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Late Mortality in Childhood Cancer Survivors according to Pediatric Cancer Diagnosis and Treatment Era in the Dutch LATER Cohort

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ABSTRACT

This multi-center cohort-study examined late mortality among 6,165 Dutch five-year childhood cancer survivors diagnosed 1963–2001. Clinical details and cause of death were based on medical records. Mortality was 12-fold that of the general population, with 51.3 additional deaths per 10,000 person-years (21.9 yrs median follow-up). Cumulative mortality 15 yrs post-diagnosis was 6.9%, predominantly from late recurrences; thereafter the absolute contribution of other health outcomes increased. Cumulative all-cause and recurrence-related mortality were highest for Central Nervous System and bone tumor survivors. All-cause, but not subsequent tumor and circulatory disease-related cumulative mortality, was highest for patients diagnosed 1963–1979 vs. later (p-trend <0.001).

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Introduction

Due to improvements in the treatment for childhood cancer, the five-year survival rate has increased up to 80% over the past decades (1). This has resulted in a growing group of childhood cancer survivors (CCS). Unfortunately, a substantial proportion of five-year CCSs are at risk to develop serious adverse health outcomes, some of which may result in premature death (2–7). CCSs experience about 8- to 17-fold higher mortality rates compared to the background population (2,3,5,6). This relative risk is highest in the first five to 10 years after diagnosis and decreases over time (5,6). Nonetheless, excess mortality has been reported in the fourth and fifth decades after childhood cancer diagnosis in several studies (5,6). All published studies rely on cause of death (COD) information from death certificates (sometimes including partial validation against medical records, according to WHO coding rules) (2,4–10). Unfortunately, WHO coding rules are not unequivocal in survivorship research; non-cancer deaths can easily be misclassified as primary cancer-related deaths in the case of established (or alleged) associations between treatment and the fatal condition (5,11). This

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Supplemental data for this article can be accessed here.

practice not only depends on the coder's knowledge of evidence in survivorship, but may also mask the true burden of non-childhood cancer related mortality while also leading to overestimation of childhood cancer-specific late mortality.

We, therefore, aim to characterize all-cause and cause-specific late mortality across pediatric cancer groups by treatment era in the national cohort of Dutch five-year CCSs using an adapted ascertainment of causes of death for late mortality from medical records.

Methods

Study population

This study is part of a nationwide collaborative effort initiated by the Long-term Effects After Childhood Cancer Consortium (LATER). The LATER cohort includes 6,165 CCSs who survived at least 5 years after childhood cancer diagnosis, originally diagnosed before the age of 18 years between 1963 and 2002, and who were treated in one of the seven former Dutch paediatric oncology & stem cell transplant centres. See the Appendix for participating institutions and for types of childhood cancer included. For all eligible CCS, information about childhood cancer diagnosis and individually received radiotherapy, chemotherapy, and hematopoietic cell transplantation was obtained from the LATER registry. Ethical review board approval, or exemption from formal review was obtained in each participating centre. Details were reported previously (12).

Vital status and cause of death ascertainment

To ascertain the vital status and date of death of all eligible subjects a record linkage with the Central Bureau for Genealogy was conducted up to 1 January 2014. COD was available through the Dutch CCSS LATER registry for part of the cohort, as previously determined based on medical record abstraction by trained data managers. We validated 20% of existing COD and ascertained new COD through medical record abstraction at the original treatment centre using a uniform medical record abstraction form (Supplemental File 1) . If unavailable, we sent questionnaires to the General Practitioner or treating medical specialist to extract information from their respective medical records. Questionnaires were completed for 95 patients, including 78 by General Practitioners. During the first period of the COD coding effort that ensued, a random sample of 20% was coded independently by two staff members to identify pitfalls and to harmonize the implementation of the coding rules.

Cause of death coding

We followed the basis of WHO rules for coding COD: The primary (underlying) COD was defined as the underlying disease that led to a chain of events resulting in death. Secondary (contributing) CODs were defined as events preceding death (13). In one particular area we changed the WHO approach, as follows: WHO coding rules encourage coding the primary COD as childhood cancer, for clinical scenarios in which the physician assumes a role of prior childhood cancer *treatment* as causal factor in the aetiology of the disease leading to death. For example, for a patient with fatal renal failure among individuals decades after high-dose abdominal radiotherapy/nephrectomy or a haemorrhagic stroke in a childhood cancer survivor who had cranial radiotherapy decades earlier, WHO rules recommend coding of the childhood cancer as the underlying COD (5). As a consequence of this approach, deaths from late recurrences/disease progression cannot be distinguished from late effects-related deaths. This approach assumes that the physician who completes the death certificate has knowledge on the full medical history of the individual who died, and has access to the evidence-base for specific treatment-related side effects.

Because we aim to obtain unbiased insight into all causes of late mortality in CCSs we adapted the WHO coding: in CCSs where the childhood cancer was inactive and the patient died of another disease (which may include new primary neoplasms) we assigned the new specific disease as underlying COD.

Trained staff-members coded COD using the International Classification of Diseases (ICD), tenth revision (ICD-10) (13). Coding discrepancies were discussed (EK, CMR, MR) until consensus was reached. Specific CODs were grouped using the WHO mortality tabulation list (list 1, general mortality, condensed list) (13). Deaths involving neoplasms were further categorized as related to recurrence/progression of the primary childhood cancer, or related to a new subsequent malignant neoplasm (SMN), based on morphology and medical information available to the study group (12).

Statistical analysis

Frequencies and percentages were used to describe distributions of characteristics by vital status at the end of follow-up and of specific CODs. Person-years at risk were calculated from five years after the original diagnosis of a childhood cancer to date of death, to 1 January 2014, or to the last date an individual was known to be alive. To quantify the relative risk of mortality compared to the background population, all-cause and cause-specific standardized mortality ratios (SMRs) and absolute excess risks (AERs) were used. SMRs were calculated by dividing the observed number of deaths by the expected number of deaths. To determine the expected number of deaths, person-years at risk were multiplied with Dutch mortality rates, for sex-specific, age-specific and calendar year-specific (per three-year) strata. Dutch mortality rates were obtained through Statistics Netherlands. AERs were calculated by subtracting the expected number of deaths from the observed number of deaths divided by the number of person-years at risk multiplied by 10,000.

