1. Title: Esophageal disease after childhood cancer therapy: Experience from three childhood cancer survivor cohorts

2. Working group and Investigators: CCSS chronic disease working group

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3. Background and rationale:

Few studies have investigated gastrointestinal disease among childhood cancer survivors, which has been recognized by the CCSS working group on chronic diseases as one of the areas where there is a gap in knowledge. One publication from the CCSS (Goldsby et al. 2011) and one manuscript from the Adult Life after Childhood Cancer in Scandinavia (ALiCCS) study (unpublished) investigated the risk of gastrointestinal disease among childhood cancer survivors. Overall, the rate ratio of gastrointestinal diseases is 1.5 to 2.1-fold in excess of sibling or population controls in the two studies, respectively. Yet, these results include a spectrum of diseases that differ both in terms of risk and disease severity.

Within the gastrointestinal system, the esophagus is one of the organs that appears to be vulnerable to injury from childhood cancer therapy. Goldsby et al. reported a 2.6-fold increased risk of esophageal disease in CCSS participants. In the ALiCCS study, survivors have a relative rate of 13 (95% CI: 9.2 – 20) for esophageal stricture, which is one of the strongest associations found in the gastrointestinal disease spectrum. Within the ALiCCS cohort, survivors of leukemia (relative

rate: 47 (95% CI: 26 – 85)) and survivors of lymphoma (relative rate: 22 (95% CI: 12 – 39)) exhibited the highest risk for this complication.

Regarding esophageal strictures, radiation has been suggested as the primary etiologic factor in a number of case-reports. (Ellenhorn et al. 1993; Mahboubi & Silber 1997) In most cases, the chest radiation has been given in rather high doses; however, it is unknown how high the dose to the esophagus has to be in order to induce fibrosis and stricture. In one study of patients with Hodgkin lymphoma, even modest doses of chest irradiation (<20 Gy) adversely affected esophageal health.(Jørgensen et al. 2013) Interestingly, a number of cases of esophageal stricture have been reported in survivors not treated with radiation. In these cases, both esophageal candida infection and radiomimetic chemotherapy like anthracyclines have been proposed as possible etiologic agents.(Kelly et al. 2010; Kassam & Mandel 2009) Another even more uncommon etiology for esophageal stricture is graft-versus-host disease after bone marrow transplantation.(Memoli et al. 1988) From the ALiCCS study, most of the cases of esophageal stricture occurred more than five years after diagnosis and some much later. How the timing of the esophageal stricture is related to treatment exposure is unknown.

To our knowledge, no studies have reported on less severe outcomes like dysphagia and gastro-esophageal reflux disease among childhood cancer survivors. As the effect of radiation from even lower doses (<20 Gy) to the esophagus have been documented, it seems reasonable to speculate that such symptoms may be more prevalent among childhood cancer survivors.

Esophageal carcinoma is an important differential diagnosis in a patient with esophageal stricture where secondary malignancies are a major concern. The disease is associated to a poor five-year overall survival of 18% (http://seer.cancer.gov/statfacts/html/esoph.html). Thoracic radiation has been associated with an increased risk of esophageal carcinomas among survivors of breast cancer. Latency among this group was at least 10 years. (Ahsan & Neugut 1998) (Pennathur et al. 2013)

4. Specific aims/objectives/research hypotheses:

Aim 1: Determine the prevalence of gastro-esophageal reflux disease, dysphagia, esophageal stricture, and esophageal cancer among childhood cancer survivors.

Hypotheses: The entire continuum of esophageal diseases will be more frequent among childhood cancer survivors than among the comparison groups. Among the esophageal diseases, the highest

relative risks will be seen for esophageal strictures. The relative risk for esophageal cancer will be increased but the number of cases will be low.

Aim 2: Identify factors associated with esophageal disease (any esophageal condition and each specific condition) among childhood cancer survivors.

Hypotheses:

Survivors of leukemia and Hodgkin lymphoma have the highest risk of esophageal strictures. The risk of esophageal disease will be associated with chest irradiation. Dosimetry to the esophagus will be the strongest predictor for esophageal disease. Secondly, anthracyclines and bone marrow transplantation will also be significant predictors of risk of esophageal stricture. Lastly, combinations of these therapies further increase the risk.

