The Dutch Childhood Oncology Group guideline for follow-up of asymptomatic cardiac dysfunction in childhood cancer survivors


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Background: The Late Effects of Childhood Cancer task force of the Dutch Childhood Oncology Group (DCOG LATER) developed a guideline for follow-up of asymptomatic cardiac dysfunction in childhood cancer survivors (CCS). In this paper, we present the methods, available evidence and final recommendations of our guideline.

Materials and methods: A multidisciplinary working group specified clinical questions that should be answered to get to recommendations for the guideline. We carried out short or extensive evidence summaries and determined methodological quality of studies and levels of evidence in order to answer all clinical questions. When evidence was lacking for CCS, we carefully extrapolated evidence from other populations. Final recommendations were based on evidence and consensus.

Results: There was high-level evidence for the increased risk of cardiac dysfunction in CCS and its main risk factors. Evidence was lacking regarding the prognosis, diagnosis and treatment of cardiac dysfunction in CCS. We recommended echocardiographic screening for asymptomatic cardiac dysfunction in CCS treated with cardiotoxic treatments and counseling about potential advantages and disadvantages of our screening recommendations.

Conclusion: The DCOG LATER guideline recommends risk-based screening for asymptomatic cardiac dysfunction in CCS, but it should be noted that recommendations are not completely supported by evidence in CCS.

Key words: cardiotoxicity, childhood cancer survivors, clinical practice guideline

introduction

Since the survival of childhood cancer approaches 75%, there is a large and growing group of young people that is confronted with health problems caused by childhood cancer treatment [1, 2]. Because of the high risk of health problems, there is consensus that childhood cancer survivors (CCS) require long-term follow-up care focused on these late effects of cancer treatment [3–5]. The Late Effects of Childhood Cancer task force of the Dutch Childhood Oncology Group (DCOG LATER) has developed a guideline to ensure optimal and uniform follow-up care for all CCS in The Netherlands, covering all potential late health problems in CCS.

One of the late effects of childhood cancer treatments that frequently causes morbidity and mortality in this population is cancer treatment-induced cardiac disease [6–8]. Especially, anthracycline- and/or radiotherapy-induced cardiac dysfunction are common and frequently present in an asymptomatic stage before progressing to symptomatic heart failure [9–13].

In this paper, we report on the DCOG LATER guideline for follow-up of asymptomatic cardiac dysfunction in 5-year CCS. We focused on the screening and treatment options for asymptomatic, cancer treatment-induced cardiac dysfunction, with the ultimate goal to prevent subsequent symptomatic heart failure in CCS. We present the methods of guideline development, the available evidence for the guideline and the final recommendations of the DCOG LATER guideline for follow-up of asymptomatic cardiac dysfunction.
methods

For the DCOG LATER guideline for follow-up of asymptomatic cardiac dysfunction, we formed a working group, including a pediatric oncologist, medical oncologist, a pediatric cardiologist, an adult cardiologist, a general pediatrician and epidemiologists. We had meetings from 2007 until 2010 to discuss the available evidence and to draft a proposal for recommendations. All steps were subsequently discussed within a wider group of the DCOG LATER task force, which coordinated all organ-based guidelines that were part of the overall DCOG LATER guideline for follow-up of CCS.

To identify relevant evidence and get to final recommendations for the guideline for follow-up of asymptomatic cardiac dysfunction, the working group first formulated clinical questions that were relevant to our guideline. We thereby focused on clinical questions regarding early detection and potential treatment of asymptomatic cardiac dysfunction. We categorized the clinical questions into four topics: (i) incidence/prevalence or etiology/risk factors, (ii) prognosis, (iii) diagnosis and (iv) therapy.