Cumulative mortality (CM) adjusted for competing causes of death was calculated and trends by calendar period, stratified by diagnosis, were estimated for the following causes of death: recurrence or progression of the primary childhood cancer (referred to as death from recurrence/progression), and for the following (potentially treatment-related) late effects: subsequent malignant neoplasm (SMN), circulatory system disease, other medical causes (i.e., all medical causes other than circulatory disease and SMNs), and external events. Expected all-cause CM was derived from Dutch mortality rates.

Statistical analyses were performed using the statistical programs R version 3.1.1 (R Foundation for Statistical Computing, Vienna, Austria) and Stata version 13 (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX, USA: StataCorp LP).

Results

The characteristics of the Dutch-LATER cohort of five-year survivors and the distribution of causes of death are described in Table 1. At the end of follow-up (1 January 2014), 621 of 6,165 cohort members (10.1%) had died, 5,544 (89.9%) were known alive, including 139 (2.3%) who were lost to follow-up and censored at the last date confirmed alive. A total of 111,130 person years were accrued after a median follow-up of 21.9 years post-diagnosis. Median and maximum ages at death were 19.2, and 61.7 years, respectively. For 286 decedents (46%), COD was available in the Dutch CCSS LATER registry, of which we validated 83 cases. In total, information on the precise COD was available for 570 decedents (92%). Progression and late recurrences of childhood cancer represented 56% of all late deaths among five-year CCS.

Comparison with general population: overall and cause-specific mortality

The all-cause and cause specific mortality risks were expressed as relative (SMR) or absolute excess risks (AER) (Table 2). All-cause mortality was 12-fold that of the general population, with 51.3 additional deaths per 10,000 person years. The SMR and AER were significantly increased for all evaluated groups in the cohort, defined by sex, diagnosis, age at diagnosis, diagnosis year, or treatment (not shown). The SMRs were significantly elevated for nearly all types of disease-related causes of death but not for pregnancy/childbirth related events (one observed death) nor for external causes of death (SMR = 0.9, 95% CI 0.5–1.4) which includes suicide.

Table 1. All-cause mortality among 6,615 five-year survivors of childhood cancer diagnosed between Jan 1963 and Dec 2001 in the Netherlands: The Dutch LATER Cohort Study.

		Cause of death: *N* of CCSs and percentages of observed deaths*									
Characteristics	Cohort: *N*	All observed death	Recurrence/ Progression		SMN		Circulatory diseases**		Other health related		External causes	
	6165	621	349	56%	109	18%	34	5%	50	8%	18	3%
Sex												
Male	3433	344	199	58%	59	17%	18	5%	29	8%	14	4%
Female	2732	277	150	54%	50	18%	16	6%	21	8%	4	1%
Childhood cancer diagnosis												
Leukemia	2092	196	142	72%	17	9%	9	5%	20	10%	1	1%
Hodgkin lymphoma	404	35	11	31%	10	29%	4	11%	3	9%	2	6%
Non-Hodgkin lymphoma	578	30	9	30%	8	27%	2	7%	4	13%	4	13%
Brain/CNS	843	146	86	59%	16	11%	4	3%	16	11%	6	4%
Bone tumors	370	68	43	63%	16	24%	4	6%	0	0%	1	1%
Soft tissue sarcoma	450	56	26	46%	15	27%	6	11%	1	2%	1	2%
Renal tumors	596	31	8	26%	10	32%	3	10%	2	6%	1	3%
Other*	832	59	24	41%	17	29%	2	3%	4	7%	2	3%
Age at diagnosis												
0–4	2798	234	133	57%	39	17%	16	7%	19	8%	9	4%
5–9	1665	173	109	63%	25	14%	7	4%	15	9%	5	3%
10–14	1314	160	86	54%	34	21%	9	6%	11	7%	4	3%
15–17	388	54	21	39%	11	20%	2	4%	5	9%	0	0%
Diagnosis year												
1963–1979	1098	240	117	49%	45	19%	10	4%	22	9%	4	2%
1980–1989	1930	208	109	52%	38	18%	18	9%	19	9%	11	5%
1990–2001	3137	173	123	71%	26	15%	6	3%	9	5%	3	2%
Time since diagnosis												
5–9	355	324	260	80%	18	6%	7	2%	16	5%	4	1%
10–14	952	99	50	51%	18	18%	9	9%	10	10%	4	4%
15–19	1315	62	22	35%	21	34%	6	10%	5	8%	2	3%
20–24	1119	38	9	24%	14	37%	4	11%	5	13%	5	13%
25–29	921	38	2	5%	15	39%	3	8%	7	18%	2	5%
30–34	787	30	4	13%	10	33%	2	7%	6	20%	1	3%
35+	716	30	2	7%	13	43%	3	10%	1	3%	0	0%
Treatment***												
No radiotherapy, no chemotherapy	598	22	13	59%	3	14%	0	0%	0	0%	1	5%
Chemotherapy only	2972	100	45	45%	22	22%	11	11%	12	12%	5	5%
Radiotherapy only	483	96	33	34%	21	22%	4	4%	15	16%	2	2%
Radiotherapy and chemotherapy	2010	352	221	63%	58	16%	18	5%	30	9%	9	3%
Hematopoietic cell transplant												
Autologous	156	49	45	92%	3	6%	0	0%	1	2%	0	0%
Allogeneic	226	43	30	70%	2	5%	3	7%	7	16%	0	0%

*139 CCSs were lost to follow-up and were censored at the last date confirmed alive. In this group, 31 patients were diagnosed between 1963 and 1979, contributing 641 person years, and 108 were diagnosed between 1980 and 2001, contributing 1,220 person years. Cause of death was missing for 51 decedents.
**Defined as ICD codes I00-I99. Fatal cases include 27 cardiac and 7 cerebrovascular disease-related deaths.
***Includes any treatment for primary tumor and recurrences.

Cumulative mortality

Figure 1 shows all-cause cumulative mortality (CM) among five-year survivors in the DUTCH LATER cohort. The CM showed a slight S-shaped curve, with a CM of 6.9% (95% CI: 6.3–7.6) at 15 years after diagnosis and 11.4% (95% CI: 10.4–12.3) 30 years after diagnosis (Table 3 first row, All Diagnoses/All Causes). Death from recurrence/progression in our survivorship cohort predominated in the first period after attainment of five-year survival, with a CM of 5.1% (95% CI: 4.6–5.7) at 15 years after diagnosis. With a longer follow-up period, the contribution of deaths from potential late effects increased, including for SMN (CM from 0.6% (95% CI: 0.4–0.8) at 15 years to 2.3% (95% CI: 1.7–2.8) at 30 years); for circulatory diseases (from 0.3% (95% CI: 0.1–0.4) at 15 years to 0.7% (95% CI: 0.4–1.0) at 30 years); and for other medical causes (CM 0.5% (95% CI: 0.3–0.6) at 15 years to 1.2% (95% CI: 0.8–1.6) at 30 years).

