

Contents

Foreword: Childhood Cancer Survival: So Much More Needs to be Done	xvii
Bonita F. Stanton	

Preface: Surviving Survival—Challenge Accepted: Perspectives on Survivorship in Pediatric Oncology	xix
Max J. Coppes and Leontine C. M. Kremer	

Surviving Survival—Challenge Accepted! Perspectives on Survivorship in Pediatric Oncology	1011
Carina Schneider, Jaap den Hartogh, Zuzana Tomášiková, and Anita Kienesberger	

Surviving childhood cancer can be a lifelong challenge: up to 75% of childhood cancer survivors must deal with late effects of their cancer and treatments. Next to keeping the balance between dealing with late-effects and adapting to a life “after cancer” many childhood cancer survivors also face the reality of inadequate or nonexistent follow-up care. Because cure is not enough, patient advocates depict why it is important to #RaiseYourHands4Survivors!

When Childhood Cancer Becomes a Family Affair, It Really Hits Home	1021
David M. Johnston and J. Martin Johnston	

In this article, a father and son describe the experience of childhood leukemia treatment and its aftermath with the unique perspective of a parent who is also a pediatric oncologist. An illness that began with an apparently favorable prognosis was transformed by an early relapse, followed by unexpected complications and difficult treatment decisions. Despite unfavorable statistics, the son is a long-term survivor with an overall excellent quality of life, despite several late events and effects. His father, in the meantime, gained insights that now inform his own practice.

Late Effects in Childhood Cancer Survivors: Early Studies, Survivor Cohorts, and Significant Contributions to the Field of Late Effects	1033
--	-------------

Filippa Nyboe Norsker, Camilla Pedersen, Gregory T. Armstrong, Leslie L. Robison, Mary L. McBride, Michael Hawkins, Claudia E. Kuehni, Florent de Vathaire, Julie Berbis, Leontien C. Kremer, Riccardo Haupt, Line Kenborg, and Jeanette Falck Winther

With improvement in cure of childhood cancer came the responsibility to investigate the long-term morbidity and mortality associated with the treatments accountable for this increase in survival. Several large cohorts of childhood cancer survivors have been established throughout Europe and North America to facilitate research on long-

Contents

term complications of cancer treatment. The cohorts have made significant contributions to the understanding of early mortality, somatic late complications, and psychosocial outcomes among childhood cancer survivors, which has been translated into the design of new treatment protocols for pediatric cancers, with the goal to reduce the potential risk and severity of late effects.

Radiotherapy and Late Effects

1051

Joshua D. Palmer, Matthew D. Hall, Anita Mahajan, Arnold C. Paulino, Suzanne Wolden, and Louis S. Constine

Advances in multimodality care for patients with pediatric cancer continues to improve long-term survival. The use of surgery, chemotherapy, and radiotherapy may lead to debilitating late effects in childhood cancer survivors. It is critically important to understand, mitigate, and screen for late effects to improve the quality of life in childhood cancer survivors. This review summarizes the use of radiotherapy in children, radiobiology of tissue injury, impact of age on late effects, important organ systems affected by radiotherapy during survivorship, and screening for radiotherapy late effects.

The Critical Role of Clinical Practice Guidelines and Indicators in High-Quality Survivorship After Childhood Cancer

1069

Renée L. Mulder, Rebecca J. van Kalsbeek, Melissa M. Hudson, Roderick Skinner, and Leontien C.M. Kremer

Childhood cancer survivors are at significant risk for late cancer treatment-related morbidity and mortality. Physicians involved in the care of childhood cancer survivors should be aware of these specific health problems and provide high-quality, long-term follow-up care to preserve and improve survivors' health. The steps required to achieve high-quality care include synthesizing evidence (systematic reviews are helpful in this regard), developing clinical policy from evidence into evidence-based clinical practice guidelines, disseminating and implementing clinical practice guidelines, and evaluating their impact on quality of care and survivor health outcomes with quality indicators. This article describes these cornerstones of evidence-based medicine.

Childhood Cancer Survivorship: Daily Challenges

1083

Fiona Schulte, Caitlin Forbes, Amanda Wurz, Michaela Patton, K. Brooke Russell, Saskia Pluijm, and Kevin R. Krull

Survivors of childhood cancer are at risk of experiencing fatigue, pain, lower levels of physical activity, increased engagement in risky health behavior, and poor social adjustment, after finishing treatment. Risks are more pronounced for survivors of specific diagnoses or receiving specific treatment protocols. Interventions to address these outcomes are in their infancy. Future research should focus on exploring the antecedents and consequences of these outcomes. In the meantime, researchers and cancer centers should attempt to provide high-quality and accessible health information to survivors through various media outlets to encourage healthy behaviors.

