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Original Research

Significant improvement in survival of advanced stage childhood and young adolescent cancer in the Netherlands since the 1990s

Maya Schulpen [a], Otto Visser [b], Ardine M.J. Reedijk [a], Leontien C.M. Kremer [a,c], Christian Michel Zwaan [a,d], Alexander M.M. Eggermont [a,c], Jan W. Coebergh [e], Rob Pieters [a,c], Henrike E. Karim-Kos [a,b,*]

[a] *Princess Máxima Center for Pediatric Oncology, Utrecht, The Netherlands*
[b] *Department of Research and Development, Netherlands Comprehensive Cancer Organisation (IKNL), Utrecht, The Netherlands*
[c] *University Medical Center Utrecht, Utrecht, The Netherlands*
[d] *Department of Pediatric Oncology, Erasmus MC-Sophia Children's Hospital, Rotterdam, The Netherlands*
[e] *Department of Public Health, Erasmus University Medical Center, Rotterdam, The Netherlands*

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Abstract ***Background:*** This is the first national study on trends in cancer survival and mortality for children and young adolescents in the Netherlands including unique information on stage at diagnosis.

Methods: All neoplasms in patients <18 years, diagnosed between 1990 and 2015 (N = 14,060), were derived from the Netherlands Cancer Registry. Cohort and period survival analyses were used to estimate observed survival (OS). Time trends in OS and mortality rates were evaluated by parametric survival models and average annual percentage change, respectively.

Results: Between 1990 and 2015, 5-year OS and 10-year OS of childhood and young adolescent cancer have improved significantly by 9 percent points, reaching 81% and 78%, respectively. Favourable trends in survival were observed for all age groups and most diagnostic (sub)groups, being particularly pronounced for advanced disease. Non-Hodgkin lymphomas Ann Arbor stage III, metastatic neuroblastomas (age ≥18 months) and Ewing bone sarcomas showed significant improvements in 5-year OS. Compared with 1990–99, the risk of dying within five years of diagnosis was decreased significantly during 2000–09 (hazard ratio

* *Corresponding author*: Princess Máxima Center for Pediatric Oncology, Heidelberglaan 25, 3584 CS Utrecht, The Netherlands.
E-mail address: h.e.karim-kos@prinsesmaximacentrum.nl (H.E. Karim-Kos).

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[HR] = 0.8) and 2010–15 (HR = 0.6), after adjustment for age, gender and follow-up time. Nonetheless, the prognosis of young patients suffering from central nervous system tumours, neuroblastoma and osteosarcomas remained modest, with 5-year OS <70% and 10-year OS <65%. Childhood and young adolescent cancer mortality decreased by an average of 2.0% annually between 1990 and 2018.

Conclusions: Significant progress has been realised in the prognosis of childhood and young adolescent cancer in the Netherlands since the 1990s. Survival improvements were especially evident for patients with advanced stages and were also reflected in the declining mortality rates.

1. Introduction

Five-year survival of childhood cancer has improved from about 40% in the 1970s to approximately 80% nowadays [1,2]. However, cancer is still one of the leading causes of death in children and adolescents [3], and about 25% of the paediatric patients with cancer eventually die from their disease [1,2,4].

Until now, no comprehensive national trend analyses on overall childhood cancer survival have been performed for the Netherlands. For the southern region of the country, a significant increase in childhood cancer survival was shown during 1973–99, reaching a 10-year estimate of 75% [5]. The EUROCARE-5 study reported an overall 5-year survival of 78% for European children (0–14 years) with cancer in 2000–07 [2]. In the United States of America, 5-year survival of childhood cancer (0–19 years) rose from 63% in 1975–79 to 83% in 2003–09 [4].

The abovementioned studies did not specify their findings by stage at diagnosis. Increased precision and wider availability of diagnostic methods may result in earlier diagnosis and increase the detection of both relatively indolent cancers and extremely aggressive and lethal cancers, potentially affecting the distribution of disease stage at diagnosis [6,7]. Stage at diagnosis is a strong indicator of prognosis depending on the state of treatment and could thus add valuable information when evaluating time trends in cancer survival [8,9].

Incidence of childhood and young adolescent cancer increased in the Netherlands between 1990 and 2017. Besides earlier diagnosis of testicular germ cell tumours and malignant melanomas, a shift occurred towards more advanced disease for Hodgkin lymphomas, rhabdomyosarcomas and non-rhabdomyosarcoma soft tissue sarcomas [7].

Young adolescents (15–17 years) with cancer in the Netherlands are increasingly referred for treatment in paediatric oncology centres since 2002, initially with haematological malignancies, gradually followed by solid tumours [10]. To further improve outcomes of childhood and young adolescent cancer, all Dutch paediatric oncologic care has been concentrated in the Princess Máxima Center for Pediatric Oncology as of 2018. To investigate the effect of this concentration of care in the future, information on the prior situation is fundamental. Therefore, an up-to-date nationwide and population-based estimate of childhood and young adolescent cancer survival in the Netherlands is desired.

In this study, we evaluated survival trends of cancer in children and young adolescents (0–17 years) in the Netherlands since the 1990s, by type of cancer and stage at diagnosis, using population-based data of the Netherlands Cancer Registry (NCR). In addition, changes in mortality due to childhood and young adolescent cancer between 1990 and 2018 were examined using data from Statistics Netherlands (CBS).

2. Patients and methods

2.1. Data collection

Data on all neoplasms in patients aged 0–17 years diagnosed in the Netherlands between 1990 and 2015 were derived from the NCR, which is a nationwide population-based cancer registry since 1989 with a completeness of at least 96% [10]. Notification of all newly diagnosed malignancies in the Netherlands occurs via the Nationwide Network and Registry of Histopathology and Cytopathology (PALGA) and the National Registry of Hospital Discharges. Retrospectively, data on patient, tumour and treatment characteristics are extracted from medical records. Information on vital status is obtained by annual linkage with the nationwide Personal Records Database (BRP, last linkage: 1st February 2020).

Since 2000, benign and borderline tumours of the central nervous system (CNS; International Classification of Diseases for Oncology [ICD-O]-3 behaviour codes/0 and/1) have been included in the NCR. These tumours are included in Fig. 1 for a comprehensive overview of childhood cancer survival and were analysed separately (Supplementary Table S1). Pilocytic astrocytomas (ICD-O-3 M9421/1, N = 818) were completely registered since