Role of treatment era

We assessed patterns in 15-year (yr) all-cause mortality by treatment era: 1963–1979, 1980–1989, and 1990–2001 in our cohort (Table 3, left panel). Overall 15-yr CM was

Table 2. Observed number of deaths and SMRs for major cause-of-death categories in the LATER Cohort Study.

Causes of death[a]	O	SMR[b]	95% CI	AER[c]	95% CI
All[d]	621	12.1	11.2–13.1	51.3	47.0–55.8
Neoplasms	458				
Childhood cancer recurrence/progression	349				
Subsequent neoplasms	109	8.9	7.3–10.8	8.7	7.0–10.7
Diseases of the circulatory system[e]	34	6.1	4.2–8.6	2.6	1.6–3.8
Cerebrovascular diseases	7	5.9	2.4–12.1	0.5	0.1–1.2
Heart diseases	26	13.5	8.8–19.8	2.2	1.4–3.3
Other diseases of the circulatory system	1	1.1	0.0–6.4	0.0	−0.1–0.4
Diseases of the nervous system	10	4.4	2.1–8.1	0.7	0.2–1.5
Diseases of the respiratory system	22	18.3	11.4–27.7	1.9	1.1–2.9
Pneumonia	4	7.7	2.1–19.8	0.3	0.1–0.9
COPD & asthma	4	10.5	2.9–26.9	0.3	0.1–0.9
Other diseases of the respiratory system	14	54.2	29.6–90.9	1.2	0.7–2.1
Diseases of the digestive system	8	6.7	2.9–13.3	0.6	0.2–1.3
Certain infectious and parasitic diseases	8	7.6	3.3–15.0	0.6	0.2–1.3
Pregnancy, childbirth and the puerperium	1	8.2	0.2–45.9	0.1	0.0–0.5
External causes	18	0.9	0.5–1.4	−0.2	−0.9–0.7
Traffic accidents	12	1.5	0.8–2.6	0.4	−0.2–1.2
Other accidents	1	2.8	0.1–15.7	0.1	0.0–0.5
Intentional self-harm	3	0.4	0.1–1.2	−0.4	−0.6–0.1
All other external causes	2	4.2	0.5–15.0	0.1	0.0–0.6

[a]Not shown are $N = 10$ deceased CCSs with unknown COD according to medical files, and $N = 51$ deceased CCSs for whom COD could not be ascertained.
[b]SMRs were calculated by dividing the observed number of deaths by the expected number of deaths.
[c]AERs were calculated by subtracting the expected number of deaths from the observed number of deaths divided by the number of person-years at risk multiplied by 10,000.
[d]In all, the 6,165 cohort members contributed 111,130 PY of observation for this study. Only 139 CCSs (2%) were lost to follow-up and were censored at the last date confirmed alive. In this group, 31 patients were diagnosed between 1963 and 1979, contributing 641 person years, and 108 were diagnosed between 1980 and 2001, contributing 1,220 person years.
[e]ICD-10 codes related to diseases of the circulatory system were grouped as follows: Cerebrovascular disease: I60–I69; Myocardial infarction: I21–I22; Other ischaemic heart disease: I20, I23–I25; Other heart disease: I30–I33, I39–I52; Remainder of diseases of the circulatory system: I00–I15, I26–I28, I34–I38, I70–I99.

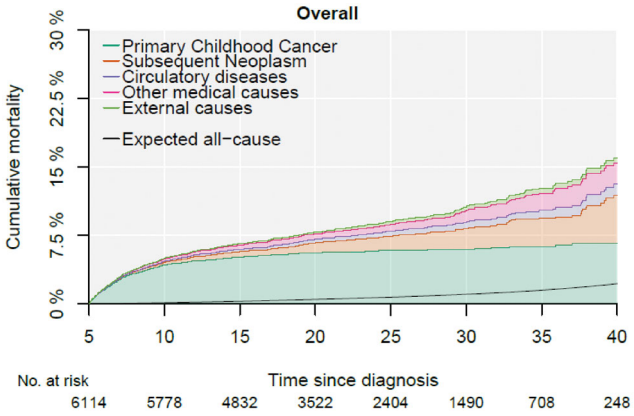

Figure 1. Cumulative mortality (%) by time since diagnosis for various COD categories in the DUTCH LATER cohort. *Corrected for sex, age and calendar year.

substantially higher among patients originally diagnosed during 1963–1979 (13.0% (95% CI: 11.1–15.0) than among patients diagnosed in later periods (6.7% (95% CI: 5.6–7.9) and 4.9% (97% CI: 4.2–5.7), respectively) ($p < 0.001$). A very similar pattern was observed for deaths from recurrence/progression. In contrast, for SMN and circulatory disease we did not observe decreases in the 15-yr CM for survivors treated in recent decades (up to 2001) compared to CCSs treated prior to 1980. This was also true for the 30-yr CM, with rates of 2.4 and 2.2% for SMN- related mortality and 0.6 and 1.0%, respectively for circulatory disease among CCSs treated <1980 and 1980–1989. We did not calculate 30-yr CM for the treatment era 1990–2001 due to insufficient years of follow-up.

Treatment exposures differed greatly across treatment era (Table 4). Patients diagnosed during 1963–1979 were treated mostly with a combination of radiotherapy and chemotherapy (57%), followed by radiotherapy only (17%) and chemotherapy only (15%). The contribution of combination therapy declined for more recent cohorts, to 22% for patients diagnosed during 1990–2001, as did the contribution of radiotherapy without chemotherapy (5% during 1990–2001). The use of chemotherapy-only regimen increased, respectively, to 48 and 60% for survivors diagnosed during 1989–1989 and 1990–2001.

Table 3. Cumulative mortality by diagnosis and period of diagnosis.

