Cardiology in the Young

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Guidelines

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Association of European Paediatric and Congenital Cardiology practical recommendations for surveillance and prevention of cardiac disease in childhood cancer survivors: the importance of physical activity and lifestyle changes:

From the Association of European Paediatric and Congenital Cardiology Working Group Sports Cardiology, Physical Activity and Prevention, Working Group Adult Congenital Heart Disease, Working Group Imaging and Working Group Heart Failure

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Abstract

Background: Childhood cancer survivors are at increased risk of developing cardiovascular diseases, presenting as the main causes of morbidity and mortality within this group. Besides the usual primary and secondary prevention in combination with screening during follow-up, the modifiable lifestyle factors of physical activity, nutrition, and body weight have not yet gained enough attention regarding potential cardiovascular risk reduction. *Objective:* These practical recommendations aim to provide summarised information and practical implications to paediatricians and health professionals treating childhood cancer survivors to reduce the risk of cardiovascular late effects. *Methods:* The content derives from either published guidelines or expert opinions from Association of European Paediatric and Congenital Cardiology working groups and is in accordance with current state-of-the-art. *Results:* All usual methods of prevention and screening regarding the risk, monitoring, and treatment of occurring cardiovascular diseases are summarised. Additionally, modifiable lifestyle factors are explained, and clear practical implications are named. *Conclusion:* Modifiable lifestyle factors should definitely be considered as a cost-effective and complementary approach to already implemented follow-up care programs in cardio-oncology, which can be actively addressed by the survivors themselves. However, treating physicians are strongly encouraged to support survivors to develop and maintain a healthy lifestyle, including physical activity as one of the major influencing factors. This article summarises relevant background information and provides specific practical recommendations on how to advise survivors to increase their level of physical activity.

Key learning objectives

These practical recommendations aim to provide information and assistance to paediatricians and healthcare professionals treating childhood cancer survivors

- with general background regarding the risk and extent of cardiovascular diseases.
- recommended diagnostic methods for surveillance and early detection of cardiovascular diseases.
- how to motivate survivors to be physically active and engage in a healthy lifestyle to reduce the risk of cardiovascular late effects.

Childhood cancer treatment has radically changed in the last few years. Since 1990, there have been attempts to reduce the intensity of treatment among children with relatively good prognosis neoplasms, with the aim of reducing the risk of treatment-related morbidity and mortality. Previous research identified that thoracic radiotherapy and specific types of chemotherapy, especially anthracycline, introduced in the late 1970s, increase the risk of heart disease among childhood cancer survivors. The survival of children with cancer has risen considerably over the last decades with 5-year survival rates exceeding 80%.[1] However, the long-term health effects in the growing population of childhood cancer survivors are of significant concern. Adverse cardiovascular events (e.g., chronic cardiomyopathy, valvular dysfunction, arrhythmias, peripheral vascular disease, pericardial disease, early coronary artery diseases, and stroke) are one of the leading causes of morbidity and mortality for cancer patients and constitute a significant health problem, considering the prevalence with a previous diagnosis of cancer.[2,3] In this scenario, cardio-oncology, a discipline aimed at the diagnosis, prevention, and treatment of cardiovascular diseases as complications of anticancer therapies, is constantly evolving. Not only in terms of clinical activity and scientific research but also regarding the development of organisational models and training courses. For this reason, the multidisciplinary Working Group Sports Cardiology, Physical Activity and Prevention, the Working Group Adult Congenital Heart Disease, the Working Group Imaging, and the Working Group Heart Failure of the Association of European Paediatric and Congenital Cardiology aimed to state the art, risk prediction, surveillance, and treatment but also the establishment about the role of physical activity in the prevention of future cardiovascular diseases.

Cardiovascular diseases in childhood cancer survivors

Survival after childhood cancer continues to improve but second malignant neoplasia and cardiovascular diseases remain among the risk of premature mortality in childhood and adolescent cancer survivors. The risk of death related to cardiovascular diseases is most common after a long survival period. Long-term survivors of childhood cancer are five to seven times more likely to develop cardiovascular diseases compared to the healthy population due to the treatments they were exposed to at a young age.[4–8] This primarily includes anthracyclines and radiation therapy targeting the chest. Over time, survivors may additionally acquire conventional risk factors for cardiovascular diseases as the general population. Certain cancers have been independently linked to the development of cardiovascular diseases, and many oncological patients have pre-existing risk factors or a genetic predisposition. Kidney cancers (Wilms tumour), bone sarcoma, lymphoma (especially non-Hodgkin lymphoma), and leukaemia are associated with a higher cardiovascular risk because of the more significant cardiotoxicity of their treatments or their association with cardiovascular risk factors[4,9] compared to other malignant diseases like some tumours of the central nervous system and some soft-tissue sarcomas not being treated with anthracyclines. However, most patients receive cardiotoxic treatment of varying doses. Oncological therapy should be considered an independent risk factor for potentially cardiotoxic events, critical after anthracycline therapy exceeding 250 mg/m^2 or after radiotherapy of > 30 Grays (or after combined therapies).