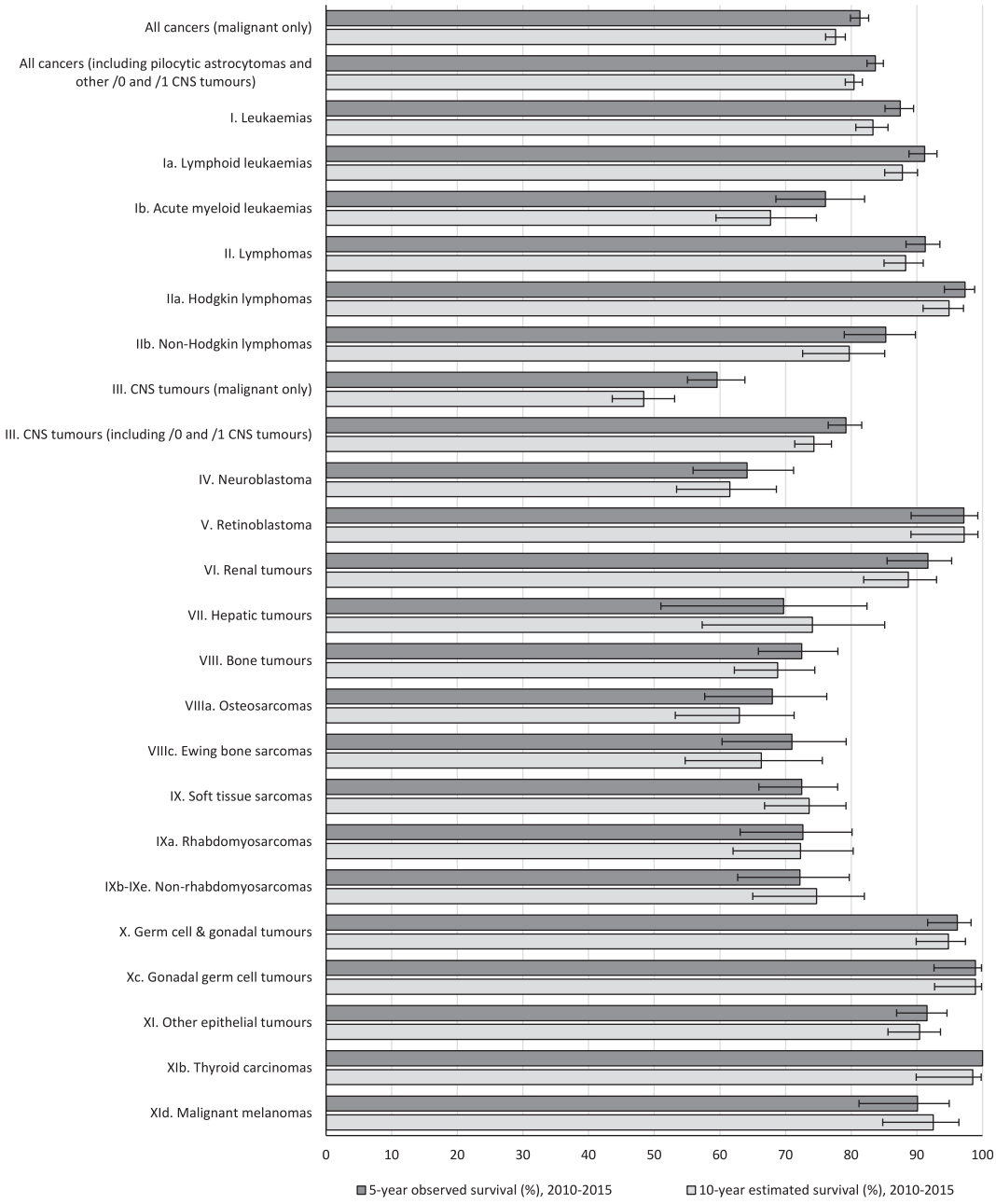

Fig. 1. Overview of 5-year observed and 10-year estimated cancer survival of children and young adolescents (aged 0–17 years) in the Netherlands in 2010–15 (Source: The Netherlands Cancer Registry). Ten-year survival has been estimated for the period 2010–15 using period-based survival analysis because follow-up was complete until 1st February 2020. The error bars depict 95% confidence intervals of the survival estimates. CNS, central nervous system.

1989. Therefore, in addition to the results for malignant cancers only, survival was also estimated for all cancers and CNS tumours including pilocytic astrocytomas. Several neoplasms were excluded because of incomplete registration during the study period: myelodysplastic syndromes (ICD-O-3 M9980–9989, N = 80), myeloproliferative neoplasms (ICD-O-3 M9950–9962, N = 24), Langerhans cell histiocytosis (ICD-O-3 M9750–9754, N = 127) and carcinoid tumour of the appendix (ICD-O-3 code C18.1, M8240–8249, N = 192). Well-differentiated chondrosarcomas (ICD-O-3 M9220/31, N = 27) and dermatofibrosarcomas (ICD-O-3 M8832, N = 66) were also excluded being now classified as borderline neoplasms.

Disease-specific mortality data from 1990 to 2018 were derived from the cause-of-death registry of Statistics Netherlands using ICD-9 codes 140–208 and ICD-10 codes C00–C97. Mortality data were obtained in 5-year age groups, where age represents age at death.

2.2. Defining diagnostic groups and stage

Neoplasms were categorised in accordance with the International Classification of Childhood Cancer (ICCC, third edition) [11]. Stage was classified using the Ann Arbor staging system for lymphomas and tumour-node-metastasis classification or extent of disease (i.e. localised, regional or distant) for other solid tumours using the Toronto Paediatric Cancer Staging guidelines (Supplementary Table S2) [12]. For astrocytomas (i.e. ICCC-3 subgroup IIIb), the World Health Organisation (WHO) grading system for CNS tumours was used [13].

Mortality data were classified into four main groups: leukaemias (ICD-9 codes 204–208, ICD-10 codes C91–C96), lymphomas (200–203, C81–C88, C90), CNS tumours (191–192, C70–C72) and non-CNS solid tumours (other ICD-9 and ICD-10 codes, except unknown primary sites [199, C77–C80]).

2.3. Statistical analyses

Survival time was calculated from the date of diagnosis until the date of death due to any cause (i.e. event) or censoring (i.e. emigration, loss to follow-up or 1st February 2020), whichever came first. Traditional cohort-based survival analysis was used to calculate 5-year and 10-year observed survival (OS) using 6-month intervals during the first year of follow-up and annual intervals onwards. Period-based survival analysis was performed to estimate 10-year survival for the latest diagnostic period [14]. OS was used instead of relative survival as competing causes of death are rare among patients with childhood cancer in developed countries [15]. Changes over time in OS were evaluated with a *p*-trend analysis for period of diagnosis using parametric survival models (streg) adjusted for follow-up time (in years) [16]. Similar models were used to estimate the risk of dying (i.e. hazard ratio, HR) within 5 years of diagnosis for three diagnostic periods: 1990–99, 2000–09 and 2010–15. Gender, age at diagnosis and disease stage (if applicable) were entered into multivariable models to adjust for case-mix. Patients who were diagnosed at autopsy were excluded from the survival models (N = 40).

Mortality rates for the age group 0–19 were standardised using the World Standard Population. Age-specific mortality rates were given for the age groups: 0, 1–4, 5–9, 10–14 and 15–19 years. Mortality rates were presented in the figures as three-year moving averages by taking the average of the rates of each given year and the rates either side of it. Changes in mortality between 1990 and 2018 were evaluated by calculating the average annual percentage change (AAPC) and corresponding 95% confidence interval (CI). AAPC was estimated from a regression line which was fitted to the natural logarithm of the rates using the calendar year as a regressor variable [17].

Survival and mortality analyses were performed using STATA/SE 16.1 (StataCorp LP, College Station, Texas, USA) and SAS software (SAS system 9.4, SAS Institute, Cary, NC, USA), respectively. Two-sided *p*-values <0.05 were considered statistically significant.

3. Results

In total, 14,060 cancers (including benign and borderline CNS tumours) newly diagnosed in children and young adolescents in the Netherlands during 1990–2015 were included.

Fig. 1 displays the most recent 5-year and 10-year OS for all childhood cancers combined and by ICCC-3 diagnostic (sub)group. Children and young adolescents diagnosed in the period 2010–15 showed a 5-year OS of 84% and a 10-year OS of 80%, including benign and borderline CNS tumours. The 5-year OS and 10-year OS were 81% and 78%, respectively, when non-malignant CNS tumours were excluded. OS rates were close to 95–100% for Hodgkin lymphomas, retinoblastomas, gonadal germ cell tumours and thyroid carcinomas, followed by lymphoid leukaemias, renal tumours and malignant melanomas of which 5-year and 10-year OS exceeded 90% and 85%, respectively. The worst prognoses (i.e. 5-year OS <70% and 10-year OS <65%) were observed for malignant CNS tumours (60% and 48%, respectively), neuroblastoma (64% and 62%, respectively) and osteosarcomas (68% and 63%, respectively).

