provides a directory of centers.
   i. www.pathintl.org
s. American Cancer Society (ACSM/ACS). Resource that provides information regarding the Certified Cancer Exercise Trainers (CET) certification that requires the trainers to tailor their fitness assessments and exercise programs specific to the cancer survivor based upon their specific cancer diagnosis, treatment and recovery status.
   i. http://certification.acsm.org/acsm-cancer-exercise-trainer
t. Herbal and Dietary Supplements: Several websites that provide various resources relevant to herbal/dietary supplements.
   i. http://www.nlm.nih.gov/medlineplus/druginfo/herb_All.html
   ii. http://www.nccam.nih.gov
   iii. http://www.mskcc.org/mskcc/html/11570.cfm
   iv. http://www.cam-cancer.org
u. World Cancer Research Fund, American Institute for Cancer Research: offers the latest evidence on food, nutrition, physical activity, body fatness and the prevention of cancer.
   i. http://www.dietandcancerreport.org

8. Screening Tools for Medical Practitioners
   a. Pediatric Symptom Checklist: A brief screening questionnaire that is used by pediatricians and other health professionals to improve the recognition and treatment of psychosocial problems in children.
      i. http://www.massgeneral.org/psychiatry/services/psc_home.aspx

b. Massachusetts General Hospital, School Psychiatry and MADI Resource Center: Provides a table of screening tools and rating scales to help measure a young person's mental health symptoms, and/or measure progress after interventions are put in place at school or at home. For each screening tool or rating scale, the table indicates: the age range for the instrument, who completes the instrument, the number of items in the instrument and how long it takes to complete, and whether free access is available on line.
   i. http://www2.massgeneral.org/schoolpsychiatry/screeningtools_table.asp
c. American Academy of Pediatrics, HEARD Alliance
   i. The Mental Health Screening and Assessment Tools for Primary Care table provides a listing of mental health screening and assessment tools, summarizing their psychometric testing properties, cultural considerations, costs, and key references. It includes tools that are proprietary and those that are freely accessible.
      1. http://www.heardalliance.org/wp-content/uploads/2011/04/Mental-Health-Assessment.pdf

9. Resources for Professionals
   a. National Cancer Institute (NCI)
      i. www.nci.nih.gov
   b. NCI's PDQ (Physician Data Query)
      i. http://www.cancer.gov/cancertopics/pdq
   c. The Childhood Cancer Survivor Study (CCSS): An Overview-National Cancer Institute.
      i. http://www.cancer.gov/cancertopics/coping/survivorship
   d. Long term follow up care of survivors of childhood cancer, Great Britain
      i. http://www.sign.ac.uk/guidelines/fulltext/132/index.html
   e. Children's Cancer and Leukaemia Group (CCLG), Great Britain, Long Term Follow Up Resources
      i. http://www.cclg.org.uk/treatment-research
   f. PanCare Childhood and Adolescent Cancer Survivor Care and Follow-Up Studies: C*onsortium* of 16 European institutions to carry out research studies into late effects of treatment for cancer, to establish guidelines for follow-up, and to disseminate the results and provide training and workshops for stakeholders.
      i. http://www.pancaresurfup.eu/
   g. Cochrane Childhood Cancer Group (CCCG) in Amsterdam
      i. www.ccg.cochrane.org
   h. National Comprehensive Cancer Network
      i. http://www.nccn.org/index.asp.
      ii. http://www.nccn.org/professionals/physician_gls/f_guidelines.asp
10. Palliative Care
   a. National Hospice and Palliative Care Organization
      i. www.nhpco.org
   b. National Consensus Project for Quality Palliative Care.
      i. www.nationalconsensusproject.org
11. Additional Resources
   a. Books for parents and health care providers
      i. Alba, O. (2010). *The hospital for sick children handbook of supportive care in pediatric oncology*. Sudbury, MA: Jones and Bartlett Publishers.
         1. A practical approach to the clinical management of problems unique to childhood cancer and its therapy.
      ii. Fromer, M. J. (1998). *Surviving childhood cancer*: *A guide for families*. Oakland, CA: New Harbinger Publications.
         1. Explains common medical procedures and offers readers sensitive and practical advice about coping with emotions and stress, talking about the illness with the child, family members and friends, and developing trusting relationships with medical caregivers.

iii. Goldman, S. & Turner, C. D. (2009). *Late effects of treatment for brain tumors*. New York, NY: Springer.
   1. Reviews the development of the medical team's awareness of late effects of brain tumor treatment and an overview of brain tumor survivorship.

iv. Green, D. & Wallace, H. (2003). *Late effects of childhood cancer*. Boca Raton, FL: CRC Press.
   1. Brings together all aspects of the long-term effects of treatment for cancer during childhood in a single comprehensive volume.

v. Grinyer, A. (2009). *Life after cancer in adolescence and young adulthood*: *Experience of survivorship*. New York, NY: Routledge.
   1. Focuses on the physical, social, cognitive, emotional and physiological consequences of surviving cancer in young adulthood. This books draws directly upon data collected from young adults who have been treated for cancer.

vi. Keene, N., Hobbie, W., & Ruccione, K. (2000). *Childhood cancer survivors*: *A practical guide to your future*. Sebastopol, CA: O'Reilly.
   1. Charts the territory for survivors by providing state-of-the-art information about: medical later effects, emotional aspects, follow up care, and challenges in the healthcare system.

vii. National Research Council. (2003). *Childhood cancer survivorship*: *Improving care and quality of life*. Washington, DC: National Academies Press.
   1. Outlines a comprehensive policy agenda that links improved health care delivery and follow-up, investments in education and training for health care providers, and expanded research to improve the long-term outlook for cancer survivors.