Cardiovascular diseases, which appear among long-term survivors of childhood cancer, may manifest in different ways as summarised in Table 1.[2,3] Adequate control of cardiovascular risk factors in people diagnosed with cancer during childhood is a priority during follow-up.

Key message: cardiovascular diseases in childhood cancer survivors

- Children and adolescents treated for cancer are at a higher risk of developing cardiovascular pathology in long-term survival.
- Certain cancers are associated with a higher cardiovascular risk due to the necessary application of cardiotoxic treatment.
- Cardiovascular diseases can manifest in various ways in long-term survivors of childhood cancer. Therefore, adequate control of cardiovascular risk factors is essential during follow-up.

Primary and secondary prevention of cardiotoxicity

Primary prevention

Extensive research has been devoted to identify possible cardioprotective interventions during anthracycline treatment that have no adverse effects on anticancer efficacy or other non-cardiac adverse effects. Below, we discuss three preventive measures mostly used and refer to the recently published Delphi consensus.[10]

Dexrazoxane. Dexrazoxane is a cardioprotective drug extensively studied in several clinical trials. Clinical heart disease and subclinical injury have been clearly demonstrated in adult patients.[11] The few published paediatric data included subjects diagnosed with leukaemia, lymphoma, and sarcoma.[12–14] These early studies demonstrate no significant differences in the occurrence of heart failure between patients treated with or without dexrazoxane.[15] In a recent review, de Baat et al.[16] posed light on the debate growth concerning the risk it may interfere with the antitumor efficacy and predisposition to secondary malignant tumours,[17] concluding that the benefits of dexrazoxane probably outweigh the risk of subsequent neoplasms. It could be linearly related to the cumulative doxorubicin dose of 250 mg/m^2 or an equivalent dose (moderate recommendation).

Liposomal anthracyclines. The purpose of this anthracycline formulation is to limit drug exposure in healthy tissues such as the heart and increase drug infusibility in malignant cells by altering

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Table 1. Most common cardiovascular diseases in paediatric cancer and underlying causes

Disease	Risk factor	Underlying cause
Cardiac structure & function		
Cardiomyocyte injury/ impairment	Anthracyclines	Damage of the myocardium due to anthracycline treatment
DCM/Heart failure	Anthracyclines Chest RT	Cardiomyocyte damage
		Mitochondrial effect and DNA disruption
		Potential progress to heart failure from systolic dysfunction Younger age and some types of cancer
Valvular heart disease	Chest RT	Relation of high dose of RT with hypertension and dyslipidaemia in young patients
		Injury to the valve cusps or leaflets, fibrosis, and calcification by direct irradiation
Pericardial disease	Chest RT	Late constrictive pericarditis after RT
Arrhythmia	Chest RT Anthracyclines (high dose)	Myocardial fibrosis caused by Chest RT
		Supraventricular and ventricular arrhythmias caused by cancer agents (e.g., cisplatin, cyclophosphamide, and tyrosine kinase inhibitors)
		Prolonged QTc interval related to medications
Vascular disease		
Coronary artery disease	Chest RT	Endothelial dysfunction, prothrombotic state
		CV risk factors as hypertension, obesity, and dyslipidaemia
Cerebrovascular disease	Cranial RT Neck RT	Endothelial dysfunction, prothrombotic state
		CV factors such as hypertension, obesity, and dyslipidaemia

DCM = dilated cardiomyopathy; RT = radiation therapy; QTc = corrected QT interval; CV = cardiovascular.
Adapted from Armenian et al.[3]

distribution in the tissue.[18] Liposomal anthracyclines have shown promising results in breast cancer patients. In a meta-analysis, liposomal doxorubicin significantly reduced clinical and subclinical heart failure.[19] To date, few randomised clinical trials or controlled trials have been performed in paediatric patients.[20]

Duration of the infusion. Time of administration and route of administration could play a role in the primary prevention of cardiotoxicity. A Cochrane systematic review compared the different durations of anthracycline infusions in children and adults with cancer.[21] An anthracycline infusion duration of six hours or more appeared to reduce the risk of both clinical heart failure and subclinical cardiotoxicity. In clinical practice, it is recommended, although no strict recommendation can be made, that an anthracycline infusion of at least one hour can prevent heart damage.[22]