3.1. Survival trends for all children and young adolescents with cancer combined

An overview of trends in cancer survival over time among children and young adolescents in the Netherlands for the period 1990–2015 is provided in Table 1, overall and by gender, age at diagnosis and ICCC-3 diagnostic (sub)group. In addition to the results for malignant cancers, survival estimates are also displayed for all cancers and CNS tumours including pilocytic astrocytomas. Benign and borderline CNS tumours (N = 1203) are separately presented in Supplementary Table S1. For all malignant childhood cancers combined, both 5-year and 10-year OS improved by 9 percent points between 1990 and 2015. The improvement in OS was seen regardless of gender and age. The largest improvement was observed among young adolescents (15–17 years), where 5-year and 10-year OS increased by 13 and 11 percent points, respectively.

Table 1
Trends in observed 5-year and 10-year cancer survival in children and young adolescents (aged 0–17 years) in the Netherlands, 1990–2015.

	Numbers at risk			5-year observed survival (%), SE								*p*-Trend	10-year observed survival (%), SE						*p*-Trend	10-year estimated[a] survival (%), SE	
	1990–99	2000–09	2010–15	1990–2015		1990–99		2000–09		2010–15			1990–2009		1990–99		2000–09			2010–15	
All cancers (malignant only)	4542	5015	3056	76.3	0.4	72.0	0.7	77.0	0.6	81.3	0.7	<0.001	72.1	0.5	69.2	0.7	74.7	0.6	<0.001	77.6	0.8
Gender																					
Boys	2554	2840	1688	75.6	0.5	71.3	0.9	75.8	0.8	81.8	0.9	<0.001	71.1	0.6	68.3	0.9	73.7	0.8	<0.001	77.6	1.0
Girls	1988	2175	1368	77.1	0.6	72.9	1.0	78.7	0.9	80.7	1.1	<0.001	73.4	0.7	70.4	1.0	76.1	0.9	<0.001	77.5	1.1
Age (in years)																					
0	344	383	228	71.2	1.5	66.8	2.5	74.2	2.2	72.8	2.9	0.12	70.1	1.7	65.6	2.6	74.2	2.2	0.03	71.0	3.0
1–4	1399	1451	835	77.3	0.7	73.0	1.2	78.0	1.1	83.5	1.3	<0.001	73.6	0.8	70.5	1.2	76.6	1.1	<0.001	80.1	1.4
5–9	935	1069	597	76.1	0.8	73.5	1.4	75.8	1.3	80.5	1.6	0.003	72.3	1.0	70.4	1.5	73.9	1.3	0.08	77.1	1.7
10–14	954	1113	728	76.2	0.8	72.8	1.4	76.1	1.3	80.8	1.5	<0.001	71.1	1.0	69.7	1.5	72.3	1.3	0.18	76.2	1.6
15–17	910	999	668	76.8	0.8	70.0	1.5	79.1	1.3	82.8	1.5	<0.001	71.7	1.0	67.0	1.6	75.9	1.4	<0.001	78.4	1.6
All cancers, including pilocytic astrocytomas[b]	*4786*	*5371*	*3272*	*77.4*	*0.4*	*73.1*	*0.6*	*78.3*	*0.6*	*82.4*	*0.7*	*<0.001*	*73.4*	*0.4*	*70.4*	*0.7*	*76.1*	*0.6*	*<0.001*	*79.0*	*0.7*
ICCC-3 diagnostic group																					
I. Leukaemias	1336	1558	900	80.1	0.6	74.0	1.2	81.1	1.0	87.5	1.1	<0.001	75.3	0.8	70.8	1.2	79.2	1.0	<0.001	83.3	1.3
Ia. Lymphoid leukaemias	1047	1222	696	85.8	0.6	80.7	1.2	87.0	1.0	91.2	1.1	<0.001	81.3	0.8	77.1	1.3	84.9	1.0	<0.001	87.8	1.3
Ib. Acute myeloid leukaemias	241	263	155	59.1	1.9	50.0	3.2	57.4	3.0	76.1	3.4	<0.001	52.1	2.2	47.9	3.2	55.9	3.1	0.04	67.7	3.9
Ic. Chronic myeloproliferative diseases	20	35	22	70.1	5.2	30.0	10.2	80.0	6.8	90.9	6.1	<0.001	60.0	6.6	30.0	10.2	77.1	7.1	0.001	84.6	8.2
Id–Ie. Other and unspecified leukaemias	28	39	27	58.0	5.1	60.7	9.2	57.8	8.0	55.6	9.6	0.68	57.5	6.1	57.1	9.4	57.8	8.0	0.98	54.6	9.3
II. Lymphomas	715	746	472	87.5	0.8	82.1	1.4	90.2	1.1	91.3	1.3	<0.001	84.9	0.9	80.4	1.5	89.2	1.1	<0.001	88.3	1.5
IIa. Hodgkin lymphomas	327	377	227	94.7	0.7	91.7	1.5	95.7	1.0	97.3	1.1	0.004	92.3	1.0	89.5	1.7	94.7	1.2	0.01	94.9	1.5
IIb. Non-Hodgkin lymphomas	248	233	170	77.7	1.6	68.5	3.0	82.0	2.5	85.2	2.7	<0.001	73.8	2.0	66.9	3.0	81.1	2.6	<0.001	79.7	3.2
IIc. Burkitt lymphomas	137	131	70	86.9	1.8	83.1	3.2	89.3	2.7	90.0	3.6	0.11	85.8	2.1	82.4	3.3	89.3	2.7	0.10	90.2	3.5
IId–IIe. Other and unspecified lymphomas	3	5	5	69.2	12.8	NA		NA		NA		NA	NA		NA		NA		NA	NA	
III. CNS tumours (malignant only)	634	683	487	50.8	1.2	50.4	2.0	45.0	1.9	59.6	2.2	0.01	43.4	1.4	46.0	2.0	41.0	1.9	0.10	48.4	2.4
IIIa. Ependymomas	102	104	50	61.0	3.1	55.5	4.9	60.4	4.8	73.3	6.4	0.05	50.5	3.5	44.6	4.9	56.4	4.9	0.22	63.4	6.7
IIIb/d. Astrocytomas and gliomas	266	301	226	47.3	1.8	56.6	3.0	36.5	2.8	50.7	3.3	0.10	43.5	2.1	55.1	3.1	33.2	2.7	<0.001	41.5	3.5
IIIc. Embryonal tumours	189	233	148	51.2	2.1	48.4	3.6	47.9	3.3	60.0	4.0	0.02	42.4	2.4	42.0	3.6	42.8	3.2	0.65	47.2	4.3
IIIe–IIIf. Other and unspecified CNS tumours	77	45	63	50.7	3.7	27.3	5.1	50.7	7.5	79.4	5.1	<0.001	34.2	4.3	26.0	5.0	48.4	7.5	<0.001	70.1	7.1
III. CNS tumours, including pilocytic astrocytomas[b]	*878*	*1039*	*703*	*64.8*	*0.9*	*62.5*	*1.6*	*62.3*	*1.5*	*71.4*	*1.7*	*<0.001*	*59.1*	*1.1*	*58.6*	*1.7*	*59.5*	*1.5*	*0.68*	*65.0*	*1.9*
IV. Neuroblastoma	220	251	151	60.9	2.0	55.9	3.3	63.2	3.0	64.1	3.9	0.046	57.7	2.3	54.1	3.4	60.8	3.1	0.07	61.5	3.9
IVa. Neuroblastoma	210	244	147	59.8	2.0	54.3	3.4	62.6	3.1	63.2	4.0	0.04	56.5	2.3	52.4	3.4	60.1	3.1	0.049	60.8	4.0
V. Retinoblastoma	129	112	71	95.5	1.2	90.7	2.6	100		97.2	2.0	0.02	95.0	1.4	90.7	2.6	100		0.99	97.2	2.0
VI. Renal tumours	255	273	134	88.2	1.3	85.9	2.2	88.6	1.9	91.7	2.4	0.10	87.1	1.5	85.9	2.2	88.2	2.0	0.43	88.7	2.8
VIa. Nephroblastoma	251	268	129	88.1	1.3	86.1	2.2	88.4	2.0	91.3	2.5	0.14	87.3	1.5	86.1	2.2	88.4	2.0	0.44	88.8	2.8