			Cumulative mortality (CI) after yrs of follow-up								Cumulative mortality (CI) after yrs of follow-up					
			15 years								30 years					
Diagnosis	Median (max) age after 15 years of follow-up (yrs)	Period of diagnosis	O*	All causes	Recurrence/ Progression	SMN	Circulatory diseases	Other medical causes	Median (max) age after 30 years of follow-up (yrs)	Period of diagnosis	O**	All causes	Recurrence/ Progression	SMN	Circulatory diseases	Other medical causes
All diagnoses	21 (38)	All	485	6.9 (6.3–7.6)	5.1 (4.6–5.7)	0.6 (0.4–0.8)	0.3 (0.1–0.4)	0.5 (0.3–0.6)	29 (52)	All	591	11.4 (10.4–12.3)	6.0 (5.4–6.6)	2.3 (1.7–2.8)	0.7 (0.4–1.0)	1.2 (0.8–1.6)
		1963–1979	156	13.0 (11.1–15.0)	9.7 (7.9–11.5)	0.9 (0.3–1.4)	0.3 (0.0–0.6)	0.9 (0.3–1.4)		1963–1979	210	17.2 (15.0–19.4)	10.6 (8.7–12.4)	2.4 (1.5–3.3)	0.6 (0.1–1.0)	1.5 (0.8–2.3)
		1980–1989	157	6.7 (5.6–7.9)	4.9 (3.9–5.8)	0.5 (0.2–0.8)	0.5 (0.2–0.8)	0.5 (0.2–0.8)		1980–1989	208	11.2 (9.6–12.7)	5.7 (4.7–6.8)	2.2 (1.4–3.0)	1.0 (0.5–1.5)	1.2 (0.7–1.7)
		1990–2001	172	4.9 (4.2–5.7)	3.7 (3.0–4.4)	0.6 (0.3–0.9)	0.1 (0.0–0.3)	0.3 (0.1–0.6)		1990–2001	173	NA	NA	NA	NA	NA
		p–Value		<.001	<.001	.51	.06	.07		*p*–Value		<.001	<.001	.99	.07	.12
Leukemia	20 (35)	All	179	7.9 (6.7–9.1)	6.6 (5.5–7.6)	0.3 (0.0–0.5)	0.2 (0.0–0.4)	0.7 (0.3–1.0)	28 (49)	1963–2001	193	10.3 (8.7–11.8)	7.0 (5.9–8.2)	0.9 (0.3–1.5)	0.7 (0.2–1.2)	1.3 (0.6–1.9)
		1963–1979	68	21.8 (17.1–26.4)	18.5 (14.1–22.9)	1.0 (0.0–2.1)	0.0 (0.0–0.0)	1.7 (0.2–3.1)		1963–1979	76	23.4 (18.6–28.1)	18.8 (14.4–23.2)	1.3 (0.0–2.6)	0.0 (0.0–0.0)	2.3 (0.6–4.0)
		1980–1989	54	7.2 (5.2–9.2)	6.0 (4.2–7.8)	0.3 (0.0–0.7)	0.3 (0.0–0.7)	0.5 (0.0–1.0)		1980–1989	60	9.5 (7.1–11.9)	6.4 (4.6–8.3)	0.9 (0.0–1.8)	1.1 (0.2–2.0)	0.9 (0.2–1.7)
		1990–2001	57	4.5 (3.3–5.7)	3.7 (2.6–4.8)	0.0 (0.0–0.0)	0.2 (0.0–0.4)	0.6 (0.1–1.0)		1990–2001	57	NA	NA	NA	NA	NA
		p–Value		<.001	<.001	.18	.37	.21		*p*–Value		<.001	< .001	.86	.18	.08
Hodgkin lymphoma	27 (38)	All	19	4,3 (2.3–6.3)	2.8 (1.2–4.5)	0.8 (0.0–1.6)	0.5 (0.0–1.2)	0.3 (0.0–0.8)	34 (49)	All	31	10.2 (6.0–14.3)	2.8 (1.2–4.5)	4.4 (1.3–7.5)	0.5 (0.0–1.2)	0.9 (0.0–2.2)
		1963–1979	5	9.3 (1.5–17.1)	10.0 (1.6–18.4)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)		1963–1979	9	14.8 (5.2–24.4)	10.0 (1.6–18.4)	4.0 (0.0–9.5)	0.0 (0.0–0.0)	0.0 (0.0–0.0)
		1980–1989	11	6.3 (2.3–10.4)	3.6 (0.5–6.6)	1.4 (0.0–3.4)	0.7 (0.0–2.1)	0.7 (0.0–2.1)		1980–1989	19	12.4 (6.5–18.3)	3.6 (0.5–6.6)	5.2 (0.9–9.5)	0.7 (0.0–2.1)	1.6 (0.0–3.7)
		1990–2001	3	1.5 (0.0–3.2)	0.5 (0.0–1.4)	0.5 (0.0–1.6)	0.5 (0.0–1.5)	0.0 (0.0–0.0)		1990–2001	3	NA	NA	NA	NA	NA
		p–Value		<.05	<.01	0.22	0.82	0.40		*p*–Value		< .01	< .01	0.35	0.52	0.39
Non-Hodgkin Lymphoma	23 (37)	All	21	3.1 (1.7–4.6)	1.6 (0.6–2.6)	0.5 (0.0–1.1)	0.2 (0.0–0.5)	0.4 (0.0–0.8)	31 (49)	All	25	4.8 (2.7–7.0)	1.6 (0.6–2.6)	1.8 (0.2–3.4)	0.2 (0.0–0.5)	0.4 (0.0–0.8)
		1963–1979	5	5.5 (0.8–10.3)	3.4 (0.0–7.1)	1.1 (0.0–3.3)	1.1 (0.0–3.3)	0.0 (0.0–0.0)		1963–1979	7	5.5 (0.8–10.3)	3.4 (0.0–7.1)	1.1 (0.0–3.3)	1.1 (0.0–3.3)	0.0 (0.0–0.0)
		1980–1989	9	4.2 (1.3–7.0)	2.1 (0.1–4.1)	0.5 (0.0–1.5)	0.0 (0.0–0.0)	0.0 (0.0–0.0)		1980–1989	11	6.5 (2.5–10.6)	2.1 (0.1–4.1)	2.9 (0.0–6.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)
		1990–2001	7	1.7 (0.2–3.2)	0.7 (0.0–1.6)	0.3 (0.0–1.0)	0.0 (0.0–0.0)	0.7 (0.0–1.6)		1990–2001	7	NA	NA	NA	NA	NA
		p–Value		0.34	0.17	0.70	0.07	0.38		*p*–Value		0.36	0.17	0.49	0.07	0.33
CNS tumors	22 (37)	All	114	11.8 (9.6–14.0)	8.3 (6.4–10.2)	1.1 (0.4–1.9)	0.1 (0.0–0.4)	0.8 (0.2–1.4)	27 (47)	All	143	21.6 (17.7–25.4)	12.2 (9.5–14.9)	2.5 (1.0–4.0)	0.4 (0.0–1.1)	3.7 (1.4–6.0)