Aim 3: Determine if survivors with a diagnosis of esophageal stricture will have an elevated risk of pulmonary disease in comparison to survivors without a history of esophageal stricture.

Hypothesis: Esophageal stricture formation and dysphagia will cause aspiration leading to an increased risk of aspiration and aspiration pneumonia. Yet, we will not have the information to infer this pathway but will have to justify it through the association between esophageal stricture and pulmonary disease.

5. Analysis framework:

To increase the likelihood of identifying factors associated with esophageal disease, particularly esophageal stricture and esophageal carcinoma, it is necessary to have an adequate sample of cases. Therefore, this study represents collaboration between the CCSS, ALiCCS, and the St Jude Lifetime Cohort study (SJLife). (Hudson et al. 2011) Outcomes in these cohorts are measured differently and therefore it may not be possible to merge the information and make inference on a single data set. Consequently, the initial approach in this analysis will be to calculate risk estimates in each study separately and discuss the finding in the context of each result. Yet, in the analysis of esophageal cancer, we believe that the outcome measure is so uniform that a pooled analysis is warranted. Below, we will give a short description of each cohort. The description will focus on the outcomes of interest for this study.

CCSS: In the study by Goldsby et al., the CCSS baseline questionnaire was used. Here, the participants were asked the following questions related to the esophagus: “Any disease in the esophagus?”, “FREQUENT heartburn?”, and if the reply is affirmative the participants were asked:

"Do you take medication for it more that once a month?". In the Follow-Up (FU) 2007 survey, participants were asked more specifically: "Esophageal strictures (narrowing of the esophagus)?" For this current study, patients who completed FU2007 survey (N=8013) or expansion baseline survey (N=10,005) are eligible for this analysis since they answered the question regarding esophageal stricture status. Among the 8013 patients who completed FU2007, 1 of them who did not complete baseline is excluded from the analysis. Furthermore, we have excluded 674 patients who died (11 in FU2007 and 663 in expansion baseline) and 28 patients who did not have a diagnosis date (Additional HIPAA form required to release this information.). After these exclusions there were 338 CCSS esophageal stricture cases and 16,977 CCSS non-cases eligible for the analysis. Among the cases, 323 reported an age of onset (205 in the original cohort and 85 in the expansion cohort). Applying the same exclusion criteria to the sibling cohort gives 2373 eligible as comparisons including 11 cases of esophageal stricture. See Table 1 for baseline characteristics and Figure 3 for a schematic overview of exclusions and dropout in the original cohort. Esophageal cancer is reported by the patient and validated by pathology reports. No questions in the CCSS questionnaire ascertain gastro-esophageal reflux disease or dysphagia. For aim three, we will use the question on repeated pneumonias (3 or more times in the past 2 years).

ALiCCS: This cohort comprises 33,160 one-year survivors of childhood cancer from the Nordic countries. Disease rates are compared to a comparison cohort from the general population (N=212,892). See Figure 2 for a flowchart. All outcome data is derived from population-based health registries. Gastro-esophageal reflux disease, dysphagia, and esophageal strictures are registered in the patient registries; hence, to capture the diagnoses the patient will have to be admitted to hospital with the disease. In the most recent follow-up period, outpatient visits are also coded. All esophageal cancers will be captured in the cancer registries, which are thought to be complete. Lastly, for some of the countries included in the ALiCCS study, we have linked to prescription registries. These registries have been operating since the mid 1990s. In our context, the registry data could be used to validate a diagnosis of e.g. dysphagia with the prescription of proton pump inhibitors.

Treatment information is not available for the entire cohort. To investigate treatment related risk factors in the ALiCCS study, we have set up a case-cohort study. For this study, we are abstracting treatment information for the cases of esophageal stricture and a sub-cohort of 600 survivors that are randomly sampled among the survivors in the original cohort. The case-cohort

study has been limited to survivors that have survived more than five years and have been diagnosed after 1970.

