EJC Paediatric Oncology 4 (2024) 100195

Contents lists available at ScienceDirect

EJC Paediatric Oncology

journal homepage: www.journals.elsevier.com/ejc-paediatric-oncology

Original research

Risk of severe esophageal stricture among childhood cancer survivors – A population-based case-cohort study within the Adult Life after Childhood Cancer in Scandinavia (ALiCCS)

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ARTICLE INFO

Keywords:
Childhood cancer
Late effects
Case-cohort study
Nordic countries
Population-based

ABSTRACT

Purpose: Due to limited data on treatment-related risk factors associated with esophageal stricture in childhood cancer survivors, this study aimed to assess such factors in long-term survivors.
Methods: A case-cohort study was conducted involving 36 cases of five-year childhood cancer survivors with esophageal stricture and a sub-cohort of 540 survivors diagnosed with cancer in 1970–2007 as identified within the Nordic 'Adult Life after Childhood Cancer in Scandinavia' program. Individualized treatment details were retrieved from medical records. Radiation doses to each body region and average dose to the esophagus were reconstructed for patients that received radiotherapy. We used a modified Cox proportional hazard model to evaluate associations between esophageal stricture and risk factors by calculating incidence rate ratio (IRR), with 95 % confidence intervals (CIs).
Results: An increased rate of esophageal stricture was found in survivors who received total body irradiation (IRR=13.7, 95 %CI 4.6–41.1), chest- and neck-directed radiotherapy (IRR=23.5, 95 %CI 8.5–64.7) and doses of ≥12 Gy to the esophagus (IRR=26.8, 95 % CI=9.0–80.3) compared to non-irradiated survivors. Treatment with chemotherapy was also associated with esophageal stricture (IRR=8.4, 95 % CI=2.9–24.4). Notably, leukemia survivors faced an elevated rate (IRR=3.8, 95 % CI 1.8–8.1) compared with survivors of CNS and other solid tumors.
Conclusions: Our findings indicate an increased risk of esophageal stricture among childhood cancer survivors, with both neck- and chest-directed radiotherapy and chemotherapy as important risk factors.

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https://doi.org/10.1016/j.ejcped.2024.100195
Received 8 April 2024; Received in revised form 20 September 2024; Accepted 1 October 2024
Available online 3 October 2024

1. Introduction

With the advancement of diagnostic methods and treatment, childhood cancer survival rates have increased over the past five decades and now exceed 80 %[1]. The improvement in survival, however, may come at a price, as many survivors face chronic late complications affecting different organ systems[2,3], including the gastrointestinal system[4]. Although gastrointestinal complications have been reported in >40 % of childhood cancer survivors[5], detailed information on these sequelae is scarce, especially in regard to the upper gastrointestinal tract[3]. Data suggest that the esophagus is susceptible to damage from radiotherapy and chemotherapy, with therapy-related esophagitis potentially leading to esophageal stricture[5–8]. Esophageal stricture, which results from narrowing of the esophageal volume, is a leading cause of dysphagia. Besides its association with cancer treatment, other known risk factors include acid reflux as well as iatrogenic or drug induced esophagitis, and infections[9].