(*continued on next page*)

Table 1 (*continued*)

	Numbers at risk			5-year observed survival (%), SE								*p*-Trend	10-year observed survival (%), SE						*p*-Trend	10-year estimated[a] survival (%), SE	
	1990–99	2000–09	2010–15	1990–2015		1990–99		2000–09		2010–15			1990–2009		1990–99		2000–09			2010–15	
VII. Hepatic tumours	58	74	33	70.1	3.6	61.3	6.5	77.0	4.9	69.7	8.0	0.27	70.2	4.0	61.3	6.5	77.0	4.9	0.05	74.1	7.0
VIIa. Hepatoblastoma	41	56	25	78.6	3.7	65.5	7.5	89.3	4.1	76.0	8.5	0.21	79.3	4.1	65.5	7.5	89.3	4.1	0.01	78.7	7.7
VIII. Bone tumours	277	348	212	67.8	1.6	61.0	2.9	70.4	2.5	72.4	3.1	0.003	60.9	2.0	55.9	3.0	64.9	2.6	0.02	68.8	3.1
VIIIa. Osteosarcomas	148	169	97	64.0	2.4	56.7	4.1	68.0	3.6	68.0	4.7	0.04	56.1	2.8	51.3	4.1	60.4	3.8	0.06	63.0	4.6
VIIIb. Chondrosarcomas	8	7	3	83.3	8.8	NA		NA		NA		NA	80.0	10.3	NA		NA		NA	NA	
VIIIc. Ewing bone sarcomas	97	129	91	65.1	2.7	60.8	5.0	64.1	4.2	71.0	4.8	0.10	57.7	3.3	54.5	5.1	60.1	4.3	0.49	66.3	5.3
VIIId–VIIIe. Other and unspecified bone tumours	24	43	21	93.0	2.7	87.5	6.8	95.2	3.3	95.2	4.6	0.30	90.8	3.6	87.5	6.8	92.8	4.0	0.40	92.0	5.5
IX. Soft tissue sarcomas	353	343	215	67.7	1.6	63.6	2.6	68.8	2.5	72.5	3.1	0.03	63.0	1.8	60.2	2.6	65.9	2.6	0.20	73.6	3.2
IXa. Rhabdomyosarcomas	203	172	107	67.3	2.1	59.8	3.5	72.7	3.4	72.7	4.3	0.01	62.5	2.5	56.8	3.5	69.2	3.5	0.01	72.3	4.6
IXb–IXe. Other and unspecified soft tissue sarcomas	150	171	108	68.2	2.3	68.9	3.8	64.9	3.6	72.2	4.3	0.67	63.6	2.7	64.8	3.9	62.5	3.7	0.43	74.7	4.3
X. Germ cell and gonadal tumours	267	240	156	89.1	1.2	85.0	2.2	89.2	2.0	96.2	1.5	0.001	86.4	1.5	84.2	2.2	88.7	2.0	0.16	94.8	1.8
Xa. Intracranial and intraspinal germ cell tumours	48	41	29	81.3	3.6	70.8	6.6	85.4	5.5	93.1	4.7	0.02	76.4	4.5	68.8	6.7	85.4	5.5	0.11	89.9	5.6
Xc. Gonadal germ cell tumours: testis	102	83	62	93.9	1.5	92.2	2.7	92.8	2.8	98.4	1.6	0.14	92.4	1.9	92.2	2.7	92.8	2.8	0.88	98.3	1.7
Xc. Gonadal germ cell tumours: ovary	53	57	31	97.2	1.4	94.3	3.2	98.2	1.7	100		0.16	96.3	1.8	94.3	3.2	98.2	1.7	0.30	100	
Xb, Xd–Xe. Other and unspecified germ cell tumours	64	59	34	80.2	3.2	76.6	5.3	78.0	5.4	91.2	4.9	0.14	75.6	3.9	75.0	5.4	76.3	5.5	0.89	87.9	5.6
XI. Other epithelial tumours	290	375	214	90.2	1.0	87.9	1.9	91.2	1.5	91.5	1.9	0.13	86.5	1.3	84.7	2.1	87.9	1.7	0.20	90.4	2.0
XIb. Thyroid carcinomas	85	84	69	99.6	0.4	100		98.8	1.2	100		0.93	98.8	0.8	98.8	1.2	98.8	1.2	0.99	98.5	1.5
XId. Malignant melanomas	120	183	82	92.5	1.3	90.0	2.7	95.1	1.6	90.1	3.3	0.60	88.7	1.8	85.0	3.3	91.2	2.1	0.10	92.5	2.8
XIa, XIc, XIe–XIf. Other and unspecified	85	108	63	77.9	2.6	72.6	4.9	78.6	4.0	84.1	4.6	0.26	72.3	3.2	70.2	5.0	73.9	4.2	0.44	79.3	5.1
XII. Other and unspecified	8	12	11	87.1	6.0	NA		100		90.9	8.7	NA	85.0	8.0	NA		100		NA	NA	

SE, standard error; ICCC, International Classification of Childhood Cancer; CNS, central nervous system.

NA, estimation of a reliable survival rate was not possible because of number at risk <10.

[a] 10-year survival has been estimated for the period 2010–15 using period-based survival analysis because follow-up was complete until 1st February 2020.

[b] Including pilocytic astrocytomas, other CNS tumours having a behaviour code/0 and/1 and completely registered since 2000 only were excluded. All benign and borderline CNS tumours are separately described in Supplementary Table S1.

Table 2
Multivariable-adjusted[a] hazards of death within five years of diagnosis by period of diagnosis for childhood and young adolescent cancer in the Netherlands, 1990–2015.