SJLife: This cohort comprises ≈3000 survivors treated at the St Jude Children's Research Hospital. Eligibility for participation in the St. Jude Lifetime Cohort (SJLIFE) is survival > 10 years from diagnosis, and attained age of > 18 years. Participation involves collection of comprehensive treatment data on all participants, provision of protocol-based medical assessments, assessment of patient-reported outcomes, validation of self-reported medical events in the patient medical file, performance of periodic longitudinal evaluations, and collection of biologic specimens. Therefore, all the esophageal outcomes under study can be investigated in this cohort. No comparison cohort has yet been established for this cohort. Approximately 2,700 survivors from this cohort are also included in the CCSS. By using these overlapping patients, we will be able to validate the diagnosis of esophageal stricture in this subset of CCSS.

Outcome grading

For esophageal stricture, we will elaborate on the possibilities to grade the severity. The most optimal strategy would be to use the Common Terminology Criteria for Adverse Events (CTCAE) but we may only be able to separate the most severe cases where a surgical procedure has been performed. See Table 2.

Exposures of interest

A number of different exposure variables will be investigated in this study. First, we will investigate the risk according to type of childhood cancer. This analysis will be done according to the International Classification of Childhood Cancer (Birch & Marsden 1987) and lymphoma will be subdivided into Hodgkin and non-Hodgkin lymphoma. We will analyze treatment related risk factors separate and in combination. Based on prior observations, radiation is likely to yield the highest risk estimates. Hence, we will investigate radiation in two different ways: first as a dichotomous variable (chest irradiation, yes/no) and secondly by the use of dosimetry. For the cohorts where the information exists, we will use the dose given directly to the esophagus. Furthermore, in a best-case scenario, we would investigate the dose given to proximal, mid, and distal part of the esophagus. As these measurements are likely not to exist for all patients, we will consider using the dose given to the thyroid gland and the heart as a proxy.

Chemotherapy will primarily be analyzed as dichotomous variables but for chemotherapeutic agents of special interest, e.g. anthracyclines, we will investigate impact of the cumulative dose. Lastly, we will investigate the risk of esophageal stricture after bone marrow transplantation.

Statistical Methods

Because only FU2007 is being used from the CCSS to ascertain outcomes, the analyses from that cohort will need to be cross-sectional. To allow for direct comparisons, similar cross-sectional analyses will be carried out for the other cohorts, although some time-to-event analyses will also be possible for SJLife and ALiCCS.

Prevalence at specific ages and times since diagnosis will be evaluated, with categories based on the natural distribution of age or time since diagnosis of survey completion, most likely divided into quartiles. To evaluate risk factors, with primary focus on radiation exposure, multivariable logistic regression models will be fit to the binary outcome of esophageal stricture. A priori, we will adjust for sex, age at cancer diagnosis, year of cancer diagnosis, and cancer type (leukemia, Hodgkin lymphoma, and other malignancies) depending on which association we will investigated (Table 3) and which is more important as an adjustment factor. Other key exposure factors are described above in detail.

Additional, similar analyses will be carried out with pneumonia as outcome and using esophageal stricture that occurred prior to pneumonia as the exposure. Like in the above-mentioned analyses, we will estimate the prevalence in each exposure group and fit multivariable logistic regression models including year of cancer diagnosis, cancer type, sex, age at cancer diagnosis, and chest irradiation.

Because we can only include participants from the CCSS original cohort who have answered the FU2007 questionnaire, we have a rather large dropout in this cohort. The dropout is likely to be related to both the exposures and outcome and may therefore cause selection problems. To account for this, we will perform inverse probability weighting of the estimates, using the inverse predicted probability of participation at FU2007 based on fitted models among the full baseline cohort with all likely risk factors included.

5. Special consideration:

This study is different in the sense that CCSS patients will be included in a study together with patients from the ALiCCS and SJLife study. It will be an international collaborative study with investigators and childhood cancer survivors from the US and from the five Nordic countries.

Appendix

Below are the suggested tables and figures that may or may not be part of the final manuscript. Table 1 shows the number of cases in each cohort and the characteristics for cases and non-cases in the three cohorts.

Table 1. Characteristics for patients that did and did not develop esophageal strictures. Adult Life after Childhood Cancer Study (ALiCCS), Childhood Cancer Survivor Study (CCSS), and St Jude Lifetime cohort study (SJLife).