Only a limited number of studies have investigated the association

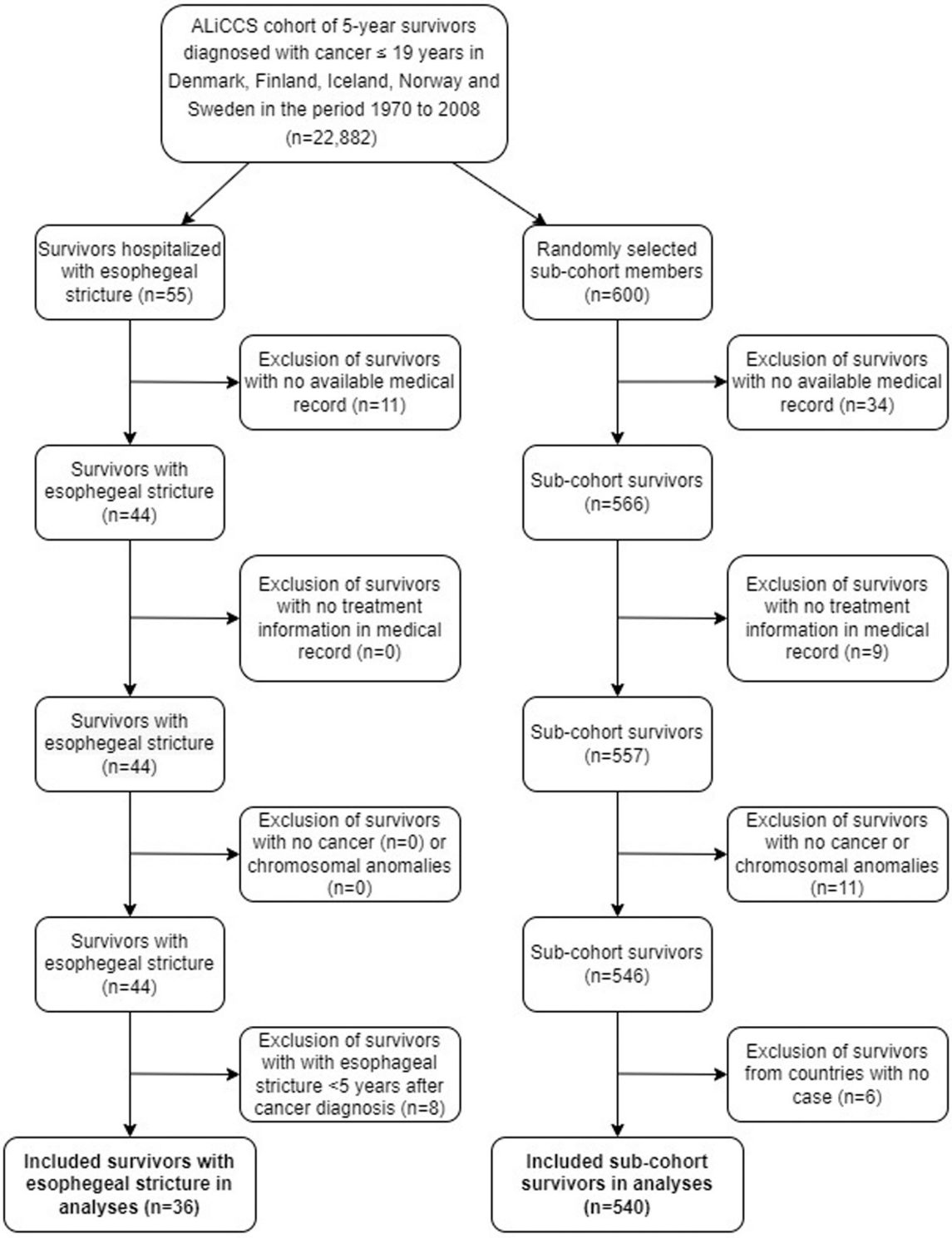

Fig. 1. Flow chart of childhood cancer survivors with esophageal stricture and sub-cohort childhood cancer survivors.

between cancer-therapy and esophageal stricture in children; several of these studies included only a small number of cases (5−13) with esophageal stricture[7,8,10]. However, recently the Childhood Cancer Survivor Study (CCSS) observed a 7.6-fold increased risk of esophageal stricture among childhood cancer survivors compared to siblings, and suggested an association between radiotherapy and risk of esophageal stricture, with indication of a dose response relationship[11]. In the Adult Life after Childhood Cancer in Scandinavia (ALiCCS) cohort, we have previously reported a 13-fold increased risk for hospitalization due to esophageal stricture based on 65 cases in a cohort of 31,132 one-year survivors but the study was limited by the lack of individual treatment information[6]. To overcome this limitation, we abstracted detailed treatment information on survivors with esophageal stricture and on a sub-cohort of randomly selected childhood cancer survivors from ALiCCS to assess the association between cancer therapy and late-onset esophageal stricture in a case-cohort study.

2. Methods

2.1. Cases and sub-cohort members

Eligible study participants were five-year survivors of childhood cancer in the ALiCCS cohort (n=22,882) registered from 1970−2008 with a cancer diagnosis in the nationwide cancer registries of Denmark, Finland, Iceland, Norway, and Sweden[12,13]. All cancer diagnoses were classified according to the International Classification Scheme for Childhood Cancer[14]. The case group included 55 childhood cancer survivors (0.2 % of the eligible survivor cohort), who had been discharged from the hospital with a primary or supplementary diagnosis of esophageal stricture according to the International Classification of Diseases 7th to 10th revisions (ICD-7 539.1; ICD-8 and ICD-9 530; ICD-9 Sweden 530.D; ICD-10 K22.2) at least five years after the cancer diagnosis in the five Nordic National Hospital Registries[15]. A sub-cohort of five-year survivors was selected from the ALiCCS cohort to represent the entire survivor cohort with respect to cancer type and treatment (n=600). The selection was done based on the number of contributing person-years of the survivors in each Nordic country[16].