		1963–1979	26	19.6 (12.3–27.0)	10.9 (4.8–17.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	3.0 (0.0–6.3)		1963–1979	41	31.3 (22.6–39.9)	14.9 (7.9–21.8)	2.0 (0.0–4.7)	1.0 (0.0–2.9)	5.9 (1.3–10.6)
		1980–1989	37	13.8 (9.4–18.3)	10.5 (6.5–14.5)	0.9 (0.0–2.1)	0.4 (0.0–1.3)	1.3 (0.0–2.8)		1980–1989	51	22.0 (16.3–27.6)	14.0 (9.4–18.7)	1.7 (0.0–3.7)	0.4 (0.0–1.3)	3.8 (1.2–6.4)
		1990–2001	51	9.1 (6.5–11.6)	6.8 (4.5–9.0)	1.5 (0.4–2.6)	0.0 (0.0–0.0)	0.0 (0.0–0.0)		1990–2001	51	NA	NA	NA	NA	NA
		p–Value		<.01	.32	.16	.31	<.01		*p*–Value		< .01	.25	.27	.40	<.01
Bone tumors	26 (38)	All	58	13.4 (9.9–16.8)	10.6 (7.5–13.8)	1.4 (0.2–2.6)	0.8 (0.0–1.8)	0.3 (0.0–0.8)	34 (52)	All	66	21.0 (16.1–25.9)	12.0 (8.6–15.4)	5.2 (2.4–8.1)	1.2 (0.0–2.3)	1.7 (0.0–3.6)
		1963–1979	19	21.1 (12.6–29.6)	16.9 (9.0–24.7)	1.1 (0.0–3.3	2.3 (0.0–5.4)	0.0 (0.0–0.0)		1963–1979	23	25.7 (16.6–34.9)	18.0 (10.0–26.1)	3.5 (0.0–7.3)	2.3 (0.0–5.4)	1.2 (0.0–3.5)
		1980–1989	15	7.6 (3.1–12.1)	5.3 (1.5–9.2)	1.5 (0.0–3.6)	0.8 (0.0–2.2)	0.0 (0.0–0.0)		1980–1989	19	16.5 (9.2–23.9)	6.9 (2.5–11.2)	5.4 (1.5–9.3)	0.8 (0.0–2.2)	1.6 (0.0–4.9)
		1990–2001	24	13.9 (8.2–19.6)	11.7 (6.4–16.9)	1.6 (0.0–3.6)	0.0 (0.0–0.0)	0.7 (0.0–2.0)		1990–2001	24	NA	NA	NA	NA	NA
		p–Value		.10	.06	.45	.55	.47		*p*–Value		.14	<.05	.63	.55	.46
Soft tissue sarcoma	21 (36)	All	43	8.5 (5.9–11.1)	5.2 (3.1–7.3)	1.0 (0.0–1.9)	0.9 (0.0–1.8)	0.0 (0.0–0.0)	30 (49)	All	54	13.6 (10.0–17.2)	6.3 (3.9–8.7)	4.3 (2.0–6.7)	1.6 (0.3–2.9)	0.0 (0.0–0.0)
		1963–1979	17	13.0 (6.9–19.2)	7.3 (2.4–12.3)	0.9 (0.0–2.7)	0.0 (0.0–0.0)	0.0 (0.0–0.0)		1963–1979	23	18.3 (11.2–25.4)	8.3 (3.1–13.5)	4.6 (0.6–8.5)	0.9 (0.0–2.7)	0.0 (0.0–0.0)
		1980–1989	13	7.0 (2.8–11.3)	4.3 (0.9–7.6)	0.0 (0.0–0.0)	2.1 (0.0–4.5)	0.0 (0.0–0.0)		1980–1989	18	13.3 (7.5–19.1)	6.1 (1.9–10.3)	3.7 (0.5–6.9)	2.9 (0.1–5.6)	0.0 (0.0–0.0)
		1990–2001	13	7.0 (3.3–10.8)	4.7 (1.7–7.7)	1.8 (0.0–3.9)	0.5 (0.0–1.6)	0.0 (0.0–0.0)		1990–2001	13	NA	NA	NA	NA	NA
		p–Value		.12	.47	.57	.08	NA		*p*–Value		.12	.62	.82	.30	NA
Renal tumors	18 (33)	All	15	1.4 (0.4–2.4)	0.9 (0.1–1.7)	0.2 (0.0–0.5)	0.2 (0.0–0.6)	0.0 (0.0–0.0)	29 (45)	All	26	5.9 (3.5–8.4)	1.3 (0.3–2.3)	1.2 (0.1–2.2)	0.9 (0.0–1.9)	0.9 (0.0–1.9)
		1963–1979	7	2.1 (0.0–4.5)	2.2 (0.0–4.6)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)		1963–1979	12	7.1 (2.9–11.4)	2.9 (0.1–5.7)	1.5 (0.0–3.5)	0.0 (0.0–0.0)	0.8 (0.0–2.2)
		1980–1989	5	1.0 (0.0–2.5)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.5 (0.0–1.6)	0.0 (0.0–0.0)		1980–1989	10	5.4 (2.1–8.7)	0.5 (0.0–1.6)	1.1 (0.0–2.5)	1.8 (0.0–3.8)	0.5 (0.0–1.6)
		1990–2001	3	1.4 (0.0–2.9)	1.0 (0.0–2.4)	0.4 (0.0–1.1)	0.0 (0.0–0.0)	0.0 (0.0–0.0)		1990–2001	4	NA	NA	NA	NA	NA
		p–Value		0.21	0.16	0.27	0.42	NA		*p*–Value		0.58	0.15	0.91	0.18	0.67
Other	18 (35)	All	36	3.8 (2.5–5.1)	2.3 (1.3–3.4)	0.7 (0.2–1.3)	0.0 (0.0–0.0)	0.5 (0.0–1.0)	28 (52)	All	53	7.7 (5.3–10.0)	2.6 (1.5–3.7)	2.6 (1.1–4.1)	0.5 (0.0–1.1)	0.7 (0.1–1.3)
		1963–1979	9	3.8 (1.0–6.5)	1.1 (0.0–2.6)	1.7 (0.0–3.5)	0.0 (0.0–0.0)	0.6 (0.0–1.6)		1963–1979	19	7.7 (3.8–11.5)	1.7 (0.0–3.5)	3.4 (0.7–6.0)	0.6 (0.0–1.7)	0.6 (0.0–1.6)
		1980–1989	13	5.0 (2.2–7.8)	3.4 (1.1–5.6)	0.4 (0.0–1.2)	0.0 (0.0–0.0)	0.8 (0.0–2.0)		1980–1989	20	8.6 (4.8–12.5)	3.4 (1.1–5.6)	2.3 (0.0–4.6)	0.4 (0.0–1.3)	1.3 (0.0–2.7)
		1990–2001	14	3.1 (1.4–4.8)	2.2 (0.8–3.7)	0.5 (0.0–1.2)	0.0 (0.0–0.0)	0.3 (0.0–1.0)		1990–2001	14	NA	NA	NA	NA	NA
		p–Value		0.64	0.55	0.21	NA	0.62		p–value		0.55	0.44	0.57	0.77	0.42