	ALiCCS cases	ALiCCS non-cases	ALiCCS sub-cohort	ALiCCS comparisons	CCSS cases (N=338)	CCSS non-cases (N=16977)	CCSS siblings (N=2373)	SJLife cases (N=73)	SJLife Non-cases (N=3026)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	
Sex									
Male	56 (70)			115,715 (54)	196 (58.0)	8715 (51.3)	1094 (46.1)	51 (69.9)	1531 (50.6)
Female	24 (30)			96,971 (46)	142 (42.0)	8262 (48.7)	1279 (53.9)	22 (30.1)	1495 (49.4)
Age at cancer diagnosis									
<5	22 (28)			-	80 (23.7)	6801 (40.1)	-	12 (16.4)	1129 (37.3)
5 – 9 years	12 (15)			-	67 (19.8)	3798 (22.4)	-	21 (28.8)	713 (23.6)
10 – 14 years	20 (25)			-	87 (25.7)	3640 (21.4)	-	21 (28.8)	695 (23.0)
15 – 20 years	26 (33)			-	104 (30.8)	2738 (16.1)	-	19 (26.0)	462 (15.3)
>20 years	-			-	-	-	-	-	27 (0.9)
Age at last contact									
<20					26 (7.7)	2178 (12.8)	9 (0.4)	-	18 (0.6)
20-24					18 (5.3)	2756 (16.2)	143 (6.0)	4 (5.5)	385 (12.7)
25-29					39 (11.5)	3793 (22.3)	348 (14.7)	2 (2.7)	582 (19.2)
30-34					46 (13.6)	3145 (18.5)	397 (16.7)	6 (8.2)	652 (21.6)
35-39					71 (21.0)	2494 (14.7)	487 (20.5)	9 (12.3)	539 (17.8)
40-44					60 (17.8)	1507 (8.9)	440 (18.5)	20 (27.4)	391 (12.9)
45-49					45 (13.3)	803 (4.7)	325 (13.7)	19 (26.0)	265 (8.8)
≥50					33 (9.8)	300 (1.8)	224 (9.4)	13 (17.8)	194 (6.4)
Missing					-	1 (0.0)	-	-	
Chest irradiation									
Yes		-		-	54 (16.0)	1282 (7.6)	-	2 (2.7)	75 (2.5)
No		-		-	284 (84.0)	15695 (92.4)	-	71 (97.3)	2951 (97.5)
Anthracyclines exposure									
No		-		-	196 (58.0)	8935 (52.6)	-	39 (53.4)	1260 (41.6)
Yes, <250 mg/m^2		-		-	68 (20.1)	4543 (26.8)	-	21 (28.8)	1315 (43.5)
Yes, ≥250 mg/m^2		-		-	56 (16.6)	3101 (18.3)	-	13 (17.8)	437 (14.4)
Yes, dose unknown		-		-	18 (5.3)	398 (2.3)	-	-	14 (0.5)
Bone marrow transplantation									
No		-		-	312 (92.3)	15464 (91.1)	-	71 (97.3)	2942 (97.2)
Yes		-		-	23 (6.8)	1169 (6.9)	-	2 (2.7)	84 (2.8)
Note sure					3 (0.9)	344 (2.0)	-	-	-
Cancer type									

Leukemias	28 (35)			-	58 (17.2)	5049 (29.7)	-	16 (21.9)	1146 (37.9)
Hodgkin lymphoma	19 (24)			-	130 (38.5)	1914 (11.3)	-	32 (43.8)	351 (11.6)
Non-Hodgkin lymphoma					23 (6.8)	1451 (8.6)		6 (8.2)	222 (7.3)
CNS tumors	6 (8)			-	47 (13.9)	3152 (18.6)	-	5 (6.9)	302 (10.0)
Neuroblastoma	3 (4)			-	14 (4.1)	1352 (8.0)	-	1 (1.4)	130 (4.3)
Retinoblastoma	0 (0)			-	-	-	-	-	91 (3.0)
Renal tumors	0 (0)			-	7 (2.1)	1605 (9.5)	-	4 (5.5)	196 (6.5)
Hepatic tumors	1 (1)			-	-	-	-	-	21 (0.7)
Malignant bone tumors	2 (3)			-	21 (6.2)	1360 (8.0)	-	-	-
Soft-tissue sarcomas	4 (5)			-	38 (11.2)	10946 (6.4)	-	5 (6.8)	399 (13.2)
Germ-cell tumors	3 (4)			-	-	-	-	-	75 (2.5)
Other malignant epithelial neoplasms	11 (14)			-	-	-	-	4 (5.5)	59 (1.9)
Other and unspecified malignant neoplasms	3 (4)			-	-	-	-	-	12 (0.4)
None-malignancy	-			-	-	-	-	-	22 (0.7)