viii. Prucha, E. J. (1999). *Pediatric cancer sourcebook*: *Basic consumer health information about leukemias*, *brain tumors*, *sarcomas*. Detroit, MI: Omnigraphics.
   1. Includes descriptions of cancers, treatments, and coping strategies along with suggestions for parents, caregivers, and concerned relatives.

ix. Schwartz, C. & Hobbie, W. (1994). *Survivors of childhood cancer*: *Assessment and management*. St. Louis, MI: Mosby.
   1. Brings together information that addresses the physical and emotional development of people surviving childhood cancer.

x. Schwartz, C. L., Hobbie, W. L., Constine, L. S., & Ruccione, K. S. (2005). *Survivors of childhood and adolescent cancer*: *A multidisciplinary Approach*. New York, NY: Springer.
   1. A comprehensive guide to the health issues in survivorship.

xi. Woodruff, T. K. & Snyder, K. A. (2007). *Oncofertility*: *Fertility preservation for cancer survivors* (*Cancer treatment and research*). New York, NY: Springer.
   1. Examines issues regarding an individual's fertility options, choice and goals in light of cancer diagnosis, treatment and survivorship.

xii. Woznick, L. A. & Goodheart, C. D. (2002). *Living with childhood cancer*: *A practical guide to help families cope*. American Psychological Association.
   1. This book draws upon the authors' own experiences with cancer as well as professional

expertise and stories from others to help families address the psychological impact of cancer.

xiii. Young, L. & Ward, J. (2011). *Hope for families of children with cancer*. (*You are not alone*). Leafwood Publishers.
1. From the initial diagnosis and throughout the daunting journey, this resource offers advice, support, and hope from fellow travelers and professionals who are experienced with what lies ahead.

b. Books for children with cancer
i. Ashley, L. B. (2009). *I am a vivor*. Halo Publishing International.
1. An inspirational story of a young girl who has survived cancer.
ii. Barber, B. (2011). *My life by me*: *A kid's forever book*. Magination Press.
1. Every page has a space for children with a chronic illness to tell their story—who they are, where they came from, what they are thinking, and hopes for their future.
iii. Brent, M. (2008). *Chemo to the rescue*: *A children's book about leukemia*. AuthorHouse.
1. The author is a mother of a child with cancer who wrote this book to encourage other children by providing a positive outlook to chemotherapy and hospital life.
iv. Cranston, L. (2001). *You and your cancer. A child's guide*. PMPH USA.
1. This book is designed to inform children with cancer of the nature of their illness.
v. Deland, M. M. (2010). *The great Katie Kate tackles questions about cancer*. Greenleaf Book Group LLC.
1. This superhero saga provides a tool for parents and medical professionals who are seeking a positive way to set young cancer patients on the road to recovery by helping them deal with their fears.
vi. Fisher, J. (2010). *I'm a kid living with cancer*. Isaiah 11:6 Publishing Co.
1. Takes the fear out of explaining cancer to a child. It offers a sense of comfort and optimism from knowing what to expect, giving the facts about cancer in an honest but gentle manner, at a child's level of understanding.
vii. Gaynor, K. (2008). *The famous hat*. Special Stories Publishing.
1. A storybook to help children with childhood cancer prepare for treatment, namely chemotherapy, and losing their hair.
viii. Gosselin, K. (2001). *Taking cancer to school*. Jayjo Books.
1. This straightforward story may help to alleviate some of the concern that accompanies the diagnosis of childhood cancer.
ix. Keene, N. (2002). *Chemo*, *craziness & comfort*: *My book about childhood cancer*. Candelighters Childhood Cancer Foundation.
1. Provides clear explanations and practical advice for children ages 6–12.
x. Krisher, T. (1992). *Kathy's hats*: *A story of hope. Albert* Whitman & Company.
1. A biographical sketch of a young girl's experiences with cancer and chemotherapy.
xi. Luttrell, A. M. (2006). *Why me*? Sand and Sea Publishing Company.
1. This book is intended to promote discussion between children and adults in discovering imaginative and positive ways to deal with life's challenges.
xii. Marchiano, M. (2010). *Grace*: *A child's intimate journey through cancer and recovery* (*coping with illness*). Happy Quail.
1. At 14-years-old, the author shares the events of her illness along with her thoughts, deep feelings and growing spirituality

through operations, radiation, drug reactions, an eating disorder and more.

xiii. Martin, K. (2005). *H is for hair fairy*: *An alphabet of encouragement and insight for kids* (*and kids at heart*) *with cancer*. Trafford Publishing.
   1. An alphabet book with a mission, this 32-page picture book will inspire, comfort, educate and encourage children being treated for cancer.

xiv. Richmond, C. (1996). *Chemo girl*: *Saving the world one treatment at a time*. Jones & Bartlett Learning.
   1. The author is a 12-year-old diagnosed with Rhabdomyosarcoma. The idea was to teach a positive, non-threatening side of chemotherapy and to realize there is always hope.

xv. Schulz, C. M. (2002). *Why Charlie Brown*, *why*? Ballantine Books.
   1. A story about what happens when a friend is very ill.

xvi. Wallace, B. (2005). *Flying with scissors*: *A different perspective on childhood cancer*. Virtualbookworm.com Publishing.
   1. A unique look at childhood cancer and the kids who have moved beyond the illness.

xvii. Wilde, D. (2005). *I'm a superhero*. Gibbs Smith.
   1. Written by a 4-year-old boy with the help of his mother, describing a superhero who battled "the bad guy named cancer" with unfailing optimism and bravery.

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