	Period of diagnosis									
	1990–99		2000–09				2010–15			
	N at risk	HR	N at risk	$HR_{adjusted}$[a]	(95% CI)	*p*-Value	N at risk	$HR_{adjusted}$[a]	(95% CI)	*p*-Value
All cancers (malignant only)	4542	Ref	5015	0.8	(0.7–0.9)	<0.001	3056	0.6	(0.6–0.7)	<0.001
All cancers, including pilocytic astrocytomas[b]	*4786*	*Ref*	*5371*	*0.8*	*(0.7–0.9)*	*<0.001*	*3272*	*0.6*	*(0.6–0.7)*	*<0.001*
ICCC-3 diagnostic group										
I. Leukaemias	1336	Ref	1558	0.7	(0.6–0.8)	<0.001	900	0.4	(0.4–0.5)	<0.001
Ia. Lymphoid leukaemias	1047	Ref	1222	0.6	(0.5–0.8)	<0.001	696	0.4	(0.3–0.6)	<0.001
Ib. Acute myeloid leukaemias	241	Ref	263	0.8	(0.6–1.0)	0.047	155	0.4	(0.3–0.6)	<0.001
Ic. Chronic myeloproliferative diseases	20	Ref	35	0.2	(0.1–0.4)	<0.001	22	0.1	(0.0–0.3)	<0.001
Id–Ie. Other and unspecified leukaemias	28	Ref	38	1.1	(0.5–2.3)	0.89	27	1.1	(0.5–2.7)	0.77
II. Lymphomas	715	Ref	746	0.5	(0.4–0.7)	<0.001	472	0.5	(0.3–0.7)	<0.001
IIa. Hodgkin lymphomas[c]	319	Ref	376	0.4	(0.2–0.8)	0.01	227	0.3	(0.1–0.7)	0.004
IIb. Non-Hodgkin lymphomas[c]	233	Ref	221	0.5	(0.3–0.7)	<0.001	132	0.4	(0.3–0.7)	0.001
IIc. Burkitt lymphomas	137	Ref	131	0.6	(0.3–1.2)	0.13	70	0.5	(0.2–1.3)	0.16
IId–IIe. Other and unspecified lymphomas[d]	3	Ref	5	NA			5	NA		
III. CNS tumours (malignant only)	634	Ref	683	1.1	(1.0–1.3)	0.09	487	0.7	(0.6–0.9)	0.001
IIIa. Ependymomas	102	Ref	104	0.9	(0.6–1.4)	0.57	50	0.5	(0.3–0.9)	0.02
IIIb/d. Astrocytomas and gliomas	266	Ref	301	1.7	(1.4–2.2)	<0.001	226	1.2	(0.9–1.6)	0.13
IIIb. Astrocytomas[e]	*206*	*Ref*	*156*	*1.0*	*(0.7–1.3)*	*0.87*	*107*	*1.1*	*(0.8–1.5)*	*0.55*
IIIc. Embryonal tumours	189	Ref	233	1.0	(0.8–1.3)	0.92	148	0.6	(0.4–0.8)	0.001
IIIe–IIIf. Other and unspecified CNS tumours	77	Ref	45	0.6	(0.4–1.0)	0.07	63	0.2	(0.1–0.3)	<0.001
III. CNS tumours, including pilocytic astrocytomas[b]	*878*	*Ref*	*1039*	*1.0*	*(0.9–1.1)*	*0.90*	*703*	*0.7*	*(0.6–0.8)*	*<0.001*
IV. Neuroblastoma	220	Ref	251	0.8	(0.6–1.0)	0.049	151	0.7	(0.5–1.0)	0.05
IVa. Neuroblastoma[f]	194	Ref	229	0.7	(0.5–1.0)	0.02	140	0.6	(0.4–0.8)	0.003
V. Retinoblastoma[d]	108	Ref	112	NA			71	NA		
VI. Renal tumours	255	Ref	273	0.8	(0.5–1.3)	0.35	134	0.6	(0.3–1.1)	0.09
VIa. Nephroblastoma[g]	221	Ref	264	0.8	(0.5–1.3)	0.36	129	0.6	(0.3–1.3)	0.18
VII. Hepatic tumours	58	Ref	74	0.5	(0.3–1.0)	0.045	33	0.7	(0.3–1.4)	0.29
VIIa. Hepatoblastoma[g]	34	Ref	56	0.2	(0.1–0.6)	0.003	23	0.5	(0.2–1.4)	0.20
VIII. Bone tumours	277	Ref	348	0.7	(0.5–0.9)	0.01	212	0.6	(0.5–0.9)	0.01
VIIIa. Osteosarcomas[g]	141	Ref	163	0.7	(0.5–1.0)	0.05	96	0.7	(0.4–1.0)	0.06
VIIIb. Chondrosarcomas[d]	8	Ref	7	NA			3	NA		
VIIIc. Ewing bone sarcomas[g]	89	Ref	120	0.7	(0.5–1.2)	0.19	90	0.5	(0.3–0.8)	0.004
VIIId–VIIIe. Other and unspecified bone tumours[d]	24	Ref	43	NA			21	NA		
IX. Soft tissue sarcomas	353	Ref	343	0.9	(0.7–1.1)	0.25	215	0.7	(0.5–1.0)	0.03
IXa. Rhabdomyosarcomas[g]	181	Ref	161	0.6	(0.4–0.9)	0.01	105	0.5	(0.3–0.8)	0.001
IXb–IXe. Other and unspecified soft tissue sarcomas[g]	123	Ref	153	1.2	(0.8–1.9)	0.46	102	0.7	(0.4–1.1)	0.13
X. Germ cell and gonadal tumours	267	Ref	240	0.7	(0.4–1.2)	0.20	156	0.2	(0.1–0.6)	0.001
Xa. Intracranial and intraspinal germ cell tumours	48	Ref	41	0.6	(0.2–1.5)	0.26	29	0.3	(0.1–1.2)	0.08
Xc. Gonadal germ cell tumours: testis[g]	101	Ref	83	0.8	(0.3–2.4)	0.22	62	0.2	(0.3–2.4)	0.72
Xc. Gonadal germ cell tumours: ovary[d]	44	Ref	50	NA			29	NA		
Xb, Xd–Xe. Other and unspecified germ cell tumours	64	Ref	59	0.9	(0.4–1.9)	0.84	34	0.5	(0.1–1.9)	0.33
XI. Other epithelial tumours	290	Ref	375	0.7	(0.4–1.1)	0.14	214	0.7	(0.4–1.2)	0.21
XIb. Thyroid carcinomas[d]	85	Ref	84	NA			69	NA		
XIb. Differentiated thyroid carcinomas[d]	24	Ref	47	NA			45	NA		
XIb. Medullary thyroid carcinomas[d]	41	Ref	17	NA			13	NA		
XId. Malignant melanomas[g]	110	Ref	170	0.5	(0.2–1.5)	0.25	74	0.8	(0.3–2.7)	0.76
XIa, XIc, XIe–XIf. Other and unspecified	85	Ref	108	0.7	(0.4–1.2)	0.18	63	0.5	(0.2–1.1)	0.08
XII. Other and unspecified[d]	8	Ref	12	NA			11	NA		

HR, hazard ratio; CI, confidence interval; ICCC, International Classification of Childhood Cancer; CNS, central nervous system.

[a] Adjusted for gender (boys/girls), age (continuous, years) and duration of follow-up (categorical, years).

[b] Including pilocytic astrocytomas, other CNS tumours having a behaviour code/0 and/1 and completely registered since 2000 only were excluded.

[c] Adjusted for gender, age, duration of follow-up and Ann Arbor stage; patients with unknown Ann Arbor stage were excluded from this analysis (ICCC-3 diagnostic group IIa, N = 9; IIb, N = 65).

[d] Regression analyses were not conducted because estimation of reliable HRs was not possible because of insufficient numbers of events ($N_{event} < 15$ for the entire study period).

[e] Adjusted for gender, age, duration of follow-up and degree of malignancy; patients with an unknown degree of malignancy were excluded from this analysis (N = 10).

[f] Adjusted for gender, duration of follow-up and stage at diagnosis, but not adjusted for age because age was included in the stage classification; patients with unknown disease stage were excluded from this analysis (N = 38).

[g] Adjusted for gender, age, duration of follow-up and stage at diagnosis; patients with unknown disease stage were excluded from this analysis (ICCC-3 diagnostic group VIa, N = 34; VIIa, N = 9; VIIIa, N = 14; VIIIc, N = 18; IXa, N = 35; IXb-e, N = 51; Xc-testis, N < 5; XId, N = 31).