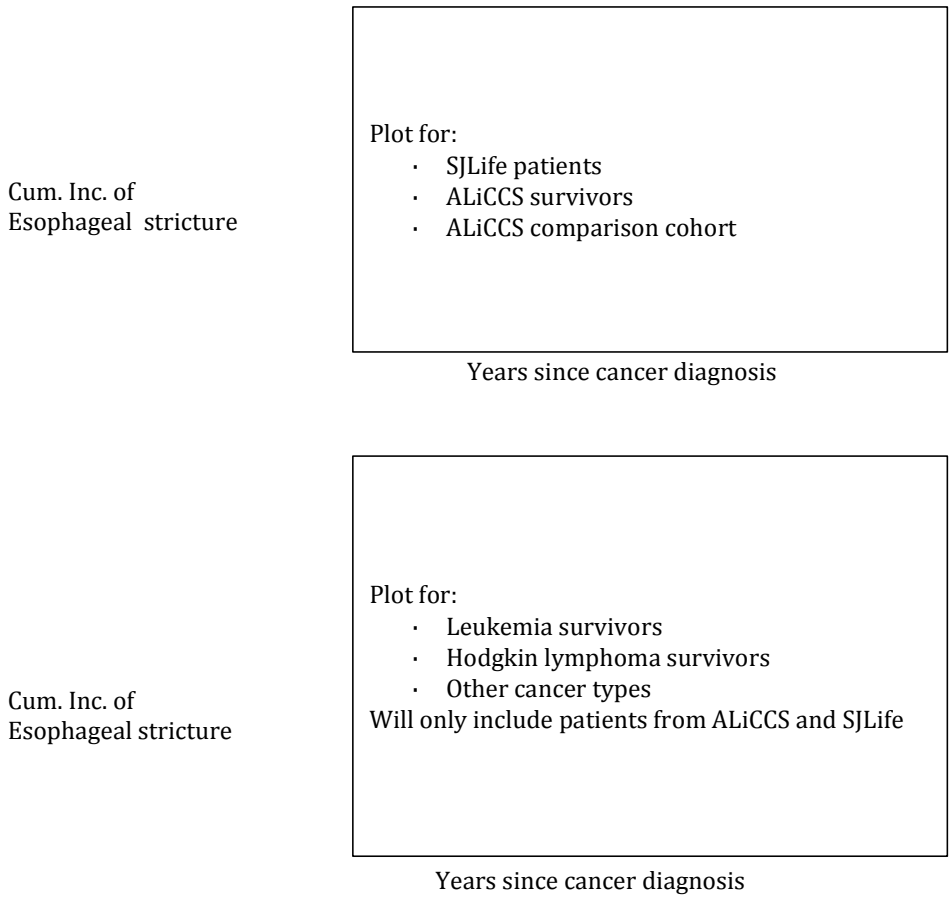

Figure 1. Cumulative incidence of esophageal stricture by time since cancer diagnosis.