2.2. Exclusion of childhood cancer patients

Medical records were requested for the 55 cases with esophageal stricture and the 600 sub-cohort members (see flow chart in Fig. 1). We excluded study participants with: no available medical records, insufficient information on cancer treatment, no confirmed cancer diagnosis, and chromosomal anomalies. Further, cases diagnosed with esophageal stricture within the first five years after cancer diagnosis were excluded. Descriptive characteristics of the survivors with early onset of esophageal stricture are seen in Table S1. Finally, we excluded sub-cohort members from Iceland as the current study did not include any Icelandic survivors with esophageal stricture. After these exclusions, 36 cases and 540 sub-cohort members remained for analysis. As the members of the sub-cohort were selected randomly from the large ALiCCS cohort of all survivors, the sub-cohort included three members with esophageal stricture, who were already included as cases[17].

2.3. Treatment information

Data on radiotherapy included information on external beam therapy, including total body irradiation (TBI). Total doses to the chest, neck and esophagus from radiation were estimated by the Late Effects Group at MD Anderson Cancer Center (MDA) Houston, Texas for 153 out of 237 survivors treated with radiotherapy (64 %; 16 survivors with esophageal stricture and 137 in the sub-cohort) for whom detailed information on radiotherapy was available. Descriptive characteristics of survivors with and without detailed information on radiotherapy are seen in Table S2. For external beam therapy, the field parameters used for dose reconstruction included age at treatment, beam energy, field location (body region, borders, size, and configuration), blocking and dose delivered. Treatment fields were reconstructed on three-dimensional computational phantoms, scaled to age at treatment. The extent of the esophagus was represented using 12 points in the phantom and the dose reported was the average of these point doses, including both direct and stray dose[18,19].

2.4. Statistical analysis

The follow-up period started five years after the date of cancer diagnosis and ended at the date of esophageal stricture diagnosis, death, emigration, second primary cancer or the end of the study period (Sweden: 31 December 2009; Denmark: 10 November 2010; Norway: 31 December 2010; Finland: 14 December 2009) whichever came first. The statistical analyses were completed according to the principles for case-cohort studies described by Prentice[16] and Barlow et al.[20]. We used a modified Cox proportional hazards model with age in years as the underlying time scale to evaluate the incidence of late-onset esophageal stricture among survivors in association with the following covariates: sex, age at cancer diagnosis in years (<5, 5–14, 15–19), type of cancer (leukemia, lymphomas, other types), and different treatment modalities. The treatment modalities included chemotherapy and specific chemotherapeutic agents, which were dichotomized as none/any. Radiotherapy was evaluated as none/any radiotherapy for all survivors. For those survivors for whom neck, chest, or esophageal doses were reconstructed, we also conducted analyses of neck- and/or chest-directed therapy (none/any) and (none, either chest or neck, both chest and neck), dose in Gy to chest (0, 2−20, >20) and neck (0, 7.5−18, >18) based on the median doses in Gy (20 and 18), average dose to the entire esophagus in Gy (0−<1, 1–11, ≥12), and TBI (none/any). Survivors treated with radiotherapy, but with incomplete information for dose calculation for either chest, neck, or esophagus, were included as a separate group in each analysis. Finally, we assessed type of cancer and treatment information combined (other solid tumors ± chemotherapy and/or radiotherapy; leukemia or lymphoma + chemotherapy only; leukemia or lymphoma + radiotherapy and CNS with radiotherapy to total spine).

Based on Wald's test of the Cox regression parameter, two-sided 95 % confidence intervals (CIs) for the incidence rate ratio (IRR) were calculated. As the population size differs between the Nordic countries, we applied sampling weights in the statistical models. All analyses were adjusted for sex and country. We used SAS version 9.4 (SAS Institute, Inc.) for the statistical analyses.

3. Results

Clinical characteristics of the study participants are presented in Table 1.

The median age at first hospitalization for esophageal stricture was 25.1 years (range 5.8–47.4); for sub-cohort members the median age at end of follow-up was 28.1 years (range 5.8–57.5).