Two clinical questions were selected for an extensive evidence summary because of relevancy and lack of knowledge within the wider DCOG LATER collaboration: (i) what is the predictive value of a reduced left ventricular ejection fraction (EF) or left ventricular fractional shortening (FS) of the heart (asymptomatic cardiac dysfunction) on the occurrence of future clinical heart failure or death? (topic diagnosis) and (ii) what is the effectiveness of medical interventions [angiotensin-converting enzyme (ACE) inhibitors, beta blockers] in patients with asymptomatic left ventricular dysfunction in general on the occurrence of heart failure and mortality? (topic therapy). For these two questions, we carried out systematic literature searches to identify relevant studies. To answer the other clinical questions formulated by the working group, we made short evidence summaries. These were based on information reported in other guidelines for follow-up of CCS [14–16], two textbooks on late effects of childhood cancer treatment [17, 18], relevant systematic reviews from a study on systematic reviews in pediatric oncology [19] and studies suggested by working group members or studies identified by performing simple Medline searches. We included studies that investigated cancer treatment-induced cardiac abnormalities that the authors of the study defined as cardiotoxicity, cardiac dysfunction, left ventricular dysfunction or heart failure. In line with studies in the pediatric oncology field, we used the terms asymptomatic cardiac dysfunction throughout the guideline to indicate abnormal function of the heart as found during a diagnostic procedure in a patient without symptoms and clinical heart failure as an abnormal function of the heart in a patient with accompanying symptoms and signs. A report on the search strategy for the two extensive evidence summaries as well as a summary of the included studies for all clinical questions are provided in the Appendix (available as supplementary data in Annals of Oncology online). We determined methodological quality of individual studies and level of evidence of all clinical questions based on the manual of the Dutch evidence-based guideline development platform (EBRO platform) [20], which was adjusted for the purpose of the DCOG LATER overall guideline (Table 1).

Within our working group, the clinical relevance of evidence and lack of evidence were discussed. When evidence was lacking for CCS, we carefully extrapolated evidence from other populations. Other considerations of the working group in addition to the available evidence were summarized. We categorized our recommendations as follows: (i) who do we need to screen?, (ii) what is the time interval for screening and for how long should we screen?, (iii) what is the diagnostic test we have to use to detect asymptomatic cardiac dysfunction? and (iv) what should be done when abnormalities are identified? The final recommendations were based on evidence, additional considerations of the working group and consensus about the estimate of the expected individual risk, the availability of a test with adequate predictive and diagnostic value to detect relevant outcomes and the availability of adequate therapy when abnormalities are detected. The working group continuously monitored evidence and updated recommendations when necessary up to April 2011.

The final recommendations of the DCOG LATER guidelines were presented to relevant professional organizations and the national organization of parents of children with cancer. Recently, the DCOG LATER task force determined indicators based on several consensus meetings. The task force has aimed to update the guideline periodically (every 3–5 years).

results

available evidence

The answers to our clinical questions, the associated levels of evidence and references for the topics: (i) incidence/prevalence or etiology/risk factors, (ii) prognosis, (iii) diagnosis and (iv) therapy are presented in supplemental Table S1, (available at Annals of Oncology online).

additional considerations of the working group

who do we need to screen? Although it has been shown that treatment with a higher cumulative anthracycline dose is associated with higher risks of cardiac dysfunction, a cut-off dose suitable for screening is difficult to determine [9, 13, 21, 25–28]. Cardiac dysfunction and clinical heart failure do occur after low anthracycline doses [12, 21, 28]. For mitoxantrone, the working group agreed that an increased risk of cardiac dysfunction is likely, but thus far no high-quality studies have been carried out to determine the risk after different cumulative doses [24]. Similarly, higher doses of cardiac irradiation are related to a higher risk of cardiac disease, but again no clear cut-off value for a safe cumulative dose can be defined, especially for asymptomatic cardiac dysfunction [8, 11, 21, 22, 29]. Other risk factors for cardiac dysfunction (like age at treatment, gender, pregnancy) were difficult to summarize because available studies analyzed different risk factors using different methods or there was conflicting or lack of evidence [8–10]. We therefore focused on results of multivariate analyses in high-quality studies [11, 13, 21, 22, 27, 30] or when no high-quality studies were available on the only available studies [31]. Based on available evidence and consensus, we recommended screening for asymptomatic cardiac dysfunction in all CCS treated with potentially cardiotoxic cancer treatment (anthracyclines, cardiac radiotherapy and mitoxantrone). We defined cardiac radiotherapy as any radiotherapy field that includes (part of) the heart (mediastinal, thoracic, spinal, left or whole upper abdominal or total body irradiation). We recommended more frequent follow-up for survivors treated with high doses of anthracyclines (cut-off 300 mg/m²), high doses of cardiac radiotherapy (cut-off 30 Gy) or a combination of the two (any dose). We felt that there is no enough evidence and consensus to further adjust these recommendations for age at treatment and/or gender of the survivor. Because of the potentially severe consequences of missing cardiac dysfunction during pregnancy [48, 49], we decided to recommend extra screening for female survivors in the third trimester of pregnancy, even though strong evidence for this recommendation is lacking [30, 31].
There is evidence for deterioration of asymptomatic anthracycline-induced cardiac dysfunction [25, 28, 32, 33], but an appropriate interval and period for screening are difficult to define. Based on studies in (adult) patients with asymptomatic cardiac dysfunction due to causes other than treatment of childhood cancer [35–43], we assumed that CCS with asymptomatic cardiac dysfunction similarly are at increased risk to develop clinical heart failure and (cardiac) death (see topic diagnosis). We considered it unlikely that this risk of deterioration decreases with longer follow-up. We agreed that frequency of screening is a balance between the risk
of missing (progressive) cardiac dysfunction and the burden of regular visits to a clinic. Based on consensus, we recommended follow-up once every 5 years or once every 2/3 years for the lower and higher risk groups, respectively. We further recommended lifelong follow-up until more evidence is available regarding very long-term risks of cardiac dysfunction.