*Includes $n = 30$ with unknown cause of death.
**Includes $n = 43$ with unknown cause of death.

Table 4. Comparison of treatment exposure across treatment era.

Treatment era	1963–1979		1980–1989		1990–2001		Total
RT and CT	624	56.9%	687	35.6%	699	22.3%	2010
RT only (+-surgery)	190	17.3%	129	6.7%	164	5.2%	483
CT only (+-surgery)	164	14.9%	928	48.1%	1880	60.0%	2972
Surgery only	95	8.7%	152	7.9%	351	11.2%	598
Unknown	23	2.1%	23	1.2%	16	0.5%	62
Other/No therapy	1	0.1%	9	0.5%	22	0.7%	32
Total	1097	100%	1928	100%	3132	99.9%	6157

Childhood cancer-specific late mortality

Figure 2(a–h) and Table 3 show the CM, overall and for specific causes, by childhood cancer type. Overall, CMs after 30 years of follow-up were highest among Central Nervous System (CNS) tumor CCSs (21.6% (95% CI: 17.7–25.4), Figure 2(d)) and bone tumor CCSs (21.0% (95% CI: 16.1–25.9), Figure 2(e)). Concurrent with the pattern in the full cohort, mortality from recurrence/progression generally increased in the first follow-up years after attaining 5 years survival in most diagnosis groups (Figure 2(a–h)). Among CCSs with CNS tumors it continued to increase thereafter; after 30-yrs of follow-up the CM for recurrence/progression of primary tumor was highest among CNS tumor CCSs (12.2% (95% CI: 9.5–14.9), Figure 2(d)) and bone tumor CCSs (12.0% (95% CI: 8.6–15.4, Figure 2(e))) and lowest, by an order of magnitude, for renal tumor CCSs (1.3% (95% CI: 0.3–2.3), Figure 2(g)) and non-Hodgkin lymphoma CCSs (1.6% (0.6–2.6), Figure 2(c)).

In all CCS, the mortality due to causes other than the primary cancer increased gradually from 10 years after diagnosis onwards (Figure 3). The large majority of these deaths were related to SMN with highest cumulative mortalities after 30 years for bone tumor CCSs (5.2% (2.4–8.1)), Hodgkin lymphoma CCS, (4.4% (1.3–7.5)) and soft tissue sarcoma CCSs (4.3% (2.0–6.7)).

Within the total group of bone tumor CCSs, those who were treated for Ewing sarcoma and osteosarcoma experienced comparable all-cause long-term mortality, while underlying patterns varied considerably: recurrence-related CM plateaued 10–15-years post-diagnosis for osteosarcoma CCS, whereas it continued to rise until at least 20 years after a Ewing sarcoma diagnosis. Moreover, osteosarcoma CCSs experienced an exceptionally high rate of SMN-related mortality (8.5% (CI 3.6–13.4)), at 30 years post-diagnosis and (13.7% (2.5–24.9)), at 40 yrs post diagnosis, which represents about 40% of cumulative mortality in very long-term osteosarcoma CCSs.

Finally, patterns of CM by treatment era also varied across childhood cancer types. The strongest and statistically significant differences for total mortality were noted among leukemia CCSs, with 21.8% 15-yr CM among patients diagnosed during 1963–1979 and 4.5% 15-yr CM in the most recent treatment cohort (p-trend <0.001); for Hodgkin lymphoma survivors (9.3% 1963–1979 to 1.5% 1990–2001) (p-trend <0.05); and for CNS tumor CCSs (19.6% 1963–1979 to 9.1% 1990–2001) (p-trend <0.01). In contrast to this typical pattern in the cohort, cumulative risk of death from progression/recurrence15-yrs after a primary diagnosis of a bone tumor did not show a difference for more recently treated CCSs with estimates of 16.9%, 5.3% and 11.7% for consecutive treatment cohorts ($p = 0.06$).

Discussion

This study shows that the cumulative risks of overall and cause-specific mortality vary between childhood cancer groups, by follow-up time, and by treatment era. We ascertained and coded causes of death from original medical files for a cohort covering a near 40 year treatment period and are able to present the results for all childhood cancer groups and treatment eras.

Three important aspects of the results should be considered: late mortality due to recurrence or progression, mortality due to late side effects, and trends over time.