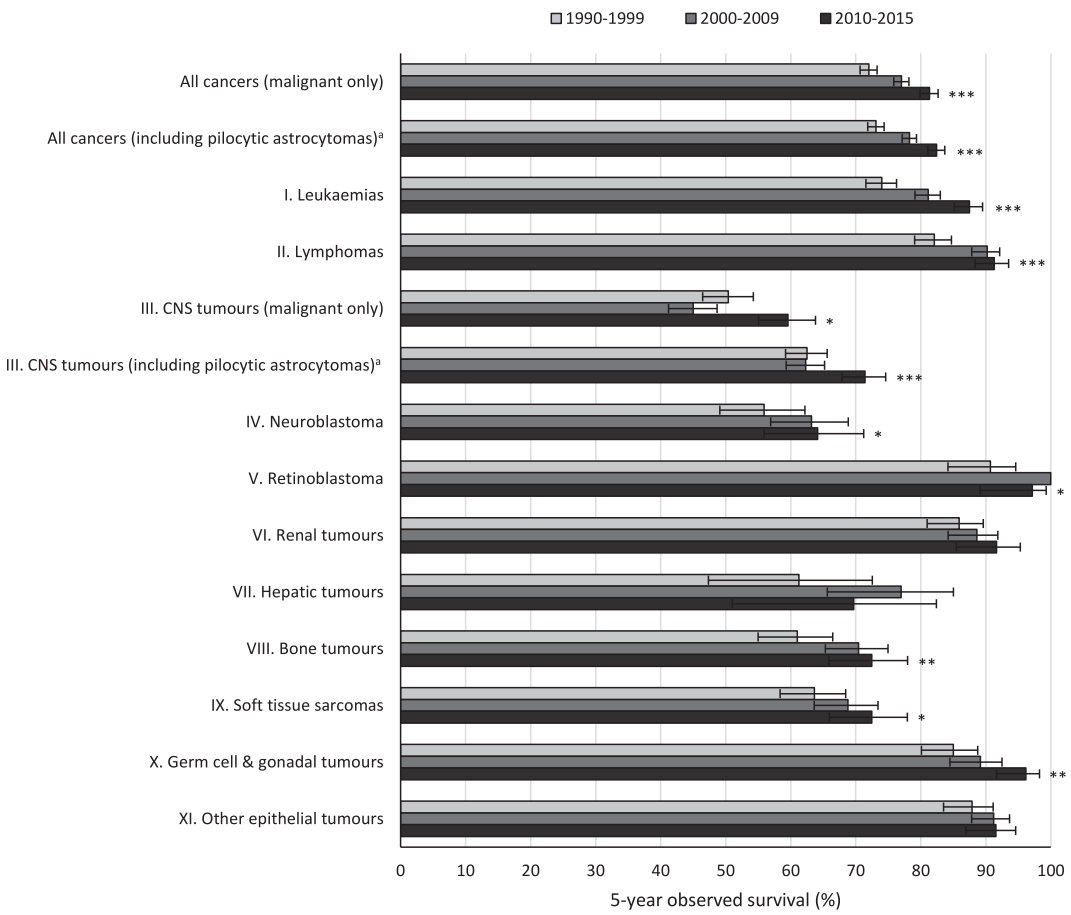

Fig. 2. Overview of time trends in 5-year observed survival of childhood and young adolescent cancer in the Netherlands by ICCC-3 diagnostic group, 1990–2015 (Source: The Netherlands Cancer Registry). The error bars depict 95% confidence intervals of the survival estimates. [a] Including pilocytic astrocytomas, other CNS tumours having a behaviour code/0 or/1 and completely registered since 2000 only were excluded. * p_{trend} over the diagnostic periods <0.05. ** p_{trend} over the diagnostic periods <0.01. *** p_{trend} over the diagnostic periods <0.001. CNS, central nervous system; ICCC, International Classification of Childhood Cancer.

Multivariable regression analysis for the risk of dying within five years of diagnosis, adjusted for follow-up time, age and gender, showed a significantly reduced HR for all malignant childhood cancers combined in the periods 2000–09 (HR = 0.8) and 2010–15 (HR = 0.6), using 1990–99 as reference (Table 2).

3.2. Survival trends in patients with haematological malignancies

Since the 1990s, 5-year OS of leukaemia has significantly improved by 14 percent points, reaching 88% for children diagnosed in 2010–15, whereas 10-year OS has increased by 12 percent points, reaching 83% (Table 1, Fig. 2). For lymphoid leukaemias, 5-year OS rose from 81% to 91%. The largest improvements in 5-year OS were seen for acute myeloid leukaemia (50–76%) and chronic myeloproliferative diseases (mostly chronic myeloid leukaemia; 30–91%). The risk of dying from leukaemia significantly decreased in the most recent time periods (2000–09: HR = 0.7; 2010–15: HR = 0.4) compared with 1990–99 (Table 2).

Significant improvements of 9 and 8 percent points in 5-year and 10-year OS, respectively, were seen for lymphomas, reaching 91% and 88%, respectively (Table 1, Fig. 2). Although the prognosis of Hodgkin lymphomas was already good in 1990–99, 5-year OS significantly increased further to 97% in 2010–15. The increase in 5-year OS was particularly evident for Ann Arbor stage II (Fig. 3). A marked improvement in survival was observed for non-Hodgkin lymphomas with 5-year OS increasing from 69% in 1990–99 to 85% in the latest period. The improvement in 5-year OS seemed to be confined to Ann Arbor stages II and III (Fig. 3). Multivariable-adjusted regression analysis showed a significantly reduced HR of dying for Hodgkin (2000–09: HR = 0.4; 2010–15: HR = 0.3) and non-Hodgkin (2000–09: HR = 0.5; 2010–15: HR = 0.4) lymphomas (Table 2).

3.3. Survival trends in patients with CNS tumours

A significantly increased survival for malignant CNS tumours was only detected for 5-year OS, which