Figure 2, flowchart of the patients from the ALiCCS study

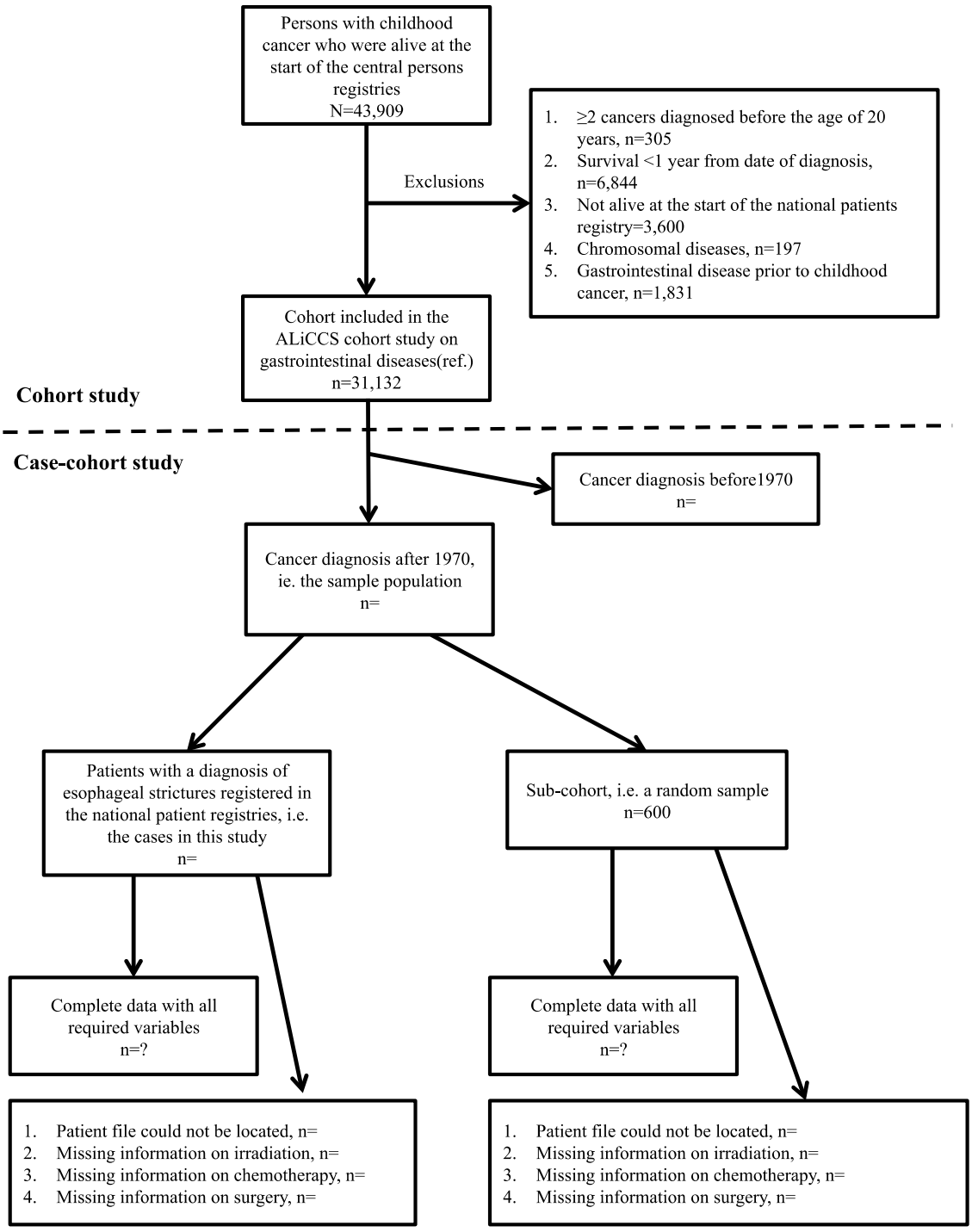

Figure 2, flowchart showing the Adult Life after Childhood Cancer in Scandinavia study population.

