



How the long-term follow-up is organized in young adult survivors of childhood cancer

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Summary The survival after childhood cancer has improved substantially, therefore the population of childhood cancer survivors is increasing. This growing population of childhood cancer survivors, however, is at risk of a spectrum of adverse health outcomes. Unfortunately, until now, there was a lack of comprehensive follow-up recommendations. The purpose of this article is to provide information on recently developed harmonized evidence-based guidelines and the structure to provide complex long term follow up for childhood cancer survivors. We pointed out the need for a multidisciplinary pediatric and adult specialist team, who together develop multidisciplinary long-term follow-up clinics.

Keywords Side effects · Guidelines · Survivorship passport · Pancare · Adolescent und young adults

Introduction

In Austria, around 300 children and adolescents up to the age of 18 are diagnosed with cancer every year [1–3]. Thanks to medical advances in recent decades, increasing numbers of patients are cured, resulting in current average survival rates around 84% [3].

However, survivors of childhood and adolescence cancer have an increased and cumulative risk of chronic diseases from cancer itself and cancer treatment side effects [4]. These late effects can affect different organ systems and range from mild and easily treatable impairments to life-threatening complications such as second cancer or organ failure caused by higher burdens of therapy (e.g., myocardial insufficiency) [4]. The prevalence of late effects increases with increasing distance from the primary oncological therapy and does not reach a plateau even decades after the end of therapy [5]. Thus, 30 years after the cancer, up to two thirds of patients are affected by new, chronic diseases [4]. Type and dose of primary therapies, additional diseases, and endogenous factors such as tumor predisposition syndromes influence the severity and type of late sequelae [6].

Aim and structure of long-term follow-up

Studies have been initiated in Europe and in the USA with the aim of assessing the individual risk for long-term complications based on evidence and to create guidelines for risk-stratified, target-group-specific follow-up care. For example, as part of the ‘PanCareFollowup Project’, guidelines for complex follow-up care have been harmonized [7].

This collection of guidelines forms the basis for modern follow-up/preventive examinations.

Pediatric oncology patients have their follow-up examinations in pediatric oncology centers at least

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5 years after the end of therapy and up to the age of 18 years, because the probability of recurrences and late effects developing are highest in the first 5 years after the end of therapy. During this period, survivors are cared according to different follow-up schedules *depending on their underlying disease*. In Austria, harmonized follow-up care plans are available for download on the survivors website (<https://www.survivors.at/survivors-austria/downloadbereich/>).

From at least 5 years after the end of therapy and above the age of 18, a transition to adult medicine specialists takes place. *Further care should follow harmonized international guidelines and based on cumulative dose and type of the therapy* [7–9].

Examination plan for late effects

We would like to present with this case, after which therapy modalities, what kind of late effects can occur, and how the survivorship care plan is set up.

If the young patient has had radiation in the thorax or upper abdomen, the following investigations are needed: Breast cancer screening is recommended for female survivors who have been treated with more than ≥ 10 Gy of breast radiation, because the risk of breast cancer in survivors after radiation is as high as in carriers of a pathogenic *BRCA* germline mutation. Initiation of breast cancer screening is recommended at the age 25 years or ≥ 8 years after radiation (whichever is later). Annual lifelong breast cancer monitoring with breast magnetic resonance imaging (MRI) is recommended [10]. Unfortunately, there is currently no data for male survivors that would allow the risk of breast cancer to be assessed after childhood radiation.

Survivors, who have been treated with 35 Gy chest radiation or 250 mg/m² anthracycline therapy or 35 Gy chest radiation and 100 mg/m² anthracycline therapy, need regular echocardiographic monitoring (as cardiomyopathy screening), starting no later than 2 years after completion of cardiotoxic therapy. The examination must be repeated every other year during the individual's lifespan. Monitoring and avoiding modifiable/unnecessary cardiovascular risk factors (e.g., hypertension, diabetes, dyslipidemia, obesity) is recommended for all survivors treated with anthracycline and/or chest radiation [11]. Thoracic irradiation can increase not only the risk of cardiomyopathies, but also the risk of other heart complications (with radiation doses > 15 Gy heart valve damage, myocardial infarction, pericarditis, and arrhythmias), of pulmonary dysfunction (after chemotherapy like bleomycin, busulfan, nitrosoureas or after pulmonary surgery the risk is even higher) and for secondary malignancies (e.g., melanoma or thyroid carcinoma).