The risk of late mortality due to recurrence or progression is low for five-year CCSs treated for non-Hodgkin lymphoma and renal tumors throughout the follow-up period. However the risk of late mortality due to recurrence or progression increases for CCSs treated for leukemia or Hodgkin lymphoma until 10 years after diagnosis. For five-year CCSs treated for a CNS tumour or bone tumour this risk of death increases up to 20 or 30 years after diagnosis to a cumulative mortality above 12% at 30 year. Previous studies in other childhood cancer survivor cohorts described that the late mortality

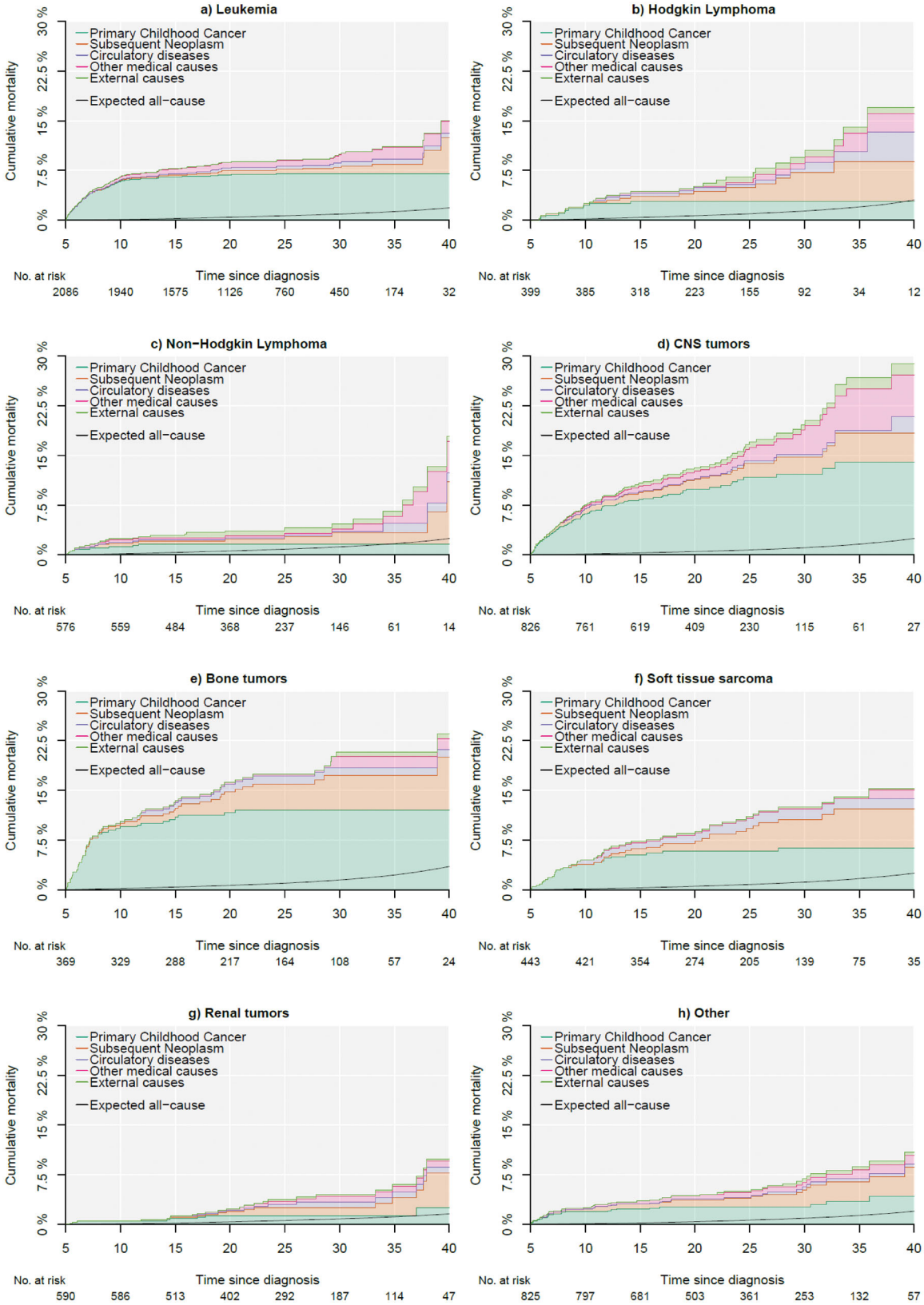

Figure 2. (a–h) Cumulative late mortality (%) of CCSs by time since diagnosis for various COD categories and stratified by primary childhood cancer type in the LATER cohort. *Corrected for sex, age and calendar year.

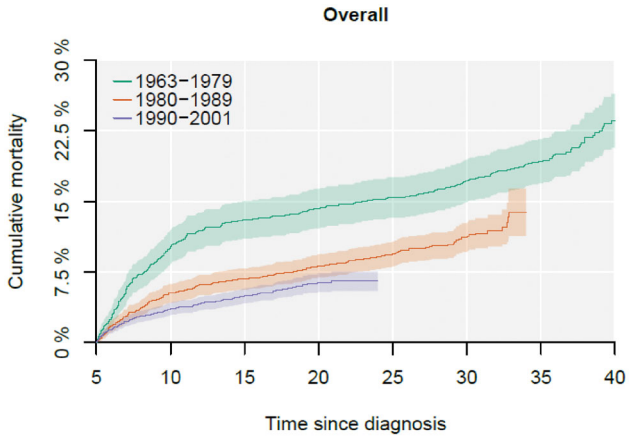

Figure 3. Cumulative late mortality (%) of CCSs by time since diagnosis for different periods of diagnosis.

from recurrence or progression predominated in the period 5–10 year after diagnosis (5,6,14,15). Fidler et al., calculated the excess late death per 10,000 person years, and also identified noticeable excesses of deaths due to recurrence or progression of the primary tumor for CCSs of CNS neoplasms, leukemia and bone sarcoma (4). For CNS tumours, two large cohort studies among long-term survivors of astrocytoma (16) and medulloblastoma (17), showed high risks of recurrence-related mortality well beyond the 10-yr follow-up mark.

The contribution of deaths from potential late effects increases with a longer follow-up time. In our study the cumulative risk of death from all late effects 30 years after diagnoses, is high (>five%) for CCSs treated for Hodgkin lymphoma, CNS tumors, bone tumors and soft tissue sarcoma. For bone tumor survivors treated in the era covered by our study, one out of 12 survivors had died due to a late effect 30 years after treatment. The pattern of late effects differs according to primary cancer diagnosis group. For example Hodgkin lymphoma, bone tumor and soft tissue sarcoma survivors have a high risk of death due to SMN at 30 years after diagnosis (cumulative mortality more than 4). CNS tumor survivors have a high risk of late mortality due to other late effects than SMN and circulatory diseases. These findings confirm a report by Huang and colleagues (2019) (18) on a Swedish record linkage study among 3,264 CNS tumour survivors and >16,000 matched population-based comparison subjects, which showed elevated risks of mortality from many different diseases. Of note, mortality from chronic conditions after a childhood cancer diagnosis and treatment, can have multiple causes, including, among others, treatment but also genetic predisposition, age, and underlying risk of chronic diseases.