Secondary prevention. Cardiomyopathy and heart failure are among the most severe conditions observed in childhood cancer survivors, so the potential for secondary prevention strategies is being evaluated. Secondary prevention involves managing asymptomatic cardiotoxicity and preventing symptoms, heart failure, and mortality.[23] The timing and appropriateness of using neurohormonal drugs, such as angiotensin-converting enzyme inhibitors and beta-blockers, in the secondary prevention of heart failure are still debated, especially in children and adolescents, due to the potential adverse effects of long-term use. Adult data are often extrapolated to paediatric cases in the absence of paediatric data. The evidence for using these drugs in long-term survivors with asymptomatic left ventricular ejection fraction < 40% is derived from published guidelines by Erhardt et al.[24] There is a lack of evidence for treating individuals with asymptomatic, mildly reduced left ventricular ejection fraction between 40 and 49% who do not have comorbidities.[24]

Apart from the initially defined approaches for secondary prevention regarding cardiotoxicity, it is essential for childhood cancer survivors to know and to be able to manage cardiovascular risk factors themselves (e.g., hypertension, obesity, dyslipidaemia, and diabetes). It is known that childhood cancer survivors show low adherence to multiple health behaviour guidelines and to improve health outcomes, multiple health behaviours should be targeted simultaneously.[25] Therefore, counselling for a healthy lifestyle by physicians and other healthcare professionals is essential.

Key messages: primary and secondary prevention of cardiotoxicity

- To reduce the risk of cardiotoxic late effects, it is important to integrate primary and secondary prevention into cancer treatment regimens.
- For primary prevention, dexrazoxane, liposomal anthracyclines, and elongated infusion time (up to six hours) appear to have cardioprotective effects and are well tolerated.[20]
- Secondary prevention aims at evading and managing occurring problems following application of cardiotoxic treatment and reducing risk factors for cardiovascular diseases on multiple levels, including cardioprotective medication and promoting a healthy lifestyle.

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Table 2. Definition of cardiovascular disease risk groups and surveillance recommendations[24]

Risk	Anthracycline dose (mg/m^2)	Chest radiation dose (Gy)	Anthracycline (mg/m^2) + chest radiation (Gy)	Cardiomyopathy surveillance
High	≥250	≥30	≥100 + ≥15	YES Strong recommendation
Moderate	100 to<250	≥15 to<30	NA	YES Moderate recommendation
Low	<100	<15	NA	NO Strong recommendation

Gy = gray; NA = not applicable.

Table 3. Summary of benefits and harms regarding primary surveillance by risk groups and modalities[24]

Risk*	Echocardiography (3D or 2D left ventricular ejection fraction)	Cardiac MRI	Blood biomarkers
High	• High risk of heart failure (>3-5 times) • Widely available (2-yearly intervals) • Reasonable agreement with cardiac MRI	• High risk of heart failure (>3-5 times) • High reproducibility but costs, waiting times, interpretability (5-yearly intervals)	• Poor diagnostic value
Moderate	• Risk of heart failure (>1-6 times) • Widely available (5-yearly intervals), cheap and cost-effective • Reasonable agreement with cardiac MRI	• High risk of heart failure (>1-6 times) • High reproducibility but costs, waiting times, interpretability (10-yearly intervals)	• Poor diagnostic value
Low	• No increased risk of heart failure	• No increased risk of heart failure	• No increased risk of heart failure

MRI = magnetic resonance imaging.
*see Table 2.

Screening for cardiovascular disease in long-term childhood cancer survivors

Long-term childhood cancer survivors are at risk of the following cardiovascular diseases:

- Myocardial damage: cardiomyopathy, heart failure
- Arterial hypertension
- Metabolic syndrome
- Valvular disease, pericardial constriction, and premature coronary artery disease (caused by mediastinal radiation).

The risk of developing cardiovascular diseases depends on the cumulative dosage of anthracycline or mediastinal irradiation administrated. A useful risk score according to Erhardt et al.[24] is shown in Table 2.

It is recommended that childhood cancer survivors with high and moderate risk should have a lifelong surveillance for development of cardiomyopathy. The screening aims to detect subtle cardiovascular system dysfunction in asymptomatic childhood cancer survivors as early as possible.

Besides taking the history and performing the physical examination of childhood cancer survivors as usual, the examinations described below should be performed

- as baseline before starting cancer treatment and
- not later than two years after completion of cardiotoxic therapy and every two years thereafter.[24]

Detection of myocardial damage. Childhood cancer survivors have a risk of > 50% to develop subclinical cardiac dysfunction in later life.

In all childhood cancer survivors, as a basis, the following examinations summarised in Table 3 should be performed.

Echocardiography. Standard echocardiography must be performed including measurement of 2D or 3D left ventricular ejection fraction to investigate asymptomatic left ventricular systolic or diastolic dysfunction or heart failure as defined by the American Society of Echocardiography[26] and the European Association of Cardiovascular Imaging recommendations[27] as previously published[24] (Table 3).