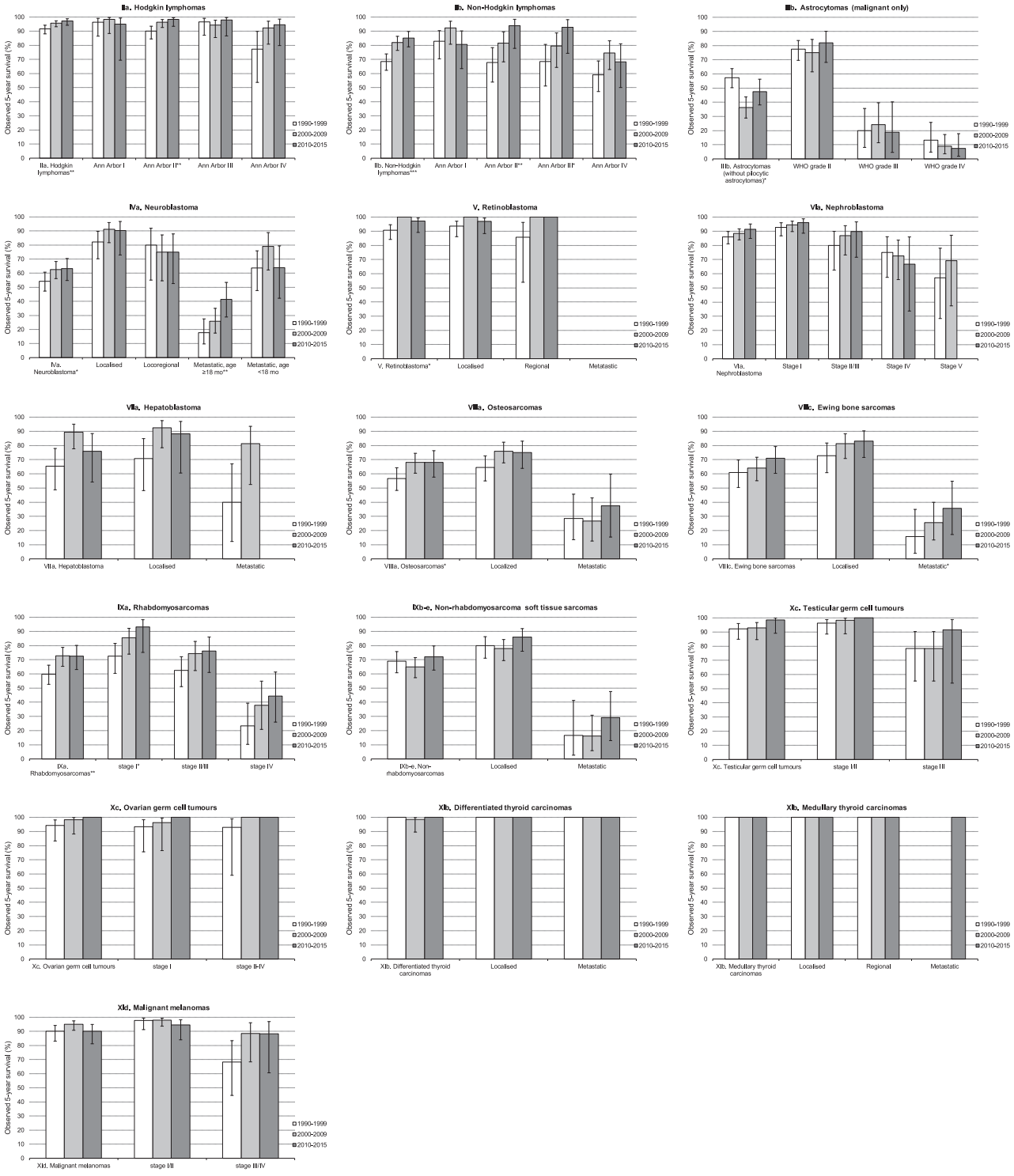

Fig. 3. Time trends in 5-year observed survival of childhood and young adolescent cancer by stage at diagnosis in the Netherlands, 1990–2015 (Source: The Netherlands Cancer Registry). The error bars depict 95% confidence intervals of the survival estimates. * p_{trend} over the diagnostic periods <0.05. ** p_{trend} over the diagnostic periods <0.01. *** p_{trend} over the diagnostic periods <0.001.

improved from 50% in the 1990s to 60% in 2010–15 (Table 1, Fig. 2). Improvements were observed for ependymomas, embryonal tumours and other and unspecified CNS tumours. The period survival estimate indicated that 10-year survival of malignant CNS tumours increased after 2009. Noteworthy is the temporary decline in 5-year OS of malignant CNS tumours between 1990–99 and 2000–09, followed by an increase

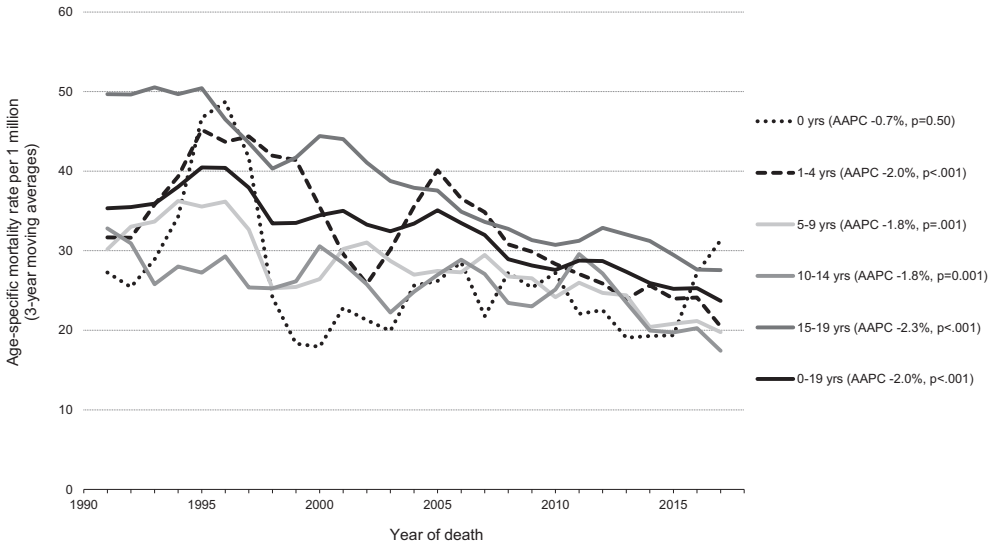

Fig. 4. Time trends in cancer mortality among 0- to 19-year-old children and young adolescents, overall and by age at death, in the Netherlands, 1990–2018 (Source: Statistics Netherlands). AAPC, average annual percentage change.

in the latest period (Table 1). This pattern was mainly observed for astrocytomas and gliomas with a decrease in 5-year OS from 57% to 37%. Within this group, a shift occurred in the distribution of the WHO grades between 1990–99 and 2000–09: the proportion of grade II tumours markedly decreased, whereas the proportion of grade IV tumours almost doubled (Supplementary Fig. S1). The 5-year OS for WHO grade IV tumours decreased from 13% in 1990–99 to 7% in 2010–15 (not significant, Fig. 3).

The risk of dying from all malignant CNS tumours, ependymomas, embryonal tumours and other and unspecified CNS tumours significantly decreased in 2010–15 (HR = 0.7, HR = 0.5, HR = 0.6 and HR = 0.2, respectively) (Table 2).

3.4. Survival trends in patients with non-CNS embryonal tumours

Concerning neuroblastoma (i.e. ICCC-3 diagnostic subgroup IVa), a significant increase was observed in 5-year and 10-year OS (both +9 percent points), reaching 63% and 61%, respectively (Table 1). This improvement was especially observed in children aged ≥18 months (Fig. 3). OS of retinoblastoma also improved over time and approached 100%. The prognosis of renal tumours did not change markedly, but was favourable during the entire period. For hepatic tumours, OS fluctuated over time without a clear pattern.

Multivariable regression analyses using 1990–99 as reference showed a reduced HR of dying from neuroblastoma (IVa) in the periods 2000–09 (HR = 0.7) and 2010–15 (HR = 0.6) and from hepatic tumours in 2000–09 (HR = 0.5) (Table 2).

3.5. Survival trends in patients with bone tumours and soft tissue sarcomas

Since the 1990s, 5-year and 10-year OS for bone tumours significantly improved by 11 and 13 percent points, respectively, reaching 5-year OS of 72% and 10-year OS of 69% in 2010–15 (Table 1, Fig. 2). The largest OS improvement was observed for osteosarcomas. For other subgroups, no statistical significance was reached. Regarding stage at diagnosis, trends in 5-year OS of localised and metastatic osteosarcomas and Ewing bone sarcomas were in the positive direction, but only reached statistical significance for metastatic Ewing bone sarcomas (Fig. 3).

For soft tissue sarcomas, 5-year OS improved from 64% in 1990–99 to 73% in 2010–15 (Table 1, Fig. 2). The period survival estimate suggested an increase in 10-year OS after 2009, reaching 74% in 2010–15. The improvement in 5-year OS was observed for rhabdomyosarcomas only. Although the prognosis improved across all disease stages, statistical significance was only attained for stage I rhabdomyosarcomas (Fig. 3).

The risk of dying using 1990–99 as reference decreased for all bone tumours combined and rhabdomyosarcomas in the periods 2000–09 (HR = 0.7 and HR = 0.6, respectively) and 2010–15 (HR = 0.6 and HR = 0.5, respectively). For Ewing bone sarcomas, the reduced mortality risk was restricted to the period 2010–15 (HR = 0.5, Table 2).

3.6. Survival trends in patients with epithelial and other childhood cancers

A significant improvement of 11 percent points in 5-year OS was seen for germ cell and gonadal tumours,

reaching 96% for patients diagnosed in 2010–15. Ten-year OS improved from 84% in 1990–99 to 95% in 2010–15 (Table 1, Fig. 2). Remarkable is the survival improvement for intracranial and intraspinal germ cell tumours. The prognosis of testicular and ovarian germ cell tumours and other epithelial tumours did not change significantly over the time period studied, but their survival was already close to or exceeded 90%. Early stages of testicular and ovarian germ cell tumours had an excellent prognosis during the entire study period with a 5-year OS of 100% in 2010–15. The same was observed for thyroid carcinomas. Finally, an improvement in 5-year OS of stage III/IV malignant melanomas was detected (from 68% in 1990–99 to 88% in 2010–15), whereas stage I/II malignant melanomas had already a favourable prognosis in 1990–99 (Fig. 3).