Figure 3, flowchart of the patients for the CCSS original cohort

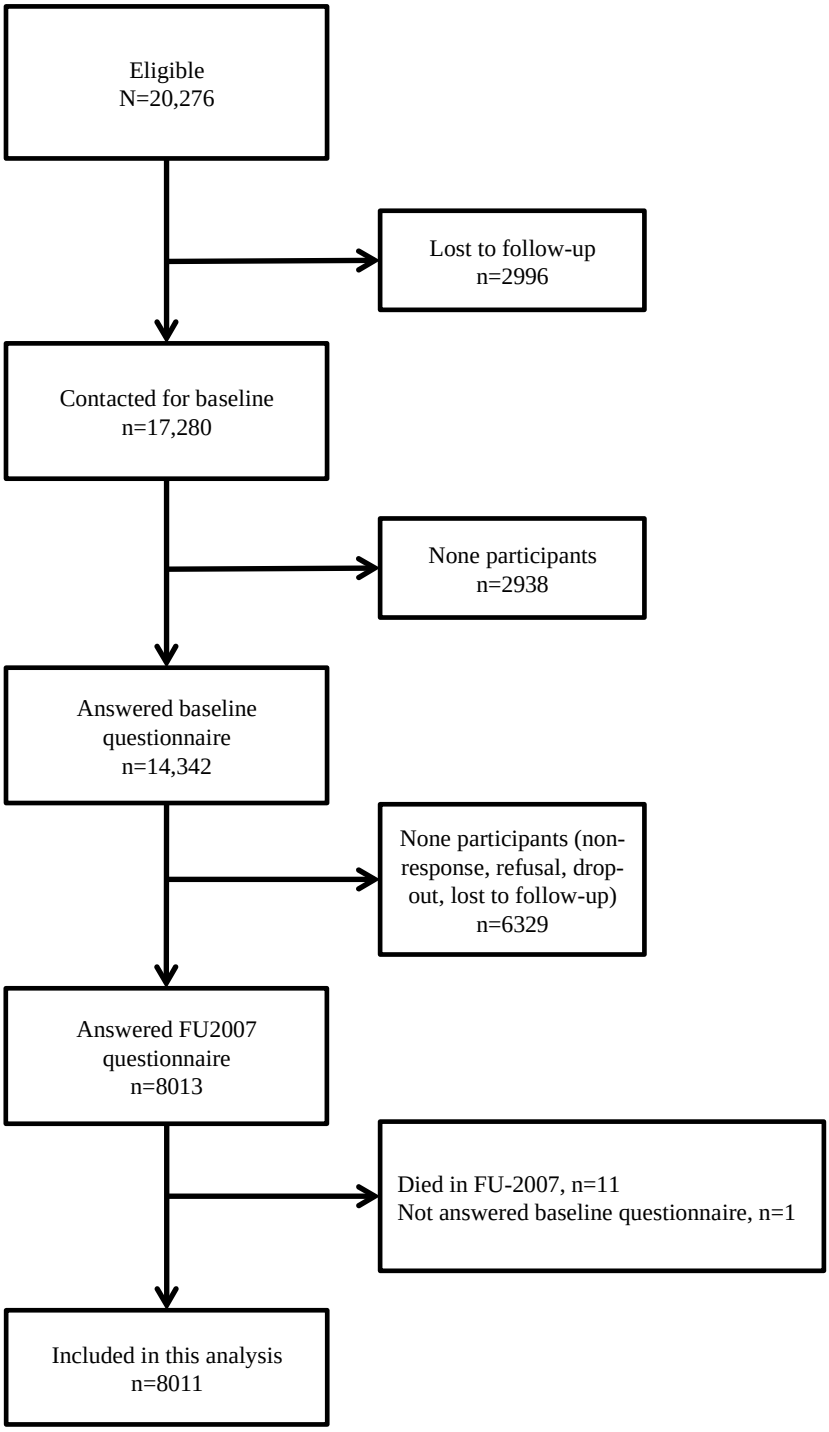

Figure 3, flowchart showing the Childhood Cancer Survivors Study original cohort exclusions and dropout.

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
CTCAE	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding; hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
CCSS		Esophageal stricture 530.3			Death coded as ICD-9: 530.3 or ICD-10: K22.2
ALiCCS		Outpatient visit coded with ICD-10 code K22.2 or equivalent	Hospital admission coded with ICD-10 code K22.2 or equivalent as the primary reason for hospital admission		Death
SJLife		The possibilities for grading is not yet known			Death

Table 2, grading of esophageal strictures. Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 for esophageal stenosis. The interpretation used in this study for the patients from the Childhood Cancer Survivors Study (CCSS), the Adult Life after Childhood Cancer in Scandinavia (ALiCCS) study, and the St Jude Lifetime Cohort study (SJLife).

Table 3. Risk factors for esophageal stricture.