It is agreed that left ventricular ejection fraction is reduced when there is a decrease by > 10 percentage points with a final value of < 53%.[28] Additional determination of diastolic left ventricular function is thought to be a marker of early myocardial damage in asymptomatic childhood cancer survivors. For this purpose, the following measurements should be performed:

- Left atrial size (area or volume)
- Peak mitral valve diastolic velocity (E- and A-wave)
- Mitral valve septal and lateral diastolic velocity (tissue Doppler with E/E´).

Recently, it has been shown that measuring global longitudinal strain with speckle tracking might detect myocardial dysfunction before a decrease in left ventricular ejection fraction is seen. A reduction of global longitudinal strain > 15% over baseline is thought to be potentially pathological. Usually, a global longitudinal strain < −18% is considered reduced.[28–30]

Electrocardiogram. Electrocardiogram is recommended when patients enter survivorship. Further testing is conducted if needed based on clinical indicators. Screening electrocardiogram is strongly recommended for heart rhythm, ST segment changes and all sorts of arrhythmia. Special attention should be paid to prolonged QT interval corrected for heart rate interval and reduced variation in circadian heart rate.

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Cardiac biomarkers. Serial measurements of blood biomarkers (natriuretic peptides and troponins) are not recommended but strongly suggested as strategy for cardiomyopathy surveillance. It is generally recommended to monitor the course of asymptomatic left ventricular systolic or diastolic dysfunction or heart failure.[24]

Cardiopulmonary exercise testing. Cardiopulmonary exercise testing can detect cardiorespiratory dysfunction, which is not seen in routine resting studies. Maximal oxygen consumption (VO_2 max) is one of the most useful parameters for assessing physical capacity. Age- and sex-adjusted measurements < 80% of normal are considered pathological. Studies have shown that patients treated with median anthracycline doses of 240 mg/m^2 (range 100–490) are at significant risk of subclinical cardiac dysfunction. De Caro et al. reported that post-exercise subclinical cardiac dysfunction could be identified in up to one-third of patients, such as reduced left ventricular posterior wall dimension or percentage thickening or increased left ventricular end-systolic wall stress.[31]

Cardiac magnetic resonance imaging. Cardiac MRI is the gold standard for evaluating left ventricular ejection fraction. MRI should be done if the echocardiography fails to give sufficient information on myocardial performance. Furthermore, cardiac MRI can measure myocardial fibrosis associated with myocardial damage via late gadolinium enhancement and T1 mapping sequences. Cardiac MRI is therefore increasingly used in cardiac surveillance.[31,31–36] One paediatric study reported that the end-systolic volume index increased, and the left and right ventricle ejection fraction decreased during anthracycline therapy without any clinical signs of dysfunction.[32] Exercise cardiac MRI is also increasingly used to detect subclinical changes in cardiac function.[36]

Comorbidities of myocardial damage

Arterial hypertension. Hypertension is the most prevalent cardiovascular risk factor in childhood cancer survivors. In the study by Chow et al.,[37] hypertension occurred among 18% of childhood cancer survivors. The prevalence is 2.6-fold (95% CI 1.6–4.7) higher than expected, based on age-, gender-, race-, and body mass index-specific rates in the general population.[38] Arterial hypertension in children under 16 years of age can easily be determined following blood pressure reference values for height percentile, age, and gender.[39] In adolescents aged 16 years or older and adults, high normal blood pressure is defined as a blood pressure ≥ 130/85 mmHg and hypertension as ≥ 140/90 mmHg, respectively.[40,41] As high-quality and moderate-quality evidence supported the association between hypertension and asymptomatic left ventricular systolic or diastolic dysfunction and heart failure, care providers must remain vigilant for hypertension in childhood cancer survivors.

Metabolic syndrome. In the study by Chow et al., the prevalence of metabolic syndrome in young adult survivors in different studies is 6.9–33.6%.[37,42] It is recommended that in all follow-up examinations, at least every two years, blood has to be taken to determine the cardiovascular risk factors, such as total cholesterol, high-density lipoprotein, low-density lipoprotein, fasting glucose and glycosylated haemoglobin.