- Psychological Outcomes, Health-Related Quality of Life, and Neurocognitive Functioning in Survivors of Childhood Cancer and Their Parents** 1103
- Gisela Michel, Tara M. Brinkman, Claire E. Wakefield, and Martha Grootenhuus
- Childhood cancer disrupts the lives of patients and their families and affects acute and long-term psychological health. This article summarizes (1) psychological challenges, including depression, anxiety, worries, and posttraumatic stress, as well as positive outcomes such as benefit finding and posttraumatic growth in young survivors and parents; (2) health-related quality of life; (3) interventions to support survivors and parents with psychological difficulties; and (4) neurocognitive problems and interventions to help alleviate them. Although many survivors and parents fare well in the long term, many survivors may benefit from interventions. Interventions should be further evaluated and integrated into routine clinical care.
- Subsequent Primary Neoplasms: Risks, Risk Factors, Surveillance, and Future Research** 1135
- Michael Hawkins, Smita Bhatia, Tara O. Henderson, Paul C. Nathan, Adam Yan, Jop C. Teepen, and Lindsay M. Morton
- The authors' objective is to provide a brief update on recent advances in knowledge relating to subsequent primary neoplasms developing in survivors of childhood cancer. This includes a summary of established large-scale cohorts, risks reported, and contrasts with results from recently established large-scale cohorts of survivors of adolescent and young adult cancer. Recent evidence is summarized concerning the role of radiotherapy and chemotherapy for childhood cancer and survivor genomics in determining the risk of subsequent primary neoplasms. Progress with surveillance, screening, and clinical follow-up guidelines is addressed. Finally, priorities for future research are outlined.
- Cardiovascular and Pulmonary Challenges After Treatment of Childhood Cancer** 1155
- Henk Visscher, Maria Otth, E.A.M. (Lieke) Feijen, Paul C. Nathan, and Claudia E. Kuehni
- Childhood cancer survivors are at risk for developing cardiovascular disease and pulmonary disease related to cancer treatment. This might not become apparent until many years after treatment and varies from subclinical to life-threatening disease. Important causes are anthracyclines and radiotherapy involving heart, head, or neck for cardiovascular disease, and bleomycin, busulfan, nitrosoureas, radiation to the chest, and lung or chest surgery for pulmonary disease. Most effects are dose dependent, but genetic risk factors have been discovered. Treatment options are limited. Prevention and regular screening are crucial. Survivors should be encouraged to adopt a healthy lifestyle, and modifiable risk factors should be addressed.
- Endocrine Health in Childhood Cancer Survivors** 1171
- Hanneke M. van Santen, Wassim Chemaitilly, Lillian R. Meacham, Emily S. Tonorezos, and Sogol Mostoufi-Moab
- Endocrine late effects, including reproductive disorders and secondary thyroid cancer, have been reported in up to 50% childhood cancer

Contents

survivors (CCS) more than 5 years after treatment. Most endocrine disorders are amenable to treatment; awareness of symptoms is therefore of great importance. Recognition of these symptoms may be delayed however because many are nonspecific. Timely treatment of endocrine disorders improves quality of life in CCS and prevents possible consequences, such as short stature, bone and cardiovascular disorders, and depression. At-risk CCS must therefore be regularly and systematically monitored. This article provides a summary of the most commonly reported endocrine late effects in CCS.

Reproductive Complications in Childhood Cancer Survivors

1187

Hanneke M. van Santen, Marianne D. van de Wetering, Annelies M.E. Bos, Marry M. vd Heuvel-Eibrink, Helena J. van der Pal, and William Hamish Wallace

Gonadal dysfunction and infertility after cancer treatment are major concerns for childhood cancer survivors and their parents. Uncertainty about fertility or being diagnosed with infertility has a negative impact on quality of survival. In this article, determinants of gonadal damage are reviewed and consequences for fertility and pregnancies are discussed. Recommendations for screening and treatment of gonadal function are provided. These should enable timely treatment of gonadal insufficiency aiming to improve linear growth, pubertal development, and sexual functioning. Options for fertility preservation are discussed.

Renal and Hepatic Health After Childhood Cancer

1203

Matthew J. Ehrhardt, Roderick Skinner, and Sharon M. Castellino

Childhood cancer survivors (CCSs) are at risk for renal and hepatic complications related to curative cancer treatments. Although acute renal and hepatic toxicities of cancer treatments are well described, data regarding long-term and late-occurring sequelae or their associations with acute sequelae are less robust. This article highlights the literature on the prevalence of and risk factors for late renal and hepatic toxicity in CCSs. Studies investigating these outcomes are needed to inform surveillance practices and the development of future frontline cancer treatment protocols.

Hearing and Other Neurologic Problems

1219

Wendy Landier, Richard J. Cohn, and Marry M. van den Heuvel-Eibrink

Ototoxicity and other neurologic toxicities are potential consequences of exposure to common therapeutic agents used during treatment of childhood cancer, including platinum and vinca alkaloid chemotherapy, cranial radiation, surgery involving structures critical to cochlear and neurologic function, and supportive care medications such as aminoglycoside antibiotics and loop diuretics. This article provides an overview of ototoxicity and other neurologic toxicities related to childhood cancer treatment, discusses the challenges that these toxicities may pose for survivors, and presents an overview of current recommendations for surveillance and clinical management of these potentially life-altering toxicities in survivors of childhood cancers.

The Future of Childhood Cancer Survivorship: Challenges and Opportunities for Continued Progress 1237

Stephanie B. Dixon, Eric J. Chow, Lars Hjorth, Melissa M. Hudson, Leontien C.M. Kremer, Lindsay M. Morton, Paul C. Nathan, Kirsten K. Ness, Kevin C. Oeffinger, and Gregory T. Armstrong

As treatment evolves and the population who survive childhood cancer ages and increases in number, researchers must use novel approaches to prevent, identify and mitigate adverse effects of treatment. Future priorities include collaborative efforts to pool large cohort data to improve detection of late effects, identify late effects of novel therapies, and determine the contribution of genetic factors along with physiologic and accelerated aging among survivors. This knowledge should translate to individual risk prediction and prevention strategies. Finally, we must utilize health services research and implementation science to improve adoption of survivorship care recommendations outside of specialized pediatric oncology centers.