Survivors of leukemia (IRR=3.8, 95 % CI 1.8–8.1) had an increased rate of esophageal stricture compared to survivors diagnosed with CNS or other solid tumors (Table 2). No significant increased risk was found for survivors of lymphoma (IRR=2.5, 95 % CI 0.8–8.1).

Relapse of primary cancer also increased the rate of esophageal stricture (IRR=5.2, 95 % CI 2.4–11.5). When we assessed radiotherapy, the IRR of esophageal stricture was 3.6 (95 % CI 1.6−8.1) for survivors treated with any radiotherapy (minus TBI) and 26.3 (95 % CI 7.6−91.2) for survivors with TBI, respectively, when compared to non-irradiated survivors. Also, chest- and neck-directed therapy were associated with an increased rate of esophageal stricture when compared to non-irradiated survivors Notably, we found that the rate of esophageal stricture was higher in survivors treated with both chest- and neck-directed (IRR=23.5, 95 % CI 8.5–64.7) than in survivors treated with

Table 1
Clinical characteristics of 36 five-year childhood cancer survivors with esophageal stricture and 540 five-year survivors in the sub-cohort.

Characteristic	Survivors with esophageal stricture (N=36) n (%)	Survivors in the sub-cohort (N=540) n (%)
Sex		
Female	10 (28)	238 (44)
Male	26 (72)	302 (56)
Country		
Sweden	21 (58)	255 (47)
Denmark, Finland, or Norway[a]	15 (42)	285 (53)
Year of cancer diagnosis		
1970–1979	6 (17)	79 (15)
1980–1989	18 (50)	137 (25)
1990–1999	12 (33)	231 (43)
2000–2007	0 (0)	93 (17)
Age at cancer diagnosis (years)		
Median (SD)	8.3 (6.2)	10.4 (6.4)
0–4	15 (42)	167 (31)
5–14	13 (36)	208 (39)
15–19	8 (22)	165 (31)
Age at outcome/end of follow-up (years)		
Median (SD)	25.1 (10.8)	28.1 (10.2)
Min	5.8	5.8
Max	47.4	57.5
Time since cancer diagnosis to esophageal stricture/end of follow-up (years)		
Median (SD)	14.7 (7.9)	17.4 (8.7)
Min	5.1	5.1
Max	33.9	39.6
Type of cancer		
Leukemia	16 (44)	132 (24)
ALL	13	118
AML	3	10
Other	0	4
Lymphomas	5 (14)	56 (10)
CNS tumors	3 (8)	117 (22)
Soft tissue sarcomas	3 (8)	25 (5)
Carcinomas and other malignant epithelial neoplasms	5 (14)	63 (12)
Other and unspecified malignant neoplasms	4 (11)	147 (27)
Relapse		
0	24 (67)	489 (91)
≥1	12 (33)	51 (9)
Radiotherapy		
None	9 (25)	330 (61)
Any	27 (75)	210 (39)
Radiation dose to esophagus		
Unknown	11	90
Yes	16	120
Median dose to esophagus in cGy, range	1495 (77−3130)	69 (1−4170)
Bone marrow transplantation		
No	28 (78)	507 (94)
Yes	8 (22)	33 (6)
Autologous	0	14
Allogeneic	8	19
Total body irradiation		
No	29 (81)	520 (96)
Yes	7 (19)	20 (4)
Chemotherapy		
None	4 (11)	239 (44)
Any	32 (89)	301 (56)

CNS, central nervous system; SD, standard deviation
[a] Denmark, Finland and Norway are combined due the low number of included survivors with esophageal stricture in each country

either chest- or neck-directed therapy when compared to survivors not irradiated to chest or neck (IRR=7.1, 95 % CI 1.2–41.0); however, <3 survivors received radiotherapy to only one of the body regions. When we assessed the average radiation dose to the esophagus, only survivors

Table 2
Risk factors for late-onset esophageal stricture among childhood cancer survivors.