What is the diagnostic test we have to use to detect asymptomatic cardiac dysfunction? Within the working group, there was consensus that echocardiography is a fairly accurate noninvasive diagnostic tool to detect cardiac dysfunction. Based on the evidence in adults with cardiac dysfunction due to causes other than treatment of childhood cancer (supplemental Table S2, available at Annals of Oncology online) [35–43], we concluded that in CCS, a decreased EF and/or FS is probably predictive for the occurrence of future clinical events. However, the exact cut-off point for abnormal cardiac function that is predictive for future clinical events is difficult to determine from included studies. We therefore recommended to consult a cardiologist when cardiac function is borderline abnormal (FS 25–29%, EF 45–49%) and referral to a cardiologist when cardiac function is clearly abnormal (FS < 25%, EF < 45%).

Studies in adults have shown that asymptomatic diastolic dysfunction can be predictive for the development of clinical heart failure [50]. However, only a few studies in CCS have suggested an increased risk of treatment-induced diastolic dysfunction and no study has evaluated the prognostic value of it [32, 51]. Also the clinical implications of other asymptomatic echocardiographic parameters in CCS, like tissue Doppler echocardiography, are unclear. We therefore did not include these abnormalities in our recommendations.

It is possible that on a routine echocardiogram, other abnormalities than a decreased FS/EF or incidental findings like anatomical variations are identified. We therefore added this possibility to our recommendations. Radionuclide angiography is an alternative to determine cardiac function when echocardiography is not suitable [52]. We found no evidence for a high prognostic value of other abnormal diagnostic tests (electrocardiogram, magnetic resonance imaging) in CCS with asymptomatic cardiac disease.

Three systematic reviews evaluated the potential of biomarkers [mainly B-type natriuretic peptide (BNP) and N-terminal pro-BNP] to detect cardiac dysfunction or clinical heart failure in the adult general population and in CCS [34, 53, 54]. These studies concluded that these biomarkers are not suitable for screening asymptomatic patients in the general population and that there is not enough evidence on their use in CCS. We therefore decided that at this point in time, there is no place for screening of asymptomatic cardiac dysfunction by biomarker assessment.

what should be done when abnormalities are identified? One randomized controlled trial (RCT) of an ACE inhibitor compared to placebo in CCS with anthracycline-induced asymptomatic cardiac dysfunction showed no positive effects on clinical end points, only a small effect on one subclinical outcome and side-effects like dizziness [44]. Because of the small sample size of this RCT and based on the effects of ACE inhibitors in other populations with asymptomatic cardiac dysfunction [35, 37, 38, 42], we felt that it is reasonable to hypothesize a positive and potentially clinical effect of ACE inhibitors in CCS. However, the working group agreed that any potential benefit should be weighed against the potential side-effects individually. Since further research is essential, we recommended providing ACE inhibitor treatment in a research setting, or when this is not possible, to at least carefully monitor the effects of treatment of future studies.