Cardiovascular diseases after mediastinal irradiation. Accelerated atherosclerosis and vascular events are significantly more likely in patients treated with radiotherapy. In childhood cancer survivors, these risks are increased 5- to 29-fold for cardiovascular mortality and 2.4- to 3.6-fold for acute myocardial infarction. Mediastinal radiotherapy has been found to increase the relative risk of death in childhood cancer survivors.[43] Mediastinal irradiation may induce fibrosis and subsequent insufficiency of the cardiac valves[44,45] and may result in pericarditis and pericardial constriction. Echocardiography is the method of choice to detect and monitor these changes. Additionally, cardiac MRI will add further information that is difficult to receive by echocardiography, such as in childhood cancer survivors with constrictive pericarditis. There are no specific diagnostic tools for the detection of premature coronary artery disease in this population. The usual examinations to rule out or to confirm myocardial ischaemia should include: Electrocardiogram at rest and under exercise, measurement of the biomarker high-sensitive troponin, and looking for regional wall motion abnormalities on echocardiography.[46]

Key message: screening for cardiovascular disease in long-term childhood cancer survivors

- Childhood cancer survivors need a lifelong screening for cardiovascular diseases with a frequency depending on the number of cardiotoxic drugs and mediastinal irradiation administered.
- Echocardiography is favourable for detecting cardiomyopathy early by assessing 2D or 3D left ventricular ejection fraction (recommended additional measurements: diastolic left ventricular function and global longitudinal strain). If the information on myocardial performance is insufficient, cardiac MRI should be done additionally.
- Cardiopulmonary exercise testing can detect cardiopulmonary changes, which are not apparent at rest. Regular testing intervals of 2–3 years are recommended.

Monitoring and treatment

Frequency of performing cardiovascular monitoring. The Children's Oncology Group and the Scottish Intercollegiate Guidelines Network have provided guidelines for the long-term follow-up of childhood cancer survivors.[47,48] The Children's Oncology Group suggested a monitoring timeframe dependent on patient age, anthracycline dosage or exposure to radiation doses.[47] The Scottish Intercollegiate Guidelines Network group recommended repeated echocardiograms during treatment and every three years after treatment in their guideline or naturally increasing the frequency of follow-up in those situations where cardiac dysfunction occurs.[48] Concordances and discordances among cardiomyopathy surveillance recommendations between different groups are summarised in Table 4 according to Armenian et al.[49]

Treatment. The most common complications after cardiotoxic therapy are: (1) dilated or restrictive cardiomyopathy, (2) arrhythmias, (3) valve disease, and (4) pericardial dysfunction.

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Table 4. Concordances and discordances among cardiomyopathy surveillance recommendations (cited from Armenian et al.)[49]

Who needs cardiomyopathy surveillance?					
At risk					
Anthracyclines	Yes	Yes	Yes	Yes	Concordance
Mitoxantrone	Yes	Yes	Yes	Yes	Concordance
Differing risk by anthracycline analogues	Yes	Not stated	Not stated	Not stated	Discordance
Chest radiation*	Yes	Yes	Yes	Yes	Concordance
CV risk factors	Yes	Yes	Yes	Yes	Concordance
Highest risk	≥300mg/m^2 anthracyclines ≥30 Gy RT involving heart Anthracycline + chest RT Younger age at treatment Pregnancy	≥300mg/m^2 anthracyclines ≥30 Gy RT involving heart Anthracycline + chest RT Pregnancy	>250mg/m^2 anthracyclines Anthracycline + chest RT Hx of transient cardiomyopathy during treatment Pregnancy	>250mg/m^2 anthracyclines ≥30 Gy RT involving heart Anthracycline + chest RT	Discordance
What surveillance modality should be used?					
Screening for cardiomyopathy					
Echocardiography	Yes	Yes	Yes	Yes	Concordance
Radionuclide angiography	Yes	Yes	No	No	Discordance
At what frequency and for how long should cardiomyopathy surveillance be performed?					
Screening begins	≥2 yrs after treatment or ≥5 yrs after dx (whichever is first)	≥5 yrs after dx	1 – 3 months after treatment	≥5 yrs after completion of treatment	Discordance
Screening frequency	Every 1 – 5 yrs	Every 2 – 5 yrs	Every 3 – 5 yrs	Every 2 – 5 yrs	Discordance
Duration of screening	Lifelong	Lifelong	Not stated	Not stated	Discordance
Closer monitoring during pregnancy	Yes	Yes	Yes	Yes	Concordance
Refer to cardiologist	Yes	Yes	Yes	Yes	Concordance
Consider ACE-inhibitors	Not stated	Yes	Not stated	Yes	Discordance

ACE = angiotensin-converting enzyme; CV = cardiovascular; Dx = diagnosis; Gy = gray; Hx = History; RT = radiation therapy; yrs = years.
*Radiation therapy involving the heart: mediastinal, thoracic, left or whole upper abdominal, or total body irradiation.
Concordance and discordance are shown across the guidelines from the Children's Oncology Group (COG), the Dutch Childhood Oncology Group (DCOG), the Scottish Intercollegiate Guidelines Network (SIGN) and the United Kingdom Children's Cancer and Leukemia Group (UKCCLG).