Screening for thyroid cancer is required in survivors who have received radiation therapy to the thyroid region. Thyroid cancer screening may also be useful for neuroblastoma survivors previously treated with 131

I-Meta-Iodo-Benzyl-Guanidine (131 I-MIBG) therapy. According to international guidelines, sonography of the thyroid gland should be performed no later than 5 years after radiation. It may be worth repeating these examinations every 3–5 years, even if no pathologies were found on previous examination [12]. Radiation that has affected the thyroid gland does not only increase the risk of thyroid cancer, but also the risk of developing hypothyroidism, and vascular diseases (arteria carotid stenosis). Unfortunately, there is currently no evidence-based data showing which preventive examinations (e.g., carotid artery Doppler) make sense and how often they have to be carried out [7].

Irradiation at any part of the body can increase the risk of skin cancer, which is why an annual dermatological examination is necessary [7].

Those survivors who received brain irradiation (including total body irradiation [TBI]) need regular neurological and endocrinological (hormones of the hypothalamus and pituitary gland) examinations, to detect second malignancies and hormonal disturbances early. Hormonal disturbances and infertility can also occur after pelvic irradiation (including the gonads) and after alkylating agent therapy.

Not only medical examinations, but also regular psychological evaluations and, if necessary, therapies, are essential elements of long-term follow-up care.

Before young adult patients are transitioned to adult care systems, they undergo thorough examinations to have a clear overall picture of the current late effects.

The survivors fill out a complex questionnaire about physical and psychosocial problems. These questionnaires help treating physicians to have an overview of the sometimes complex complaints from the survivor's point of view [13].

After the final examinations, a meeting takes place, in which the possible late effects and the necessary follow-up examinations are discussed with the survivors.

The survivors receive survivorship care plans, which were developed as part of the European project "PanCareFollowUp" and contains all relevant information to their therapy (including cumulative doses of anticancer therapies), family history, other illnesses, and recommendations for follow-up care [13].

Young adults not only receive a printed survivorship care plan, but also a folder, which contains all results of their final examinations and important previous letters.

As part of the European project PanCareSurPass, these summary briefs are transmitted into electronic form in the so-called "Survivorship Passport" and will be available as an electronic (ELGA) document for the survivors.

Summary

Follow-up care (which is preventive care) enables early prevention, detection, and treatment of recurrences and appearance of new secondary tumors as well as organ damage to maintain and to improve the quality of life of the survivors. In survivors who are in regular long-term follow-up care, long-term effects could be discovered earlier, and hospital stays could be reduced [8]. In addition, these patients should have better knowledge about their disease and their risk of long-term side effects and should have a greater health-related self-efficacy [8, 14].

The results of long-term follow-up examinations could be recorded centrally in a database in the future, so that they are available for further scientific research. Such data will be generated in a project (the SUPA-BIO register) recently initiated in St. Anna Children's Hospital together with St. Anna Children's Cancer Research.

In order to function, these scientific projects require a cooperative collaboration between pediatric oncology and internal medicine oncology. In Vienna, this need has been recognized and is supported by the responsible public health authorities. Since 2020, the interdisciplinary oncological aftercare outpatient clinic (IONA) has been enabling both structured medical (in the sense of a personalized “precision survivorship” strategy based on individual risk factors) and comprehensive psychosocial care for survivors.

With these advances, the quality of care, education, and health awareness of survivors has increased. As a result, healthier young adults should be able to actively participate as functional members of society.

Take home messages

Structured, risk-adapted, evidence-based follow-up care in young adults after childhood cancer can help to identify and treat potentially life-threatening secondary diseases early on and, through lifestyle modifications, to avoid them and improve the health-related self-efficacy and quality of life of survivors. This requires screening standards, an appropriately structured transition, and close cooperation between pediatric oncology, internal oncology, and various specialist areas of adult medicine.

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Conflict of interest E. Bardi, L. Kager and W. Holter declare that they have no competing interests.

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