Additional considerations. Because of lack of evidence regarding several important topics within the field of cancer treatment-induced cardiac dysfunction, we additionally recommended that CCS should be counseled regarding this lack of evidence and the potential advantages and disadvantages of screening for asymptomatic cardiac dysfunction after childhood cancer treatment. After careful counseling, the individual survivor and the health care professional together should decide on the optimal follow-up of the survivor.

Final recommendations for screening and follow-up

Based on the available evidence and the stated considerations, we formulated recommendations for screening and follow-up for cardiac dysfunction in CCS. These are summarized in Table 2.

guideline implementation and quality indicator

The implementation of the DCOG LATER guidelines has been an ongoing process. The final recommendations of the DCOG LATER guidelines were presented to relevant professional organizations and the national organization of parents of children with cancer, who agreed on them. A website with patient information has been launched and a booklet comprising the recommendations of all organ-based guidelines was published [55]. Also, all Dutch pediatric cancer centers now have an outpatient clinic for late effects after childhood cancer treatment. In 2010, DCOG LATER members defined indicators that can be used to evaluate guideline adherence in the outpatient clinics. The indicator for cardiac screening is the percentage of CCS treated with a cumulative anthracycline dose of ≥300 mg/m² that has received an echocardiogram during a 3-year period. In the nearby future, all outpatient clinics will be evaluated.

discussion

In this article, we described the development of the DCOG LATER guideline on asymptomatic cardiac dysfunction after cancer therapy in CCS, the available evidence and our final recommendations for screening. Based on evidence summaries and consensus, we recommended regular medical follow-up of CCS treated with potential cardiotoxic therapies and additional screening for asymptomatic dysfunction with referral to a cardiologist in case of abnormalities.

The DCOG LATER guideline for follow-up of asymptomatic cardiac dysfunction is based on a comprehensive summary of evidence in CCS and when necessary careful extrapolation of evidence from other populations. Ideally, we would have carried out a systematic review for all clinical questions
There is extensive evidence to support the increased risk of cardiac dysfunction in CCS treated with anthracyclines and/or cardiac radiotherapy. An important finding was that few studies have evaluated the prognosis and diagnostic and therapeutic options for CCS with asymptomatic cardiac dysfunction. Also, studies evaluating benefits, risks and costs of screening of this population are lacking. Although there is lack of evidence with regard to prognostic, diagnostic and therapeutic questions in CCS treated with potentially included in the guideline. However, because of the time-consuming process of a systematic review, this was not possible within the available time. Although we did not perform extensive evidence searches for all clinical questions, we tried to be transparent in the choices we made regarding extensive or less extensive evidence searches. All studies were methodologically judged and the levels of evidence of conclusions of clinical questions were systematically summarized.
cardiotoxic therapies, there was consensus across the working group to recommend regular risk-based screening by echocardiography, mainly based on evidence from other populations. However, the number needed to screen or treat was impossible to define with the available evidence. The working group additionally recommended that CCS should be counseled regarding the potential advantages and disadvantages of screening for cardiac dysfunction after childhood cancer treatment. A potential advantage is that early treatment of asymptomatic cardiac dysfunction might decrease the risk of deterioration to clinical heart failure. Potential disadvantages of screening are false-positive results, uncertainty about the course and outcome of an abnormality, potential impediments in purchasing an insurance/mortgage and side-effects of the treatment. The survivor and healthcare professional should discuss all possibilities and together decide on the optimal follow-up of the survivor.

It should be noted that our guideline is focused on asymptomatic cardiac dysfunction. It does not cover other cardiac late effects, such as valvular disease, ischemic heart disease or arrhythmia’s. Cardiovascular risk factors, such as hypertension, hypercholesterolemia and endocrine abnormalities, have been covered by other guidelines within the overall DCOG LATER guideline [55]. Furthermore, our recommendations are suited for the Dutch situation. In The Netherlands, distances to the nearest late effects outpatient clinic are relatively small and all inhabitants of the country have health insurance and access to medical care. Also, all Dutch pediatric cancer centers had already started initiatives to provide care and follow-up for CCS. Therefore, implementation of a follow-up guideline for CCS was feasible. This may not be true in other countries. However, regardless of the medical system, the levels of evidence are universal and recommendations could therefore easily be adjusted to other health care systems.