Moreover, a combination of these is not uncommon. Medical therapy is then initiated (Table 5). Late dilated cardiomyopathy is considered a progressive disease, and the medical treatment initiation seems still too late. Elevated biomarkers, progressive exercise intolerance, and deep echocardiographic phenotyping of myocardial muscle function (standard echocardiographic measurements, tissue Doppler, strain and strain rate analysis) could be used as a marker to start medical therapy. In this setting, angiotensin-converting enzyme inhibitors, beta-blockers, statins, and spironolactone have been tried.[50–54] Medical treatment is initiated according to the current heart failure guidelines.[55,56]

For restrictive cardiomyopathy or constrictive pericarditis, medical therapy is mainly initiated to suppress symptoms and clinical signs of heart failure.[55] It involves using loop diuretics and sodium-glucose cotransporter-2 inhibitors that might improve outcomes. Therapeutic strategies are adapted from standard cardiology treatment.[55]

When drug therapy fails, fenestration of the interatrial septum, mechanical support to decompress the left atrium, pericardiectomy, or heart transplantation (if in remission) may be considered as alternative therapeutic choices.

Arrhythmias can be either bradycardia or tachycardia. For the approach, reference is made to the existing guidelines for treating arrhythmias.[57–59] Besides medication, ablations and implantation of devices may also be necessary.

Finally, managing valve disease due to past oncological treatment is no different from managing degenerative valve disease. Both valve pathologies are progressive and require timely intervention. As it involves damaged valve tissue, valve replacement rather than valve-sparing therapy will be preferred. Also here, valve guidelines can be referred to existing guidelines.[60]

Key message: monitoring and treatment of cardiovascular diseases in long-term childhood cancer survivors

- Treatment of the wide range of cardiovascular diseases in long-term childhood cancer survivors should start as early as possible to minimise their progression and limit late effects.

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Table 5. Medical therapy for late complications in cardio-oncology patients

	Recommendation	Level of evidence
For asymptomatic and symptomatic congestive cardiomyopathy, standard heart failure therapy is recommended to be initiated.	I	C
For symptomatic restrictive cardiomyopathy and/or pericarditis constrictive, loop diuretics are recommended to be initiated.	I	C
For symptomatic restrictive cardiomyopathy consider starting SGLT-2 inhibitors.	IIa	C
For asymptomatic restrictive cardiomyopathy with increased biomarkers, diuretics may be initiated.	IIb	C
For brady and/or tachyarrhythmia, medical treatment according to the standard guidelines[57–59] is recommended to be initiated.	I	C
For valvular disease, medical treatment should be initiated when structural repair cannot be performed.	IIa	C

SGLT-2 = sodium-glucose cotransporter-2.

- Elevated biomarkers, progressive exercise intolerance, and deep echocardiographic phenotyping of myocardial muscle function are valuable markers for early initiation of medical therapy.
- Guidelines provide long-term follow-up monitoring and treatment recommendations, including medical and surgical interventions tailored individually to the survivor.

Physical activity and lifestyle changes

All previously described recommendations and methods to reduce the risk of cardiovascular diseases in childhood cancer survivors are passive actions from the survivors' perspective. Beyond that, there is a spectrum of influencing factors that have not received enough attention yet, however, with a promising potential: modifiable lifestyle risk factors. These factors include physical activity, body weight, and nutrition. Lack of physical inactivity, unhealthy nutrition, and most commonly associated obesity increase the risk of cardiovascular diseases in the generally healthy population.[61]

Physical activity

Physical and cardiorespiratory fitness are usually used as a measurable surrogate marker for physical activity behaviour and one of the most important predictors of overall health. An active and healthy lifestyle can reduce the risk of developing cardiovascular diseases in the group of survivors,[62] and encouraging physical activity may even positively reduce overall mortality.[63] Meta-analytic evidence supports the effectiveness of physical exercise to improve cardiorespiratory fitness and highlights the effectiveness of the cardiovascular system in childhood cancer survivors.[64,65] Schindera et al.[66] recently showed that increased physical fitness is also associated with fewer cardiovascular risk factors. This potential cardioprotective effect, or at least the increase in physical capacity, should convince childhood cancer survivors to engage in a long-term active lifestyle. However, a high number of this population is physically inactive compared to healthy controls. Innovative strategies (Table 6) tailored to the survivors' physical limitations and preferences to encourage physical activity are needed.[67,68] Although knowledge of chemotherapy-related cardiotoxicity and exercise interventions is at an early stage,[69] the importance of engagement in exercise for childhood cancer survivors to mitigate and manage treatment-related cardiovascular dysfunction is obvious.[70]

Body weight

Body weight significantly impacts oncogenesis, the outcome of cancer therapy, the patient's different lifespan, and their quality of life. Although there is no data available for paediatric patients, it is recognized that an increased body mass index in childhood raises the risk of several malignancies in adulthood.[71] There are 430 million children with excessively high body weight worldwide.[72] After stabilisation on a high level, increases are obvious due to global events like the COVID-19 pandemic.[73,74] Body weight is crucial already in diagnosing cancer in children since being overweight, obese, and even underweight increases the risk of morbidity and mortality during therapy and beyond.[75,76]