	Survivors with esophageal stricture/survivors in sub-cohort (n)	IRR[a] (95 % confidence interval)
Sex		
Female	10/238	Ref.
Male	26/302	1.8 (0.9–3.8)
Age at cancer diagnosis		
0–4	15/167	1.6 (0.6–4.0)
5–14	13/208	1.4 (0.5–3.6)
15–19	8/165	Ref.
Cancer type		
Diagnoses other than leukemia and lymphomas	15/352	Ref.
Leukemia	16/132	3.8 (1.8–8.1)
Lymphoma	5/56	2.5 (0.8–7.6)
Relapse		
0	24/489	Ref.
≥1	12/51	5.2 (2.4–11.5)
Radiotherapy		
None	9/330	Ref.
Any (minus TBI)	20/190	3.6 (1.6–8.1)
TBI	7/20	26.3 (7.6–91.2)
Chest-directed therapy[b,c]		
None	12/420	Ref.
Any (minus TBI)	7/25	11.8 (3.9–36.0)
TBI	6/16	28.3 (8.1–98.1)
Maximum chest radiation dose (Gy)		
None	12/420	Ref.
2–20	7/20	23.4 (7.3–76.3)
>20–64	6/20	11.9 (7.4–74.7)
Neck-directed therapy[b,c]		
None	10/420	Ref.
Any (minus TBI)	9/24	17.6 (5.7–54.2)
TBI	6/16	33.4 (9.1–122.9)
Maximum neck radiation dose (Gy)		
None	10/420	Ref,
7.5–18	6/22	20.1 (5.8−69.5)
>18–64	9/17	23.5 (7.4−74.7)
Chest and/or neck directed therapy		
None	10/413	Ref.
Chest or neck	<3[d]/14	7.1 (1.2−41.0)
Chest and neck	<15[d]/33	23.5 (8.5−64.7)
Average dose to esophagus (Gy)[b]		
0–<1	9/330	Ref.
1–11	3/90	1.1 (0.3–4.3)
≥12	13/30	26.8 (9.0–80.3)
Total body irradiation		
No	29/520	Ref.
Yes	7/20	13.7 (4.6–41.1)
Chemotherapy		
None	4/239	Ref.
Any	32/301	8.4 (2.9–24.4)
Anthracyclines		
None	11/337	Ref.
Any	25/203	6.0 (2.8–13.0)
Alkylating agents		
None	15/348	Ref.
Any	21/192	3.5 (1.7–7.2)
Corticosteroids		
None	15/368	Ref.
Any	21/172	3.6 (1.8–7.3)
Antimitotic drugs		
None	11/297	Ref.
Any	25/243	3.1 (1.5–6.6)
Asparaginase		
None	26/428	Ref.
Any	10/112	2.0 (1.0–4.4)
Antimetabolites		
None	14/374	Ref.
Any	22/166	4.7 (2.3–9.6)

(*continued on next page*)

Table 2 (*continued*)

	Survivors with esophageal stricture/survivors in sub-cohort (n)	IRR[a] (95 % confidence interval)
Platinum drugs		
None	30/487	Ref.
Any	6/53	2.9 (1.0–8.3)
Cancer type and treatment		
Other solid tumors ± chemotherapy and/or radiotherapy	14/349	Ref.
Leukemia or lymphoma + chemotherapy only	7/104	2.3 (0.9–5.9)
Leukemia or lymphoma + radiotherapy CNS with radiotherapy to total spine	15/87	5.2 (2.4–11.6)

[a] All analyses were adjusted for sex and country (except the analysis of sex)

[b] For some survivors, the information on radiation abstracted from medical records was insufficient to estimate dose to chest, neck or esophagus. Thus, the included numbers of cases and survivors in the sub-cohort are lower than 36 and 540, respectively.

[c] The doses to chest and neck were calculated as the maximum delivered radiation treatment dose to each body region from all overlapping fields in each region. Doses from TBI are also included.

[d] The exact number of cases cannot be reported due to reporting restrictions.

treated with doses of ≥12 Gy to the esophagus were at increased risk for esophageal stricture compared to non-irradiated survivors (IRR=26.8, 95 % CI=9.0–80.3). In 15 of the 43 survivors (35 %) treated with doses ≥12 Gy, radiotherapy was given as TBI as part of conditioning for hematopoietic stem cell transplantation (HSCT) (data not shown). TBI was also associated with an increased rate of esophageal stricture (IRR=13.7, 95 % CI=4.6–41.1). Six of the leukemia survivors with esophageal stricture had received TBI and three had received whole brain radiation. Additionally, the average radiation dose to esophagus was higher in leukemia survivors with esophageal stricture than in leukemia survivors in the sub-cohort (Table S3).