Other collaborative groups have published guidelines with recommendations for the surveillance of CCS [14–16]. There are similarities between these guidelines and ours, e.g. in including survivors treated with anthracyclines and/or cardiac radiotherapy and in using echocardiography as the main screening tool. But there are also marked differences, e.g. in the exact definitions of risk groups, the associated frequency of screening and the use of additional tests. In addition, two other guidelines do not clearly describe the exact process of summarizing evidence and getting to recommendations [15, 16]. The American Childhood Oncology Group (COG) summarized levels of consensus, while we summarized methodological quality and the level of evidence [14, 56]. International collaboration in guideline development for CCS and possible harmonization of the recommendations will be the focus of future international research.

The lack of evidence that we described signifies that future studies should focus on the prognosis, diagnosis and therapeutic options of cardiac dysfunction in CCS as well as on advantages and disadvantages of screening of asymptomatic survivors, including cost-effectiveness analyses. Especially, studies evaluating the effect of screening practices and medical interventions for cardiac dysfunction need well set up designs. These studies should preferably be RCTs, but we recognize that performing an RCT in clinics where screening or medical treatment is already recommended is not always feasible. For these situations, alternative study designs, adjusting for the potential selection bias i.e. related to nonrandomized studies, are essential [57].

In conclusion, we summarized the method of guideline development, available evidence and final recommendations of the DCOG LATER guideline for follow-up of asymptomatic cardiac dysfunction. We recommend risk-based follow-up primarily based on echocardiography in 5-year CCS. Each individual CCS should be counseled on potential advantages and disadvantages of our screening recommendations.

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disclosure

The authors declare no conflicts of interest.

references


Cruciferous vegetables and cancer risk in a network of case–control studies

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Background: Cruciferous vegetables have been suggested to protect against various cancers, though the issue is open to discussion. To further understand their role, we analyzed data from a network of case–control studies conducted in Italy and Switzerland.

Patients and methods: The studies included a total of 1468 cancers of the oral cavity/pharynx, 505 of the esophagus, 230 of the stomach, 2390 of the colorectum, 185 of the liver, 326 of the pancreas, 852 of the larynx, 3034 of the breast, 367 of the endometrium, 1031 of the ovary, 1294 of the prostate, 767 of the kidney, and 11 492 controls. All cancers were incident, histologically confirmed; controls were subjects admitted to the same network of hospitals as cases for a wide spectrum of acute nonneoplastic conditions.

Results: The multivariate odds ratio (OR) for consumption of cruciferous vegetables at least once a week as compared with no/occasional consumption was significantly reduced for cancer of the oral cavity/pharynx (OR = 0.83), esophagus (OR = 0.72), colorectum (OR = 0.83), breast (OR = 0.83), and kidney (OR = 0.68). The OR was below unity, but not significant, for stomach (OR = 0.90), liver (OR = 0.72), pancreatic (OR = 0.90), laryngeal (OR = 0.84), endometrial (OR = 0.93), ovarian (OR = 0.91), and prostate (OR = 0.87) cancer.

Conclusion: This large series of studies provides additional evidence of a favorable effect of cruciferous vegetables on several common cancers.

Key words: brassicaceae, cancer, case–control study, cruciferous vegetables, risk factor, vegetables

Introduction

The issue of vegetables and cancer risk has long been considered in the absence, however, of definite quantification [1, 2].

Cruciferous vegetables have been of specific interest due to their content in glucosinolates, whose major breakdown products [isothiocyanates (ITCs) and indoles] have anticarcinogenic properties in in vitro and animal studies [3–5]. Glucosinolates are converted to ITCs and indoles through myrosinase activity, a β-thioglucosidase enzyme found in vacuoles and activated following mastication or cutting of plant tissue [6]. Most of the ITCs are metabolized in vivo through the mercapturic acid pathway; indole compounds can react...