Furthermore, if the patient is considered a normal weight at the beginning of treatment, unwanted weight gain is often caused by certain therapies such as higher cranial radiation dose, abdominal radiation, total body radiation, surgery in suprasellar region, corticosteroids or being younger age at treatment (age < 4 years), and female sex. Conversely, weight loss is also a common consequence of the oncotherapy. More than 50% of cancer patients suffer from cachexia, which impairs quality of life, responsiveness to cancer therapy, and survival.[77] Consequently, successful primary prevention of increased body mass index is pivotal in children in general, moreover it is highly recommended to perform a precise follow-up of the patient's body weight and composition during and after cancer therapy, to minimise the overall morbidity and mortality among childhood cancer survivors.

Nutrition

Adequate nutrition plays an important role both in prevention and treatment of childhood cancer. Besides its known positive impact on the cardiovascular system, it may contribute to the reduction of overweight and obesity, which are associated with reduced disease-free survival and overall survival in cancer.[78–83] In adults, a high intake of vegetables/fruits and whole grains has been shown to be associated with reduced mortality and cancer recurrence when compared with a high intake of refined grains, processed and red meats, and high-fat dairy products.[84–86] Successful personalised nutrition must be based on the patients' and parents' knowledge of the long-term impact of the child's nutritional status. This includes proper counselling regarding avoidance of restrictive or alternative nutrition.[87]

Besides usual nutrition recommendations, the link between nutrition and physical activity behaviour should not be overlooked. Physical activity is positively associated with healthier

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Table 6. Practical implications for physicians to address the topic of physical activity with childhood cancer survivors

How to explain the importance of physical activity?
• Use of easily understandable explanations (less medical terminology).
• Name the potential benefits of physical activity and the consequences of physical inactivity – Benefits of physical activity: e.g., increased aerobic capacity, muscle strength, flexibility, and balance, reduced risk of health problems, weight control – Consequences of physical inactivity: e.g., increased risk of health problems like some types of cancer in adulthood, diabetes, hypertension, osteoporosis, risk of falling, and bone fractures
• Explain the different levels of intensity: e.g., low – no sweating and normal breathing, moderate – light sweating and moderate breathing, vigorous – intense sweating and intense breathing.
How to advise childhood cancer survivors to be physically active?
• Most important: Fun, motivation, and maintenance!
• Some physical activity is better than physical inactivity, but the aim is regularity and a long-term active lifestyle.
• Explain the difference between daily physical activities (e.g., mobility, way to school or work) and exercise training (e.g., structured, regular training sessions to increase aerobic capacity and strength)
• Give examples: e.g., increase your daily physical activity by walking stairs instead of escalators and elevators, take the bike or a walk, and plan moderate-to-vigorous exercise sessions in your weekly routine.
• Appropriate types of exercise: – Endurance training: e.g., walking, jogging, cycling, and rowing outdoors or in a gym – Resistance training: e.g., training of the big muscle groups, joining a group, and searching for clips
What questions could be asked to detect problems and potential barriers?
• Are you physically active?
• How often are you physically active during the week and for how long? (e.g., in comparison with age-related physical activity recommendations)
• If not, which barriers do you face? (e.g., physical, personal, social, and organisational)
• What kind of physical activity do you like?
• What is motivating you?
Who can further advise childhood cancer survivors to be physically active and how to develop a long-term active and healthy lifestyle?
• Exercise professionals (e.g., exercise physiologist, physiotherapist, trainer, and a teacher for physical education at school)
• Social environment (family, friends)
• Provide information and contact to experienced persons in charge (e.g., the Network ActiveOncoKids in Germany or the International Pediatric Oncology Exercise Guideline Group in Canada/worldwide)

eating habits as shown in healthy adults in Brazil during the COVID-19 pandemic.[88] Furthermore, interventions must target multiple health behaviours as healthy adolescents often show risk behaviour patterns and fail to meet dietary and physical activity guidelines.[89]

Apart from an unhealthy diet, alcohol, drug abuse, and smoking habits might increase the risk of late effects and other health problems in childhood cancer survivors.[90] Therefore, advice regarding this risk-taking behaviour should be provided for survivors by their treating physician and other healthcare professionals and specialists.

The risk factors mentioned above are modifiable and probably a cost-effective measure to reduce long-term sequelae concerning cardiovascular health. The most apparent problem in interventions aiming at lifestyle changes in childhood cancer survivors is the lack of sustainability, due to the complexity of behaviour change. Future research focusing on targeted and effective interventions should be supported by advice from treating physicians (e.g., oncologist, cardiologist) as a different approach to encouraging an active and healthy lifestyle in childhood cancer survivors. Exercise professionals should further assist survivors in maintaining and consolidating this behaviour and, most importantly, avoiding physical inactivity. Practical implications for treating physicians are summarised in Table 6.