Treatment with any chemotherapeutic agent, irrespective of radiotherapy status, was a risk factor for esophageal stricture, with an IRR of 8.4 (95 %, CI 2.9–24.4). In the analyses of specific chemotherapeutic drugs, the risk for esophageal stricture was increased for all included drugs, except asparaginase, with the highest associations seen for anthracyclines (IRR=6.0, 95 % CI 2.8–13.0) and antimetabolites (IRR=4.7, 95 % CI 2.3–9.6). Nine (26 %) of the cases with esophageal stricture had been treated with chemotherapy (+/- surgery), of which seven were diagnosed with leukemia. Finally, we observed that the rate of esophageal stricture was 2.3 (95 % CI 0.9–5.9) for survivors of leukemia or lymphoma treated with chemotherapy only and 5.2 (95 % CI 2.4–11.6) for survivors of leukemia or lymphoma who also received radiotherapy and CNS tumors with total spine radiotherapy when compared to survivors of solid tumors treated with chemotherapy and/or radiotherapy.

4. Discussion

In this population-based case-cohort study including five-year survivors of childhood cancer from Denmark, Finland, Norway, and Sweden, we found that radiotherapy and chemotherapy were associated with an increased risk of esophageal stricture. According to our knowledge, this is the first study to assess the association between esophageal stricture and irradiation of the esophagus using dosimetry data.

Our results support the association between radiotherapy and the development of esophageal stricture among five-year survivors of childhood cancer as suggested by the CCSS on late-onset esophageal stricture in childhood cancer patients[11]. We found a 3.6-fold increased risk among irradiated survivors, which is slightly higher than the risk of 2.4 (95 % CI 1.8–3.2) reported by the CCSS[11]. When we assessed radiotherapy doses to the esophagus, survivors who received doses ≥ 12 Gy had the highest risk for esophageal stricture. Survivors of leukemia or lymphoma treated with radiotherapy had an increased risk for esophageal stricture when compared to survivors of CNS and other solid tumors. In the CCSS, an increased risk of esophageal stricture was reported only in survivors of Hodgkin lymphomas (prevalence ratio=2.8, 95 % CI 2.2−3.6), not in those with leukemia (0.71, 95 % CI 0.54–0.94). Hodgkin lymphoma patients have typically been treated with high doses to the chest or neck[21], whereas some high-risk or relapsed ALL or AML patients undergo BMT including TBI as part of conditioning[22,23]. In our study, a substantial number of leukemia survivors with esophageal stricture had received TBI (6/16), potentially accounting for the observed elevated risk. Variations in radiotherapy practices between the US and Europe have been reported, with irradiation being more commonly used and administrated at higher doses in the US[24], could also explain the observed differences between the studies.

Survivors of leukemia or lymphoma treated with chemotherapy also showed an elevated risk, but it was not statistically significant. We observed an eight-fold increased risk for esophageal stricture among survivors treated with any type of chemotherapy, and the risk was increased for all the chemotherapeutic groups, except asparaginase. An association between anthracyclines and esophageal stricture has previously been suggested[25,26]. Platinum agents have also been associated with an increased risk for esophageal stricture in survivors who received chest-directed radiotherapy[11]. Due to the limited number of survivors with esophageal stricture, we were not able to stratify our chemotherapy analyses on chest-directed radiotherapy or to conduct combined analyses of chemotherapy and radiotherapy. Treatment with chemotherapy including anthracyclines, antimetabolites, alkylating agents, and corticosteroids might cause gastrointestinal (GI) toxicity, particularly vomiting, mucositis or candidiasis, and thereby may contribute to late onset radiotherapy-related GI toxicity[27]. Candidiasis causes severe inflammation that may lead to scarring and formation of strictures[28]. In addition, scarring of the esophagus may cause stricture formation later in life as the child grows[10]. None of the survivors diagnosed with cancer after 2000 developed severe esophageal stricture causing hospitalization, which could indicate better prophylaxis of vomiting, mucositis, and candidiasis, or may be due to short follow-up. Finally, more recent treatment protocols with less use of radiotherapy may reduce the risk of esophageal stricture in the survivors or result in less severe toxicity requiring only outpatient treatment.