From our study we can conclude that late mortality due to all causes is lower for survivors treated in the more recent treatment period. Other studies also showed a decrease in all-cause late mortality (4,5,7,15), including a recent pan-European evaluation among 77,234 survivors (19). We could confirm this finding for late mortality due to all causes for survivors of leukemia, Hodgkin lymphoma and CNS tumors. We also identified a decrease in death due to recurrence and progression when we analysed this for all survivors including for the subgroups of survivors of pediatric leukemia and Hodgkin lymphoma. The 15-yrs recurrence-related cumulative mortality declined from 10% for Hodgkin lymphoma CCSs treated in the 1970s to less than 1% for those treated in the 1990s. Of interest in this regard are findings for a large cohort of medulloblastoma survivors which showed a strong decrease in recurrence-related mortality for children treated most recently: in parallel, though, in the most recently treated subgroup, survivors reported higher rates of morbidity and multimorbidity than children treated earlier, most likely related to highly intensified protocols over time.

Since we changed the coding convention for decedents who died while suffering from certain established treatment-specific side effects, it is possible that the trends in CODs related to recurrence, are no longer detected for specific small subgroups in the cohort.

With regard to side effects, colleagues from the Northern American Childhood Cancer Survivor Study reported a decrease in late mortality related to side effects among CSS treated in the 1990s compared to those treated earlier and attributed this change to diminished treatment intensity in leukemia, renal tumor, astrocytoma and Hodgkin lymphoma patients (8). Overall, mortality rates are expected to gradually decrease for cohorts treated with less intensive radiotherapy protocols in the 1990s, and to a lesser extent, decreased

intensity and alternative chemotherapy. Also Fidler et al. showed in the British Cancer Survivors study a decrease in excess risk of specific causes of death from late side effects for some tumour groups (4). They could not confirm the decrease of late mortality from circulatory diseases for CCSs treated in more recent years. Albeit for a short follow-up period, a recent report from Australia (20) also showed no decrease in non-cancer mortality risk 5–10 yrs post-diagnosis for survivors treated most recently. When we evaluate the cumulative mortality from SMN, circulatory disease and other diseases across treatment periods we also did not confirm a decrease over time. Only for CNS tumor survivors the risk of death due to late side effects other than SMN and circulatory disease significantly decreased over time. One explanation could be that we investigated a smaller cohort and that we had a lack of power to detect a difference. However, in our study SMN-related 30-yr cumulative mortality is generally similar for patients treated in the 1980s and those treated earlier. These results confirm findings reported in our earlier LATER subsequent tumor incidence study, in which no decreased SMN risk was observed for survivors treated in more recent calendar periods (12,21), although treatments changed considerably over time Given the discrepancies in conclusions across these large cohort studies to date, and the fact that 20-yr follow-up data are not available yet for most recent treatment cohorts, we feel it is too early to conclude that recent treatment regimens are less toxic.

The following methodological aspects need to be considered when interpreting our results. We report from a very well-characterized cohort, with near-national coverage of childhood cancer patients diagnosed from the 1990s onwards. Information on COD was based on medical records and was coded according to the standard classification system for COD, the ICD-10. To avoid obvious ambiguity in coding health conditions potentially caused by medical treatments many years earlier, and associated risk of bias, we applied a new rule for assignment of putative causality: if there was no evidence of active disease (i.e., childhood cancer) the chronic condition of interest was coded as the underlying COD rather than the childhood cancer. In 13 cases, the physician's letter determining COD spoke of a direct iatrogenic effect of the treatment of childhood cancer leading to death (for example, 'chemotherapy-induced cardiomyopathy after childhood cancer'). Furthermore, in 9 cases this iatrogenic effect was also suggested but not explicitly stated as COD. Thus, we expect our estimates of the burden of mortality of late chronic conditions to be slightly different from those reported earlier, and in our opinion, more appropriate compared to those based on official cause of death registration (11).

Limitations include the fact that patients treated most recently cannot be followed for the full 20- or 30 year period yet. Also, we recognize that cumulative mortality is influenced by age-specific patterns of underlying mortality in the general population. There are childhood-cancer specific differences in attained age in our cohort, owing to underlying differences in typical ages at diagnosis (depicted in Table 3). Finally, survivorship cohorts do not capture nor take into account trends in five-yr survival. Nonetheless, the role of attained age does not seem apparent in the patterns of cumulative mortality. Finally, dedicated surveillance programs for CCS, started in the mid-1990s in the Netherlands with nation-wide coverage nowadays, which may have influenced mortality rates for second cancers (in particular breast cancer) and circulatory diseases (in particular cardio-myopathy).

In conclusion, late mortality from recurrence/progression of childhood cancer predominated until 15 years after diagnoses, thereafter, the contribution of deaths from potential late effects increased. Overall, CNS and bone tumor survivors carry the highest- and lymphoma patients carry the lowest cumulative late mortality. The risk of late mortality as well as the ratio of mortality from recurrences and from late side effects varies between childhood cancer groups, by treatment era, and by follow-up time.

With respect to clinical relevance, our data suggest that (1) CCSs, in bone tumor and CNS tumor survivors may benefit from further integration of follow-up care for the primary tumor and surveillance for late side effects (including

SMN) in survivorship clinics until at least 15 years after diagnosis. Such integrated care likely strengthens awareness for initial clinical signs of very late recurrences; and (2) that it is reasonable to maintain surveillance for late effects for ageing survivors because no plateau of mortality from late effects has been reached yet, and (3) efforts should remain focused on developing adapted treatment protocols for new children with cancer to further decrease the risk of late mortality due to late effects while at the least maintaining tumor survival rates.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

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Appendix

Participating pediatric oncology centers

LATER collaborating institutions include Emma Children's Hospital/Academic Medical Center (EKZ/AMC) Amsterdam, VUmc Amsterdam, LUMC Leiden, ErasmusMC-Sophia Children's Hospital/Rotterdam, Beatrix Kinderkliniek UMCG Groningen, Radboud Nijmegen, and UMCU Wilhelmina Children's Hospital/Princess Máxima Center for Pediatric Oncology Utrecht.

Inclusion criteria: childhood cancer diagnoses

All malignant childhood tumors according to the International Classification of Childhood Cancer (ICCC) 3rd edition as well as systemic multifocal/poly-ostotic/Class 3 Langerhans Cell Histiocytoses (LCH).