General physical activity recommendations for different groups of childhood cancer survivors

- For adult childhood cancer survivors: Physical activity, including aerobic training three times per week for at least 30 minutes with moderate intensity and resistance training at least twice per week dependent on the individual health status and treatment-related outcomes, according to the exercise guidelines for cancer survivors.[91]
- For young childhood cancer survivors: According to the 11 consensus-based recommendations by the Network ActiveOncoKids[92] and the International Pediatric Oncology Exercise Guidelines,[93] childhood cancer patients and survivors should be supported to be physically active following their health status during all phases of treatment.

Apart from particular recommendations for cancer survivors, the World Health Organization's guidelines[94] on physical activity and sedentary behaviour for the healthy population may be the aim to achieve for survivors considering disease- and treatment-related impairments.

- Healthy adults (18–64 years) are recommended to be physically active for at least 150–300 minutes with moderate-intensity aerobic physical activity per week or at

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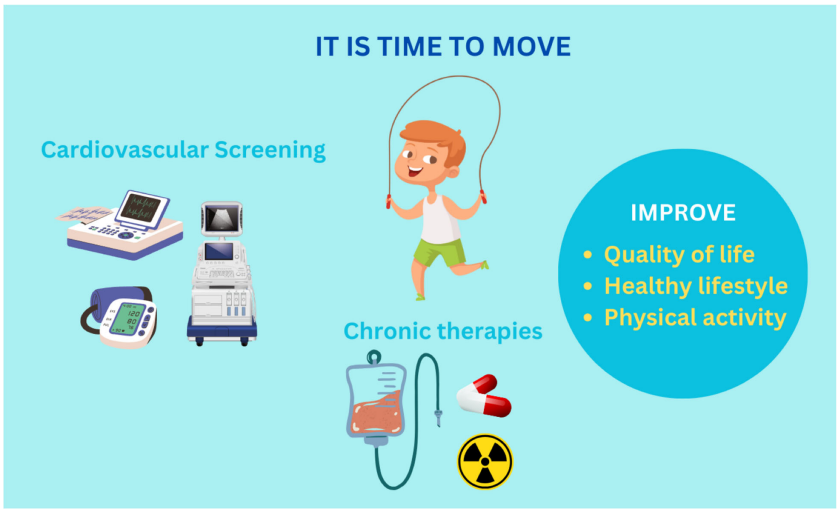

Figure 1. Summary of prevention and surveillance to decrease the risk of cardiovascular diseases in childhood cancer survivors.

least 75–150 minutes of vigorous aerobic physical exercise. Muscle-strengthening activities involving all major muscle groups should be added twice a week, and the number of sedentary activities should be limited for extended periods.
- Healthy children and adolescents (5–17 years) should be physically active for an average of 60 minutes of moderate-to-vigorous intensity per day with mostly aerobic but strengthening exercises for muscles and bones at least three days per week. Moreover, the amount of recreational screen time and time spent being sedentary should be limited for extended periods.

All these modifiable risk factors can only be reduced with the active participation of childhood cancer survivors themselves. The key word is health literacy to achieve this competence and knowledge regarding a healthy lifestyle. Although health literacy in childhood cancer patients and survivors is still understudied, this critical construct must be considered and addressed in the future[95] and first examples of educating childhood cancer survivors regarding these risk factors already exist.[96]

Key messages: physical activity and lifestyle changes

- Physical activity, adequate nutrition, and body weight management are promising and actively modifiable factors to reduce the risk of cardiovascular diseases associated with childhood cancer.
- Personalised strategies to incorporate an active and healthy lifestyle during treatment and follow-up are needed.
- Treating physicians and exercise professionals should assist survivors in maintaining an active and healthy lifestyle by explaining the importance, giving advice, and helping to detect potential barriers in realisation.

Conclusion

Although successful treatment results in high survival rates in paediatric oncology, childhood cancer survivors are at increased risk of cardiovascular diseases due to the necessary cardiotoxic treatment regimen. Therefore, primary, and secondary prevention, in combination with systematic screenings during follow-up in long-term survivors are highly recommended to detect myocardial damage as early as possible (Figure 1). Emerging cardiovascular diseases should be monitored and treated to avoid further progression. Regulation of actively modifiable factors like physical activity, adequate nutrition, and body weight management to reduce the risk of cardiovascular diseases needs to receive increased attention as these can be influenced by the survivors themselves. Active encouragement by treating physicians and healthcare professionals as summarised in these practical recommendations is needed to support childhood cancer survivors both to engage in and maintain an active and healthy lifestyle.

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