	All grades of esophageal strictures				Severe esophageal strictures		
	Total number of cases (ALiCCS/CCSS/SJLife)	ALiCCS OR (95% CI)	CCSS OR (95% CI)	SJLife OR (95% CI)	Total number of cases (ALiCCS/SJLife)	ALiCCS OR (95% CI)	SJLife OR (95% CI)
Cancer type[a]							
Any other than leukemia and Hodgkin lymphoma		Ref.	Ref.	Ref.		Ref.	Ref.
Leukemia							
Hodgkin lymphoma							
Age at cancer diagnosis[b]							
<5 years		Ref.	Ref.	Ref.		Ref.	Ref.
5-<10 years							
10-<15 years							
15-<20 years							
Radiation[c]							
None		Ref.	Ref.	Ref.		Ref.	Ref.
Yes but other than the chest							
≥5 Gy to the chest							
Maximum esophageal radiation dose[c]							
None		Ref.	Ref.	Ref.		Ref.	Ref.
<40 Gy							
40-49 Gy							
50-59 Gy							
60-69 Gy							
≥70 Gy							
Anthracyklin[c]							
None		Ref.	Ref.	Ref.		Ref.	Ref.
<250 mg/m^2							
≥250 mg/m^2							
Alkylating agents (excluding platinums)[c]							
None		Ref.	Ref.	Ref.		Ref.	Ref.
Any							
Platinum agent[c]							
None		Ref.	Ref.	Ref.		Ref.	Ref.
Any							
Vinca-alkaloid[c]							
None		Ref.	Ref.	Ref.		Ref.	Ref.
Any							
Methotrexate[c]							
None		Ref.	Ref.	Ref.		Ref.	Ref.
Any							
Topoisomerase inhibitors[c]							
None		Ref.	Ref.	Ref.		Ref.	Ref.
Any							
Bone marrow transplantation[c]							
No		Ref.	Ref.	Ref.		Ref.	Ref.
Yes							
Combinations of treatments[c]							
No radiotherapy or anthracyklin		Ref.	Ref.	Ref.		Ref.	Ref.
≥35 Gy to the chest and ≥250 mg/m2 of anthracyklin							

a= adjusted for sex.
b= adjusted for sex and cancer type (leukemia, Hodgkin lymphoma, and other).
c= adjusted for sex, age at diagnosis, year of cancer diagnosis, and cancer type (leukemia, Hodgkin lymphoma, and other).

References

Ahsan, H. & Neugut, A.I., 1998. Radiation Therapy for Breast Cancer and Increased Risk for Esophageal Carcinoma. *Annals of internal medicine*, 128(2), pp.114–117.

Birch, J.M. & Marsden, H.B., 1987. A classification scheme for childhood cancer. *International journal of cancer. Journal international du cancer*, 40(5), pp.620–624.

Ellenhorn, J.D. et al., 1993. Treatment-related esophageal stricture in pediatric patients with cancer. *Cancer*, 71(12), pp.4084–4090.

Goldsby, R. et al., 2011. Survivors of childhood cancer have increased risk of gastrointestinal complications later in life. *Gastroenterology*, 140(5), pp.1464–71.e1.

Hudson, M.M. et al., 2011. Prospective medical assessment of adults surviving childhood cancer: Study design, cohort characteristics, and feasibility of the St. Jude Lifetime Cohort Study. *Pediatric blood & cancer*, 56(5), pp.825–836.

Jørgensen, A.Y.S. et al., 2013. The effect on esophagus after different radiotherapy techniques for early stage Hodgkin's lymphoma. *Acta oncologica (Stockholm, Sweden)*, 52(7), pp.1559–1565.

Kassam, A. & Mandel, K., 2009. Chemotherapy induced esophageal stricture. *Pediatric blood & cancer*, 52(4), pp.551–551.

Kelly, K. et al., 2010. Esophageal strictures during treatment for acute lymphoblastic leukemia. *Journal of pediatric hematology/oncology*, 32(2), pp.124–127.

Mahboubi, S. & Silber, J.H., 1997. Radiation-induced esophageal strictures in children with cancer. *European radiology*, 7(1), pp.119–122.

Memoli, D. et al., 1988. Acute esophageal stricture after bone marrow transplantation. *Bone marrow transplantation*, 3(5), pp.513–516.

Pennathur, A. et al., 2013. Oesophageal carcinoma. *Lancet*, 381(9864), pp.400–412.