The higher prevalence observed in the CCSS compared to our study may be explained by the inclusion of less severe cases and cases diagnosed before 5 years after cancer diagnosis in the CCSS. The prevalence of self-reported esophageal stricture in the CCSS was 2 % compared to a crude prevalence of esophageal stricture leading to admission in this study of 0.2 % (of 22,882 survivors in the ALiCCs cohort). Thus, while esophageal stricture may cause severe manifestations with a need for hospital admission in a smaller fraction of patients, there is a larger group of patients that can be managed in an outpatient setting. The impact on quality of life in childhood cancer survivors is unknown, but given that symptoms of esophageal stricture include dysphagia, regurgitation, heartburn, and, over time, aspiration and pneumonia, the impact may be considerable[29]. Besides the difference in reporting, another possible explanation for the difference in prevalence between the two studies is restrictions to time of stricture developments. In the CCSS, no specific time point from diagnosis was set from where stricture could be reported. In the current study, we only included patients admitted to hospital for the first time with esophageal stricture >5 year from cancer diagnosis. Finally, we observed a higher proportion of males than females in our case group (72 % vs. 28 %), a pattern similarly reported in the CCSS study of esophageal stricture (57 % vs. 44 %). However, due to the small number of cases, we were not able to conduct any analyses stratified by sex.

5. Strengths and limitations

The strengths of our study include the population-based design with clinically validated information on cancer treatment from medical records. Due to the unique personal identification number of all inhabitants in the Nordic countries, we were able to identify childhood cancer survivors through nationwide registries with virtually complete registration and follow-up. The national health services in the Nordic countries provide tax-supported health care, guaranteeing free or nearly free access to health care for all citizens. This limits bias based on income and availability of health care[15]. Finally, as both cases and sub-cohorts are survivors of childhood cancer, the risk of surveillance bias is limited.

Our study also has limitations. Though we included survivors from all the Nordic countries, our case group of survivors with esophageal stricture was small, which limited the statistical power. Thus, we were not able to estimate the effect of chemotherapy in analyses stratified by radiotherapy treatment. Furthermore, the small number of patients in dosimetry analyses resulted in broad CIs, making it challenging to precisely estimate the increased risk for esophageal stricture. As we only included survivors with a hospitalization due to esophageal stricture, cases with less severe disease outcome are not included. We excluded eight cases due to diagnosis of esophageal stricture before a five-year survival was achieved and all eight survivors had repeated hospitalizations due to esophageal stricture after the five-year mark. Thus, by only including outcome $\geq$5 years after cancer diagnosis, we may underestimate the association between cancer-therapy and esophageal stricture. Furthermore, we did not have any information on location or date of the first symptoms of the stricture. Therefore, we do not know whether the process was already initiated during or shortly after cancer therapy or the first symptoms were registered years after end of therapy.

6. Conclusion and clinical implications

In this Nordic population-based case-cohort study, we found an increased risk for esophageal stricture among five-year childhood cancer survivors treated with neck- and chest-directed radiotherapy, TBI or who received doses to the esophagus $\geq$12 Gy. We also observed an increased risk for treatment with chemotherapy. Healthcare providers should be aware of this rare, but serious late complication, especially in survivors of leukemia or lymphoma treated with radiotherapy. Our findings illustrate the importance of long-term follow-up for childhood cancer survivors, considering their treatment history, including fungal infections, and at-risk organs. Providers should remain vigilant for gastrointestinal symptoms like dysphagia that may indicate esophageal stricture and ensure appropriate examinations are conducted, including gastroscopy.

Ethical approval

The study was originally approved by national or regional ethics committee or institutations: Denmark: The National Board of Health (j. nr. 3–3013–71/1/); Sweden: Regionala Etikprövningsnämnden, Lund (Dnr 2012/682); Norway: REK Nord (2011/884/REK nord); Finland: National Institute for Health and Welfare (No. THL/1284/5.05.00/2013). The project is listed in a local archive (2018-DCRC-0042) at the Danish Cancer Institute, which provides an accurate, updated overview of ongoing projects and of ongoing research projects involving personal data under the GDPR.

Author contributions

Conceptualization: HKH, PHA, ASH, LH, TB, TG, SL, CR, HH, JFW, and LK. Investigation: PHA, ASH, LH, TW, TG, SL, HØ, PL, YRL, KS, MJ, RTL, SAS, and RH. Methodology: PHA, HH, JFW, JC, CP, and LK. Software and data curation: AK, SAS, and RH. Formal analyses: HKH, JC, CP, and LK. Writing – original draft: HKH. Writing – review and editing: all authors. Supervision: LK. Funding acquisition: HH and JFW.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Funding

This work was funded by the Danish Council for Strategic Research (grant number 09–066899), the Danish Childhood Cancer Foundation/Børnecancerfonden (grant number 2015–46), the Danish Cancer Society, and the Swedish Childhood Cancer Foundation.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejcped.2024.100195.

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