For germ cell and gonadal tumours, the multivariable-adjusted HR of dying was significantly reduced when comparing 2010–15 with 1990–99 (HR = 0.2, Table 2).

3.7. Mortality trends in children and young adolescents with cancer

Fig. 4 presents trends in cancer mortality in the Netherlands between 1990 and 2018 among children and young adolescents (0–19 years). Overall, cancer mortality decreased by 2.0% annually from 37 per million person-years in 1990 to 20 in 2018. This significant decline extended over all age groups with AAPC values ranging from −2.3% for 15- to 19-year-olds to −1.8% for 5 to 9 and 10 to 14-year-olds, except for infants where the mortality trend remained stable over time. Of the total 3449 childhood and young adolescent cancer deaths between 1990 and 2018, 1189 were due to haematological malignancies (936 leukaemia and 253 lymphoma), 1015 to CNS tumours, 1212 to non-CNS (extracranial) solid tumours and 33 to an unknown primary site. Age-specific mortality trends for leukaemias, lymphomas, CNS tumours and non-CNS solid tumours are visualised in Supplementary Fig. S2. From the age of 1 year, mortality due to haematological malignancies (leukaemias and lymphomas) and non-CNS solid tumours generally declined in subsequent age groups. For CNS tumours, the decrease in mortality seemed to be restricted to 15- to 19-year-olds.

4. Discussion

This is the first nationwide, population-based study on time trends in survival and mortality of childhood and young adolescent cancer in the Netherlands. Since the 1990s, the OS of malignant cancers has improved, reaching 81% 5 years after diagnosis and 78% after 10 years. This improvement was observed for both genders, all age groups and most diagnostic (sub)groups and was particularly pronounced for advanced disease. The increasing OS was supported by steadily decreasing mortality rates among all age groups, except infants. However, the prognosis of patients with malignant CNS tumours, neuroblastoma and osteosarcomas remains unfavourable.

Our results for the Netherlands are in line with findings of large population-based studies from Europe showing increasing trends in 5-year OS of childhood and young adolescent cancer with rates approximating 75–80% around 2000 [2,18]. In addition, survival estimates of the most common ICCC-3 diagnostic groups (5-year OS 2010–15: 88% for leukaemias, 91% for lymphomas and 60% for malignant CNS tumours [71% including pilocytic astrocytomas]) were in accordance with rates reported in Europe as a whole and individual European countries, as is shown in a selected overview in Supplementary Table S3. With respect to non-CNS solid tumours, the present observations were generally similar as previously published Europe-wide results as well [2,18]. Survival comparisons of CNS tumours across countries are hampered by differences in diagnosis, classification and registration practices (inclusion or exclusion of borderline and benign tumours) and should take the incidence of the various subtypes into account [2,7]. The drop in OS of astrocytomas and gliomas for patients diagnosed in 2000–09 might be attributable to refined diagnostics, that is, imaging, and—in comparison with the 1990s—increasing completeness of registration of CNS tumours with a very poor prognosis. This is reflected by the increasing incidence of brain stem tumours with a dismal outcome and a shift in the classification of these tumours from 'other and unspecified CNS tumours' (i.e. ICCC-3 diagnostic group IIIe–IIIf) to 'gliomas, not otherwise specified (NOS)'. Furthermore, optic nerve tumours with a favourable prognosis were mainly classified as 'pilocytic astrocytomas' in 2000–09 whereas as 'Gliomas, NOS' in 2010–15 and were therefore increasingly considered to be malignant in the latter period (Hoogendijk R, personal communication).

This study showed an increase in survival of young patients with cancer in the Netherlands, which was especially evident for patients with advanced stages. The improved prognosis of advanced disease can partially be attributed to advances in diagnostic technologies, which on the one hand led to better tumour localisation and severity assessment, but also may have resulted in stage migration and thus artificial increases in stage-specific survival by upstaging [6,7,19]. During 1990–2017, stage migration towards advanced disease has been observed in the Netherlands in children and young adolescents diagnosed with Hodgkin lymphomas, rhabdomyosarcomas and non-rhabdomyosarcoma soft tissue sarcomas [7].

At the group level, we observed increases in survival and substantially decreased HRs of dying over time for

most of the diagnostic (sub)groups. Therefore, progress has undoubtedly been made in the treatment of paediatric cancer, for example, by improved classification of tumours, development of new effective (chemo)therapeutic agents, better use of (combinations of) classical treatments in a risk-stratified and/or response-adapted fashion and improved supportive care [20–27]. For example, the optimal use of anti-leukaemic agents, progress in supportive care and precise risk assessment have been listed as important contributors to the improved outcome of paediatric patients with acute lymphoblastic leukaemia (ALL) [21,24], whose 5-year OS in the Netherlands reached 91% in 2010–15.

Finally, concentration of paediatric oncologic care may have had a favourable influence on the prognosis of young patients with cancer [28,29]. Reedijk et al. [10] showed that between 2004 and 13, 82% of children and young adolescents diagnosed with cancer in the Netherlands were treated in paediatric oncology centres. The proportion of 15- to 17-year-old patients who were referred to a paediatric oncologist increased markedly over time from 33% to 54%. Coincidentally, the largest survival improvement was observed among these patients following previous results for ALL and Hodgkin lymphoma [30,31].

The improved survival of patients with childhood and young adolescent cancer in the Netherlands between 1990 and 2015 coincided with a decline in mortality and a minimal increase in incidence, supporting that true progress has been made [7,32,33]. Furthermore, increases in 5-year OS were not exclusive to the most incident paediatric cancers (i.e. leukaemias, lymphomas and CNS tumours) and were observed for the vast majority of the main ICCC-3 diagnostic groups.

A major strength of this study is the use of quality controlled, population-based data from the NCR, which registers all morphologically verified cancers diagnosed in each hospital in the Netherlands. In addition to overall 5-year and 10-year survival, we also presented survival estimates for several subgroups, including stage at diagnosis. Stage-specific survival of childhood and young adolescent cancer has seldom been reported before. Finally, tumours that were only consistently registered during part of the study period were excluded to reduce the effect of registration artefacts. The limitations encompass the missing stage information for some tumours and changes in stage registration over time.

5. Conclusion

Significant progress has been realised in the prognosis of childhood and young adolescent cancer in the Netherlands since the 1990s. This was demonstrated by increases in survival of most tumours and accompanying decreases in the multivariable-adjusted risk of dying. The increase in survival was also reflected in the markedly declining cancer mortality rates. Survival improvements were especially evident for patients with advanced stages.

Author contribution

H.E.K-K., L.C.M.K., J.W.C. and R.P. conceived and designed the study. M.S. and H.E.K-K. did the literature search. H.E.K-K. prepared the database and carried out the analysis. M.S. and H.E.K-K. drafted the manuscript. All authors contributed to the interpretation of the results and critically revised the manuscript. M.S. and H.E.K-K. directly accessed and verified the raw data and take responsibility for the integrity and accuracy of the analyses. All authors had full access to all the data reported in the study and accept responsibility to submit the article for publication.

Data statement

The data that support the findings of this study are available on request from the Netherlands Cancer Registry and Statistics Netherlands. To obtain data of children diagnosed with cancer in the Netherlands since 2014, an additional permission from the Biobank and Data Access Committee of the Princess Máxima Center for Pediatric Oncology is required. Further information is available from the corresponding author on request.

Conflict of interest statement

The authors declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2021.08.001.

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