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Endocrine and Metabolic late effects following cancer treatment – challenges and controversies

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In 2020 there were 19.3 million new cancer cases diagnosed globally[1,2], and numbers continue to rise. During the last decades, cancer survival has improved considerably; in the 1960's children had a 5 year cancer survival rate of around 25% which has risen to over 80% in high income countries[3,4]. Rising incidence and improved survival rates have resulted in a growing number of long-term cancer survivors; currently over 43 million worldwide.[5,6]

Although cured of their cancer, these patients continue to present a challenge to health systems as the majority will develop sequelae from their cancer or cancer treatments occurring years to decades after the end of cancer treatment (figure 1). These late consequences are reflected in a range of different organs and functions with varying severity, from mild restrictions to new life-threatening diseases and can have significant effects on quality and quantity of life thus requiring a multi-disciplinary approach to care[7]. Up to half of them will develop endocrine or metabolic consequences.

Childhood cancer survivors represent a comparably small group of patients in this large cohort that have been studied for decades due to their excellent long-term survival rates and the long life span ahead of them after end of treatment. Much knowledge about late effects is therefore derived from this patient group and serves as the basis for guidelines and recommendations, for example the International Guideline Harmonisation Group (https://www.ighg.org/) promoting risk-adapted long-term follow-up with the aim of facilitating early detection and treatment of possible sequelae [8]. With focus shifting from survival to living beyond cancer in many, optimal long-term follow

up is essential to reduce long-term morbidity and mortality as well as to ensure good quality of life in all long-term cancer survivors.

Developing evidence based research and guidance for late effects is challenging for a number of reasons, including; rapidly evolving oncology treatments, individualized cancer regimens and the duration of time between cancer treatments and development of sequelae. This has been compounded by relatively few studies investigating underlying pathophysiology of late effects and lower levels of research funding compared to other areas of oncology research. These challenges need to be addressed as cancer incidence and cancer survival rates rise.

Despite increasing awareness of late effects, implementation of long-term follow up care still varies considerably between nations and patient cohorts. Specialized late-effects centers have been established in some countries during the last decade offering standardized care for a few, however large numbers of patients receive only basic follow-up care or, after the end of oncological follow-up care, no long-term follow-up care at all. Therefore, it is of enormous importance to address this inequity and determine which examinations at which frequency should be performed to detect possible long-term health consequences in a timely fashion without overburdening the resources of the health care systems and without exposing patients to unnecessary risks that may arise from overdiagnosis.

The first article published in this special series discusses the effect of different surveillance strategies for differentiated thyroid carcinoma in childhood cancer survivors who have received radiotherapy to the thyroid field. It reviews differences in survival rates between these surveillance strategies, with the aim of determining the benefits of surveillance against potential harm of overdiagnosis. Other articles in the series will highlight other current controversies in the field of late effects of cancer in order to present pragmatic approaches to optimal care. Moreover, expert authors from different nations and specialties will explore their topic from a range of angles, representing the multidisciplinary approach as well as the need for continuous international collaboration between specialists. Topics will cover bone health, growth hormone deficiency, impact of different radiotherapy techniques on hypothalamic-

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pituitary axis, risk assessment for second cancers as well as strategies for international collaboration and different approaches to data analysis.

This special series is designed to initiate discussions and critique of currently available recommendations; to evaluate current knowledge and to highlight the importance of continuous adaption and development of clinical and mechanistic research around late effects and surveillance strategies to ensure optimal long-term follow up for every cancer survivor . To accompany the invited short review articles we welcome the submission of original research articles in the field of late effects to complement and enhance this special series.

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Figure 1: Relative risks for chronic health conditions in childhood cancer survivors (compared to their siblings) [9]: