Progress against childhood and young adolescent cancer in the Netherlands since 1990

Ardine M.J. Reedijk

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Voortuitgang in de strijd tegen kanker bij kinderen en adolescenten in Nederland sinds 1990
(met een samenvatting in het Nederlands)

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Leef!

en geniet

– geinspireerd op Leef! van Laura Maaskant

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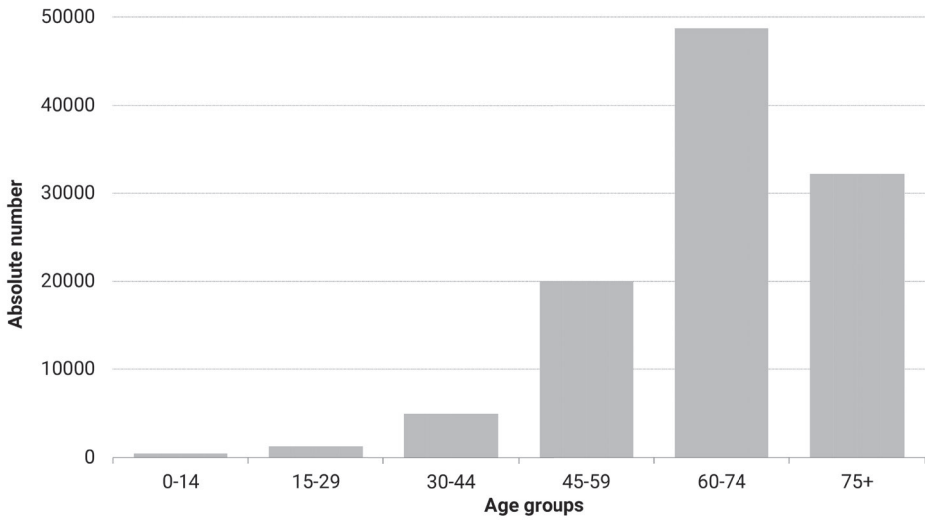
CHAPTER 1

General introduction and outline of this thesis

In the Netherlands, almost 460 children and 145 young adolescents were diagnosed with cancer in 2015 (definition; children: age at diagnosis <15 years and young adolescents: age at diagnosis 15-17 years). This is less than 2% of the total cancer occurrence, **figure 1.1**. Despite its rarity, cancer remains an important burden of disease in children and young adolescents, because it is the leading cause of disease-related mortality for children and adolescents in developed countries.[1,2] Moreover, the incidence of childhood cancer is, albeit modestly, increasing worldwide, and modest survival variation exists between European countries.[3-6] Recent national trend analyses in incidence, treatment patterns, survival, and mortality from childhood and young adolescent cancer are lacking for the Netherlands.



Source: website of the Netherlands Cancer Registry
Figure 1.1 Number of patients diagnosed with cancer in 2015 by age group

Childhood and young adolescent cancers: types and pathogenesis

Childhood cancer is not one disease, there are over 100 subtypes, grouped into 12 main diagnostic groups. The types of cancer affecting children and adolescents are quite different from the cancers affecting adults. The childhood cancers are also differently distributed depending on the age of the child or young adolescent. Embryonal tumours such as neuroblastoma, nephroblastoma, retinoblastoma, medulloblastoma, rhabdomyosarcoma and teratomas predominantly occur in children, some already in infants. These tumours originate in the embryonal development in utero as a consequence of unrepaired random mutations.[7,8] Epithelial malignancies, or carcinomas, on the other hand are very uncommon in children. These malignancies usually occur after long-time exposure to risk factors like smoking, alcohol consumption, excessive

sun exposure and overweight, which is not applicable to childhood cancers. All in all, the underlying mechanisms of childhood cancers are largely unknown. Some associations with other syndromes or cancer-predisposing genes exists, but they explain less than 10% of the cancers in this young age group.[9]

The main groups of childhood cancer, defined according to the international classification of childhood cancers (ICCC-3)[10], are listed in **table 1.1**, together with the subtypes that are studied in more detail for this thesis. Haematological malignancies are the most common types of childhood and young adolescent cancers and comprise the diagnostic groups I Leukaemias and II Lymphomas. The diagnostic group III CNS and miscellaneous intracranial and intraspinal neoplasms represents the brain tumours. All tumours in the other diagnostic groups are so called solid tumours.

Leukaemias originate from the lymphoid progenitors (acute lymphoblastic leukaemias (ALL)) or myeloid progenitors (acute myeloid leukaemias (AML)) of blood cells. Normal haematopoiesis mostly resides in the bone marrow, where multipotential hematopoietic stem cells can give rise to either myeloid or lymphoid progenitors. The progenitors further develop into the different blood cell types. Due to a differentiation arrest, hyperproliferation and accumulation in one of the differentiation stages, uncontrolled expansion of leukemic blasts might occur.

Lymphoma, on the other hand, is not just one disease but a group of cancers that originate in lymphocytes. Both types of lymphocytes, B- and T-cell lymphocytes, may undergo a malignant change and become one of the subtypes of non-Hodgkin lymphomas (NHL). Hodgkin lymphoma (HL) is distinguished from the other lymphoma types because of the presence of Reed-Sternberg cells, mature B-cell lymphocytes that are unusually large. Lymphomas often begin in the lymph nodes, but may rise in any organ of the body and are often suspected or even diagnosed by a variety of organ specialists.

Neuroblastoma (NBL) is a cancer of specialized nerve cells, called neural crest cells, involved in the development of the adrenal medulla, sympathetic ganglia and other autonomic sites. Neuroblastoma occurs in the adrenal glands in the abdomen or in the prevertebral sympathetic ganglia. The pathogenesis of other solid tumours and brain tumours will be omitted in this introduction.

Table 1.1 Groups of childhood cancers and some general descriptive

Main groups	General descriptive		Distribution age groups (years)
I Leukaemias, myeloproliferative diseases, and myelodysplastic diseases	age characteristics	peak <5 years	
	gender distributions (m:f ratio)	1.2	
	average number of patients per year	155	
acute lymphoblastic leukaemia (ALL) ***(Chapter 4)***	age characteristics	peak at 1-4 years	
	gender distributions (m:f ratio)	1.3	
	average number of patients per year	114	
acute myeloid leukaemia (AML) ***(Chapter 5)***	age characteristics	peak at 0 years	
	gender distributions (m:f ratio)	1.1	
	average number of patients per year	26	
II Lymphomas and reticuloendothelial neoplasms	age characteristics	occurs mainly in teenagers	
	gender distributions (m:f ratio)	1.5	
	average number of patients per year	88	
Hodgkin Lymphoma (HL) ***(Chapter 6)***	age characteristics	occurs mainly in teenagers	
	gender distributions (m:f ratio)	1.0	
	average number of patients per year	36	
Non-Hodgkin Lymphoma and Burkitt lymphoma (taken together as NHL) ***(Chapter 7)***	age characteristics	occurs mainly in teenagers	
	gender distributions (m:f ratio)	2.0	
	average number of patients per year	38	
III CNS and miscellaneous intracranial and intraspinal neoplasms	age characteristics	many types with own age peaks	
	gender distributions (m:f ratio)	1.0	
	average number of patients per year	162	
IV Neuroblastoma and other peripheral nervous cell tumours (NBL) (***Chapter 8)***	age characteristics	peak <5 years	
	gender distributions (m:f ratio)	1.1	
	average number of patients per year	25	

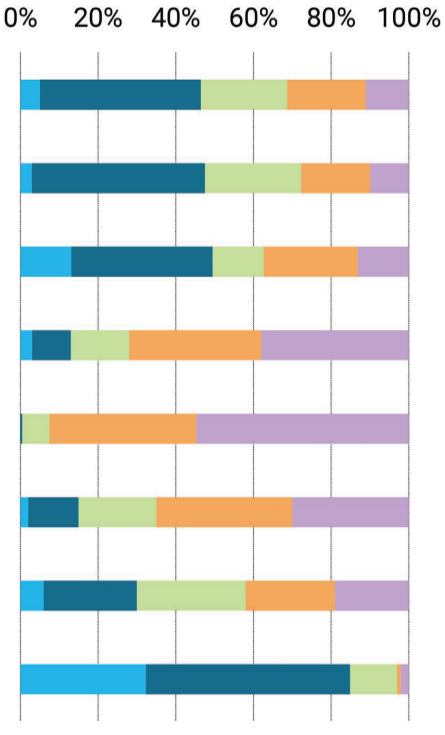
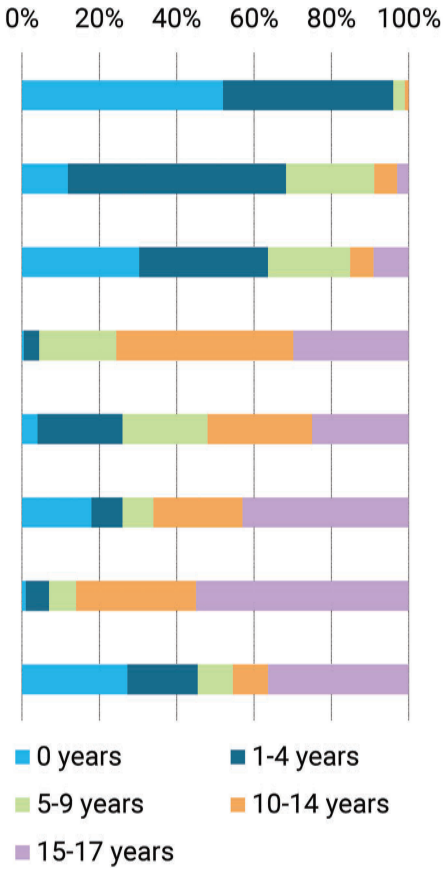


Table 1.1 Groups of childhood cancers and some general descriptive *continued*

Main groups	General descriptive		Distribution age groups (years)
V Retinoblastoma	age characteristics	peak at 0 years	
	gender distributions (m:f ratio)	2.0	
	average number of patients per year	16	
VI Renal tumours	age characteristics	peak <5 years	
	gender distributions (m:f ratio)	0.9	
	average number of patients per year	23	
VII Hepatic tumours	age characteristics	peak <5 years	
	gender distributions (m:f ratio)	1.2	
	average number of patients per year	6	
VIII Malignant bone tumours	age characteristics	occurs mainly in teenagers	
	gender distributions (m:f ratio)	1.1	
	average number of patients per year	36	
IX Soft tissue and other extraosseous sarcomas	age characteristics	no specific age peak	
	gender distributions (m:f ratio)	1.6	
	average number of patients per year	39	
X Germ cell tumours, trophoblastic tumours, and neoplasms of gonads	age characteristics	peak at 0 years and teenagers	
	gender distributions (m:f ratio)	1.6	
	average number of patients per year	28	
XI Other malignant epithelial neoplasms and malignant melanomas	age characteristics	occurs mainly in teenagers	
	gender distributions (m:f ratio)	0.6	
	average number of patients per year	46	
XII Other and unspecified malignant neoplasms	age characteristics	very infrequent	
	gender distributions (m:f ratio)	0.4	
	average number of patients per year	2	



Source: data from the Netherlands Cancer Registry.

Childhood and young adolescent cancer care in the Netherlands

National guidelines for diagnosis and treatment of childhood leukaemia started in 1972 for children with ALL. The first national treatment protocol for AML was introduced in 1982 and for different types of NHL in 1994. Protocol committees from the Dutch Childhood Leukemia Study Group (DCLSG) updated their multi-modality treatment protocols based on their own results and results from other childhood cancer groups worldwide.

Until 2002 some treatment protocols included patients aged ≤14 years at diagnosis and some up to 18 years. Thereafter the paediatric oncologists, supported by the parent association, increasingly treated adolescents with cancer up to the age of 18 years. With the transition from DCLSG to Dutch Childhood Oncology Group (DCOG) in 2003, the treatment for HL, solid tumours and brain tumours was harmonized between the 7 paediatric oncology centres. More than 40 multidisciplinary protocol committees for specific types of cancer came into existence within the DCOG. The patients treated according to such a DCOG treatment protocol are participating in a clinical trial. Randomized controlled phase 3 clinical trials are the gold standard to assess the efficacy of new (combinations of) therapies.

In 2014, the care for children with solid tumours was centralized in the new national childhood cancer centre, the Princess Máxima Center for Pediatric Oncology in Utrecht, followed by the other cancer types in 2018. In that year, the former 7 centres for paediatric oncology were closed.

Data sources applied in the work described in this thesis

The research presented in this thesis was based on data from three registries, the DCLSG/DCOG, the Netherlands Cancer Registry (NCR), and Statistics Netherlands. Since 1972, data on childhood leukaemia is collected by the DCLSG, based on verification of the diagnosis in a central laboratory. Leukaemia specific data regarding subtype and treatment protocol were obtained from the DCLSG/DCOG registry. From 2003 onwards the DCOG started its own basis clinical registry, for all patients seen and treated by the paediatric oncologists in the seven paediatric oncology centres. Data managers collect information on patient and tumour characteristics from medical records.

The NCR is hosted by the Netherlands Comprehensive Cancer Organisation (IKNL). Preceded by, among others, the Eindhoven Cancer Registry which became complete since the early 1970s[11], the nationwide population-based NCR became operational in 1989. The NCR's primary notification source is the Nationwide Network and Registry of Histopathology and Cytopathology

(PALGA), supplemented with data from the National Registry of Hospital Discharge Diagnoses (LMR). The NCR records a minimal dataset for every newly diagnosed cancer patient. Trained registrars of the NCR collect data through medical records review, according to standardized procedures set by the NCR, which follows guidelines of the World Health Organisation (WHO) and the International Association of Cancer Registries (IACR). The dataset includes information on patient (date of birth, sex), tumour (morphology, topography, stage of the tumour) and general categories of primary treatment characteristics. The NCR is one of the few registries in the world that also registers stage and initial treatment. Information on vital status (i.e., alive, dead or emigration) is obtained by annual linkage of the NCR with the Nationwide Population Registries Network that provides vital statistics of all Dutch residents; follow-up is accurate and complete. The NCR provides pseudonymized data on all cancer patients at a national level, regardless of age and collected at all possible sites of treatment since 1989.

Statistics Netherlands holds a registration based on causes of death from all deceased persons registered in the Netherlands since 1901. The (formerly called primary) cause of death is the disease or injury which started the chain of morbid events leading to death and is determined by the attending physician and anonymously registered on a cause of death certificate.[12] Causes of death are accessible via Statistics Netherlands as tables, by year of death, sex, area and age at death (0 years, 1-4 years and 5-9 years, 10-14 years up to 95+).

Definitions for (epidemiological) outcome studies on childhood cancer

Clinical trials have improved outcome of childhood and young adolescent cancer patients substantially. Since 2003, most of the children and adolescents with cancer are treated according to a DCOG treatment protocol and are registered in a clinical trial database and in the DCOG basis registry. On the other hand there are population-based registries, like the NCR. The essential features of clinical trials and population-based registries are presented in **table 1.2**. Randomized clinical trials and population-based observational studies have different objectives and outcome parameters.

Table 1.2 Clinical trials and population-based cancer registries in context

	Clinical cancer trials	Population-based cancer registries
Objectives	– Specific questions, which treatment is more effective (randomized groups) – On selected patient and tumour series	– Include all cases arising in a defined population – No age, tumour or hospital restrictions, registration according to international standards
Duration	– During limited periods	– Continuous, permanent
Data output	– Detailed standardised diagnostic data – Detailed information on treatments – Detailed information on outcomes: toxicities, adverse events, cause of death	– Standardised data on diagnosis – Succinct information on treatments – Vital status
Outcome measures	– Number of included patients – Tests for efficacy for given α and 1-β – Event Free Survival – Disease Free Survival – Overall Survival – Cumulative incidence of relapse – Numbers needed to treat	– Incidence rates/ year of diagnosis – Prevalence – Relative Survival – Overall Survival – Mortality rates/ year of death

The NCR participates in international epidemiological projects from for example Eurocare, ACCIS and CI 5.[3,5,13,14] The DCLSG participated in these projects in the 1990s.[14] These descriptive epidemiological studies report about trends in:

incidence; $\frac{\text{number of children and young adolescents with (a specific newly diagnosed) cancer}}{\text{total number of children and young adolescents in the population}}$

survival; the % of patients with (a specific) cancer alive at 5 or 10 years after diagnosis

mortality; $\frac{\text{number of deceased children and young adolescents with (a specific) cancer}}{\text{total number of children and young adolescents in the population}}$

Populations statistics are also accessible via Statistics Netherlands as tables by age (0 years, 1-4 years and 5-9 years, 10-14 years up to 95+), sex, area and year of interest.

As mentioned previously, recent national trend analyses in incidence, treatment patterns, survival, and mortality from childhood and young adolescent cancer are lacking for the Netherlands. Furthermore, international epidemiological comparison studies are also limited as they mostly group countries and only report about incidence, survival or mortality individually, and never combined. Nevertheless, these studies report increases in incidence, overall and

for several childhood cancer subgroups,[4] whereas 81% of European children with cancer are alive 5 years after diagnosis.[5,15] Furthermore, Bonaventura *et al.*[6] showed that the survival rate of children with AML in the Netherlands was only average compared to that in other European countries; whilst mortality rates were decreasing between 2000 and 2007 in surrounding European countries, that in the Netherlands remained stable.[1] Ranking survival percentages and mortality rates by country is not supposed to be a competition, but reasons for marked differences need to be investigated.

Conceptual framework for progress against cancer in this thesis

In **figure 1.2** the relationship between incidence, survival and mortality is depicted. Incidence, survival and mortality rates are summary measures that provide snapshots of a long-term process that is time-dependent. These outcome measures are useful to evaluate whether and where progress has been made by (earlier) cancer detection, improved diagnostics and treatment, and where further improvements might be needed. Optimal progress should be reflected in a stable or even decreasing incidence and/or improving survival accompanied by decreasing mortality.[16] By combining the three outcome measures per tumour a balanced discussion on progress against cancer is generated.

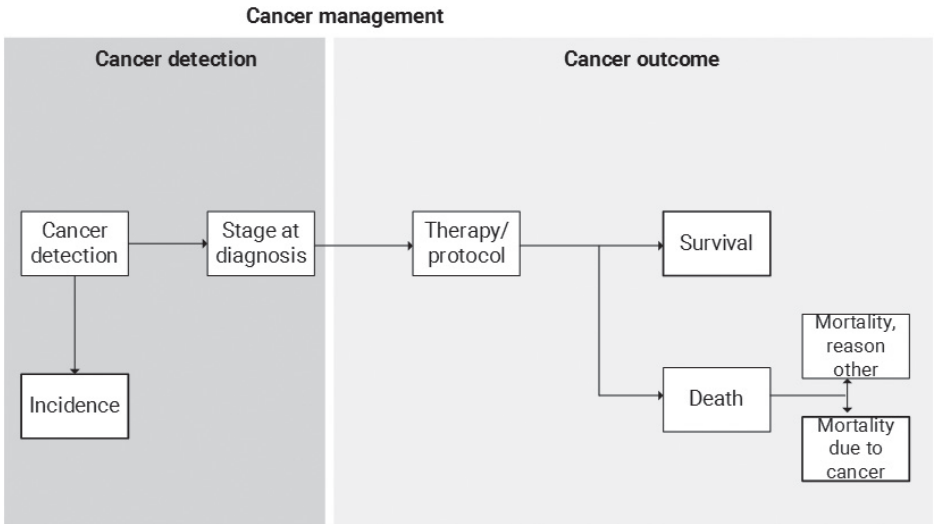


Figure 1.2 Schematic overview of the conceptual framework with the interplay between cancer detection and cancer outcome and the outcome measures used in thesis.
Incidence, survival and mortality due to cancer are the main parameters of interest. Inspired on figure 1.5 in the introduction of Henrike Karim-Kos' thesis (2012) and figure 1 in the discussion of Mieke Aarts' thesis (2012).

Differences in survival may be related to differences in stage at diagnosis and/or treatment, as depicted in **figure 1.2**. Furthermore, the cause-of-death data from Statistics Netherlands will be used as an independent 'rough' population-based source of outcomes for evaluating progress against the major types of childhood cancers.

Objective and outline of this thesis

The general objective of this thesis is to assess and clarify epidemiologic progress against childhood cancers occurring during the last decades in the Netherlands (1990-2015). This has been done by measuring and interpreting trends in incidence and stage at diagnosis, treatment and survival patterns, ultimately reflected in widening the gap between incidence and mortality. The resulting outcomes presented in this thesis will also serve as baseline measurement for the Princess Máxima Center for Pediatric Oncology, that has opened its doors for all children and young adolescents with cancer in 2018.

The two main research questions in this thesis are:

1. What are the trends in incidence for cancer in children and young adolescents, in general and for five of the main cancers?
2. What is the impact of changes in cancer management on paediatric and young adolescent cancer trends?

First, in **chapter 2**, we performed a methodological linkage study to confirm the diagnoses in the NCR with the diagnoses in the DCOG registry for children and young adolescents with cancer diagnosed during 2004-2013. This in order to report about the coverage of both registries. In **chapter 3** we summarize the trends in the overall and tumour-type specific incidence of childhood and young adolescent cancer with data from the NCR during 1990-2017.

The second part of this thesis describes trends in incidence, survival and mortality for the most common hematologic malignancies in childhood and young adolescence; ALL, AML, HL and NHL (**chapters 4-7)**. For these studies data are used from the NCR, DCOG and Statistics Netherlands during the diagnostic years 1990-2015. Incidence and outcome data of the most common embryonal tumour, neuroblastoma, are described in **chapter 8**, using data from the NCR during the period 1990-2014. In **chapter 9**, the main findings of these studies are discussed in the perspective of public health, clinical implications and recommendations for future research.

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CHAPTER 2

Site of childhood cancer care in the Netherlands

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ABSTRACT

Due to the complexity of diagnosis and treatment, care for children and young adolescents with cancer preferably occurs in specialised paediatric oncology centres with potentially better cure rates and minimal late effects. This study assessed where children with cancer in the Netherlands were treated since 2004.

All patients aged under 18 diagnosed with cancer between 2004 and 2013 were selected from the Netherlands Cancer Registry (NCR) and linked with the Dutch Childhood Oncology Group (DCOG) database. Associations between patient and tumour characteristics and site of care were tested statistically with logistic regression analyses.

This population-based study of 6,021 children diagnosed with cancer showed that 82% of them were treated in a paediatric oncology centre. Ninety-four percent of the patients under 10 years of age, 85% of the patients aged 10-14 and 48% of the patients aged 15-17 were treated in a paediatric oncology centre. All International Classification of Childhood cancers (ICCC), 3rd edition, ICCC-3 categories, except embryonal tumours, were associated with a higher risk of treatment outside a paediatric oncology centre compared to leukaemia. Multivariable analyses by ICCC-3 category revealed that specific tumour types such as chronic myelogenous leukaemia (CML), embryonal carcinomas, bone tumours other type than osteosarcoma, non-rhabdomyosarcomas, thyroid carcinomas, melanomas and skin carcinomas as well as lower-staged tumours were associated with treatment outside a paediatric oncology centre.

The site of childhood cancer care in the Netherlands depends on the age of the cancer patient, type of tumour and stage at diagnosis. Collaboration between paediatric oncology centre(s), other academic units is needed to ensure most up-to-date paediatric cancer care for childhood cancer patients at the short and long term.

INTRODUCTION

Children with cancer are treated in paediatric oncology units, other academic units or non-academic hospitals. Expert opinions and evidences suggest that specialised paediatric oncology care is essential to guarantee most up-to-date treatments (i.e. maximal cure rates and minimal late effects) for children and young adolescents with cancer.[1-6] Effective therapies have been developed for most types of paediatric cancers in the last decades.[5,7-13] Where and how to treat an adolescent cancer patient (15-19 years) is a difficult question because the adolescents can have specific childhood cancers, but also adult types of tumours. [14,15] Previous hospital-based studies showed better survival rates for adolescents and young adults with leukaemia treated on paediatric protocols compared to adult protocols.[16-18] Also patients older than 16 years with Wilms tumours can often be cured by multimodal treatment following the Society of Paediatric Oncology (SIOP) 93/ Society for Paediatric Oncology and Haematology (GPOH) protocol.[19]

The upper age limit for referral to a paediatric oncology centre differs among countries from 14 to 21.[1,3,19-23] In the Netherlands, parents and paediatric oncologists expressed the intention to treat children and young adolescents aged under 18 with cancer in a paediatric oncology centre. Population-based cancer registries in Ontario (Canada), Utah and Georgia (USA) as well as in France, Switzerland and the United Kingdom [UK] (Europe) showed that over 80% of children (≤14 years) and 32-65% of young adolescents (15-19 years) with cancer were treated in paediatric centres (**supplementary table S2.1**). [3,20,22-25] However no in-depth analyses on the type of tumour have been described.

The overall aim of this study was to investigate the trends in the site of treatment for children (0-17 years) with cancer in the Netherlands. Furthermore, differences in: (1) age groups, (2) gender, (3) time and (4) types of cancer were studied in relation to the site of treatment.

PATIENTS AND METHODS

Study population

To get insight into the trends in the site of treatment for children with cancer we identified children with cancer in the existing registries of the Netherlands Cancer Registry (NCR) and the tumour registry of the Dutch Childhood Oncology Group (DCOG) for a 10-year period since January 2004.

Netherlands Cancer Registry

Registration of patients with cancer is covered by the population-based NCR since 1989. Notification occurs primarily through the national registry of all pathology and haematology departments, with additional reporting by hospital discharge registries. Following notification, trained registration personnel collect relevant information from the medical records at the hospitals. The NCR showed a completeness of 96% of all patients diagnosed with cancer in the Netherlands.[26] In 2013, 81 general hospitals and eight academic centres were included, seven of the latter with a paediatric oncology centre.

Dutch Childhood Oncology Group tumour registry

Since 2003, children with cancer (aged under 18) treated in one of the seven paediatric oncology centres are registered in the DCOG tumour registry. Trained personnel collect relevant information from medical records. Until now there are no studies which evaluated the completeness of this registry.

Types of childhood cancer

Both registries (i.e. NCR and DCOG) code topography and morphology according to the International Classification of Diseases for Oncology (ICD-O), 3rd edition published by the World Health Organization (WHO) in 2000. The ICD-O codes were classified in main diagnostic groups and subgroups according to the international classification of childhood cancers (ICCC), 3rd edition.[27] This classification includes tumours with malignant behaviour, except for tumours of the central nervous system (CNS) and intracranial germ cell tumours, these tumours may have a non-malignant behaviour code. The number of ICCC-3 categories was reduced by combining: CNS tumours and intracranial/intraspinal germ cell tumours (ICCC main group III and ICCC group Xa), embryonal tumours (ICCC main groups IV-VII. Of note; this category also contains carcinomas and unspecified tumours (n = 31)), bone and soft tissue tumours (ICCC main groups VIII and IX), germ cell tumours, epithelial and other unspecified (referred as epithelial and other tumours; ICCC group Xb-e and ICCC main groups XI and XII).

Contralateral tumours occurring simultaneously in the eyes or kidneys (retinoblastomas and nephroblastomas) were only counted once (n = 45 and n = 4, respectively). Second primary benign tumours in the CNS (n = 13) and tumours found at autopsy only (n = 15) were excluded. Until 2013, the NCR did not register Langerhans cell histiocytosis (n = 59) and was possibly incomplete for benign intracranial and intraspinal germ cell tumours (n = 11), therefore these entities were also excluded.

Site of treatment

In this study, three categories of centre for primary treatment were used: (1) a paediatric oncology centre, (2) a specialised academic unit other (like surgical oncology or haematology) and (3) a non-academic hospital. In the Netherlands there may be the unique situation that, in the study period, children with cancer have mostly been treated at a university medical centre. The neuro- and orthopaedic surgical and haemato-oncology units as well as the paediatric oncology units and radiotherapy departments were located in these centres. Multidisciplinary patient meetings have increasingly been held in the major five paediatric oncology centres. In these meetings, patients only needing surgery were likely to have been discussed as well. In addition to being registered in the NCR this resulted in a notification for the DCOG registry personnel and these patients were classified as paediatric oncology patients.

Linkage of the NCR and DCOG data files

From both databases all children with cancer treated before the age of 18 and diagnosed between 1st January 2004 and 31st December 2013 were selected. The linkage of the two databases was done in three steps (**supplementary figure S2.1**). First, data files were merged with a probabilistic method using the following fields: date of birth, family name, gender, first initial, date of death and postal code. All records with a complete match were included at the first step (n = 4,404). For the second step of the linkage, records with one or two discrepancies in the matching variables were checked by AR. This resulted in 377 matched records. In the third step unlinked records were checked by registrars from the other registry why they were missing and whether their inclusion in the registry was correct or not. Doubtful records (n = 226) were discussed by AR and OV, 110 of them were treated in a paediatric oncology centre (61 were missed by the NCR; mainly cytological missed cases, 49 were missed by the DCOG). Another 44 records were in both databases but with a year of diagnosis outside the selected range in one of the two databases. And 72 records were excluded (50 from the NCR and 22 from the DCOG) mainly because these were children with a doubtful residence in the Netherlands at time of diagnosis or a malignancy could not be confirmed. The three steps resulted in 4,935 childhood cancers treated in a paediatric oncology centre. And last, 1,086 additional records

were included, these were childhood cancers not treated in any of the paediatric oncology centres and were registered in the NCR only. The records of patients seen and treated at another unit in an academic centre were also checked by registrars from DCOG for correct inclusion. The total study population of children with cancer diagnosed before the age of 18 years treated in the Netherlands between 2004 and 2013 consisted of 6,021 cancer patients.

Statistical analyses

Characteristics of the study population in relation to the site of initial treatment were described as percentages and tested with χ 2 test. Logistic regression analysis was used to explore the determinants of treatment of children with cancer outside a paediatric oncology centre, therefore also dichotomising place of treatment in a paediatric oncology centre or not (i.e. another unit in an academic centre or a non-academic hospital). The logistic regression analysis was also used to assess significance in referral to a paediatric oncology centre for age, gender and time by ICCC-3 category (p for trend). After univariate testing the following variables were included in the multivariable model: age group (0-9, 10-14 and 15-17 years), gender, 2-year period of diagnosis and ICCC-3 category. Logistic regression analysis was performed for the total group of children with cancer and separately by ICCC-3 category. Diagnostic subgroups within the ICCC-3 category and stage of the tumour (if applicable) were considered as independent variables for the multivariable regression analyses by ICCC-3 category. These analyses were adjusted for gender, age and period of diagnosis. Hodgkin lymphoma (n = 354) and non-Hodgkin lymphoma (n = 395) were analysed separately because of differences in age, gender and stage distributions. Seven patients with an unspecified lymphoma (IIe Unspecified lymphomas) were excluded for the analyses by ICCC-3 category. Statistical analyses were performed using Stata 14.0 (StataCorp LP).

Ethical consideration

According to the Central Committee on Research involving Human Subjects (CCMO), this type of study does not require approval from an ethics committee in the Netherlands. Use of data for this study was approved by the Privacy Review Board of the NCR and the research committee of the DCOG.

RESULTS

Site of primary treatment

In total, 4,935 (82%) children were treated at any of the paediatric oncology centres, 742 (12%) at another academic unit and 344 (6%) in a non-academic hospital (**table 2.1**). Boys were more often treated in a paediatric oncology centre than girls (83% versus 80%). Most patients in the youngest age group (aged 0-9) were treated in a paediatric oncology centre (94%), 85% of 10-14 year olds and only 48% of 15-17 year olds. Patients with leukaemia and embryonal tumours (blastomas, carcinomas) were mostly treated at any of the paediatric oncology centres (96% and 98%, respectively), patients with CNS tumours and the combined category of epithelial and other tumours were less seen at such a centre (79% and 38%, respectively).

Table 2.1. Characteristics of 6,021 childhood cancer patients and the site of primary treatment in the Netherlands, period 2004-2013

	Total	Paediatric oncology centre		Non paediatric oncology centre				p-value[a]
				Academic unit other		Non-academic hospital		
Variable		*N*	%[b]	*N*	%	*N*	%	
	6,021	4,935	*82.0%*	742	*12.3%*	344	*5.7%*	
Sex								
Male	3,234	2,698	*83.4%*	378	*11.7%*	158	*4.9%*	<0.01
Female	2,787	2,237	*80.3%*	364	*13.1%*	186	*6.7%*	
Age at diagnosis (years)								
0 – 9	3,324	3,122	*93.9%*	165	*5.0%*	37	*1.1%*	<0.01
10 – 14	1,423	1,206	*84.8%*	150	*10.5%*	67	*4.7%*	
15 – 17	1,274	607	*47.6%*	427	*33.5%*	240	*18.8%*	
Year of diagnosis								
2004-05	1,230	979	*79.6%*	172	*14.0%*	79	*6.4%*	0.08
2006-07	1,183	963	*81.4%*	147	*12.4%*	73	*6.2%*	
2008-09	1,170	950	*81.2%*	158	*13.5%*	62	*5.3%*	
2010-11	1,264	1,069	*84.6%*	133	*10.5%*	62	*4.9%*	
2012-13	1,174	974	*83.0%*	132	*11.2%*	68	*5.8%*	
Main diagnostic group[c]								
I Leukaemia	1,573	1,511	*96.1%*	51	*3.2%*	11	*0.7%*	<0.01
II Lymphoma	756	625	*82.7%*	81	*10.7%*	50	*6.6%*	
III & Xa CNS & intracranial germ cell	1,578	1,247	*79.0%*	270	*17.1%*	61	*3.9%*	
IV-VII Embryonal tumours	703	687	*97.7%*	15	*2.1%*	1	*0.1%*	
VIl & XI Bone & soft tissue tumours	740	609	*82.3%*	100	*13.5%*	31	*4.2%*	
X – XII[d] Epithelial & Other	671	256	*38.2%*	225	*33.5%*	190	*28.3%*	

[a] From chi-square test for differences across categories

[b] Row percentages for total, sex, age, year of diagnosis and main diagnostic subgroup

[c] Main diagnostic groups adapted from the International Classification of Childhood Cancers ICCC-3[27]

[d] Group X without Xa Intracranial and intraspinal germ cell tumours

Within the study period, the percentage of young adolescents aged 15-17 year treated at a paediatric oncology centre increased (**figure 2.1**). The proportion of referral for this age group increased from 33% in 2004 to 54% in 2013 (*p* for trend <0.01).

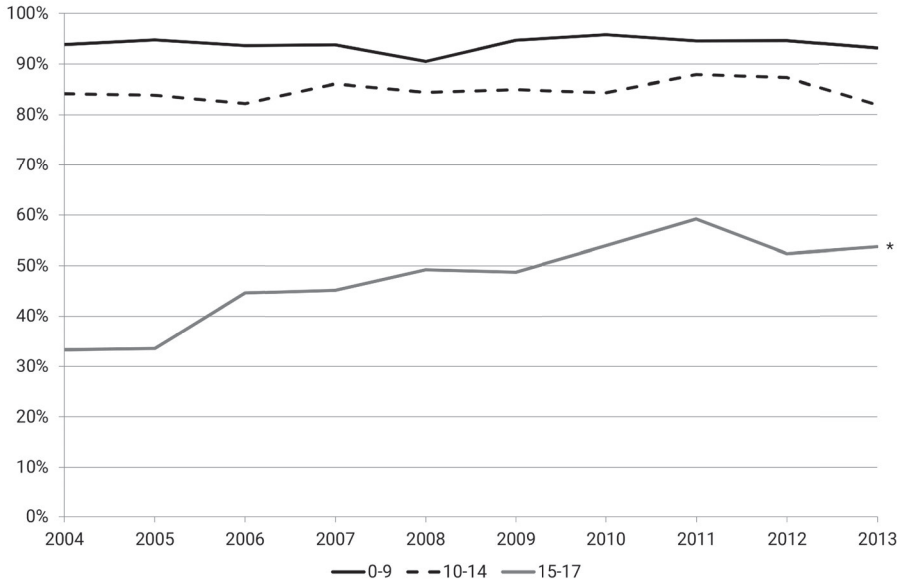

Figure 2.1. Percentage of treatment at a paediatric oncology centre in time by age groups. Percentage of patients 15-17 years at diagnosis treated at a paediatric oncology centre significantly increased during the study period (33·3% to 53·7% in 2004 and 2013, respectively). * *P* for trend < 0·01.

Determinants for treatment outside a paediatric oncology centre

Table 2.2 shows the multivariable logistic regression including gender, age at diagnosis, year of diagnosis and ICCC-3 categories. Female gender (OR 1.2; 95%CI 1.0-1.4) and older age were associated with treatment outside a paediatric oncology centre (OR 1.9; 95%CI 1.6-2.4 and OR 13.0; 95%CI 10.5-16.0 for age groups 10-14 and 15-17, respectively). All ICCC-3 categories, except embryonal tumours, were associated with treatment outside a paediatric oncology centre compared to leukaemia. A diagnosis in the later periods 2010-11 and 2012-13 was associated with treatment in a paediatric oncology centre (OR 0.6; 95%CI 0.4-0.7 and OR 0.7; 95%CI 0.5-0.9, respectively).

Table 2.2 Determinants of primary treatment outside a paediatric oncology centre in the Netherlands, period 2004-13

	Total	Patients treated outside a paediatric oncology centre		Univariate analysis			Multivariable analysis		
Variable		*N*	%[a]	OR	95% CI	*p-value*	OR	95% CI	*p-value*
Sex									
Male	3,234	536	16.6%	Ref			Ref		
Female	2,787	550	19.7%	1.2	1.1 - 1.4	<0.01	1.2	1.0 - 1.4	0.03
Age at diagnosis (years)									
0 - 9	3,324	202	6.1%	Ref			Ref		
10 – 14	1,423	217	15.2%	2.8	2.3 - 3.4	<0.01	1.9	1.6 - 2.4	<0.01
15 – 17	1,274	667	52.4%	17	14 - 20	<0.01	13	11 - 16	<0.01
Year of diagnosis									
2004-05	1,230	251	20.4%	Ref			Ref		
2006-07	1,183	220	18.6%	0.9	0.7 - 1.1	0.26	0.8	0.6 - 1.1	0.16
2008-09	1,170	220	18.8%	0.9	0.7 - 1.1	0.32	0.8	0.6 - 1.0	0.05
2010-11	1,264	195	15.4%	0.7	0.6 - 0.9	<0.01	0.6	0.4 - 0.7	<0.01
2012-13	1,174	200	17.0%	0.8	0.6 - 1.0	0.04	0.7	0.5 - 0.9	<0.01
Main diagnostic group[b]									
I Leukaemia	1,573	62	3.9%	Ref			Ref		
II Lymphoma	756	131	17.3%	5.1	3.7 - 7.0	<0.01	2.5	1.8 - 3.6	<0.01
III & Xa CNS & intracranial germ cell	1,578	331	21.0%	6.5	4.9 - 8.6	<0.01	7.0	5.2 - 9.4	<0.01
IV-VII Embryonal tumours	703	16	2.3%	0.6	0.3 - 1.0	0.05	1.1	0.6 - 1.9	0.31
VII & XI Bone & soft tissue tumours	740	131	17.7%	5.2	3.8 - 7.2	<0.01	3.4	2.5 - 4.8	<0.01
X – XII[c] Epithelial & Other	671	415	61.8%	39	29 - 53	<0.01	24	17 - 33	<0.01

[a] Row percentages

[b] Main diagnostic groups adapted from the International Classification of Childhood Cancers[27]

[c] Group X without Xa Intracranial and intraspinal germ cell tumours

Site of treatment by ICCC-3 category

Site of primary treatment by ICCC-3 category according to age, gender and year of diagnosis are presented in **supplementary figures S2.2a-c**. The 10-14 year olds with CNS and epithelial other tumours were significantly more often treated outside a paediatric oncology centre, compared to 0-9 year olds (both *p* <0.01) (**supplementary figure S2.2a**). For every ICCC-3 category, the oldest age group was treated significantly more often outside a paediatric oncology centre compared to the youngest (*p* <0.01) (**supplementary figure S2.2a**). Girls were significantly more often treated outside a paediatric oncology centre when diagnosed with a CNS tumour (*p* =0.01) (**supplementary figure S2.2b**). Over time significantly more patients with a lymphoma (*p* =0.01) or bone or soft tissue tumour (*p* =0.05) were treated in a paediatric oncology centre (**supplementary figure S2.2c**).

Table 2.3 shows the multivariable logistic regression by ICCC-3 category adjusted for gender, age and 2-year period of diagnosis. In the category of leukaemia a diagnosis of CML was associated with treatment outside a paediatric oncology centre (OR 9.7; 95%CI 3.8-25). In the category Hodgkin lymphoma Ann Arbor stage 2 and stage 4 were more likely treated in a paediatric oncology centre (OR 0.3; 95%CI 0.1-0.9 and OR 0.2; 95%CI 0.0-0.6, respectively). In the category non-Hodgkin lymphoma unknown stage was associated with treatment outside a paediatric oncology centre (OR 8.2; 95%CI 2.4-28). On the other hand, a diagnosis of Burkitt lymphoma was associated with treatment at a paediatric oncology centre (OR 0.2; 95%CI 0.1-0.8). In diagnostic group IIb.4 Non-Hodgkin lymphomas, NOS only four patients were included, all diagnosed and treated at a paediatric oncology centre. A diagnosis of an intracranial and intraspinal embryonal tumour was associated with treatment in a paediatric oncology centre (OR 0.2; 95%CI 0.1-0.6), whereas a diagnosis of other and unspecified CNS tumours (ICCC-3 groups IIIe and f) was associated with treatment outside a paediatric oncology centre (OR 4.6; 95%CI 2.6-8.1 and OR 4.7; 95%CI 2.3-9.5, respectively). If grading of the CNS tumours was considered, 31.8% of the children with low-grade tumours were treated outside a paediatric oncology centre compared to 7.6% of the high grade tumours. To be more precise, children with low grade tumours who were treated outside a paediatric oncology centre (n = 252) these are mainly tumours from the ICCC-category IIIe.1 (Pituitary adenomas and carcinomas) and IIIe.4 (Neuronal and mixed neuronal-glial tumours) (n = 67 and n = 66, respectively) and pilocytic astrocytomas (n = 63, ICCC-3 category IIIb).

Table 2.3. Determinants of primary treatment outside a paediatric oncology centre in the Netherlands by ICCC-3 category

	Total	Patients treated outside a paediatric oncology centre		Multivariable analysis		
ICCC category		*N*	%[a]	OR	95%CI	*p-value*
Leukaemia						
Tumour detail						
Ia. ALL	1,162	29	2.5%	Ref.		
Ib. AML	261	12	4.6%	1.4	0.7 - 3.0	0.36
Ic. CML	41	15	36.6%	9.7	3.8 - 25	<0.01
Id&e. Other & unspec.	109	6	5.5%	1.5	0.6 - 4.0	0.44
Hodgkin's lymphoma						
Ann Arbor stage						
1	42	12	28.6%	Ref.		
2	184	45	24.5%	0.3	0.1 - 0.9	0.03
3	75	17	22.7%	0.5	0.1 - 1.6	0.23
4	53	7	13.2%	0.2	0.0 - 0.6	0.01
Non-Hodgkin's lymphoma						
Ann Arbor stage						
1	84	12	14.3%	Ref.		
2	77	9	11.7%	0.7	0.2 - 2.3	0.60
3	85	4	4.7%	0.3	0.1 - 1.2	0.09
4	116	9	7.8%	0.4	0.1 - 1.3	0.14
X	33	14	42.4%	8.2	2.4 – 28	<0.01
Tumour detail						
IIb. NHL	263	45	17.1%	Ref.		
IIc. Burkitt	132	3	2.3%	0.2	0.1 - 0.8	0.03
CNS tumours						
Tumour detail						
IIIa. Ependymomas and choroid plexus tumours	146	19	13.0%	Ref.		
IIIb. Astrocytomas	586	96	16.4%	1.2	0.7 - 2.1	0.56
IIIc. Intracranial embryonal	233	7	3.0%	0.2	0.1 - 0.6	<0.01
IIId Other glioma	144	17	11.8%	0.9	0.5 - 2.0	0.90
IIIe. Other specified CNS	342	157	45.9%	4.6	2.6 - 8.1	<0.01
IIIf. Unspecified CNS	77	31	40.3%	4.7	2.3 - 9.5	<0.01
Xa. Intracranial germ cell	50	4	8.0%	0.3	0.1 - 1.0	0.06
Embryonal tumours						
Tumour detail						
Blastoma	672	5	0.7%	Ref.		
Carcinoma	31	11	31 %	80	17 - 380	<0.01

Table 2.3. (continued)

	Total	Patients treated outside a paediatric oncology centre		Multivariable analysis		
ICCC category		*N*	%[a]	OR	95%CI	*p-value*
Bone & soft tissue tumours						
Tumour detail						
Osteosarcoma	178	20	11.2%	Ref.		
Ewing sarcoma	139	9	6.5%	1.2	0.5 - 3.0	0.75
bone other	53	38	71.7%	54	19 - 151	<0.01
Rhabdomyosarcoom	157	8	5.1%	0.7	0.3 - 2.0	0.52
non-rhabdomyosarcoom	213	56	26.3%	4.3	2.1 - 9.1	<0.01
Stage						
I	270	73	27.0%	Ref.		
II	221	17	7.7%	0.2	0.1 - 0.5	<0.01
III	40	7	17.5%	0.3	0.1 - 1.1	0.08
IV	115	11	9.6%	0.2	0.1 - 0.5	<0.01
X	94	23	24.5%	0.2	0.1 - 0.5	<0.01
Epithelial and other						
Tumour detail						
Xb. Extracranial germ cell	61	11	18.0%	Ref.		
Xc Gonadal germ cell	157	85	54.1%	1.2	0.5 - 3.2	0.69
XIb. Thyroid ca	107	77	72.0%	3.4	1.3 - 8.5	0.01
XId. Melanoma	163	140	85.9%	13	5.3 - 33	<0.01
XIa&c Adrenocortical & nasopharyngeal carcinomas	26	4	15.4%	0.8	0.2 - 3.4	0.81
XIe&f. Skin & other	138	95	68.8%	3.4	1.4 - 8.5	0.01
XIIa&b. Other and unspecified	19	3	15.8%	0.4	0.1 - 2.1	0.29
Stage						
I	358	246	68.7%	Ref.		
II	73	45	61.6%	0.7	0.3 - 1.5	0.36
III	46	16	34.8%	0.2	0.1 - 0.5	<0.01
IV	43	10	23.3%	0.1	0.1 - 0.3	<0.01
X	151	98	64.9%	0.9	0.5 - 1.6	0.63

[a] Row percentages

All analyses are adjusted for sex, age and year of diagnosis.

Used abbreviations ICCC: International Classification of Childhood Cancers, ALL: Acute lymphoblastic leukaemia, AML: Acute myeloid leukaemia; CML Chronic myeloid leukaemia, NHL: non-Hodgkin lymphoma, CNS: Central nervous system tumours

On the other hand children with tumours of the sellar region (craniopharyngiomas) (IIIe.2) and pineal parenchymal tumours (IIIe.3) are almost all (86/95) treated at a paediatric oncology centre. In the category of embryonal tumours a carcinoma tumour type instead of a blastoma

was highly associated with treatment outside a paediatric oncology centre, OR 80 (95%CI 17-380). With respect to bone and soft tissue tumours, tumour types belonging to ICCC-3 category 'Bone other' or non-rhabdomyosarcoma were associated with treatment outside a paediatric oncology centre (OR 54; 95%CI 19-151 and OR 4.3; 95%CI 2.1-9.1, respectively). Compared to stage I tumours, higher stages as well as stage unknown were associated with treatment in a paediatric oncology centre (stage III, not statistical significant).

In the ICCC-3 category epithelial and other tumours, thyroid carcinomas (OR 3.4; 95%CI 1.3-8.5), melanomas (OR 13; 95%CI 5.3-33) and skin and other carcinomas (OR 3.4; 95%CI 1.4-8.5) were associated with treatment outside a paediatric oncology centre. Higher staged epithelial and other tumours were more likely treated in a paediatric oncology centre (stage III OR 0.2; 95%CI 0.1-0.5 and stage IV OR 0.1; 95%CI 0.1-0.3).

DISCUSSION

This population-based study of 6,021 children with cancer diagnosed before the age of 18 years showed that 18% of them were treated outside a paediatric oncology centre. Treatment at a paediatric oncology centre diminished greatly with age: 94% of the patients under 10 years, 85% of the 10- to 14-year olds and 48% of the 15- to 17-year olds with childhood cancer were treated at a paediatric oncology centre. This is a high percentage especially because previous studies suggested better survival rates for adolescents and young adults with leukaemia treated on paediatric protocols compared to adult protocols.[16-18] Over time more 15- to 17-year olds were treated at a paediatric oncology centre during the study period: 33% in 2004 and 54% in 2013. This was mainly attributable to the referral of more patients with Hodgkin lymphoma and bone and soft tissue tumours.

The longstanding European networks for Hodgkin lymphoma, European networks for Hodgkin lymphoma (EuroNet-PHL)[10] and sarcoma (Euro-Ewing)[12] The European Paediatric Soft Tissue Sarcoma Study Group (EpSSG)[28], in which the Netherlands also participates since the early 2000s could be the reason for more referral and treatment at a paediatric oncology centre for these tumours at ages 15-17.

Type of tumour was also associated with treatment outside a paediatric oncology centre. All ICCC-3 categories, except embryonal tumours, were more often treated outside a paediatric oncology centre compared to leukaemia. The high percentage of patients with leukaemia treated at a paediatric oncology centre (96%) might be explained by the fact that it has been proven that

better survival rates are achieved for adolescents and young adults when treated on paediatric protocols compared to adult protocols.[16-18] Treatment data from the NCR revealed that patients who only needed surgical removal of the tumour, remained very often on the surgical unit only (45%, or 557/1233 patients with surgery only, data not shown). These surgery only patients were mainly patients in the ICCC-3 categories of CNS tumours and epithelial and other tumours.

Previous articles which evaluated site of treatment for children with cancer in a state- or country-wide population-based registry are summarised in **table S2.1.**[3,20,22-25] Our results are consistent with these publications and also showed that older children were referred less often to a paediatric oncology centre. None of the existing studies did a multivariate analyses to investigate possible associations between type of tumour and site of treatment in more detail. Our multivariable analyses by ICCC-3 category revealed that specific tumour types such as CML, embryonal carcinomas, bone tumours other type than osteosarcoma (ICCC subgroup VIIIb, d and e), non-rhabdomyosarcomas, thyroid carcinomas, melanomas and skin carcinomas as well as lower stages tumours were associated with treatment outside a paediatric oncology centre. For these specific tumours, except CML, Ewing sarcoma and non-rhabdomyosarcoma, the paediatric oncologists in the Netherlands have no (multidisciplinary) treatment protocol. In addition, some of the localised tumours are not treated with chemotherapy.

We observed that five in six boys and four in five girls with childhood cancer were treated at a paediatric oncology centre. It is unclear how gender difference is an explanatory factor in overall analysis, but not in the multivariable specific tumour group analyses. This is probably caused by smaller numbers. A more theoretical explanation for our gender difference is that girls have a more adult appearance and may therefore be referred more often to an adult ward.

Children diagnosed with types of cancer that are more common in young adults (e.g. gonadal germ cell tumours and Hodgkin disease) are referred to paediatric oncologists, urologists, gynaecologists or haematologists. Since these relatively young patients do receive chemotherapy and sometimes radiotherapy, and both modalities can result in late effects as these children grow older, it is important that these survivors also receive appropriate follow-up care after treatment has ended.[4] This kind of care is well organised in paediatric oncology centres.[6] For very rare tumour types in the age groups 15-19 and 20-39, specialists do consider broader age spectra and treat a person after consultation with the professional with most experience in that tumour type. More consensus recommendations like the management of adults with Wilms tumour[29] may seem to improve outcome. Active collaboration between paediatric and

(adolescent and young) adult units treating these relatively young patients is needed to have the best chances for cure and less side-effects at the long term.

A strength of our study is the completeness of our cohort. We included two independent childhood cancer registries (one population-based and one registry from the paediatric oncology centres) and cross-checked all discrepancies. A regular exchange and validation of data should take place in the Netherlands. This should be worked out for the Netherlands with the NCR, DCOG, DCOG Long-Term Effects After Childhood Cancer Registry (DCOG LATER) and the new national paediatric oncology centre, the Princess Máxima Center for paediatric oncology, within the near future. A limitation of this study is that there is possibly a group of patients not detected by the NCR nor by the DCOG. For example very aggressive (brain) tumours without pathology confirmation can be missed by both registries. The death statistics could not be checked as death certificates are not available to cancer registries in the Netherlands. Also we did not aim to evaluate accuracy and completeness of case ascertainment by both registries and to evaluate differences in morphology or topography as was done by Schouten *et al.*[30] If there was a difference the NCR record was used. In our study we did not investigate the outcome for children with cancer in relation to the site of treatment because there are many confounders and corrections for age and stage had to be made. Especially since some patients who died within one week after diagnosis could not have had the chance to reach a paediatric oncology centre. In our cohort 60 patients (including 30 children with a CNS tumour) died within one week and 40% of them were not known at the paediatric oncology centre (data not shown).

CONCLUSION

This population-based study of 6,021 children with cancer diagnosed before the age of 18 years showed that 82% of them were treated in a paediatric oncology centre, 12% at another academic unit and 6% in a non-academic centre during 2004-2013 in the Netherlands. Most of the patients under the age of ten (94%) and 85% of the children aged 10- to 14-year were treated at a paediatric oncology centre. Over time there was an increase in the proportion of treatment at a paediatric oncology centre for 15-17 year olds, in 2013 54% was treated at a paediatric oncology centre. Patients with leukaemia or a blastoma were mostly treated inside a paediatric oncology centre. Other types of tumours (e.g. carcinomas and lower staged tumours) were associated with treatment outside a paediatric oncology centre. Active collaboration between paediatric oncology centre(s), other academic paediatric units and other academic (adolescent and young) adult wards is needed to ensure most up to date paediatric cancer care for childhood cancer patients at the short and long term.

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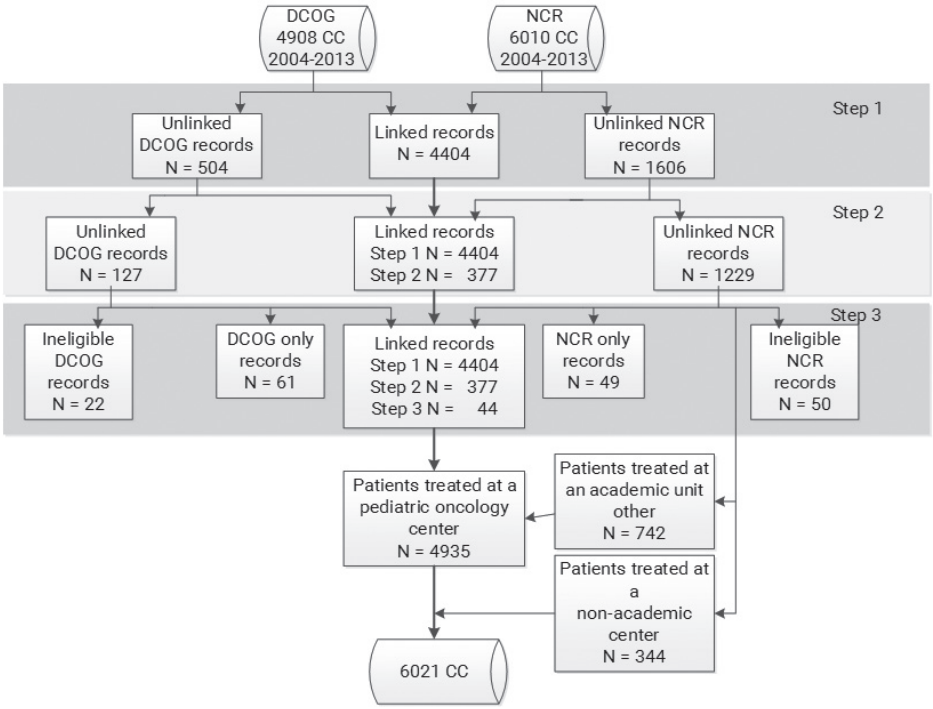
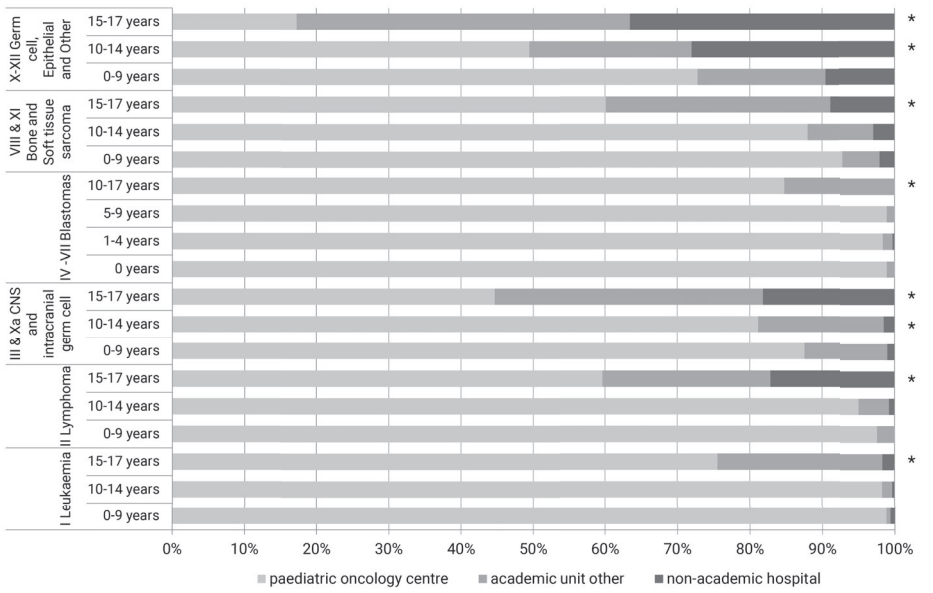
Supplementary table S2.1 Overview of the literature, site of treatment for children and adolescents with cancer

first author	**Klein-Geltink**
country and state	Canada, Ontario
ages included	15-19 years
diagnostic years	1995-2000
total number	3070 average number/ year =512
no. of paediatric oncology centres	5
performed analyses	Report about percentages of adolescents treated in paediatric versus adult centres by age group and type of tumour. Report about median number of days before start treatment
outcome	47% treatment in paediatric oncology centre for 15-17 year olds and 10% for 18-19 year olds. Carcinomas 11% treated in paediatric oncology centre and leukaemia most likely (51%) in paediatric oncology centre
first author	**Albritton**
country and state	USA, Utah
ages included	0-24 years
diagnostic years	1994-2000
total number	1355 average number/ year =226
no. of paediatric oncology centres	1
performed analyses	Report about percentages by age and site of treatment. Multivariable logistic regression predicting adolescents receipt of care at a paediatric oncology centre included diagnosis and age (categorical) and distance (linear)
outcome	97% treatment in paediatric oncology centre for the 0-9 year olds and 82% for the 10-14 year olds and 34% for the 15-19 Half of the leukaemia and soft tissue sarcoma patients and one third of the brain tumour and lymphoma patients aged 15-19 were seen at paediatric oncology centre.
first author	**Howell**
country and state	USA, Georgia
ages included	0-19 years
diagnostic years	1998-2002
total number	1751 average number/ year =350
no. of paediatric oncology centres	5
performed analyses	Report about percentages by age and site of treatment. Multivariable logistic regression to compare the distribution of age, sex, race and cancer site to attend a paediatric oncology centre or not. Also survival analyses, though not corrected for age and stage
outcome	87% treatment in paediatric oncology centre for the 0-14 year olds and 36% for the 15-19. The 5-year actuarial survival rates for more paediatric-specific cancers were significantly lower in all leukemias and ALL patients not treated at a paediatric oncology centre.

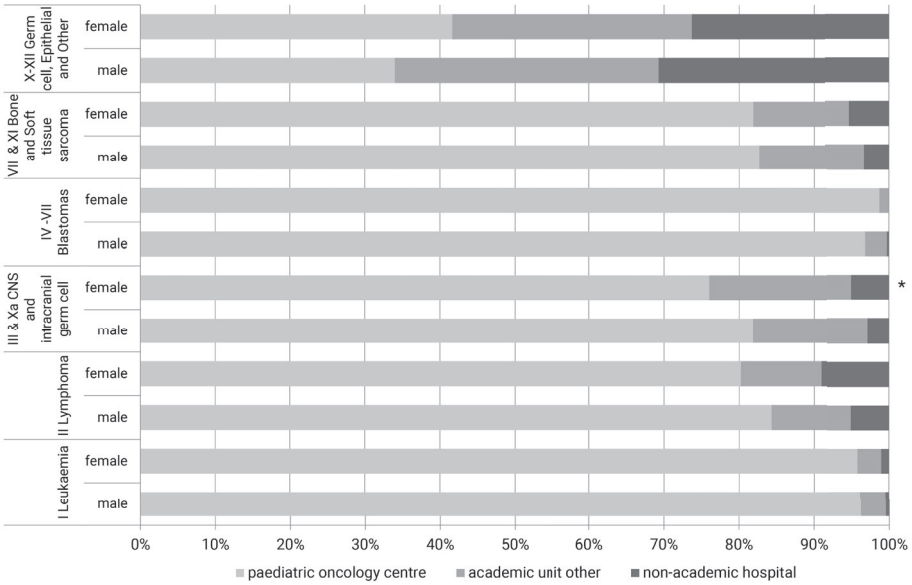
first author	Adam
country and state	Switzerland, seven regions
ages included	0-15 years
diagnostic years	1990-2004
total number	1077 average number/ year =72
no. of paediatric oncology centres	9
performed analyses	Report about percentages for treatment outside a paediatric oncology centre. Multivariable logistic regression to find potential predictors for treatment outside a paediatric oncology centre.
outcome	65% treatment in paediatric oncology centre for the 14-15 year olds. Malignant bone tumours and soft tissue sarcomas and malignant epithelial neoplasms and older children more often treated outside a paediatric oncology centre
first author	Desandes
country and state	France, six regions
ages included	15-19 years
diagnostic years	2006-07
total number	594 average number/ year =297
no. of paediatric oncology centres	47
performed analyses	Report about percentages of adolescents treated in paediatric versus (young) adult centres by age and type of tumour. Report about median number of days before start treatment
outcome	33% treatment of 15-19 year olds in paediatric oncology centre, declining with age (at diagnosis), varying significantly for tumour types. Time to diagnosis is significant less in paediatric centres.
first author	Whelan
country and state	UK, Southeast England
ages included	10-24 years
diagnostic years	1998-2002
total number	2260 average number/ year =452
no. of paediatric oncology centres	4
performed analyses	Report about percentages treatment at paediatric oncology units, teenage care units or adult care units. Age-specific percentages and tumour types and cancer network.
outcome	53% of the 10-14 year olds and 32% for the 15-19 34% of the 10-14 year olds and 23% of the 15-19 year olds were treated in a teenage care unit.



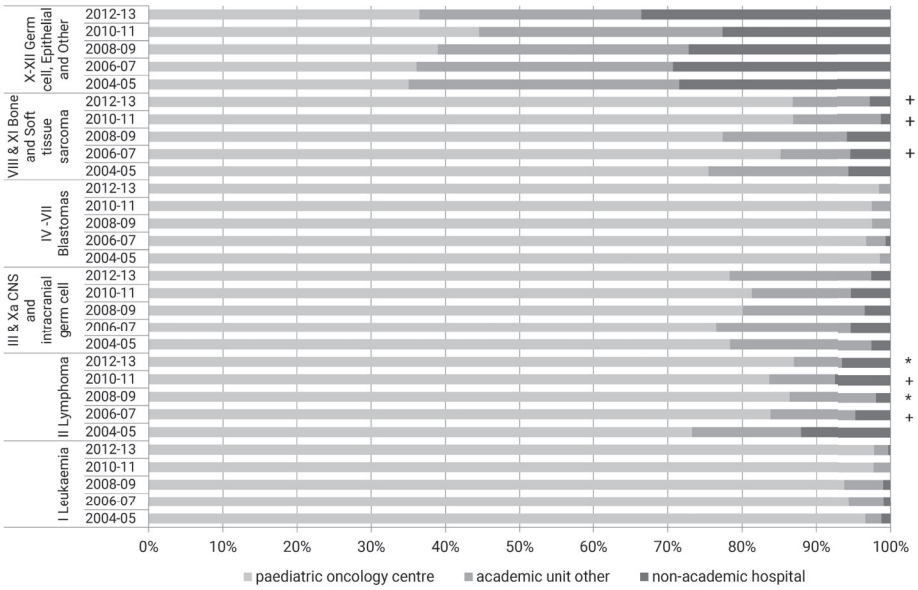
Supplementary figure S2.1. Flowchart linkage DCOG and NCR registries over the period 2004-2013. In total 6021 childhood cancers were included. *DCOG* Dutch Childhood Oncology Group, *CC* childhood cancers, *NCR* Netherlands Cancer Registry



Supplementary figure S2.2A



Supplementary figure S2.2B



Supplementary figure S2.2C

Supplementary figure 2.2. Site of treatment by the ICCC-3 categories A) Site of treatment according to age for the six ICCC-3 categories. B) Site of treatment according to sex for the six ICCC-3 categories. C) Site of treatment according to year of diagnosis for the six ICCC-3 categories. * *P* for trend < 0.01 + *P* for trend < 0.05

CHAPTER 3

Increasing incidence of cancer and stage migration towards advanced disease in children and young adolescents in the Netherlands, 1990-2017

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ABSTRACT

This is the first national study on trends in cancer incidence for children and young adolescents in the Netherlands, including stage at diagnosis as a potential marker of early diagnosis and better staging.

All neoplasms in patients younger than 18 years, diagnosed between 1990 and 2017 (n = 15,233), were derived from the Netherlands Cancer Registry. Incidence rates and the average annual percentage change with 95% CIs were calculated for all cancers combined and diagnostic (sub)groups. The stability of trends was examined by joinpoint analyses. Potential changes in early detection or improved staging over time were evaluated through proportional alterations in stage at diagnosis.

The annual overall cancer incidence increased significantly over time by 0.6% (95% CI 0.3-0.8) from 144 per million person-years in 1990-1999 to 162 in 2010-2017 and was significant for both boys (+0.5%, 0.2-0.8) and girls (+0.7%, 0.3-1.1), for infants (aged 0 years; +1.5%, 0.4-2.5), teenagers (aged 10-14 years;+0.6%, 0.3-1.0) and young adolescents (aged 15-17 years; +0.7%, 0.2-1.2), with no trend interruptions. The incidence of leukaemia (+0.7%, 0.3-1.2), malignant CNS tumours including pilocytic astrocytomas (+1.0%, 0.5-1.5), neuroblastoma (+1.2%, 0.1-2.2) and Ewing bone tumours (+2.4%, 0.9-4.0) increased significantly, whereas temporal variation in trends was observed in boys diagnosed with leukaemia, in pilocytic astrocytoma and malignant melanoma. The proportion of early-stage disease increased in patients with testicular germ cell tumours (+21%) and malignant melanomas (+14%), whereas stage migration towards advanced disease was seen for Hodgkin lymphomas, soft tissue sarcomas and medullary thyroid carcinomas.

The increasing childhood cancer incidence could not be explained by a rise in early diagnosis which suggest that background risk factors seem of more importance.

INTRODUCTION

The incidence of childhood cancer is increasing over time in Europe.[1] Fortunately, survival of childhood cancer improved from about 40% in the 1960s to nearly 80% nowadays.[2,3] However, cancer is still one of the leading causes of death in children and adolescents.[4]

In a recent analysis of data from 19 European countries, incidence trends of three common diagnostic groups of childhood cancer were studied.[1] Increasing incidence was observed for leukaemia in both children and adolescents (+0.7% and +0.9% per year, respectively), lymphoma in adolescents (+1.0% per year), and malignant tumours of the central nervous system (CNS) in children (+0.5% per year). Those increases are generally attributed to improved diagnostics and registration practices, and/or changes in the prevalence of risk factors.[1,5] New and improved methods for cancer diagnosis are often more precise and may result in earlier diagnosis and even more diagnosis of indolent cancers or cancers with a bad prognosis previously not diagnosed during a patient's lifetime. More precise diagnostics may also lead to an increase in the occurrence of advanced-stage disease resulting in the so-called stage-migration. Therefore, information on stage at diagnosis could be useful to understand trends in incidence.

In the Netherlands, since 2002, young adolescents until the age of 18 years are usually treated in paediatric oncology centres as in many other European countries.[6] Until now, no comprehensive national trend analyses on incidence of childhood cancer for the Netherlands have been performed. The incidence of childhood cancer has been only described for the ages 0-14 years in the South of the Netherlands until 1999. In this study, an increasing incidence trend (+3% per year) was observed until 1997 and this flattened out afterwards.[7] Therefore, an up-to-date population-based estimation of the incidence of childhood cancer, including young adolescents, is needed.

In this present study, we evaluate incidence trends of cancer in children and young adolescents aged below 18 years and potential changes in early detection and staging through proportional alteration in disease stage at diagnosis in the Netherlands between 1990 and 2017 using population-based data of the Netherlands Cancer Registry (NCR).

PATIENTS AND METHODS

Data collection

Data on all malignant neoplasms in patients younger than 18 years, diagnosed between 1990 and 2017, were derived from the NCR, a nationwide population-based cancer registry since 1989. The NCR is based on notification of all newly diagnosed malignancies in the Netherlands by the automated national pathological archive PALGA with additional reporting by hospital discharge registries and the haematology departments. After notification, trained registration personnel collect relevant information from medical records at the hospitals. Since 2000, benign and borderline tumours of the CNS (ICD-O-3, behaviour codes /0 and /1) are included in the NCR. Those tumours were taken into account in **figure 3.1 and 3.2** only, to give a comprehensive overview of all childhood cancers. Pilocytic astrocytomas (ICD-O-3 M9421/1) were completely registered for the period 1990-2017 and therefore included in all analyses. Several other neoplasms were excluded because of no complete registration during the study period: myelodysplastic syndromes (ICD-O-3 M codes starting with 998, registered since 2001, n = 94), myeloproliferative neoplasms (ICD-O-3 M9950-9962, registered since 2001, n = 26), Langerhans cell histiocytosis (ICD-O-3 M9750-9754, not consistently registered before 2012, n = 152), carcinoid tumour of the appendix (ICD-O-3 site code C18.1, M8240-M8249, before 2013 not consistently registered as /3, n = 221). Well-differentiated chondrosarcomas (ICD-O-3 M9220/31, n = 28) and dermatofibrosarcomas (ICD-O-3 M8832, n = 74) were also excluded as they are classified as borderline neoplasms in the newest ICD-O classification (ICD-O-3.2).

Neoplasms were categorised according to the International Classification of Childhood Cancer (ICCC, third edition).[8] The stage was classified using the Ann Arbor staging system for lymphomas[9] and TNM classification or the extent of disease (i.e., localised, regional, and distant) for other solid tumours.[10] Early-stage disease at diagnosis was defined as Ann Arbor stage I for lymphomas, and as localized disease for other solid tumours defined by the Toronto Paediatric Cancer Staging guidelines.[11] Early-stage disease of malignant melanomas and thyroid carcinomas are not defined by the Toronto guidelines and therefore based on TNM classification: M0/X for papillary/follicular, T1-4 N0/X M0/X for medullary thyroid carcinomas and T1-2 N0/X M0/X for malignant melanomas (**supplementary table S3.1**). For astrocytomas (i.e., ICCC-3 diagnostic subgroup IIIb), the degree of malignancy, WHO grade was used.[12] WHO grade was derived from the sixth digit of the ICD-O morphology code and cross-checked with the first four digits of the morphology code. In case of discrepancies, registry files were checked by one of the authors (OV). Low degree of malignancy was defined as WHO grade I/II.

Statistical analyses

Descriptive analysis of the average number per year and proportions of diagnosis by ICCC-3 diagnostic groups and main subgroups was performed. Incidence was calculated as the average annual number of cases per million person-years. Age-standardised incidence rates (ASR) were calculated for the age group 0-17 years using the weights of the world standard population[13], and age-specific incidence rates were given to the age groups: 0, 1-4, 5-9, 10-14 and 15-17 years. Incidence 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. The study period was divided into three periods: 1990-99, 2000-09 and 2010-17.

Changes in incidence over time were evaluated by calculating the average annual percentage change (AAPC) and corresponding 95% confidence interval (CI) calculated for the period 1990-2017. AAPC was derived from a regression line that was fitted to the natural logarithm of the rates using the calendar year as a regressor variable and calculated for the period 1990-2017.[14] The null hypothesis corresponds to no change in the annual rate during the study period, which was equivalent to 0 lying within the 95% CI of the AAPC. Benign and borderline CNS tumours were not taken into account in those trend analyses, and trends were separately described for the period 2000-17 in **supplementary table S3.2**. Joinpoint regression program (version 4.5.0.1) was used to check for trend transitions during the study period.[15,16] The null hypothesis assumed that the AAPC was constant throughout the study period. The permutation test [16] was used to determine the number of joinpoints, by default set to a maximum of four. For each detected joinpoint, the AAPC and corresponding 95% CIs were reported for each of the linear segments identified prior and next to the detected joinpoint. AAPC and joinpoint analyses were performed for all cancers combined and by gender, age, diagnostic groups and main subgroups.

To determine changes in disease stage at diagnosis, proportional alterations in all stages and early stage versus advanced stage over time were evaluated and tested by $\chi 2$ test for each diagnostic group, except for group I. Leukaemias and group XII. Other and unspecified tumours. Unknown stages were excluded for this analysis (n = 767, 8% of the total included cancer diagnosis, **supplementary table S3.1**)

All analyses were performed using SAS software (SAS system 9.4, SAS Institute, Cary, NC).

RESULTS

In total 15,233 cancer diagnoses in children and young adolescents were registered during 1990-2017, including 706 diagnoses of benign and borderline CNS tumours which were included in the NCR since 2000. For the period 2000-17, those CNS tumours comprised 7% of all cancer diagnoses, and almost 30% of all new CNS cancer diagnoses. The proportion of benign and borderline CNS tumours varied by age from 5% of all new cancer diagnosis and 18% of all new CNS cancer diagnosis in children aged below 10 years to 10% and 50% in young adolescents aged 15-17 years.

Figure 3.1 describes the distribution of the different diagnostic childhood cancer groups during 2000-17. About one-third (34%) was diagnosed before the age of 5 years and 21% in the age range 15-17 years. The most common cancer types among infants (0 years) were leukaemia and neuroblastomas, including other peripheral nervous cell tumours, comprising 40% of all new cancer diagnoses in infants. Leukaemia was the most common type of cancer in children of 1-9 years (31% of all new cancer diagnoses in this age group). Lymphoma became more common from the age of 10 years: 21% of all new cancer diagnosis in 10-17 years old compared to <5% in children below 5 years. In the younger age, Burkitt lymphoma was common, whereas Hodgkin lymphoma was more present at the older ages. Bone tumours were also common in 10-17 years old patients resulting in about 10% of all new cancer diagnoses in this age group. Epithelial cancers became an important group in the age group of 15-17 years, comprising 16% of all new cancer diagnoses in those young adolescents.

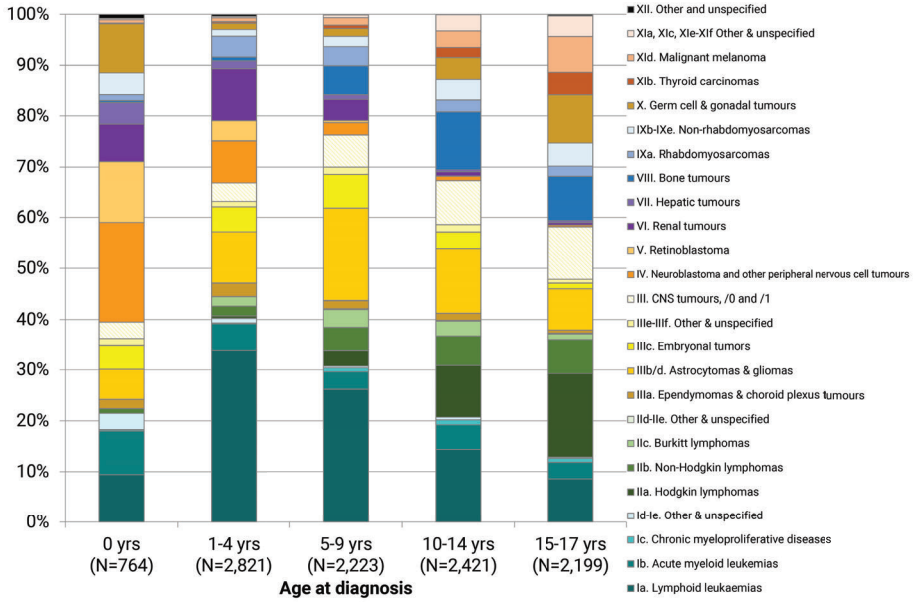


Figure 3.1. Relative frequencies (in %) of diagnostic (sub)groups according to the International Classification of Childhood Cancer (ICCC)-3 classification including benign and borderline central nervous system (CNS) tumours by age group in children and young adolescents in the Netherlands, 2000-17 (Source: The Netherlands Cancer Registry).

Cancer incidence

In the period 2000-17, on average, 579 children and young adolescents were diagnosed with cancer in the Netherlands annually, including the benign and borderline CNS tumours (**figure 3.2A**). The average ASR of childhood cancer was 168 per million person-years (**figure 3.2B**). The boys were slightly more affected than girls with an M:F ratio of 1.2 (ASR was 180 per million in boys versus 156 in girls). The average incidence rate also differed by age group. Children aged 5-9 years had the lowest incidence with 127 per million person-years, followed by teenagers aged 10-14 years with 135 per million. The highest incidence was observed in infants (0 years) with 230 per million person-years.

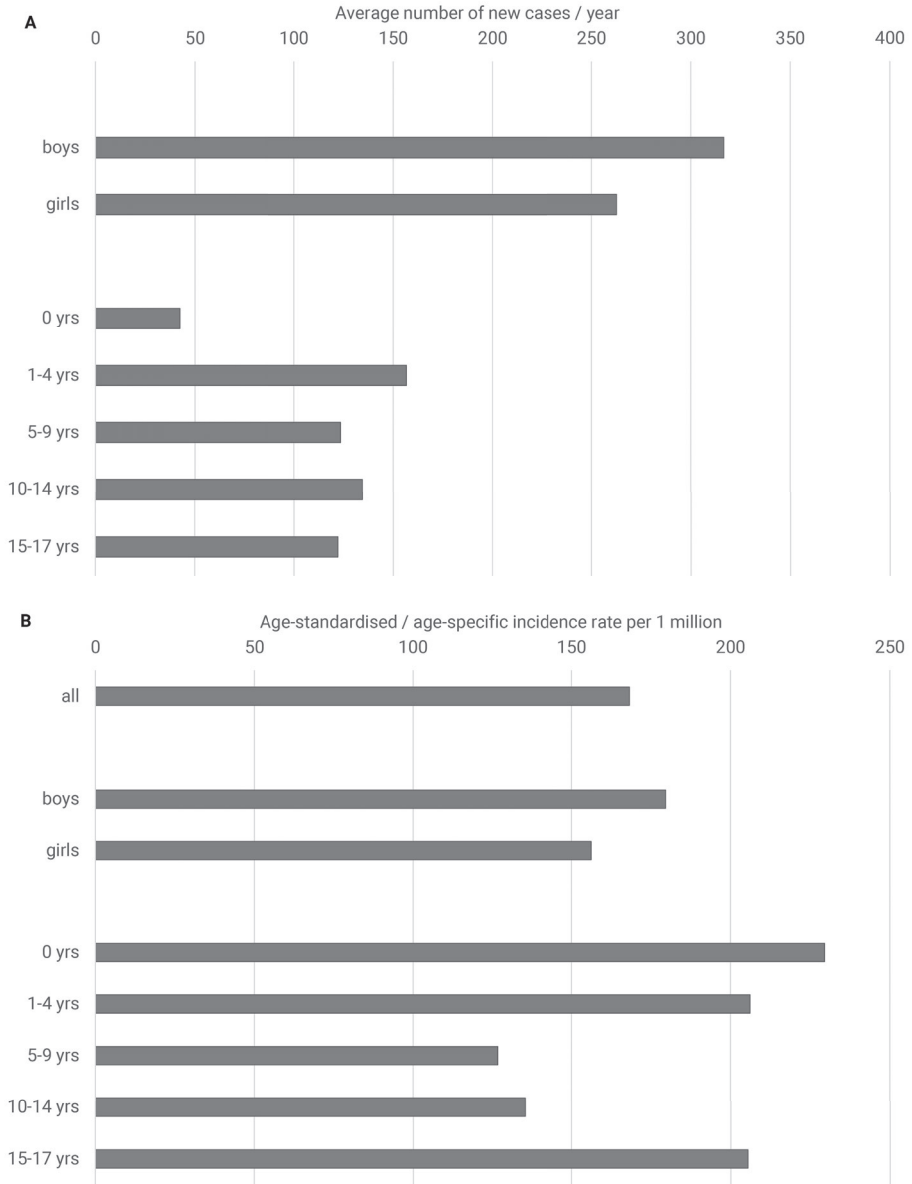


Figure 3.2. Incidence of childhood and adolescent cancer by gender and age (including benign and borderline CNS tumours) in the Netherlands, 2000-17. A) Average number of new cases per year by gender and age. In total, on average 579 children and young adolescents were diagnosed with cancer in the Netherlands annually. B) Incidence rates by gender and age. Age-standardised rates were calculated for all, boys and girls[13], and age-specific rates for the given age groups.

Cancer incidence trends over time

The average number of new cancer cases, ASR per million person-years and AAPC by diagnostic (sub)group in children and young adolescents (aged 0-17 years) are shown in **table 3.1**. Benign and borderline CNS tumours were not taken into account in these trend analyses, but are separately presented in **supplementary table S3.2**. Childhood cancer incidence increased significantly over time by 0.6% per year (95% CI 0.3-0.8) from 144 per million person-years in 1990-1999 to 162 in 2010-17, and was seen in both sexes, in infants (aged 0 years), teenagers (aged 10-14 years) and young adolescents (aged 15-17 years; **table 3.1 and figure 3.3A and 3.3B**). Significant increases were observed for leukaemia (+0.7% per year, 95% CI 0.3-1.2), CNS tumours (+1.0% per year, 0.5-1.5), neuroblastoma (i.e. diagnostic subgroup IVa; +1.2% per year, 0.1-2.2) and Ewing bone tumours (+2.4% per year, 0.9-4.0). Evaluation of trend transitions during the study period using joinpoint analysis are shown in **table 3.2**.

Incidence increases of leukaemia were observed in girls (from 35 per million person-years in 1990-99 to 44 in 2010-17; a rise of 1.1% annually, 95% CI 0.4-1.8) and in infants (from 31 in 1990-99 to 50 in 2010-17; +3.1% per year, 1.2-5.1) with no trend transitions. Except for the boys, a temporary incidence increase was seen during the time segment 1990-97 by 4.8% per year (95% CI 0.4-9.4) followed by a stable incidence at 52 per million. In young adolescents, incidence tended to increase by 1.4% per annum (95% CI -0.0-2.9), from 23 per million person-years in 1990-99 to 29 in 2010-17. Lymphoid leukaemia (LL) represented 77% of all leukaemia's and mainly responsible for the significant increase of leukaemia (LL +0.6% per year, 95% CI 0.1-1.1; **table 3.1**). Incidence of three main types of lymphomas remained stable over time (**table 3.1**).

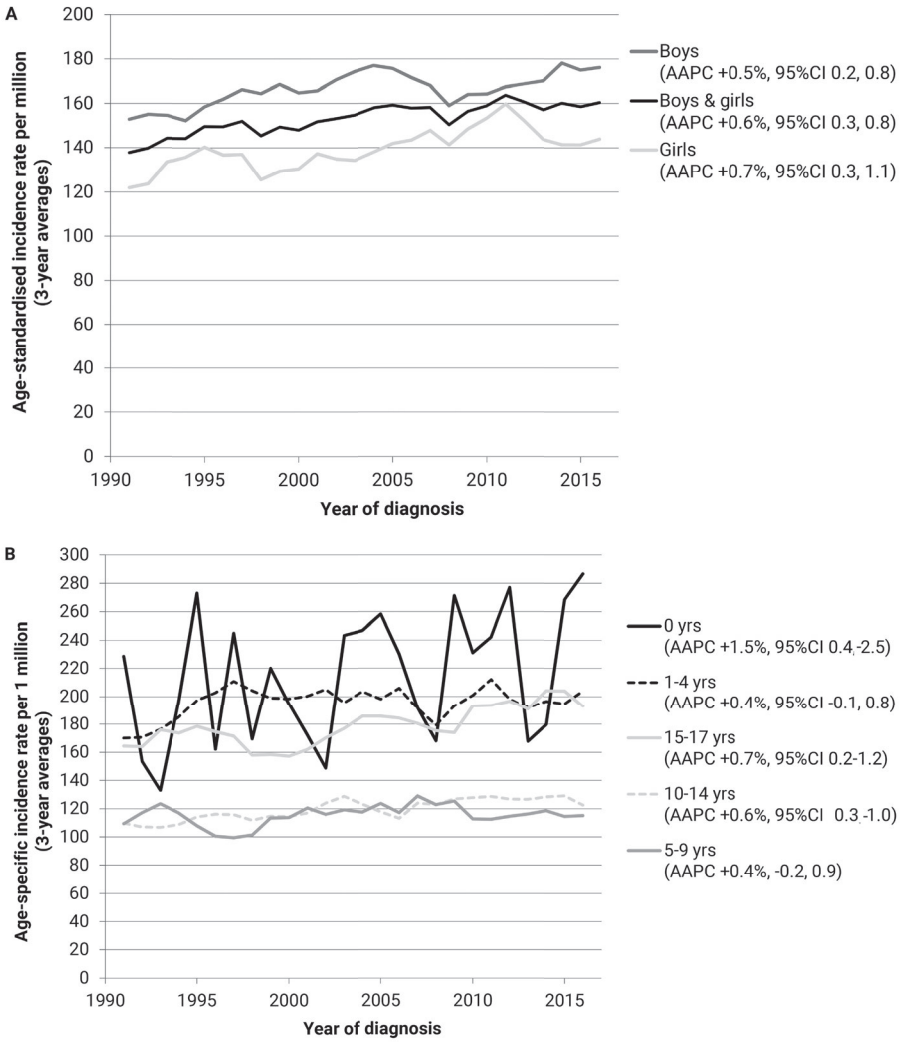


Figure 3.3. Trends in incidence of childhood and adolescent cancer by gender and age in the Netherlands, 1990-2017. A) Age-standardised incidence rates[14] by gender over time. B) Age-specific incidence rates by age group over time. AAPC estimated from a regression line, which was fitted to the natural logarithm of the rates using calendar year as regressor variable. Note: Benign and borderline CNS tumours were excluded. *AAPC*, Average Annual Percentage Change; *CI*, confidence interval.

Table 3.1. Average number of new cancer cases per year, incidence rate per million person-years, and AAPC over time by diagnostic (sub)group in children and young adolescents (aged 0-17 years) in the Netherlands, 1990-2017

	Total number of cases	Average number of new cases per year				Average incidence rate per million person-years#				AAPC (%)	95% CI
	1990-2017	1990-2017	1990-99	2000-09	2010-17	1990-2017	1990-99	2000-09	2010-17		
All cancers	14,527	519	481	538	542	152.7	144.2	154.1	161.5	0.6	0.3 to 0.8
Gender											
Boys	8,079	289	269	301	297	166.0	158.3	168.1	172.9	0.5	0.2 to 0.8
Girls	6,448	230	211	237	245	138.8	129.5	139.4	149.7	0.7	0.3 to 1.1
Age (in years)											
0	1,099	39	36	40	42	208.8	184.8	207.4	240.5	1.5	0.4 to 2.5
1-4	4,188	150	147	154	147	195.3	189.4	194.1	204.2	0.4	-0.1 to 0.8
5-9	3,101	111	102	121	109	114.8	108.0	121.3	115.2	0.4	-0.2 to 0.9
10-14	3,228	115	102	120	126	119.2	111.3	121.2	126.5	0.6	0.3 to 1.0
15-17	2,911	104	94	103	118	178.4	168.0	175.3	195.2	0.7	0.2 to 1.2
All cancers without pilocytic astrocytomas	*13,653*	*488*	*456*	*503*	*508*	*143.6*	*137.0*	*144.0*	*151.5*	*0.5*	*0.3 to 0.7*
ICCC-3 diagnostic group											
I. Leukaemia's	4,103	147	134	156	151	44.8	41.4	46.2	47.3	0.7	0.3 to 1.2
Ia. Lymphoid leukaemia's	3,189	114	105	122	115	35.0	32.6	36.3	36.3	0.6	0.1 to 1.1
Ib. Acute myeloid leukaemia's	728	26	24	26	28	7.8	7.3	7.7	8.5	0.8	-0.1 to 1.7
Ic. Chronic myeloproliferative diseases	83	3	2	4	4	0.8	0.6	0.9	1.0	NA	
Id-Ie. Other & unspecified leukaemia's	103	4	3	4	5	1.2	0.9	1.2	1.4	NA	
II. Lymphomas	2,098	75	72	75	79	20.2	20.1	19.8	20.8	0.2	-0.3 to 0.8
IIa. Hodgkin lymphomas	1,013	36	33	38	38	9.4	8.9	9.7	9.7	0.6	-0.3 to 1.4
IIb. Non-Hodgkin lymphomas	711	25	25	23	29	7.0	7.2	6.3	7.7	0.3	-0.7 to 1.4
IIc. Burkitt lymphomas	359	13	14	13	11	3.7	4.0	3.7	3.2	-0.8	-2.3 to 0.7
IId-IIe. Other & unspecified lymphomas	15	1	0	1	1	0.1	0.1	0.1	0.2	NA	

Table 3.1. (continued)

	Total number of cases	Average number of new cases per year				Average incidence rate per million person-years#				AAPC (%)	95% CI
	1990-2017	1990-2017	1990-99	2000-09	2010-17	1990-2017	1990-99	2000-09	2010-17		
III. CNS tumours[a]	2,819	101	88	104	112	29.7	26.5	29.8	33.6	1.0	0.5 to 1.5
IIIa. Ependymomas and choroid plexus tumours	272	10	10	10	8	3.0	3.2	3.1	2.6	-1.0	-2.4 to 0.5
IIIb/d. Astrocytomas & gliomas	1,727	62	51	66	70	17.9	15.2	18.5	20.4	1.3	0.7 to 1.9
Pilocytic astrocytomas (ICD-O-3 M9421)	*874*	*31*	*25*	*36*	*34*	*9.1*	*7.3*	*10.1*	*10.1*	*1.8*	*0.8 to 2.8*
Astrocytomas NOS (ICD-O-3 M9400 and 9430)	*212*	*8*	*13*	*4*	*5*	*2.2*	*3.7*	*1.2*	*1.5*	*NA*	
Gliomas NOS (ICD-O-3 M9380)	*265*	*9*	*2*	*11*	*17*	*2.8*	*0.6*	*3.2*	*5.0*	*NA*	
IIIc. Embryonal tumours	616	22	19	24	24	6.7	5.8	6.9	7.5	1.2	0.1 to 2.3
IIIe-IIIf. Other & unspecified CNS tumours	204	8	8	5	10	2.2	2.3	1.3	3.1	1.3	-1.5 to 4.1
III. CNS tumours without pilocytic astrocytomas	*1,945*	*65*	*64*	*69*	*78*	*20.6*	*19.2*	*19.2*	*23.5*	*0.7*	*0.1 to 1.4*
IV. Neuroblastoma and other peripheral nervous cell tumours	689	25	22	26	26	8.2	7.4	8.2	9.2	1.0	0.1 to 2.0
Iva Neuroblastoma	667	24	21	25	26	8.0	7.1	8.1	9.0	1.2	0.1 to 2.2
V. Retinoblastoma[b]	341	12	13	11	13	6.9	7.2	6.1	7.5	-0.6	-2.6 to 1.4
VI. Renal tumours	723	26	26	27	24	8.5	8.4	8.7	8.3	-0.2	-1.4 to 1.0
VII. Hepatic tumours	175	6	6	7	5	2.0	1.9	2.3	1.7	1.3	-1.2 to 3.8
VIII. Bone tumours	895	32	28	35	34	8.5	7.7	9.0	8.9	0.8	-0.2 to 1.8
VIIIa. Osteosarcomas	437	16	15	17	15	4.1	4.0	4.3	3.8	-0.5	-2.2 to 1.1
VIIIb. Chondrosarcomas	21	1	1	1	1	0.2	0.2	0.2	0.2	NA	
VIIIc. Ewing bone tumours	340	12	10	13	14	3.3	2.8	3.4	3.8	2.4	0.9 to 4.0
VIIId-VIIIe. Other & unspecified bone tumours	97	3	2	4	4	0.9	0.7	1.1	1.0	NA	

Table 3.1. (continued)

	Total number of cases	Average number of new cases per year				Average incidence rate per million person-years#				AAPC (%)	95% CI
	1990-2017	1990-2017	1990-99	2000-09	2010-17	1990-2017	1990-99	2000-09	2010-17		
IX. Soft tissue sarcomas	977	35	35	34	35	10.1	10.5	9.8	10.0	-0.6	-1.5 to 0.3
IXa. Rhabdomyosarcomas	514	18	20	17	17	5.5	6.2	5.0	5.2	-1.2	-2.4 to -0.1
IXb-IXe. Other & unspecified soft tissue sarcomas	463	17	15	17	18	4.6	4.3	4.8	4.	0.2	-1.0 to 1.4
X. Germ cell & gonadal tumours	727	26	27	24	27	7.3	7.9	6.5	7.6	-0.1	-1.0 to 0.8
Xa. Intracranial and intraspinal germ cell tumours	126	5	5	4	4	1.2	1.4	1.1	1.1	-1.0	-3.9 to 1.8
Xb. Extracranial and extragonadal germ cell tumours	138	5	5	4	6	1.7	1.7	1.4	2.0	1.4	-0.7 to 3.5
Xc. Gonadal germ cell tumours: testis	269	10	10	8	11	5.1	5.7	4.2	5.5	-0.8	-2.5 to 0.9
Xc. Gonadal germ cell tumours: ovary	154	6	5	6	6	3.0	3.0	3.0	2.8	0.4	-1.9 to 2.7
Xd-Xe. Other & unspecified gonadal tumours	40	1	2	2	1	0.4	0.4	0.4	0.2	NA	
XI. Other epithelial tumours	942	34	29	38	35	8.9	8.0	9.7	9.0	0.9	-0.1 to 1.9
XIb. Thyroid carcinomas	255	9	9	8	11	2.4	2.4	2.2	2.8	1.7	-0.5 to 4.0
XId. Malignant melanoma	414	15	12	18	14	3.9	3.3	4.8	3.6	1.1	-0.2 to 2.5
XIa, XIc, XIe-XIf Other & unspecified epithelial tumours	273	10	9	11	10	2.6	2.3	2.8	2.6	0.3	-1.5 to 2.1
XII. Other and unspecified tumours	37	1	1	1	2	0.4	0.3	0.4	0.6	NA	

[a] Including pilocytic astrocytomas, other CNS tumours having a behaviour code /0 and /1 and completely registered since 2000 only were excluded and those tumours are separately described in **supplementary table S3.2**

[b] Numbers, rates and average annual percentage change calculated for 0-9 years, only

[#] Incidence rates were standardised following the World Standard Population[13]; age-specific incidence rates were calculated for age groups consisting ≤ 5 years

NA, estimation of a reliable average annual percentage change was not possible because of n = 0 in ≥ 1 incidence year

Table 3.2. Trends in incidence of cancer in children and young adolescents (aged 0-17 years) for the entire study period and for any time segment identified in joinpoint analysis by diagnostic ICCC-3 (sub)group, gender and age at diagnosis in the Netherlands, 1990-2017[a, b]

	Average number of new cases per year	Average incidence rate per million person-years#	Overall trend AAPC, % (95% CI)	AAPC during a time segment (95% CI) identified by joinpoint analysis Year of incidence					
				1990	1995	2000	2005	2010	2015
I. Leukaemia's	147	44.8	0.7 (0.3 to 1.2)						
Gender									
Boys	85	50.2	0.5 (-0.1 to 1.1)	4.8 (0.4 to 9.4)		-0.4 (-1.3 to 0.5)			
Girls	62	39.1	1.1 (0.4 to 1.8)						
Age (in years)									
0	8	42.8	3.1 (1.2 to 5.1)						
1-4	62	81.3	0.4 (-0.2 to 1.1)						
5-9	36	37.4	0.6 (-0.2 to 1.4)						
10-14	26	26.3	0.6 (-0.5 to 1.6)						
15-17	15	25.1	1.4 (-0.0 to 2.9)						
III. CNS tumours	101	29.8	1.0 (0.5 to 1.5)						
Gender									
Boys	55	31.6	1.0 (0.4 to 1.7)						
Girls	46	27.9	1.0 (0.2 to 1.9)						
Age (in years)									
<5	34	35.3	1.3 (0.5 to 2.0)						
5-9	31	32.6	0.9 (-0.3 to 2.1)						
10-14	24	24.6	0.3 (-0.8 to 1.4)						
15-17	12	21.1	1.2 (-0.4 to 2.7)						

Table 3.2. (continued)

	Average number of new cases per year	Average incidence rate per million person-years#	Overall trend AAPC, % (95% CI)	AAPC during a time segment (95% CI) identified by joinpoint analysis Year of incidence					
				1990	1995	2000	2005	2010	2015
IIIb. Pilocytic astrocytomas (ICD-O-M9421/1)	31	9.1	1.8 (0.8 to 2.8)	3.4 (2.0 to 4.8)				-5.5 (-11.7 to 1.0)	
Gender									
Boys	15	8.7	1.5 (0.3 to 2.8)						
Girls	16	9.5	1.9 (0.2 to 3.6)	4.2 (2.0 to 6.5)				-11.6 (-23.5 to 2.1)	
Age (in years)									
<5	9	9.6	2.3 (0.6 to 4.1)						
5-9	11	10.9	1.0 (-0.7 to 2.7)	4.4 (2.0 to 6.9)				-10.0 (-17.4 to -1.8)	
10-14	7	7.7	0.7 (-0.9 to 2.3)						
15-17	4	7.0	NA						
IV. Neuroblastomas	24	8.0	1.2 (0.1 to 2.2)						
Gender									
Boys	13	8.8	1.1 (-0.1 to 2.4)						
Girls	11	7.7	0.7 (-0.8 to 2.2)						
Age (in years)									
0	8	42.7	0.6 (-1.1 to 2.3)						
1-4	12	16.3	1.1 (-0.2 to 2.4)						
5-17	4	1.7	2.2 (-0.4 to 4.7)						
VIIIc. Ewing bone tumours	12	3.3	2.4 (0.9 to 4.0)						
Gender									
Boys	7	3.6	3.0 (1.0 to 5.1)						
Girls	5	3.0	2.1 (-0.5 to 4.7)						

Table 3.2. (continued)

	Average number of new cases per year	Average incidence rate per million person-years#	Overall trend AAPC, % (95% CI)	AAPC during a time segment (95% CI) identified by joinpoint analysis Year of incidence					
				1990	1995	2000	2005	2010	2015
Age (in years)									
<10	4	2.0	NA						
10-17	8	5.3	NA						
IXa. Rhabdomyosarcomas	18	5.5	-1.2 (-2.4 to -0.1)						
Gender									
Boys	11	6.3	-1.2 (-3.1 to 0.6)						
Girls	8	4.7	-1.4 (-2.9 to 0.1)						
Age (in years)									
<5	8	8.0	-1.9 (-4.2 to 0.3)						
5-9	5	5.0	-0.4 (-2.4 to 1.5)						
10-17	6	3.7	-0.4 (-2.4 to 1.5)						
XId. Malignant melanomas	15	3.9	1.1 (-0.2 to 2.5)	6.4 (2.6 to 10.4)			-2.5 (-5.0 to 0.1)		
Gender									
Boys	6	3.0	2.1 (-0.7 to 4.9)						
Girls	9	4.8	0.7 (-1.1 to 2.4)						
Age (in years)									
<15	7	2.1	NA						
15-17	8	13.9	-0.3 (-1.7 to 1.1)						

[a] No trend transitions were observed for the total group

[b] Joinpoint analyses were also performed for II. Lymphomas, IIIc. Embryonal tumours, V. Retinoblastomas, VI. Renal tumours, VII. Hepatic tumours, VIII. Bone tumours, IX. Soft tissue sarcomas,
X. Germ cell and gonadal tumours and XI. Other epithelial tumours, but no significant changes in incidence were found during the entire study period or during any time segment.

[#] Incidence rates were standardised following the World Standard Population[14]; age-specific incidence rates were calculated for age groups consisting =< 5 years

NA: joinpoint analysis and estimation of a reliable average annual percentage change was not possible because of N=0 in >=1 incidence years

Incidence increases of CNS tumours were seen in both sexes with a rise of 1.0% per year (boys: from 28 per million person-years in 1990-99 to 36 in 2010-17; girls: from 25 in 1990-99 to 32 in 2010-17) and in young children below the age of 5 years with a rise of 1.3% annually (95% CI 0.5-2.0; from 31 per million in 1990-99 to 42 in 2010-17), with no significant changes in trend (**table 3.2**). The increase of CNS tumours was caused by increases of astrocytomas/gliomas and embryonal CNS tumours (+1.3% annually, 95% CI 0.7-1.9 and +1.2% per year, 0.1-2.3, respectively) comprising 83% of all CNS tumours. Pilocytic astrocytomas represented half of the astrocytomas/gliomas and mainly responsible for the significant increase in incidence of astrocytomas/gliomas (+1.8% per year, 95% CI 0.8-2.8; **table 3.1**). In joinpoint analysis, the trend of pilocytic astrocytomas increased until 2010 by 3.4% per annum (95% CI 2.0-4.8) followed by a stable incidence at 10 per million person-years. The same pattern was visible in girls and 5-9 years old ones (**table 3.2**).

The incidence of neuroblastoma (i.e. diagnostic subgroup IVa) has risen significantly from 7.1 per million person-years in 1990-99 to 9.0 in 2010-17 with no joinpoints. The increase of Ewing bone tumours was observed in boys with a rise of 3% annually (95% CI 1.0-5.1), from 3.0 per million person-years in 1990-99 to 4.1 in 2010-17 with no trend transitions (**table 3.2**). The same pattern was seen in all tumours of the Ewing sarcoma family (diagnostic subgroups VIIIc and IXd.1-d.2), incidence increased by 2.3% (95% CI 0.8-3.7) from 3.4 per million person-years in 1990-99 to 4.8 in 2010-17, mainly seen in boys in which the incidence rate rose to 5.3 in 2010-17 (+3% annually, 95% CI 0.9-5.1).

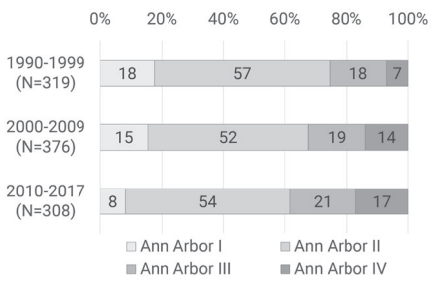
From the epithelial tumours, thyroid cancer seemed to increase in young adolescents from 5.9 per million person-years in 1990-99 to 10 in 2010-17 (+3% per annum, 95% CI -0.2 to6.2). A temporary increase in the incidence of malignant melanomas was observed during 1990-2002 by +6.4% per year (95% CI 2.6-10), and tended to decrease afterwards with -2.5% per year (-5.0 to 1.0; **table 3.2**).

Changes in stage at diagnosis over time

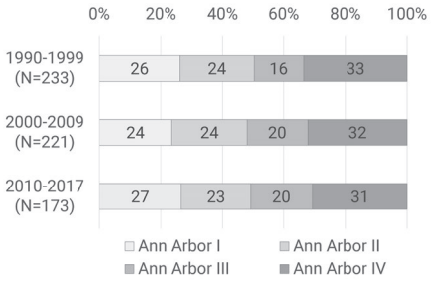
Time trends in stage at diagnosis by diagnostic (sub)group in children and young adolescents are presented in **figure 3.4**. Shifts in stage were observed for Hodgkin lymphoma, CNS tumours, non-rhabdomyosarcomas, testicular germ cell tumours, medullary thyroid carcinomas and malignant melanomas. For testicular germ cell tumours and malignant melanomas early-stage disease increased over time: stage I testicular germ cell tumours rose from 55% in 1990-2009 to 76% in 2010-17 (p =0.01), and stage I melanomas showed a rise from 48% in 1990-99 to 62%

in 2000-17 (p =0.047). The degree of malignancy in astrocytomas shifted towards WHO grade I and increased from 51% in 1990-99 to 67% in 2010-17 (p <0.01).

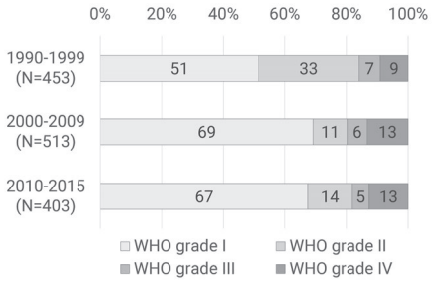
A shift to more advanced disease at diagnosis was seen in Hodgkin lymphomas, CNS tumours, rhabdomyosarcomas, non-rhabdomyosarcomas and medullary thyroid carcinomas. Hodgkin's Ann Arbor I declined from 18% in 1990-99 to 8% in 2010-17 (p <0.01) mainly due to an increase in Ann Arbor IV. Early-stage disease of rhabdomyosarcomas slightly decreased from 83% in 1990-99 to 73% in 2010-17 (p =0.05) mainly due to a decrease in stage II/III and a rise in stage IV. The same pattern was observed in non-rhabdomyosarcomas (from 90% to 79%, p =0.03) due to an increase in metastatic disease. Localised medullary thyroid carcinoma declined from 93% in 1990-99 to 64% in 2010-17 (p =0.01), whereas regional and metastatic disease increased (**figure 3.4**).



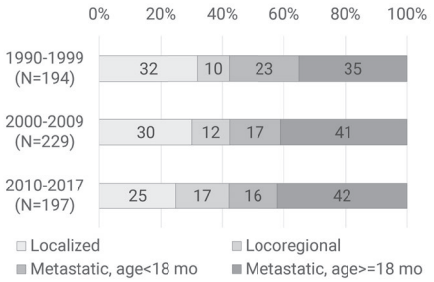
IIa. Hodgkin lymphoma
(proportional alteration of stage over time, p_{all}<.001; proportional alteration of Ann Arbor I vs. rest, p_{early}=.002)



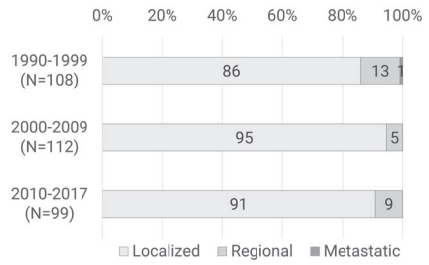
IIb. Non-Hodgkin lymphoma
(p_{all}=.92 ; Ann Arbor I vs. rest, p_{early}=.74)



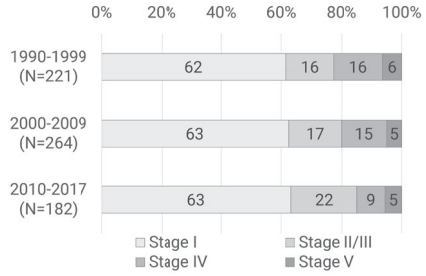
IIIb. Astrocytomas
(p_{all}<.001; WHO grade I/II vs. rest, p_{early}=.31)



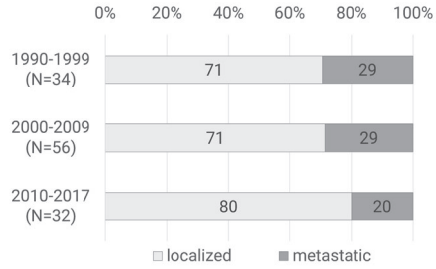
IVa. Neuroblastoma
(p_{all}=.11; localized vs. rest, p_{early}=.27)



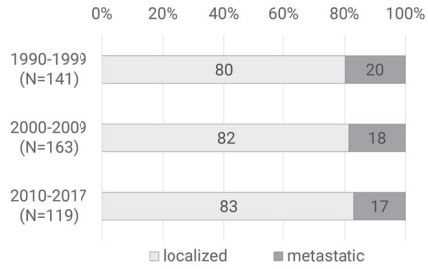
V. Retinoblastoma, <10 yrs
(p_{all}=.21; localized vs.rest, p_{early}=.09)



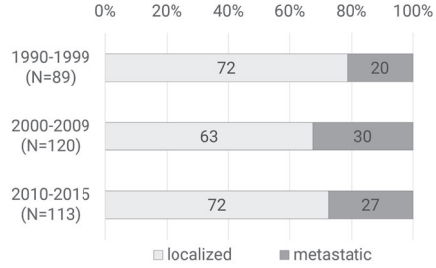
VIa. Nephroblastoma
(p_{all}=.36; Stage I-III vs. rest, p_{early}=.14)



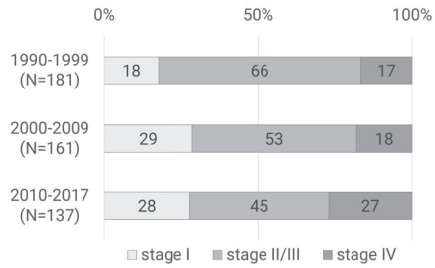
VIIa. Hepatoblastoma
(p_{all}=.63; localized vs. rest, p_{early}=.63)



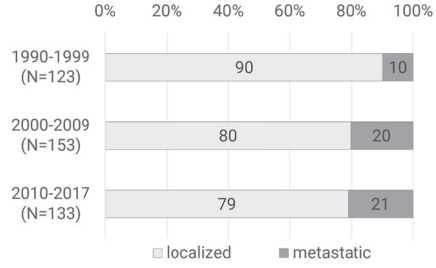
VIIIa. Osteosarcoma



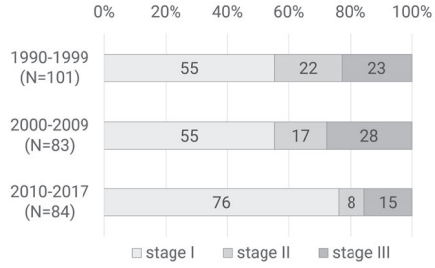
VIIIc. Ewing tumour(p_{all}=.82; localized vs. rest, p_{early}=.82)
(p_{all}=.20; localized vs. rest, p_{early}=.20)



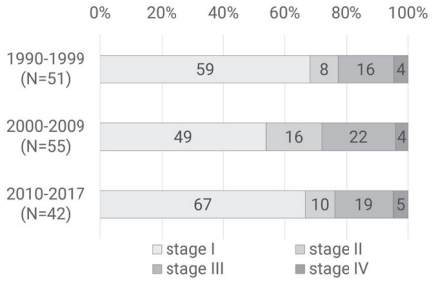
IXa. Rhabdomyosarcoma
(p_{all}=.20; stage I-III vs. rest, p_{early}=.05)



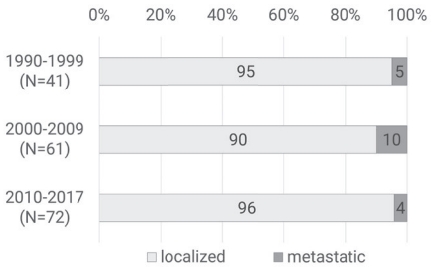
IXb-e. Non-rhabdomyosarcoma
(p_{all}=.02; localized vs. rest, p_{early}=.02)



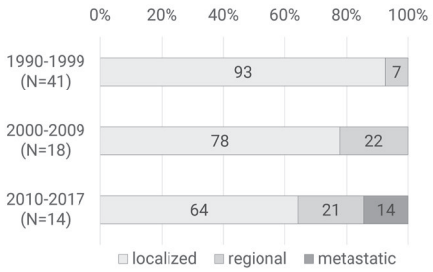
Xc. Testicular germ cell tumour
(p_{all}=.02; Stage I vs. rest, p_{early}=.01)



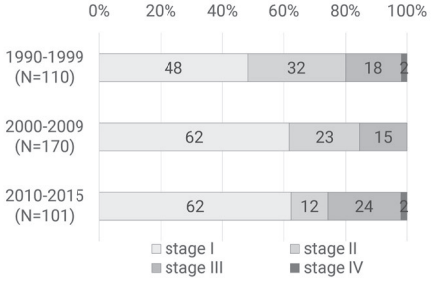
Xc. Ovarian germ cell tumour
(p_{all}=.77; Stage I vs. rest, p_{early}=.29)



XIb. Thyroid carcinoma, papillary/follicular
(p_{all}=.37; localized vs. rest, p_{early}=.37)



XIb. Thyroid carcinoma, medullary
(p_{all}=.02; localized vs. rest, p_{early}=.03)



IXd. Malignant melanoma
(p_{all}=.01; Stage I vs. rest, p_{early}=.047)

Figure 3.4. Time trends in stage at diagnosis by diagnostic ICCC-3 (sub)groups and period of diagnosis in children and young adolescents (aged 0-17 years) in the Netherlands, 1990-2017. Staging criteria of each ICCC-3 diagnostic (sub)group are described in **supplementary table S3.1**. Early-stage disease is highlighted in orange shades. Note: Benign and borderline CNS tumours were excluded.

DISCUSSION

This is the first nationwide, population-based study on time trends in incidence of childhood and young adolescent cancer in the Netherlands. Over a 28-year period the overall cancer incidence increased by an average of +0.6% annually. This increase in incidence was especially seen in infants, teenagers and young adolescents, and in the diagnostic (sub)groups: leukaemia, malignant CNS tumours, neuroblastoma and Ewing sarcoma. Rise in early-stage disease was seen in testicular germ cell tumours and malignant melanomas only, whereas a stage migration to more advanced stages was observed for Hodgkin lymphomas, soft tissue sarcomas and medullary thyroid carcinomas.

The slight increase in the overall cancer incidence since the 1990s is in line with a recent international pooling of European data, which showed an average increase of +0.5% per year in children younger than 15 years, and +1.0% in adolescents (aged 15-19 years) during 1991-2010[1]. A steady rise in cancer incidence among children has been seen in the developed countries since the 1950s.[2,17] Reasons for this rise are difficult to pin down as changes in diagnostic procedures and imaging, but also in registry procedures have taken place, and the aetiology of cancer in children is still largely unknown.[2,18]

Advances in diagnostic technology may result in an increased (earlier) detection and/or stage migration. In this study, increased detection was observed for low grade pilocytic astrocytomas until 2010, especially in young children (<10 years), which partly caused the total increase of CNS tumours. This finding is a result of a shift from unspecified astrocytomas towards pilocytic astrocytomas and might be explained by an increasing use of magnetic resonance imaging (MRI). This is consistent with a study from Great Britain in the 1990s[18], although the incidence increase started later in the Netherlands. Probably, the rise in unspecified gliomas at the brain stem is partially also due to the increased use MRI. Simultaneously, a rise in high-grade embryonal CNS tumours was observed. This might be a result of increasing use of molecular diagnostic tools combined with a higher diagnostic awareness of atypical teratoid/rhabdoid tumours because its recognition as a distinct pathologic entity since the mid-1990s.[19] However, in other countries a simultaneous decreasing trend for unspecified embryonal CNS tumours was detected and even a decreasing trend for medulloblastomas.[20-22] In this study, detailed trend analyses of the subtypes were not performed and therefore the exact cause of the observed rise in embryonal CNS tumours remains unclear.

Stage migration towards advanced-stage disease as a result of improved and more precise diagnostics was seen in Hodgkin lymphomas, soft tissue sarcomas and medullary thyroid carcinomas (MTC). However, these changes did not result into an increasing incidence.[23] For MTCs even a lower incidence was observed which might be the result of prophylactic surgery for multiple endocrine neoplasia 2a and 2b. Since 1993, genetic screening has been introduced in the Netherlands to identify carriers of these syndromes to prevent MTC by early prophylactic thyroid surgery which resulted in more frequent finding of thyroids with C-cell hyperplasia instead of MTC.[24,25] This might also explain the stage shift in MTCs. The opposite, an increased proportion of early-stage disease, was observed in malignant melanomas and testicular germ cell tumours. For melanomas, this is due to the increased diagnostic awareness among general practitioners, dermatologists and the general population as a result of prevention campaigns.[26] Causes for the rise in early disease of testicular germ cell tumours is less clear and probably a mix of increased diagnostic awareness among general practitioners and the use of more sensitive imaging modalities.[27]

The effect of improved diagnostics and diagnostic awareness on the rising incidences of leukaemia, neuroblastoma and Ewing tumours is less clear. The largest increase of leukaemia was made during the 1990s and most visible in infants. Under-diagnosis in the past could be a reason as shown in a study from the United Kingdom where acute lymphoblastic leukaemia was under-diagnosed in poorer communities.[28] However, this seems not valid for our finding as the Netherlands has a high quality system of child health care. Over 90% of all children up to the age of 4 years visit the free public service of child health clinics that monitor health and social development on a regular basis.[29] A recent publication of our group showed that the rising incidence of neuroblastoma could not be explained by registration artefacts, immigration of paediatric patients to the Netherlands or improved diagnostics.[30] For the observed increase in Ewing tumours, we do not expect that diagnostics play a role. Despite of the difficulty in interpretation of biopsy specimens, a pathology review in the Netherlands showed that agreement on original diagnosis was almost perfect for Ewing tumours.[31]

The possibility of real changes in background risk factors cannot be excluded as a cause of the observed increasing childhood cancer incidence. Etiological factors are largely unknown for most childhood cancers, but changes in social structures (e.g. older maternal age, increasing percentage of Caesarean deliveries, birth weight, family size, attitudes regarding breastfeeding and immunisation, daycare attendance), socioeconomic situation, exposure to artificial and natural substances (e.g. ionising radiation, electromagnetic fields, pesticides, etc.) during the last decades might have some impact on the development of childhood cancer.[1,2,32-35] Most of those risk factors have been associated with leukaemia.[36]

The strength of our study was its population-based nature and the NCR not having age or hospital limits (i.e. inclusion of children and young adolescents who might not have been treated by a paediatric oncologist). In a previous study, we have linked the NCR with the Registry of the Dutch Childhood Oncology Group, which showed that 18% of children and adolescents with cancer below the age of 18 years were not known in paediatric oncology centres.[6] A limitation of this study is the missing stage information of ependymomas and embryonal CNS tumours. The Toronto staging guidelines were implemented in the NCR since 2018 and therefore it was not possible to report on stage distribution of those diagnostic subgroups. Furthermore, there were changes in stage registration over time: during 1990-2002 TNM classification was used for blastomas, whereas since 2003, the extent of disease was used. However, it was possible to generate stage categories based on both staging classifications (**supplementary table S3.1**), and the distribution of stages was in line with a population-based study from Australia which described the distribution of cases by stage at diagnosis for the first time.[37] Moreover, we have tried to minimise the influence of registration artefacts by excluding those tumours that were not registered completely during our study period.

CONCLUSION

In conclusion, this is the first study that describes the incidence for children and young adolescents in the Netherlands including the unique information on stage at diagnosis. Rise in early-stage disease was found for a few childhood cancers only, but could not explain the total increase in cancer incidence. Improved diagnostics and increased diagnostic awareness have mainly led to higher proportions of advanced disease. Real changes in background factors seem of more importance in explaining the incidence increase.

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SUPPLEMENTARY TABLES

Table S3.1. Childhood cancer staging criteria, definition of localized disease and included numbers of paediatric patients used in Figure 3

Diagnostic group/subgroup[a]		Staging criteria[b]	1990-2017 N
IIa. Hodgkin lympoma	Early stage disease	Ann Arbor I: Involvement of single lymph node region (I) or localized involvement of a single extralymphatic organ site (IE)	139
		Ann Arbor II: Involvement of two or more lymph node regions on same side of the diaphragm (II) or localized involvement of a single associated extralymphatic organ or site and its region on the same side of the diaphragm (IIE)	543
		Ann Arbor III: Involvement of lymph node regions on both sides of the diaphragm (III), which may also be accompanied by localized involvement of an associated extralymphatic organ or site (IIIE), or by involvement of the spleen (IIIS) or both (IIIE+S)	195
		Ann Arbor IV: Disseminated involvement of one or more extralymphatic organs, with or without associated lymph node involvement; or isolated extralymphatic organ involvement with distant (non-regional) nodal involvement	126
		Unknown stage	10
IIb. Non-Hodgkin lymphoma	Early stage disease	Ann Arbor I: Involvement of a single tumour mass or nodal area, excluding the abdomen and mediastinum	159
		Ann Arbor II: Involvement of two or more lymph node regions on same side of the diaphragm (II) or localized involvement of a single associated extralymphatic organ or site and its region on the same side of the diaphragm (IIE)	149
		Ann Arbor III: Involvement of lymph node regions on both sides of the diaphragm (III), which may also be accompanied by localized involvement of an associated extralymphatic organ or site (IIIE), or by involvement of the spleen (IIIS) or both (IIIE+S)	117
		Ann Arbor IV: Disseminated involvement of one or more extralymphatic organs, with or without associated lymph node involvement; or isolated extralymphatic organ involvement with distant (non-regional) nodal involvement	202
		Unknown stage or not applicable	84
IIIb. Astrocytomas[c]	Early stage disease	WHO grade I: lesions with low proliferative potential and the possibility of cure after surgical resection alone	860
		WHO grade II: lesions are usually infiltrative and often recur, despite having low levels of proliferative activity	263

Table S3.1. (continued)

Diagnostic group/subgroup[a]		Staging criteria[b]	1990-2017 N
		WHO grade III: lesions with clear histological evidence of malignancy, including nuclear atypia and sometimes brisk mitotic activity	86
		WHO grade IV: cytologically, malignant, mitotically active, necrosis-prone neoplasms that are often associated with rapid pre- and postoperative disease evolution and fatal outcome	160
		WHO grade unknown	11
IVa. Neuroblastoma	Early stage disease	Localized: Localized tumour not involving vital structures and confined to one body compartment (EoD=2 OR any T, N0/X, M0/X)	180
		Locoregional: Locoregional tumour with spread (EoD=3, 4, 5 OR any T, N+, M0/X)	82
		Metastatic: Distant metastatic disease (except stage MS; EoD=6 OR any T, any N, M+)	245
		INRGSS-MS disease: Metastatic disease confined to skin, liver, and/or bone marrow in a patient less than 18 months (EoD=6 OR any T, any N, M+)	113
		Unknown stage	47
V. Retinoblastoma	Early stage disease	Localized: Intraocular (EoD=2 OR T1-T3, N0/X, M0/X)	289
		Regional: Orbital extension or regional lymph nodes (EoD=3, 4, 5 OR T4 or N+, M0/X)	29
		Metastatic: Distant metastases present (EoD=6 OR any T, any N, M+)	<10
		Unknown stage	22
VIa. Nephroblastoma	Early stage disease	Stage I: Tumour is limited to the kidney (EoD=2 OR T1-T2, N0/X, M0/X)	416
		Stage II/III: Tumour extends beyond kidney (EoD=3, 4, 5 OR T3-T4, N+, M0/X)	121
		Stage IV: Haematogenous metastases or spread beyond abdomen at diagnosis (EoD=6 OR any T, any N, M+)	93
		Stage V: Bilateral renal involvement at diagnosis	37
		Unknown stage	36
VIIa. Hepatoblastoma	Early stage disease	Localized: Tumour confined to the liver including regional lymph nodes (EoD=2,3, 4, 5 OR any T, any N, M0/X)	88
		Metastatic: Distant metastases present (EoD=6 OR any T, any N, M+)	32

Table S3.1. (continued)

Diagnostic group/subgroup[a]		Staging criteria[b]	1990-2017 N
		Unknown stage	<10
VIIIa. Osteosarcomas	Early stage disease	Localized: Tumour confined to the area of origin including regional lymph nodes (EoD=2, 3, 4, 5 OR any T, any N, M0/X)	345
		Metastatic: Distant metastases present (EoD=6 OR any T, any N, M+)	78
		Unknown stage	14
VIIIc. Ewing tumours	Early stage disease	Localized: Tumour confined to the area of origin including regional lymph nodes (EoD=2, 3, 4, 5 OR any T, any N, M0/X)	233
		Metastatic: Distant metastases present (EoD=6 OR any T, any N, M+)	89
		Unknown stage	18
IXa. Rhabdomyosarcoma	Early stage disease	Stage I: Tumour confined to the area of origin including the regional lymph nodes (EoD=2, 3, 4, 5 OR any T, any N, M0/X) at favourable sites: orbit (ICD-O-3 site C69.6), head and neck (ICD-O-3 sites C00-C14) and genitourinary sites (ICD-O-3 sites C51-C68, excluding bladder, C67 and prostate tumours, C61)	116
		Stage II/III: Tumour confined to the area of origin including the regional lymph nodes (EoD=2, 3, 4, 5 OR any T, any N, M0/X) at nonfavourable sites (i.e., all sites not noted as favourable)	267
		Stage IV: Distant metastases present, any site (EoD=6 OR any T, any N, M+)	96
		Unknown stage	35
IXb-IXe. Non-rhabdomyosarcoma	Early stage disease	Localized: Tumour confined to the area of origin including the regional lymph nodes (EoD=2,3,5 OR any T, any N, M0/X)	338
		Metastatic: Distant metastases present (EoD=6 OR any T, any N, M+)	71
		Unknown stage	54
Xc. Gonadal germ cell tumours - testicular	Early stage disease	Stage I: Tumour confined to the testis (any T, N0/X, M0/X)	166
		Stage II: Tumour extension to regional lymph nodes (any T, N+, M0/X)	43
		Stage III: Distant metastases present (any T, any N, M+)	59
		Unknown stage	<10

Table S3.1. (continued)

Diagnostic group/subgroup[a]		Staging criteria[b]	1990-2017 N
Xc. Gonadal germ cell tumours - ovarian	Early stage disease	Stage I: Tumour confined to ovaries (one or both) (T1, N0/X, M0/X)	85
		Stage II: Tumour involves one or both ovaries with pelvic extension (below the pelvic brim) (T2, N0/X, M0/X)	17
		Stage III: Tumour involves one or both ovaries with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes (T3 or N+, M0/X)	28
		Stage IV: Distant metastasis (any T, any N, M+)	<10
		Unknown stage	18
XIb. Thyroid carcinomas - papillary/follicular	Early stage disease	Localized: any T, any N, M0/X	163
		Metastatic: distant metases present (any T, any N, M+)	11
		Unknown stage	<10
XIb. Thyroid carcinomas - medullary	Early stage disease	Localized: any T, N0/X, M0/X	61
		Regional: any T, N+, M0/X	10
		Metastatic: distant metastases present (any T, any N, M+)	<10
		Unknown stage	<10
XId. Malignant melanomas	Early stage disease	Stage I (T1-2, N0/X, M0/X)	221
		Stage II (T3, N0/X, M0/X)	86
		Stage III (T4 or N+, M0/X)	70
		Stage IV (any T, any N, M+)	<10
		Unknown stage	33

[a] neoplasms were categorized according to the International Classification of Childhood Cancer (ICCC, third edition)[8]

[b] pathological stage was used and if unknown, clinical stage was taken; staging was based as much as possible on the Toronto Childhood Cancer Staging Guidelines [12]

[c] WHO grading system for astrocytomas [10] was used instead of the Toronto Childhood Cancer Staging Guidelines

Table S3.2. Average number of new cancer cases per year, incidence rate per million person-years, and average annual percentage change (AAPC) over time for CNS tumours with behaviour code /0 and /1 in children and young adolescents (0-17 years) in the Netherlands, 2000-2017

	Total number of cases	average number of new cases/year			average incidence rate per million person-yearsb			AAPC (%)	95%CI	p-value
		2000-2017	2000-2009	2010-2017	2000-2017	2000-2009	2010-2017			
III. Benign and borderline CNS tumours[a]	706	39	36	43	10.8	9.8	11.9	2.3	0.5 - 4.0	0.02
IIIa. Ependymomas & choroid plexus tumours	70	4	4	4	1.2	1.0	1.3	1.7	-2.0 - 5.5	0.35
IIIb/d. Astrocytomas and gliomas	31	2	2	2	0.5	0.4	0.5	NA		
IIIe/f. Other & unspecified	605	34	31	37	9.1	8.3	10.1	0.8	-2.6 - 4.3	0.63
Gender										
Boys	312	17	17	18	9.4	9.0	9.9	1.6	-0.6 - 3.8	0.16
Girls	394	22	19	25	12.2	10.6	14.1	2.7	0.4 - 5.0	0.03
Age (years)										
<5	128	7	7	7	7.5	7.1	8.1	1.7	-0.6 - 4.0	0.16
5-9	140	8	7	9	8.0	6.7	9.6	5.8	1.9 - 9.7	0.01
10-14	211	12	12	12	11.8	11.6	12.0	2.1	-2.2 - 6.3	0.34
15-17	227	13	11	15	21.2	18.6	24.6	1.6	-1.8 - 4.9	0.35

[a] excluding pilocytic astrocytomas (ICD-O-M9421)

[b] Incidence rates were standarised following the World Standard Population [13]; age-specific incidence rates were calculated for age groups consisting =< 5 years

NA, estimation of a reliable average annual percentage change was not possible because of N=0 in >=1 incidence years

CHAPTER 4

Progress against childhood and adolescent acute lymphoblastic leukaemia in the Netherlands, 1990-2015.

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Leukemia: accepted for publication

ABSTRACT

Against the background of environmental changes and therapeutic improvements, we assessed the epidemiologic progress against childhood and adolescent acute lymphoblastic leukaemia (ALL) in the Netherlands over a 26 year period.

ALL patients <18 years at diagnosis were selected from both the Netherlands Cancer Registry and the Dutch Childhood Oncology Group. Incidence and mortality trends per 1,000,000 person years were evaluated by the average annual percentage change (AAPC). Traditional actuarial survival analysis estimated overall survival (OS) was calculated in 5-year periods after diagnosis. The effect of sex, age, ALL subtype, and site of treatment on changes in survival over time were analysed by multivariable analysis.

Between 1990 and 2015, a total of 2,997 children and young adolescents were diagnosed with ALL, an average of 115 patients (range 87-147) per year. Overall incidence remained stable at 37 per million children, despite increases for B-cell precursor ALL (BCP-ALL) at age 10-14 years (AAPC +1.4%, p =0.04) and T-cell ALL at age 15-17 years (AAPC +3.7%, p =0.01). Five-year OS increased from 80% in 1990-94 to 91% in 2010-15 (p <0.01). Multivariable analyses demonstrated a 60% reduction in risk of death for patients treated in 2010-15 compared to 1990-94 (p<0.01). Simultaneously, mortality decreased by 4% annually (p <0.01). Patients aged 15-17 years were increasingly treated in a paediatric oncology centre, from 35% in 1990-94 to 87% in 2010-15 and experienced a 70% reduction of risk of death compared to those treated outside such a centre (p <0.01).

Significant progress against childhood ALL has been made in the Netherlands, visible by improved survival rates coinciding with declining mortality rates. These outcomes were accompanied by stable incidence rates, despite increases for BCP-ALL at age 10-14 years and T-cell ALL at age 15-17 years.

INTRODUCTION

Increases in incidence of childhood acute lymphoblastic leukaemia (ALL) have been reported at the beginning of the 21st century.[1-5] No clear explanations for these increases could be given in the absence of specific causes. ALL is the most common cancer among children, as well as the most frequent cause of death from cancer below the age of twenty.[6,7] Incidence and mortality trends are summary measures that provide snapshots of a long-term, time-dependent process.[8] Recent population-based studies for paediatric ALL focusing on incidence and mortality are limited in literature and are lacking for the Netherlands.

Since the early 1970s, treatment of children with ALL has been organized with national treatment protocols in the Netherlands. At that time the Dutch Childhood Leukemia Study Group (DCLSG, since 2002 extended to the Dutch Childhood Oncology Group [DCOG]) was established. The DCLSG/DCOG has a trial and data centre, with a reference diagnostic laboratory for leukaemias, and it also coordinates clinical trials, since 2003 also for solid tumours. Most recent changes in therapy were improvements in chemotherapy and better ways to stratify patients to receive less or more intensive therapy.[9-12] Trends in childhood ALL survival have been published in relation to therapeutic developments in several European countries, Japan and the US.[13] Both Pastore and colleagues[14] and Stiller and colleagues[15] have examined that changes in population-based survival parallel those reported by the relevant clinical trials. The increasing level of participation in trials, facilitated by the organisation of specialised care, has underpinned the substantial improvements in survival seen at the population level.[15]

The overall aim of this study was to assess the progress made for children and young adolescents with ALL in the Netherlands since 1990 by analysing trends in incidence and survival against the background of subsequent treatment regimens. Data from the Netherlands Cancer Registry (NCR) were combined with detailed leukaemia and treatment characteristics from the DCOG registry. Mortality data on cause of death were derived from the website of Statistics Netherlands. In addition, detailed analyses were made regarding ALL subtype and site of treatment.

PATIENTS AND METHODS

Study population

Patients aged <18 years and diagnosed with ALL (ICD-O-3 M9811-9818 and M9835-9837) from January 1990 to December 2015 were extracted from the NCR. For completeness a linkage with DCOG was performed and after this linkage the ALL subtype, site of treatment and treatment protocol could be determined for patients known at the DCOG registry. A total of 2,947 patients with ALL from the NCR were linked with 2,882 patients from the DCOG, yielding 2,997 patients eligible for inclusion (**supplementary figure 4.1**). In case of discrepancies in morphology, DCOG data were preferred over NCR data because of their role as a reference laboratory. For patients ascertained in the NCR only, morphology codes (according to the International Classification of Diseases for Oncology (ICD-O)) as registered in the NCR were taken. ALL may be of B-cell precursor (BCP) or T-cell (T-cell) lineage.[16] For 11 patients (<1%) the subtype was unknown.

The Netherlands Cancer Registry

The nationwide population-based NCR is maintained and hosted by the Netherlands Comprehensive Cancer Organisation (IKNL) and has a national coverage since 1989 with a completeness of at least 96% of all newly diagnosed malignancies in the Netherlands.[17] The NCR is notified by the Nationwide Network and Registry of Histopathology and Cytopathology, and the National Registry of Hospital Discharges. Retrospectively, data is extracted on patient, tumour and treatment characteristics. Primary therapy started within 9 months after diagnosis is recorded following order of administration and includes radiotherapy, systemic chemotherapy, and stem cell transplantation (SCT). Information on vital status (alive, dead, or emigration) is obtained by annual linkage of the NCR with the Nationwide Population Registries Network that holds vital statistics on all residents in the Netherlands. Last linkage was at February 1st 2019.

Registry of the Dutch Childhood Oncology Group

The centrally reviewed results of bone marrow, peripheral blood and spinal fluid samples taken at diagnosis are registered at the DCOG database. ALL diagnosis is based on a combination of cytomorphology, immunophenotyping and –increasingly– (molecular) cytogenetics.[12] Baseline patient and leukaemia characteristics (e.g., sex, age, white blood cell count at diagnosis, pre-existing syndromes and cytogenetics) are collected from the treating hospitals and included in the database. Eligibility and inclusion in specific clinical trials or treatment protocols are centrally registered at the DCOG. For these "in-trial patients" details regarding diagnosis, treatment, response to treatment, toxicity and outcome including relapse(s), second malignancy, and death were also registered. Five consecutive ALL treatment protocols (ALL7 – ALL11) were

active during our study period[9-12], plus specific protocols for infants, patients aged <1 year, since 1999 (Interfant)[18,19] and for Philadelphia-chromosome-positive ALL (EsPhALL) since 2005[20] (**supplementary figure 4.2**). Only patients treated in the seven paediatric oncology centres in the Netherlands were included in the DCOG registry. In the 1990s treatment was also performed in some non-university hospitals, under supervision of one of the paediatric centres. For the site of treatment analyses patients were considered as being treated outside a paediatric oncology centre if they were unknown in the DCOG registry.

Mortality data

Disease-specific mortality rates from 1980 to 2016 were derived from Statistics Netherlands (CBS). Because of privacy regulations, linkage between the NCR and CBS is not allowed in the Netherlands on a routine base. The lymphoid leukaemia (LL) specific ICD-9 code "204" and ICD-10 code "C91" were used to identify the number of persons who died from LL. Mortality data by age at death were presented by 5-year age groups (i.e., 0-4, 5-9, 10-14, and 15-19 years).

Statistical analyses

Characteristics of the study population were described as percentages in relation to the following five periods of diagnosis: 1990-94, 1995-99, 2000-04, 2005-09, and 2010-15. Differences among categorical variables were tested with the $\chi 2$ tests.

Annual incidence and mortality rates were calculated per million person years, using the annual mid-year population size as obtained from Statistics Netherlands. Rates were age-standardised according to the age structure of the World standard population for age ranges 0-14 year, 0-17 year for estimation of incidence rates, and 0-19 year for mortality rates.[21] Linear regression modelling assessed trends over time (i.e. time period 1990-2015 for incidence and time period 1980-2016 for mortality). A regression line was fitted to the natural logarithm of the incidence and mortality rates, including calendar year as a continuous variable.[21] Results were reported as average annual percent changes (AAPC) along with the corresponding 95% confidence interval (CI) and p-values.

Survival time was calculated as the time elapsed between the date of diagnosis and the date of death due to any cause (event) or date at last follow-up (i.e. alive or censored). Traditional actuarial survival analysis was used to calculate overall survival (OS) at 5 and 10 years after diagnosis. Changes over time in observed 5-and 10-year survival were evaluated with a p-trend analysis for period of diagnosis, sex, age at diagnosis, ALL subtype, and site of treatment by using parametric survival models (streg), adjusted for follow-up time (in years). To evaluate

their effect on the risk of dying per period of diagnosis, these parameters were entered in a multivariable analysis model. For survival analyses according to treatment protocol, patients eligible and treated according to the protocol were included (DCOG patients only).

All analyses were performed with STATA/SE 14.1 (StataCorp LP, College Station, Texas, USA). Joinpoint regression program (version 4.5.0.1) was used to check for incidence trend transitions during the study period.[22] A *p*-value <0.05 was considered statistically significant.

Role of the funding source

The funding source had no role in the study design, data collection, analyses and interpretation of the results, nor in writing of this manuscript.

RESULTS

Patient and leukaemia characteristics

Between 1990 and 2015, 2,997 children and adolescents aged <18 years were diagnosed with ALL in the Netherlands and analysed in this study. The majority of patients had a diagnosis confirmed by the reference laboratory of the DCOG (96%). Median age at diagnosis was 5 years (interquartile range 3 - 9 years). More boys than girls were diagnosed with ALL (male to female ratio (M:F ratio) being 1.4) (**table 4.1**). Patients below five years were mainly diagnosed with BCP-ALL (94%), decreasing with age to 73% of the patients aged 15-17 years.

Over time patients were increasingly treated at a paediatric oncology centre, 94% in the period 1990-94 compared to 98% in the period 2010-15 (*p* <0.01) (**table 4.1**).

Table 4.1 Patient characteristics of patients aged <18 years with acute lymphoblastic leukaemia in the Netherlands between 1990 and 2015

	Total		average per year	1990-94		1995-99		2000-04		2005-09		2010-2015*		*p-Chi2*
	N	%	N	N	%	N	%	N	%	N	%	N	%	
	2997		115	481	*16%*	589	*20%*	640	*21%*	585	*20%*	702	*23%*	
Age groups (years)														0.04
0	90	*3%*	3	10	*2%*	16	*3%*	24	*4%*	22	*4%*	18	*3%*	
1-4	1385	*46%*	53	237	*49%*	292	*50%*	295	*46%*	244	*42%*	317	*45%*	
5-9	796	*27%*	31	129	*27%*	149	*25%*	166	*26%*	180	*31%*	172	*25%*	
10-14	479	*16%*	18	65	*14%*	89	*15%*	114	*18%*	84	*14%*	127	*18%*	
15-17	247	*8%*	10	40	*8%*	43	*7%*	41	*6%*	55	*9%*	68	*10%*	
Sex														0.02
male	1744	*58%*	67	266	*55%*	373	*63%*	383	*60%*	325	*56%*	397	*57%*	
female	1253	*42%*	48	215	*45%*	216	*37%*	257	*40%*	260	*44%*	305	*43%*	
Site of treatment														<0.01
paediatric oncology centre	2882	*96%*	111	452	*94%*	558	*95%*	619	*97%*	567	*97%*	686	*98%*	
outside paediatric oncology centre	115	*4%*	4	29	*6%*	31	*5%*	21	*3%*	18	*3%*	16	*2%*	
Immunophenotype[&]														0.16
BCP-ALL	2562	*86%*	99	412	*87%*	502	*86%*	556	*87%*	489	*84%*	603	*86%*	
T-cell ALL	424	*14%*	16	64	*13%*	84	*14%*	83	*13%*	95	*16%*	98	*14%*	
unknown (<1% of total) ^	11		0	5		3		1		1		1		
Down syndrome (only for pts in DCOG registry)														0.31
yes	77	*3%*	3	9	*2%*	16	*3%*	14	*2%*	22	*4%*	16	*2%*	
no	2805	*97%*	108	443	*98%*	542	*97%*	605	*98%*	545	*96%*	670	*98%*	
unknown	115			29		31		21		18		16		

[&] As confirmed by the DCOG laboratory, if not known in the DCOG registry, the NCR morphology code was taken. BCP-ALL: B-cell precursor acute lymphoblastic leukaemia

^ unknown if not known in the DCOG registry

* 6yr period

In the last period, 2010-15, only 16 patients were not known in a DCOG centre because of treatment abroad (n = 4), treatment at an adult ward (n = 9) or death at first presentation at a hospital (n = 3).

Trends in incidence rates

On average, 115 patients (range 87-147) were diagnosed with ALL annually. The world standardised incidence rate for patients aged 0-17 years (WSR 0-17) increased over time by 0.6% per year (p =0.05), from 30 per million person-years in 1990-94 to 37 in 2010-15. This increase did not pertain to any age group (**figure 4.1**) or gender (**supplementary table S4.1**). BCP-ALL increased over time by 0.6% per year (p =0.06), from 26 per million person-years in 1990-94 to 32 in 2010-15 (**supplementary table S4.1**). However, for patients aged 10-14 years the increase was significant (AAPC +1.4%, p =0.04). T-cell ALL only showed an increasing trend for young adolescents (15-17 years) from 2 patients per year on average in the 1990s to 4 in 2010-15 (AAPC +3.7%, p =0.01) (**supplementary table S4.1**).

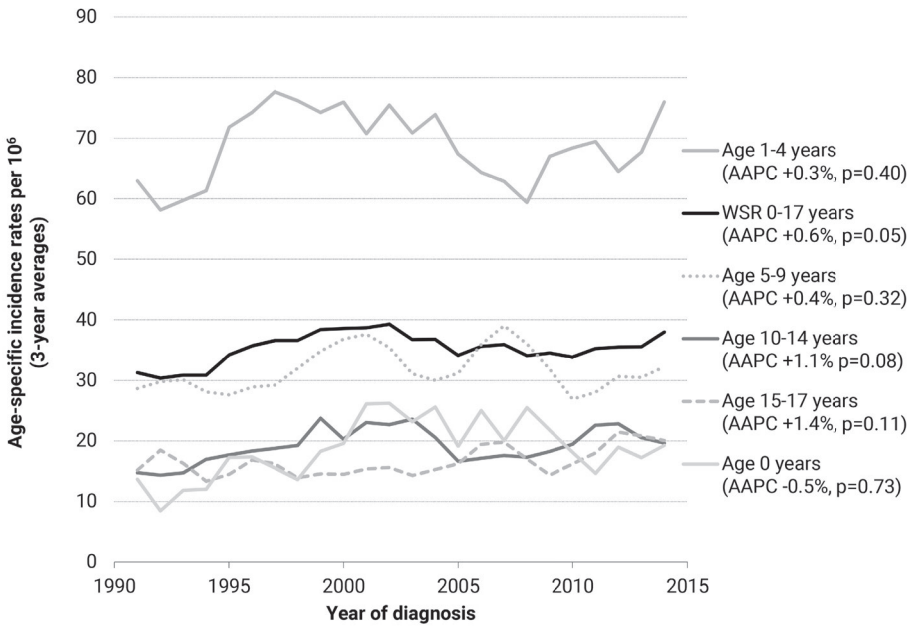

Figure 4.1 Time trends in incidence of patients aged <18 years with ALL by age groups in the Netherlands, 1990-2015
Three year moving averages of the age standardised incidence rate of ALL (standardised according to the World Standard Rate, WSR) and age specific incidence rates are shown. The average annual percentage change (AAPC) was estimated for each year of diagnosis with linear regression analyses.

Trends in overall survival

Five year overall survival increased from 80% (SE 2%) in 1990-94 to 91% (SE 1%) in 2010-15 (*p* <0.01) (**figure 4.2)**. Ten year overall survival increased from 76% (SE 2%) in 1990-94 to

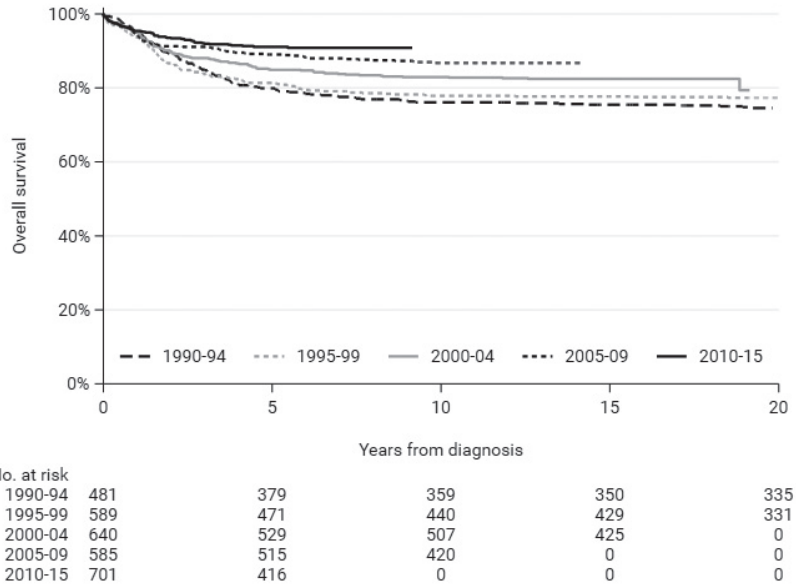

Figure 4.2 Time trends in overall survival of patients aged <18 years with ALL in the Netherlands, 1990-2015. The 1-year overall survival did not improve over time, *p*=0.70. The 5- and 10-year overall survival did improve over time, both *p*<0.01. The *p* for trend was tested with *streg* and adjusted for follow-up time.

87% (SE 1%) in 2005-09 (p <0.01) (**figure 4.2**). Five-year survival significantly increased for infants aged <1 year from 27% in 1990-99 to 66% in 2000-15 (*p* <0.01); for patients aged 1-4 years from 86% in 1990-94 to 95% in 2010-15 (*p* <0.01); for patients aged 5-9 years from 86% in 1990-94 to 96% in 2010-15 (*p* <0.01); for patients aged 10-14 years from 72% in 1990-94 to 85% in 2010-15 (*p* <0.01); for patients aged 15-17 years from 57% in 1990-94 to 74% in 2010-15 (*p* =0.02) (**figure 4.3a and supplementary table S4.2**). The 10-year overall survival did also increase significantly for all age groups, only non-significantly for patients aged 10-14 years. (**figure 4.3b and supplementary table S4.2**).

Five-year overall survival significantly increased for both boys and girls; for boys from 75% in 1990-94 to 90% in 2010-15 (*p* <0.01); for girls from 86% to 91% (*p* =0.04) (**supplementary table S4.2**). Ten year overall survival also significantly increased for boys, from 72% in 1990-94 to 89% in 2005-09 (*p* <0.01). Five- and 10-year overall survival significantly increased for BCP-ALL, from 81% in 1990-94 to 93% in 2010-15 (*p* <0.01) and from 77% in 1990-94 to 89% in 2005-09 (*p* <0.01), respectively. Five and 10-year overall survival for T-cell ALL did not improve (**supplementary table S4.2**).

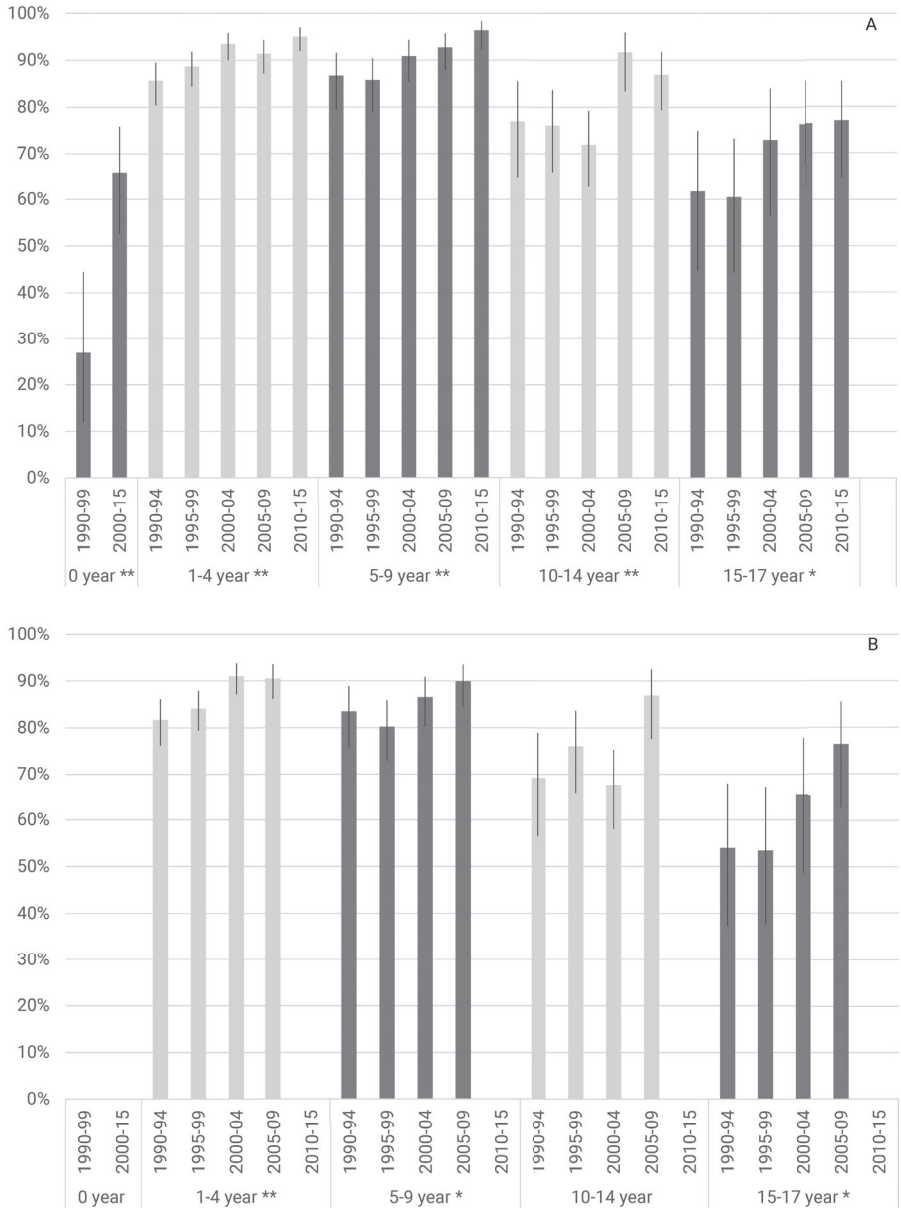

Figure 4.3 Time trends in overall survival of patients aged <18 years with ALL by age groups in the Netherlands, 1990-2015. Five (A) and 10-year (B) overall survival with corresponding confidence intervals, corrected for follow-up time. Ten-year overall survival for infants, patients aged <0 years is not given due to <20 patients in this group. And for patients diagnosed in the last period, follow-up time is not sufficient to report 10-year survival.

* Indicates significant improvement of survival over time for that age group, p >=0.01 and p <0.05

** Indicates significant improvement of survival over time for that age group, p <0.01

P for trend adjusted for follow-up time

Determinants for risk of death

The multivariable analysis for the risk of dying within 5-years after diagnosis, adjusted for follow-up time, demonstrated a significant decrease in the hazard ratio (HR) during the periods 2005-09 and 2010-15 (HR 0.5, *p* <0.01 and HR 0.4, *p* <0.01) compared to 1990-94 (**table 4.2**). Infants, children aged 10-14 years and young adolescents of 15-17 years exhibited an increased risk of death compared with children of 1-4 years at diagnosis (HR 8.2, *p* <0.01, HR 2.1, *p* <0.01 and HR 3.5, *p* <0.01, respectively). Patients with a T-cell ALL were at higher risk of dying compared to patients with BCP-ALL (HR 1.9, *p* <0.01) (**table 4.2**).

Table 4.2. Multivariable analysis for the risk of dying from acute lymphoblastic leukaemia for patients aged <18 years in the Netherlands between 1990 and 2015

		N	HR[a]	95% CI	p-value
Period	1990-94	481	Ref.		
	1995-99	589	0.9	0.7-1.2	0.56
	2000-04	640	0.7	0.5-0.9	0.01
	2005-09	585	0.5	0.1-0.3	<0.01
	2010-15	702	0.4	0.1-0.3	<0.01
Sex	male	1744	Ref.		
	female	1253	0.9	0.7-1.1	0.19
Age groups (years)	0	90	8.2	5.8-12	<0.01
	1-4	1385	Ref.		
	5-9	796	1	0.8-1.4	0.79
	10-14	479	2.1	1.6-2.8	<0.01
	15-17	247	3.5	2.6-4.7	<0.01
Immunophenotype	BCP-ALL	2562	Ref.		
	T-cell ALL	424	1.9	1.5-2.4	<0.01
	unknown	11	ND		

[a] In this multivariable analysis, each covariate is simultaneously adjusted for all other covariates and follow-up time. Hazard ratios represent risk of death within 5 years from diagnosis compared to the reference category.
BCP-ALL B-cell precursor acute lymphoblastic leukaemia, *HR* hazard ratio, *CI* confidence interval, *ND* not done

Site of treatment and trends in overall survival for patients aged 15-17 year

The percentage of patients aged 15-17 year and treated at a paediatric oncology centre increased significantly (*p* <0.01) over time, being 87% (n = 59) during 2010-15 compared with 35% (n = 14) during 1990-94 (**figure 4.4**). To determine whether the site of treatment also affected outcome, we developed two multivariable analyses models. The first demonstrated a decreased risk of death over time for the two most recent periods (2005-09 HR 0.4, *p* =0.03

and 2010-15 HR 0.5, *p* =0.04, respectively). Addition of site of treatment, i.e. adult oncology versus paediatric oncology resulted in the loss of significance for the HRs of the recent periods of diagnosis (HR 0.6, *p* =0.25 and HR 0.8, *p* =0.56, respectively). In this second model, site of treatment appeared to be the most discriminative factor for reduced risk of death, i.e. an HR 0.3 for patients treated at a paediatric oncology centre compared to treatment outside a paediatric oncology centre (*p* <0.01, **table 4.3**)

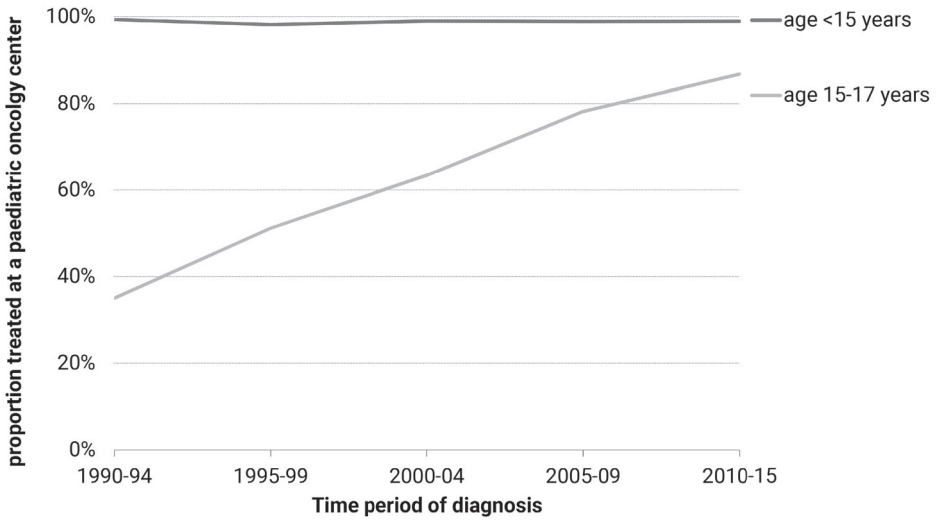

Figure 4.4: Proportion of patients with ALL, aged <15 years and aged 15-17 years, treated at a paediatric oncology centre, 1990-2015

Trends in mortality rates

Mortality rates below the age of 20 years at time of death decreased remarkably from 9.5 per million children in 1980-84 to 2.8 in 2010-16 (a decline of 4.0% per annum, *p* <0.01). In the first period on average 40 young people died per year compared to 11 per year in 2010-16 (**supplementary table S4.3**). Also for the period 1990-2016 the AAPC trend analysis remained significant. Low numbers did not allow to observe a trend in girls below age 5 nor aged 10-14 year at death (**supplementary table S4.3**).

DISCUSSION

This is the first population-based study describing trends in incidence, survival and mortality for children and adolescents aged <18 years with ALL in the Netherlands. Over a 26-year period we observed stable incidence rates and increasing survival rates for all ages. The progress made is supported by steadily decreasing, independently assessed, mortality rates for all age groups. Markedly more patients of 15-17 year were treated at a paediatric oncology centre which - in a subgroup analysis - improved their outcome significantly compared with those who were not treated at a paediatric oncology centre.

The age-standardised incidence rate (WSR) of ALL increased with a modest 0.6% per year. For the last period the WSR was 37 cases per million children aged 0-17 years. This incidence rate is similar to other western countries[23,24], although epidemiologic trend papers report mostly incidence trends for children aged <15 years or including adolescents <20 years. Compared to the reported increase in incidence in the 1990s[4,5] we can safely assume that incidence remained almost stable after 2000. We were also able to study occurrence of BCP- or T-cell ALL specifically and notice an increase for BCP- ALL in 10-14 year olds and for T-cell ALL in 15-17 year olds. Although we did not correct for multiple testing, it is not rare that one or two of the results became positive, due to temporal variation. All in all, substantial influences of environmental factors, either or not pregnancy related, were unlikely to have affected risk of childhood leukaemia in the Netherlands.

Table 4.3. Univariate and multivariable analyses for the risk of dying from acute lymphoblastic leukaemia for patients aged 15-17 years in the Netherlands between 1990 and 2015

		univariate analysis					multivariable analysis, 1st model				multivariable analysis, 2nd model			
		N	HR	95% CI		p-value	HR[a]	95% CI		p-value	HR[a]	95% CI		p-value
Period	1990-94	40	Ref.				Ref.				Ref.			
	1995-99	43	0.9	0.5	1.8	0.85	0.9	0.5	1.7	0.73	1.0	0.5	1.9	0.94
	2000-04	41	0.6	0.3	1.3	0.23	0.6	0.3	1.3	0.18	0.7	0.3	1.4	0.30
	2005-09	54	0.5	0.2	1.0	0.04	0.4	0.2	0.9	0.03	0.6	0.3	1.4	0.25
	2010-15	68	0.5	0.3	1.0	0.06	0.5	0.3	1.0	0.04	0.8	0.4	1.7	0.56
Sex	male	169	Ref.				Ref.				Ref.			
	female	77	1.2	0.7	1.9	0.48	1.2	0.8	2.0	0.41	1.5	0.9	2.4	0.14
Immunophenotype	BCP-ALL	179	Ref.				Ref.				Ref.			
	T-cell ALL	67	1.5	0.9	2.4	0.12	1.6	1.0	2.6	0.06	1.6	1.0	2.6	0.07
Site of treatment	outside paediatric oncology centre	83	Ref.								Ref.			
	paediatric oncology centre	163	0.3	0.2	0.5	<0.01					0.3	0.2	0.5	<0.01

[a]In the multivariable analysis, each covariate is simultaneously adjusted for all other covariates, and follow-up time. Hazard ratios represent risk of death within 5 years from diagnosis compared to the reference category. In the first multivariable model we did not consider site of treatment, and this model shows significantly lower risk of death in recent periods of diagnosis compared to the reference period 1990—1994. In the second multivariable model we added site of treatment which results in disappearance of the discriminative effect of period of diagnosis and a significantly lower risk of death for patients treated in a paediatric oncology centre. *BCP-ALL* B-cell precursor acute lymphoblastic leukaemia, *HR* hazard ratio, *CI* confidence interval

Our population-based survival data demonstrated increasing rates over time, with 5-year overall survival of 80% in 1990-94 versus 91% in 2010-15. The population-based study from the CONCORD working group showed similar results for patients aged 0-14 years and year of diagnosis between 1995 and 2009 for north-western European countries comparable with the Netherlands.[25] The COG has reported on the outcome of over 20,000 patients registered in their trials between 1990-2005, in which 5-year OS increased from 84% in 1990-94 to 90% in 2000-05[26] indicating very similar improvements in outcome in both North-America and Europe. Infants, older children and young adolescents had a less favourable prognosis compared to children aged 1-9 years. This might be explained by the higher incidence of unfavourable features such as KMT2A rearrangements[19] in infants and a higher incidence of BCR-ABL like abnormalities[27] and lower incidence of favourable prognostic features such as ETV6-RUNX1 and hyperdiploidy in older patients.[12] The increase in survival rate from 27% in 1990-99 to 66% in 2000-15 in infants is likely due to implementation of the Interfant treatment schemes including more intensive use of cytosine arabinoside. [18,19] It should be mentioned that the confidence intervals for infants are broad due to small numbers. Also, 5-year survival rate of 80% for T-cell ALL in 2010-15 was lower than the 93% for BCP-ALL. Historically, T-ALL patients have had a worse prognosis than other ALL patients.[12,13,28] With the better treatment stratifications based on MRD, the outcome for T-ALL patients improved to 81% in 2010-15 but there is still a gap with B-lineage ALL.

Five and 10-year overall survival rates for adolescents aged 15-17 years increased from <60% in 1990-94 to ~75% in 2010-15. The better hospital-based survival rates for adolescents (and young adults) were attained when adolescents were treated on paediatric ALL protocols compared to adult protocols about 15 years ago.[29-31] The percentage of patients aged 15-17 years treated at a paediatric oncology centre increased over time from 35% to 87% in the past 25 years in our study. Interestingly, a multivariable analysis showed that treatment of patients aged 15-17 years in a paediatric oncology centre led to a better outcome. Since the early 2000s young adult ALL treatment protocols have been adapted to the more paediatric like treatment approaches with dose-intensity of non-myelotoxic therapies and stricter timing of subsequent courses.[32] Possibly, there are still differences in management of treatment-related toxicities and/or trial participation in adult versus paediatric centres.[33]

In agreement with other studies, mortality rates declined constantly over time at each age group.[34,35]. Increased intensity of induction and reinduction therapy were the first important components of successful ALL treatment protocols at the end of the 1970s and 1980s.[36] We could not report on the incidence and survival in the 1980s because this was before initia-

tion of the NCR. Improvements in chemotherapy and better ways to stratify patients based upon genetic abnormalities and on initial treatment response measured by minimal residual disease[18-20], together with specific protocols for infants and BCR-ABL positive patients, further improved outcome for ALL patients. **Supplementary table 4.4** shows outcome data of the DCOG protocols used during the time period of the present study. There was no change in death before remission or death in remission over time. The improved survival has been achieved by better initial treatments leading to significantly improved EFS (from 66% to 89%) but part of patients is still rescued by relapse therapy illustrated by the gap between EFS and OS. The rate of stem cell transplantation did not significantly change over time. The proportion of secondary malignancies is below 2% on all DCOG protocols in the time period of the present study.[12,37]

Although detailed information on treatment schemes (initial and relapse treatment), risk group or response status are lacking in the NCR for individual patients, we did not have the intention with this descriptive epidemiological study to study outcome by treatment protocol or risk group. We just wanted to show whether there was progress. Strengths of our study include the linkage with the DCOG clinical registry over the whole study period. We could thus obtain morphology codes of almost all patients by centralized expert haemato-pathology review and determine the proportion of patients treated in a paediatric oncology centre. The latter improvement may be a stimulus for other groups.

CONCLUSION

All in all, by combining incidence, survival and mortality data we attained a comprehensive picture of the progress against ALL in children and young adolescents in the Netherlands by showing improved survival, especially improved survival of adolescents treated in a paediatric oncology centre, and supported by steadily declining mortality rates. The overall incidence rate was stable, despite two age and type specific increases.

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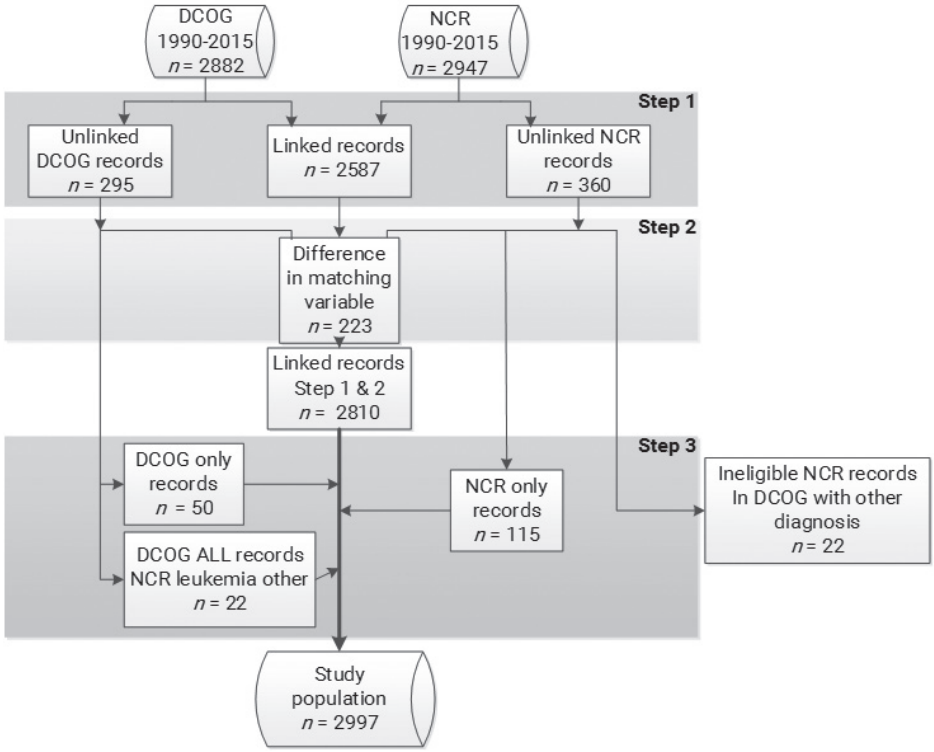
Supplementary figure S4.1

Linkage between the Dutch Childhood Oncology Group and Netherlands Cancer Registry data



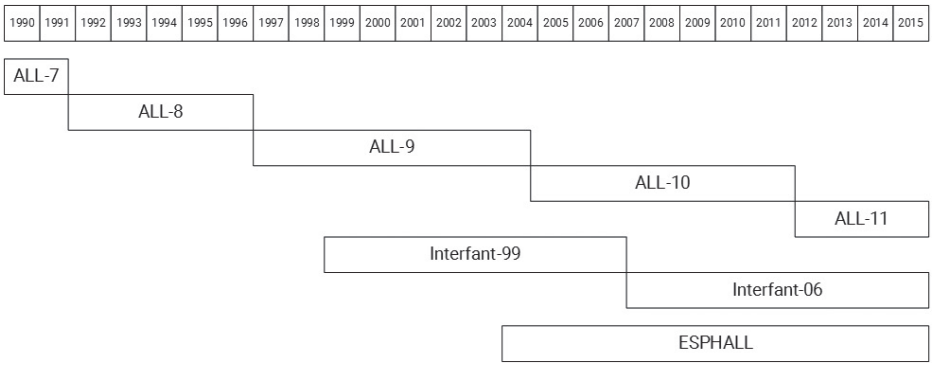
Legend Supplementary Figure S4.1

In order to check for completeness all children below age 18 and diagnosed with acute lymphoblastic leukemia (ALL) between 1 January 1990 and 31 December 2015 were selected from both databases. Linkage between the data files from the Dutch Childhood Oncology Group (DCOG) and Netherlands Cancer Registry (NCR) was performed in three steps. First, data files were merged by date of birth, gender and year of diagnosis which resulted in 2,587 linked records. 223 records had an inconsistency in one of the three merging variables of step 1, but could be added to the linked records. After step 2, 2,810 records were linked. In the third step remaining unlinked records were checked in the other registry by date of birth only. Fifty records were present in the DCOG registry, but could not be identified in the NCR. Another 22 records were also registered in the NCR, but with a different diagnosis; acute myeloid leukemia (AML, n=6), non-Hodgkin lymphoma (NHL, n=9), mixed phenotype acute leukemia (MPAL, n=3) and leukemia not otherwise specified (n=4). With respect to the unlinked NCR records, 115 records were not in the DCOG registry. These patients were included, but additional clinical information and treatment specifics were missing for them. Twenty-two records were registered by the NCR as ALL, but with a different diagnosis by the DCOG; NHL (n=18), leukemia not otherwise specified (n=1) and chronic myeloid leukemia (CML, n=3). These records were excluded, because the diagnosis by the DCOG was assumed to be most reliable, since they function as a reference laboratory.

After the final step, 2,997 patients could be included in the study.

Supplementary figure S4.2

Overview of the DCOG treatment protocols active during the study period



Footnotes Supplementary Figure S4.2

ALL-7: Jul 1988-Sep 1991, 0-15 years of age (total treatment duration was 18 months for all patients)[1];
ALL-8: Oct 1991-Dec 1996, 0-18 years of age (total duration of chemotherapy for all patients was 24 months)[2];
ALL-9: Jan 1997-Oct 2004, 0-18 years of age (total treatment duration was 109 weeks)[3];
ALL-10: Nov 2004-Mar 2012 1-18 years of age (total treatment duration was 24 months)[4];
ALL-11: Apr 2012-current, 1-18 years of age (2 years of treatment and 3 years for Ikaros positive patients);
Interfant-99:January 1999-January 2006, 0 years of age[5];
Interfant-06: February 2006-current 0 years of age[6];
ESPHALL: January 2004-June 2018, irrespective the patient's age including Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) only[7].

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Supplementary table S4.1: Incidence for children, aged <18 years and diagnosed with ALL in the Netherlands between 1990 and 2015

							AAPC				
Incidence Males & Females		**1990-94**	**1995-99**	**2000-04**	**2005-09**	**2010-15**	**1990-2015**	**SE**	**95% CI low**	**95% CI high**	**p-value**
	Average number of new cases/ year	96	118	128	117	117					
	Age adjusted incidence rate (per 10^6)	*30.4*	*36.2*	*37.8*	*34.9*	*36.6*	*0.6*	*0.3*	*0.0*	*1.2*	*0.05*
Age (years)											
0	Average number of new cases/ year	2	3	5	4	3					
	Incidence rate (per 10^6)	*10.2*	*16.5*	*23.7*	*23.7*	*17.0*	*-0.5*	*1.5*	*-3.7*	*2.7*	*0.73*
1-4	Average number of new cases/ year	47	58	59	49	53					
	Incidence rate (per 10^6)	*61.7*	*74.6*	*72.9*	*62.9*	*72.7*	*0.3*	*0.4*	*-0.4*	*1.1*	*0.40*
5-9	Average number of new cases/ year	26	30	33	36	34					
	Incidence rate (per 10^6)	*28.4*	*30.4*	*33.5*	*35.8*	*30.1*	*0.4*	*0.4*	*-0.4*	*1.3*	*0.32*
10-14	Average number of new cases/ year	13	18	23	17	21					
	Incidence rate (per 10^6)	*14.4*	*19.3*	*23.0*	*17.0*	*21.1*	*1.1*	*0.6*	*-0.1*	*2.4*	*0.08*
15-17	Average number of new cases/ year	8	9	8	11	11					
	Incidence rate (per 10^6)	*14.2*	*15.6*	*14.3*	*18.3*	*19.0*	*1.4*	*0.9*	*-0.3*	*3.2*	*0.11*

							AAPC				
Incidence Males		**1990-94**	**1995-99**	**2000-04**	**2005-09**	**2010-15**	**1990-2015**	**SE**	**95% CI low**	**95% CI high**	**p-value**
	Average number of new cases/ year	53	75	77	65	66					
	Age adjusted incidence rate (per 10^6)	*32.6*	*44.8*	*43.8*	*37.5*	*39.9*	*0.4*	*0.4*	*-0.4*	*1.3*	*0.31*
Age (years)											
0	*Average number of new cases/ year*	1	1	2	2	2					
	Incidence rate (per 10^6)	*8.0*	*12.1*	*21.2*	*21.2*	*20.2*	*1.4*	*1.5*	*-1.8*	*4.6*	*0.36*
1-4	Average number of new cases/ year	24	38	33	25	27					
	Incidence rate (per 10^6)	*61.1*	*93.9*	*78.7*	*63.0*	*71.6*	*-0.1*	*0.6*	*-1.3*	*1.1*	*0.87*
5-9	Average number of new cases/ year	16	18	22	21	19					
	Incidence rate (per 10^6)	*34.0*	*36.3*	*43.0*	*40.1*	*33.4*	*0.0*	*0.6*	*-1.3*	*1.4*	*0.95*

Supplementary table S4.1: (continued)

10-14	Average number of new cases/ year	7	12	15	10	13					
	Incidence rate (per 10^6)	*14.7*	*25.0*	*29.2*	*20.5*	*26.1*	*1.8*	*0.9*	*0.0*	*3.6*	*0.05*
15-17	Average number of new cases/ year	6	6	5	7	8					
	Incidence rate (per 10^6)	*20.1*	*20.5*	*17.8*	*22.7*	*27.3*	*1.4*	*1.3*	*-1.3*	*4.1*	*0.31*
							AAPC				
Incidence Females		**1990-94**	**1995-99**	**2000-04**	**2005-09**	**2010-15**	**1990-2015**	**SE**	**95% CI low**	**95% CI high**	**p-value**
	Average number of new cases/ year	43	43	51	52	51					
	Age adjusted incidence rate (per 10^6)	*28.1*	*27.2*	*31.5*	*32.2*	*33.2*	*0.8*	*0.4*	*-0.1*	*1.7*	*0.08*
Age (years)											
0	*Average number of new cases/ year*	1	2	3	2	1					
	Incidence rate (per 10^6)	*12.6*	*21.1*	*26.3*	*26.4*	*13.5*	*-1.8*	*1.6*	*-5.1*	*1.5*	*0.26*
1-4	Average number of new cases/ year	23	21	26	24	26					
	Incidence rate (per 10^6)	*62.3*	*54.4*	*66.9*	*62.8*	*73.9*	*0.8*	*0.6*	*-0.5*	*2.1*	*0.21*
5-9	Average number of new cases/ year	10	12	11	15	15					
	Incidence rate (per 10^6)	*22.5*	*24.3*	*23.6*	*31.4*	*26.7*	*1.0*	*0.7*	*-0.5*	*2.5*	*0.18*
10-14	Average number of new cases/ year	6	6	8	6	8					
	Incidence rate (per 10^6)	*14.0*	*13.3*	*16.5*	*13.3*	*15.9*	*0.6*	*1.1*	*-1.7*	*3.0*	*0.59*
15-17	Average number of new cases/ year	2	3	3	4	3					
	Incidence rate (per 10^6)	*8.1*	*10.4*	*10.7*	*13.6*	*10.3*	*1.4*	*1.3*	*-1.4*	*4.1*	*0.32*
							AAPC				
Incidence B cell precursor type		**1990-94**	**1995-99**	**2000-04**	**2005-09**	**2010-15**	**1990-2015**	**SE**	**95% CI low**	**95% CI high**	**p-value**
	Average number of new cases/ year	82	100	111	98	101					
	Age adjusted incidence rate (per 10^6)	*26.3*	*31.1*	*33.2*	*29.6*	*31.9*	*0.6*	*0.3*	*0.0*	*1.2*	*0.06*
Age (years)											
0	*Average number of new cases/ year*	2	3	5	4	3					
	Incidence rate (per 10^6)	*10.2*	*13.4*	*23.7*	*23.7*	*16.0*	*-0.5*	*1.7*	*-4.0*	*3.1*	*0.78*

Supplementary table S4.1: (continued)

1-4	Average number of new cases/ year	44	54	56	45	50					
	Incidence rate (per 10^6)	*57.5*	*69.3*	*69.5*	*58.2*	*68.3*	*0.3*	*0.4*	*-0.5*	*1.1*	*0.40*
5-9	Average number of new cases/ year	20	24	27	28	24					
	Incidence rate (per 10^6)	*22.2*	*24.5*	*27.5*	*27.5*	*25.2*	*0.7*	*0.4*	*-0.2*	*1.6*	*0.15*
10-14	Average number of new cases/ year	10	13	17	13	16					
	Incidence rate (per 10^6)	*10.6*	*14.3*	*17.1*	*13.0*	*16.3*	*1.4*	*0.6*	*0.1*	*2.6*	*0.04*
15-17	Average number of new cases/ year	6	6	6	8	8					
	Incidence rate (per 10^6)	*11.4*	*11.6*	*10.5*	*13.0*	*12.9*	*0.6*	*1.0*	*-1.4*	*2.7*	*0.52*
									AAPC		
Incidence T cell type		**1990-94**	**1995-99**	**2000-04**	**2005-09**	**2010-15**	**1990-2015**	**SE**	**95% CI low**	**95% CI high**	**p-value**
	Average number of new cases/ year	13	17	17	19	16					
	Age adjusted incidence rate (per 10^6)	*3.8*	*4.9*	*4.5*	*5.3*	*4.6*	*0.8*	*0.8*	*-0.7*	*2.4*	*0.28*
Age (years)											
0	*Average number of new cases/ year*	0	<1	0	0	<1					
	Incidence rate (per 10^6)	*0.0*	*2.1*	*0.0*	*0.0*	*0.9*	*NA*				
1-4	Average number of new cases/ year	3	4	3	4	3					
	Incidence rate (per 10^6)	*3.9*	*5.1*	*3.5*	*4.6*	*4.4*	*1.0*	*1.5*	*-2.2*	*4.2*	*0.52*
5-9	Average number of new cases/ year	5	6	6	8	4					
	Incidence rate (per 10^6)	*5.9*	*5.9*	*5.8*	*8.4*	*4.8*	*-0.4*	*1.3*	*-2.9*	*2.2*	*0.78*
10-14	Average number of new cases/ year	3	4	6	4	5					
	Incidence rate (per 10^6)	*3.1*	*4.8*	*5.8*	*4.0*	*4.8*	*1.4*	*1.3*	*-1.2*	*4.1*	*0.28*
15-17	Average number of new cases/ year	2	2	2	3	4					
	Incidence rate (per 10^6)	*2.9*	*4.0*	*3.9*	*5.0*	*6.2*	*3.7*	*1.2*	*1.2*	*6.2*	*0.01*

Supplementary table S4.2: Trends in 1, 5 and 10-yr overall survival for patients aged <18 years with ALL according to age, gender, subtype between 1990 and 2015

	1990-1994							1995-1999							2000-2004						
	n at risk	1-yr OS	*SE*	5-yr OS	*SE*	10-yr OS	*SE*	n at risk	1-yr OS	*SE*	5-yr OS	*SE*	10-yr OS	*SE*	n at risk	1-yr OS	*SE*	5-yr OS	*SE*	10-yr OS	*SE*
	481	**95%**	***1%***	**80%**	***2%***	**76%**	***2%***	**589**	**94%**	***1%***	**81%**	***2%***	**78%**	***2%***	**640**	**95%**	***1%***	**85%**	***1%***	**83%**	***2%***
Age groups (years)																					
0	**26** [2]	58%	*10%*	27%	*9%*										**64** [3]	75%	*5%*	62%	*6%*	62%	*6%*
1-4	**237**	97%	*1%*	86%	*2%*	81%	*3%*	**292**	97%	*1%*	88%	*2%*	84%	*2%*	**295**	98%	*1%*	92%	*2%*	91%	*2%*
5-9	**129**	96%	*2%*	86%	*3%*	83%	*3%*	**149**	95%	*2%*	84%	*3%*	80%	*3%*	**166**	96%	*1%*	88%	*3%*	87%	*3%*
10-14	**65**	97%	*2%*	72%	*6%*	69%	*6%*	**89**	91%	*3%*	76%	*5%*	75%	*5%*	**114**	93%	*2%*	70%	*4%*	67%	*4%*
15-17	**40**	82%	*6%*	57%	*8%*	51%	*8%*	**43**	88%	*5%*	58%	*8%*	53%	*8%*	**41**	83%	*6%*	70%	*7%*	65%	*7%*
Sex																					
male	**266**	93%	*2%*	75%	*3%*	72%	*3%*	**373**	94%	*1%*	81%	*2%*	77%	*2%*	**383**	94%	*1%*	83%	*2%*	81%	*2%*
female	**215**	96%	*1%*	86%	*2%*	81%	*3%*	**216**	93%	*2%*	82%	*3%*	79%	*3%*	**257**	96%	*1%*	88%	*2%*	85%	*2%*
Site of treatment																					
paediatric oncology centre	**452**	96%	*1%*	83%	*2%*	79%	*2%*	**558**	95%	*1%*	83%	*2%*	80%	*2%*	***619***	95%	*1%*	85%	*1%*	83%	*2%*
outside paediatric oncology centre	**29**	75%	*8%*	40%	*9%*			**31**	77%	*8%*	45%	*9%*			***21***	86%	*8%*	76%	*9%*		
Immunophenotype[&]																					
BCP-ALL	**412**	96%	*1%*	81%	*2%*	77%	*2%*	**502**	95%	*1%*	84%	*2%*	80%	*2%*	***556***	96%	*1%*	86%	*1%*	84%	*2%*
T-cell ALL	**64**	83%	*5%*	73%	*6%*	72%	*6%*	**84**	85%	*4%*	67%	*5%*	64%	*5%*	**83**	89%	*3%*	75%	*5%*	75%	*5%*
unknown (<1% of total) ^	**5**							**3**							***1***						
Down syndrome (only for pts in DCOG registry)																					
yes	**9**	89%	*10%*					**16**	94%	*6%*					**14**	100%	*0%*				

Supplementary table S4.2: (continued)

	2005-2009							2010-2015[1]							
	n at risk	1-yr OS	*SE*	5-yr OS	*SE*	10-yr OS	*SE*	n at risk	1-yr OS	*SE*	5-yr OS	*SE*	p at 1-yr OS	p at 5-yr OS	p at 10-yr OS
	585	**94%**	***1%***	**89%**	***1%***	**87%**	***1%***	**701**	**95%**	***1%***	**91%**	***1%***	0.77	*<0.01*	*<0.01*
Age groups (years)															
0													0.09	*<0.01*	*ND*
1-4	**244**	96%	*1%*	91%	*2%*	91%	*2%*	**316**	97%	*1%*	95%	*1%*	0.57	*<0.01*	*<0.01*
5-9	**180**	97%	*1%*	92%	*2%*	89%	*2%*	**172**	99%	*1%*	96%	*1%*	0.43	*<0.01*	*0.03*
10-14	**84**	94%	*3%*	92%	*3%*	84%	*4%*	**127**	94%	*2%*	86%	*3%*	0.64	*<0.01*	0.12
15-17	**55**	84%	*5%*	76%	*6%*	76%	*6%*	**68**	90%	*4%*	76%	*5%*	0.80	*0.02*	*0.01*
Sex															
male	**325**	95%	*1%*	89%	*2%*	87%	*2%*	**397**	97%	*1%*	91%	*1%*	0.23	*<0.01*	*<0.01*
female	**260**	93%	*2%*	89%	*2%*	86%	*2%*	**304**	93%	*1%*	91%	*2%*	0.29	*0.04*	0.08
Site of treatment															
paediatric oncology centre	**567**	95%	*1%*	89%	*1%*	87%	*1%*	**686**	96%	*1%*	92%	*1%*	0.82	*<0.01*	*<0.01*
outside paediatric oncology centre	**18**	77%	*10%*	77%	*10%*			**15**	80%	*10%*			0.92	0.06	0.05
Immunophenotype[&]															
BCP-ALL	**489**	95%	*1%*	91%	*1%*	88%	*1%*	**602**	96%	*1%*	93%	*1%*	0.93	*<0.01*	*<0.01*
T-cell ALL	**95**	89%	*3%*	81%	*4%*	79%	*4%*	**98**	92%	*3%*	81%	*4%*	0.40	0.17	0.14
unknown (<1% of total) ^	**1**							**1**							
Down syndrome (only for pts in DCOG registry)															
yes	**22**	77%	*9%*					**16**	81%	*10%*			ND	ND	ND

[&] As confirmed by the DCOG laboratory, if not known in the DCOG registry, the NCR morphology code was taken. BCP-ALL: B-cell precursor acute lymphoblastic leukaemia
^ unknown if not known in the DCOG registry
* 6yr period

Supplementary table S4.3 Mortality for children, aged <20 years at death, dying from ALL in the Netherlands between 1980 and 2016

mortality males & females		1980-1984	1985-1989	1990-1994	1995-1999	2000-2004	2005-2009	2010-2016	1980-2016 AAPC	SE	95% CI low	95% CI high	p-value
	Average number of deaths/ year	40	35	21	21	14	14	11					
	Age adjusted mortality rate (per 10^6)	*9.5*	*8.5*	*5.4*	*5.6*	*3.5*	*3.5*	*2.5*	*-4.0*	*0.4*	*-4.8*	*-3.4*	*<0.01*
Age (years)													
0	Average number of deaths/ year	1	1	<1	1	1	<1	1					
	mortality rate (per 10^6)	*4.6*	*4.4*	*2.0*	*4.2*	*3.9*	*2.2*	*2.4*	*-6.2*	*6.4*	*-22.9*	*10.1*	*0.36*
1-4	Average number of deaths/ year	7	5	3	4	1	3	2					
	mortality rate (per 10^6)	*10.4*	*6.5*	*3.6*	*5.6*	*1.7*	*3.6*	*3.0*	*-17.8*	*8.2*	*-40.6*	*1.3*	*0.06*
5-9	Average number of deaths/ year	10	9	6	6	5	3	2					
	mortality rate (per 10^6)	*10.6*	*10.1*	*6.6*	*6.5*	*4.7*	*3.0*	*1.6*	*-24.5*	*3.0*	*-35.8*	*-20.3*	*<0.01*
10-14	Average number of deaths/ year	11	7	3	5	3	3	3					
	mortality rate (per 10^6)	*9.5*	*7.4*	*3.5*	*5.4*	*3.4*	*3.2*	*2.7*	*-17.2*	*4.5*	*-30.4*	*-7.4*	*0.01*
15-19	Average number of deaths/ year	11	13	9	5	4	5	3					
	mortality rate (per 10^6)	*8.5*	*11.2*	*8.8*	*5.0*	*4.2*	*4.6*	*2.6*	*-18.3*	*4.1*	*-30.6*	*-9.7*	*<0.01*

mortality males		1980-1984	1985-1989	1990-94	1995-99	2000-04	2005-09	2010-16	1980-2016 AAPC	SE	95% CI low	95% CI high	p-value
	Average number of deaths/ year	24	21	14	13	11	8	6					
	Age adjusted mortality rate (per 10^6)	*10.9*	*9.9*	*6.9*	*6.5*	*5.1*	*3.9*	*2.9*	*-4.0*	*0.4*	*-4.8*	*-3.3*	*<0.01*
Age (years)													
0	Average number of deaths/ year	<1	<1	<1	<1	<1	0	0					
	mortality rate (per 10^6)	*2.2*	*2.1*	*2.0*	*2.0*	*1.9*	*0.0*	*0.0*	*-3.3*	*0.7*	*-5.6*	*-1.1*	*0.02*

Supplementary table S4.3 (continued)

1-4	Average number of deaths/ year	4	3	2	3	1	2	1					
	mortality rate (per 10^6)	*10.5*	*8.3*	*5.5*	*7.0*	*2.4*	*4.0*	*3.9*	*-17.2*	*6.3*	*-34.9*	*-2.8*	*0.03*
5-9	Average number of deaths/ year	7	4	3	4	4	2	1					
	mortality rate (per 10^6)	*13.3*	*9.7*	*7.3*	*8.0*	*7.9*	*3.9*	*1.5*	*-24.4*	*6.3*	*-44.1*	*-11.8*	*0.01*
10-14	Average number of deaths/ year	8	5	2	3	3	2	2					
	mortality rate (per 10^6)	*12.5*	*9.7*	*4.3*	*5.9*	*5.9*	*3.6*	*3.1*	*-18.3*	*5.0*	*-32.9*	*-7.4*	*0.01*
15-19	Average number of deaths/ year	6	9	6	3	2	3	2					
	mortality rate (per 10^6)	*9.4*	*14.1*	*11.8*	*6.4*	*4.9*	*5.5*	*3.9*	*-15.8*	*4.9*	*-29.9*	*-4.5*	*0.02*

											AAPC		
mortality females		**1980-1984**	**1985-1989**	**1990-94**	**1995-99**	**2000-04**	**2005-09**	**2010-16**	**1980-2016**	**SE**	**95% CI low**	**95% CI high**	**p-value**
	Average number of deaths/ year	16	14	7	8	4	6	4					
	Age adjusted mortality rate (per 10^6)	*7.9*	*7.1*	*3.9*	*4.5*	*1.9*	*3.0*	*2.0*	*-4.0*	*0.6*	*-5.2*	*-3.0*	*<0.01*
Age (years)													
0	Average number of deaths/ year	1	1	0	1	1	<1	1					
	mortality rate (per 10^6)	*7.0*	*6.8*	*2.1*	*6.4*	*6.1*	*4.4*	*5.0*	*0.1*	*9.1*	*-23.3*	*23.6*	*0.99*
1-4	Average number of deaths/ year	4	2	1	2	<1	1	1					
	mortality rate (per 10^6)	*10.4*	*4.6*	*1.6*	*4.2*	*1.0*	*3.2*	*2.0*	*-18.0*	*12.9*	*-53.1*	*13.3*	*0.19*
5-9	Average number of deaths/ year	4	5	3	2	1	1	1					
	mortality rate (per 10^6)	*7.7*	*10.6*	*5.9*	*5.0*	*1.2*	*2.1*	*1.8*	*-26.6*	*8.8*	*-53.6*	*-8.2*	*0.02*
10-14	Average number of deaths/ year	4	2	1	2	<1	1	1					
	mortality rate (per 10^6)	*6.3*	*5.0*	*2.7*	*4.9*	*0.8*	*2.9*	*2.3*	*-17.1*	*11.2*	*-47.5*	*10.0*	*0.16*
15-19	Average number of deaths/ year	5	5	3	2	2	2	1					
	mortality rate (per 10^6)	*7.5*	*8.1*	*5.7*	*3.5*	*3.5*	*3.7*	*1.2*	*-24.0*	*5.9*	*-42.5*	*-12.4*	*<0.01*

Supplementary table S4.4 Outcomes of consecutive Dutch Childhood Oncology Group Protocols during the period 1990-2015

Protocol	**ALL-7** [1] Period 1990-91	**ALL-8** [2] Period 1991-97	**ALL-9** [3] Period 1997-2004	**ALL-10** [4] Period 2004-2012
% death - before remission	2%	1%	1%	2%
- in remission	3%	2%	3%	3%
% relapse	32%	25%	15%	9%
5-year EFS % (SE) [$]	66 (3)	75 (2)	83 (1)	89 (1)
5-year OS % (SE) [$]	80 (3)	85 (2)	88 (1)	94 (1)
5-year CIR % (SE) [$]	30 (3)	22 (2)	13 (1)	8 (1)
% alloSCT - in first CR	~3%	2%	2%	6%
% sec malignancy	2%	1%	0.1%	1%

Protocol ALL-11 is still ongoing, this data cannot be presented yet.

[$] Excluding children older than 15 years, patients with DS, infants and Philadelphia chromosome-positive ALL because of differences in inclusion, adapted from Pieters et al. JCO 2016[4], table 3.

Abbreviations: alloSCT, allogenic hematopoietic stem cell transplantation, CIR, cumulative incidence of relapse, CR, complete remission, DS, Down syndrome, EFS, event free survival, OS, overall survival, SE, standard error

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CHAPTER 5

Improved survival for children and young adolescents with acute myeloid leukaemia: a Dutch study on incidence, survival and mortality

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ABSTRACT

Variation in survival of paediatric acute myeloid leukaemia (pAML) over time and between Western European countries exists. The aim of the current study is to assess the progress made for the Dutch pAML population (0–17 years) during 1990–2015, based on trends in incidence, survival and mortality.

Data from the population-based Netherlands Cancer Registry were merged with leukaemia-related characteristics and treatment specifics from the Dutch Childhood Leukemia Study Group (Dutch Childhood Oncology Group (DCOG) from 2002 onwards). Mortality data (1980–2016) were obtained from the cause of death registry of Statistics Netherlands. Trend analyses were performed over time and by treatment protocol.

Between 1990 and 2015, a total of 635 children aged 0–17 years were diagnosed with AML for an average of 25 patients (range 18–36) per year. There was a slight increase in the incidence at age 1–4 years (average annual percentage change (AAPC) of +2.2% per year (95% CI 0.8–3.5, p <0.01)). Overall, the 5-year survival significantly improved over the past 26 years and nearly doubled from 40% in the early 1990s to 74% in 2010–15. Multivariable analysis showed a 49% reduction in risk of death for pAML patients treated according to the latest DB-AML 01 protocol (p =0.03). The continuing decrease of mortality (AAPC −2.8% per year (95% CI −4.1 to −1.5)) supports the conclusion of true progress against pAML in the Netherlands.

INTRODUCTION

Leukaemia is the most common form of cancer in children (<15 years), accounting for almost one-third of all childhood malignancies. Acute myeloid leukaemia (AML) contributes to 15–20% of the childhood leukaemias.[1] Prognosis for AML improved remarkably during the past decades, due to optimizing existing treatment strategies.[2-4] However, within Northwest Europe, the 5-year survival varied from 57 to 78% for the period 2005–09 as recently published by the CONCORD-2 study.[5] This variation in survival suggests that improvements in clinical practice have not been implemented in all countries in the same way and/or at the same time.

The Dutch Childhood Oncology Group (DCOG) harbours a reference laboratory and coordinates treatment protocols and clinical trials in the field of paediatric haemato-oncology since 1972. For childhood leukaemias, 96% of the patients (<18 years) were treated at a paediatric oncology centre in the period 2004–13.[6] All paediatric AML (pAML) patients diagnosed in the Netherlands from the early 1980s onwards are treated according to international treatment protocols.[7]

Six consecutive treatment protocols for pAML were active since 1990 (**supplementary figure S5.1**). Several changes were introduced concerning first- and second-line treatment. In the 1990s, allogenic stem cell transplantation (alloSCT) in first complete remission (CR1) at the end of chemotherapy was standard of care for patients with an available human leukocyte antigen (HLA)-identical donor, and later this was restricted to specific risk groups. Since 2010, upfront alloSCT was completely omitted in the DBAML01 protocol. Furthermore, this protocol used a response-guided induction. Lastly, concerning second-line therapy, two blocks of reinduction therapy and alloSCT directly or after consolidation seem to be most effective for patients with relapsed or refractory AML. This was applied since 2001 within the I-BFM-AML consortium.[8]

Population-based studies for pAML focusing on incidence, survival and mortality are limited in literature and are lacking for the Netherlands. Combining these three parameters is essential to understand the progress in treatment of AML.[9,10] The main aim of this study was to gain insight into the progress made for pAML patients diagnosed between 1990 and 2015 by describing trends in incidence, survival and mortality against the background of various treatment regimens. We have combined the information from the Netherlands Cancer Registry (NCR) with detailed leukaemia and treatment characteristics from the DCOG registry and used the mortality data from cause of death statistics Netherlands.

PATIENTS AND METHODS

Study population

All patients aged below 18 years and diagnosed with AML during the period January 1990 to December 2015 were selected from the NCR and the clinical registry of the DCOG. A total of 622 patients with pAML from the NCR were linked with 578 patients with pAML from the DCOG registry, yielding 635 patients eligible for inclusion (**supplementary figure S5.2**). In case of discrepancies in morphology results, DCOG data were preferred over NCR data because of their role as a reference laboratory.

AML diagnoses were coded according to ICD-O-3 (**supplementary table S5.1**). Extramedullary AML (myeloid sarcoma without bone marrow involvement), acute promyelocytic leukaemia (APL), and myeloid leukaemia associated with Down syndrome (ML-DS) were included, whereas transient abnormal myelopoiesis, acute undifferentiated leukaemia and acute bi-phenotypic leukaemia were excluded. Patients with primary myelodysplastic syndromes and therapy-related AML were also excluded, because these patients were not eligible for treatment according to one of the treatment protocols in our study.

Based on patient- and leukaemia-specific characteristic, cases were classified into the following four categories: AML, APL, ML-DS and myeloid sarcoma. Patients with available (molecular) cytogenetic data were categorized as having core-binding factor (CBF) leukaemia (i.e., t(8;21)(q22;q22)/*RUNX1-RUNX1T1* [t(8;21)] or inv(16)(p13.1q22)/t(16;16)(p13.1;q22)/ *CBFB-MYH11* [inv(16)/t(16;16)) or non-CBF leukaemia. Molecular testing for CBF abnormalities increased over time in the university medical centres and became a standard diagnostic procedure in the DCOG laboratory from 2010 onward. For patients ascertained in the NCR but not in the DCOG registry, information regarding CBF leukaemia and FAB (French–American–British) type was based on morphology code as registered in the NCR. Initial treatment was registered in the NCR for these patients, but type of SCT and treatment protocol were not.

The Netherlands Cancer Registry

The nationwide population-based NCR is maintained and hosted by the Netherlands Comprehensive Cancer Organisation (IKNL) and has a national coverage since 1989 with a completeness of at least 96% of all newly diagnosed malignancies in the Netherlands.[6,11] The NCR relies on comprehensive case notification through the Nationwide Network and Registry of Histopathology and Cytopathology, and the National Registry of Hospital Discharges. Trained registrars of the NCR extract data on patient and tumour characteristics and primary treatment

through retrospective medical records review. Primary therapy started within 9 months after diagnosis is coded following order of administration and includes radiotherapy, systemic chemotherapy and SCT. The NCR codes disease topography and morphology according to the International Classification of Diseases for Oncology (ICD-O). Information on vital status (alive, dead or emigration) is obtained by annual linkage of the NCR with the Nationwide Population Registries Network that holds vital statistics on all residents in the Netherlands. Last linkage was at 1 February 2018.

Registry of the Dutch Childhood Oncology Group

The centrally reviewed results of bone marrow, peripheral blood and spinal fluid samples taken at diagnosis are all registered at the DCOG laboratory database. AML diagnosis is based on a combination of cytomorphology, immunophenotyping and –increasingly-(molecular) cytogenetics.[3] Baseline patient and leukaemia characteristics (e.g., sex, age, white blood cell count at diagnosis, pre-existing syndromes and cytogenetics) are collected from the treating hospitals and included in the database. Data managers also registered if a patient was eligible for treatment and included in the treatment protocol. For these so-called "in-trial patients" details regarding treatment, type of SCT, response to treatment, date of relapse(s) and cause of death were also registered. Only patients treated in the seven paediatric oncology centres in the Netherlands are included in the DCOG registry.

Mortality data

Disease-specific mortality rates from 1980 to 2016 were derived from Statistics Netherlands (CBS). Because of privacy regulations, linkage between the NCR and the CBS is not allowed in the Netherlands on a routine base. The myeloid leukaemia (ML)-specific ICD-9 code "209" and ICD-10 code "C92" were used to identify patients who died from ML. Of note, this also includes potential deaths of chronic myeloid leukaemia subgroups and myeloid sarcoma. Mortality rates represent age at the time of death and were obtained in 5-year age groups (e.g., ages 0–4, 5–9, 10–14 and 15–19).

Statistical analyses

Characteristics of the study population were described as percentages in relation to the following five periods of diagnosis: 1990–94, 1995–99, 2000–04, 2005–09 and 2010–15. Differences among categorical variables were tested with the $\chi 2$ tests.

Annual incidence and mortality rates were calculated per 1 million person-years, using the annual mid-year population size as obtained from Statistics Netherlands. Rates were age

standardized according to the age structure of the World standard population for age ranges 0–14 years and 0–17 years for estimation of incidence rates, and 0–19 years for mortality rates.[12] Linear regression modelling was used to assess trends over time. A regression line was fitted to the natural logarithm of the incidence and mortality rates, including calendar year as a continuous variable.[12] Results were reported as average annual percent changes (AAPC) along with the corresponding 95% confidence interval (CI) and *p* values.

Traditional cohort-based survival analyses were performed to calculate the observed survival (OS) and standard errors (SE) at 5 years after diagnosis. For the patients in the last period, median follow-up time was 3.8 years. Observed survival was used instead of relative survival, because competing causes of death are rare among childhood cancer patients in developed countries such as the Netherlands.[13] Changes over time in observed 5-year survival were evaluated using parametric survival models (*streg*). The year of diagnosis was entered as a continuous variable in the model adjusted for follow-up time (in years). In a second multivariable analysis model, adjusted for follow-up time, we included sex, age at diagnosis and type of treatment protocol.

For the different analyses performed, we used different study cohorts (**figure 5.1**). Incidence analyses included all AML patients, irrespective of AML category and treatment received (cohort 1). For survival analyses we analysed separately the outcome of ML-DS and APL because these are distinct entities of myeloid leukaemias (cohorts 1a and 1b).[14] For survival analyses according to treatment protocol, patients eligible and treated according to the protocol were included (cohort 1c). Excluded from this cohort were patients registered in the NCR only as well as patients treated on the current NOPHO-DBH AML 2012 protocol, since this trial is still ongoing.

Incidence and mortality analyses were performed with SAS software (SAS system 9.4, SAS Institute, Cary, NC). Survival analyses were performed with STATA/SE 14.1 (StataCorp LP, College Station, Texas, USA). A *p* value <0.05 was considered statistically significant.

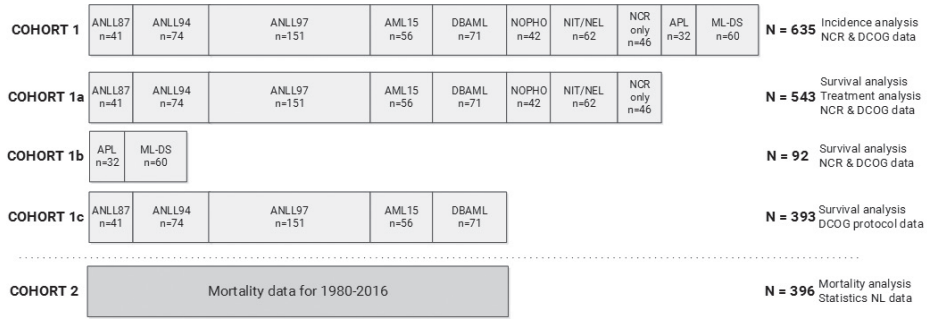

Figure 5.1. Inclusion of patients for the different analyses performed
In total 635 paediatric acute myeloid leukaemia (pAML) patients were included and used for the incidence analysis (cohort 1). The first six boxes represent the patients treated according one of the six treatment protocols, active during the period 1990-2015 (**supplementary figure 5.1**). The box NIT/NEL is for patients not in trial (NIT): no informed consent had been obtained or it was physicians' decision to treat otherwise (n = 48); patients not eligible (NEL) received corticosteroids or chemotherapy longer than two weeks before diagnosis or had a severe comorbidity (n = 14). The box NCR only consists of pAML patients that are unknown at the DCOG. The last two boxes are for patients with acute promyelocytic leukaemia (APL) and myeloid leukaemia associated with Down syndrome (ML-DS).
Cohort 1a are the pAML patients without APL and ML-DS, used for the survival and treatment analyses.
Cohort 1b are the APL and ML-DS patients for whom a subsequent survival analysis was performed.
Cohort 1c are the pAML patients treated according to one of the first five treatment protocols, used for protocol survival analysis.
Cohort 2 is based on the mortality data from Statistics Netherlands, deceased patients with cause of death myeloid leukaemia during 1980-2016. This cohort is used for the mortality analysis.

RESULTS

Patient and tumour characteristics

Between 1990 and 2015, 635 children <18 years were diagnosed with de novo AML in the Netherlands and included in this study. Median age at diagnosis was 6 years (interquartile range, 1–13 years). Slightly more boys than girls were diagnosed with pAML (male to female (M:F) ratio=1.2), whereas the M:F ratio was <1 in children below 1 year of age (**table 5.1**).

The majority of the patients (91%) had a diagnosis of pAML confirmed by the reference laboratory of the DCOG. Over time, more patients had their diagnosis centrally confirmed by the DCOG laboratory, increasing from 85% in 1990–94 to 97% in 2010–15 (p <0.01). In 2010–15, 19% of the pAML patients had a CBF abnormality. Most patients received chemotherapy only (n=479, 78%). The use of alloSCT in CR1 decreased from 22% in 1990–94 to 12% in 2010–15 (p <0.01). From 1999 onwards, autologous SCT (autoSCT) was no longer applied.

Table 5.1. Characteristics of patients aged <18 years and diagnosed with AML in the Netherlands between 1990 and 2015

	Total		average/ year	1990-1994		1995-1999		2000-2004		2005-2009		2010-2015[a]		
Characteristic	**n**	**%**		**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**p-value**
	635		**25**	**107**	***17***	**114**	***18***	**123**	***19***	**135**	***21***	**156**	***25***	
Age groups (years)														0.97
0	82	*13*	3	16	*15*	12	*10*	12	*10*	22	*16*	20	*13*	
1-4	210	*33*	8	30	*28*	38	*33*	43	*35*	43	*32*	56	*36*	
5-9	92	*15*	4	17	*16*	18	*16*	15	*12*	21	*16*	21	*14*	
10-14	156	*25*	6	27	*25*	27	*24*	35	*28*	29	*21*	38	*24*	
15-17	95	*15*	4	17	*16*	19	*17*	18	*15*	20	*15*	21	*14*	
Sex														0.29
male	355	*56*	14	57	*53*	60	*53*	79	*64*	76	*56*	82	*53*	
female	281	*44*	11	50	*47*	54	*47*	44	*36*	59	*44*	74	*47*	
Diagnosis confirmed by the DCOG[b]														<0.01
yes	578	*91*	22	91	*85*	96	*84*	113	*92*	127	*94*	151	*97*	
no	57	*9*	2	16	*15*	18	*16*	10	*8*	8	*6*	5	*3*	
AML FAB types[b]														[c]
M0	45	*8*	2	8	*8*	10	*9*	9	*8*	12	*9*	6	*4*	
M1	49	*8*	2	10	*10*	7	*7*	9	*8*	12	*9*	11	*8*	
M2	95	*16*	4	20	*20*	14	*13*	26	*22*	18	*14*	17	*13*	
M3	32	*5*	1	6	*6*	6	*6*	10	*8*	4	*3*	6	*4*	
M4	140	*24*	5	22	*22*	28	*26*	26	*22*	25	*19*	39	*29*	
M5	131	*22*	5	23	*23*	26	*24*	21	*18*	27	*21*	34	*25*	
M6	13	*2*	1	4	*4*	5	*5*	1	*1*	2	*2*	1	*1*	
M7	81	*14*	3	7	*7*	10	*9*	15	*13*	28	*22*	21	*16*	

Table 5.1. (continued)

	Total		average/ year	1990-1994		1995-1999		2000-2004		2005-2009		2010-2015[a]		
Characteristic	**n**	**%**		**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**p-value**
Unknown (7.7% of total)	49		2	7		8		6		7		21		
Subtype														0.10
APL, FAB M3	32	*5*	1	6	*6*	6	*5*	10	*8*	4	*3*	6	*4*	
ML-DS	60	*9*	2	8	*7*	8	*7*	10	*8*	19	*14*	15	*10*	
Myeloid sarcoma	18	*3*	1	3	*3*	4	*3*	7	*6*	2	*1*	2	*1*	
CBF leukaemia: t(8;21) or inv(16)[d]	97	*15*	4	8	*7*	19	*17*	23	*19*	18	*13*	29	*19*	
AML other	429	*67*	17	82	*77*	77	*67*	73	*59*	92	*68*	104	*67*	
Initial therapy														<0.01
CT only	479	*78*	18	58	*56*	68	*62*	101	*84*	116	*89*	136	*88*	
CT + autoSCT	35	*6*	1	22	*21*	13	*12*	0		0		0		
CT + alloSCT[e]	103	*17*	4	23	*22*	28	*26*	19	*16*	15	*11*	18	*12*	
No or unknown therapy (2.8% of total)	18		1	4		5		3		4		2		

[a] 6-year period.
[b] As confirmed by the DCOG laboratory, if not known in the DCOG registry, the NCR morphology code was taken.
[c] Not applicable to calculate differences because many cells have < 5 observations.
[d] Tested more structurally from 2001 onwards and tested in structural manner from 2010 onwards.
[e] Including n=19 patients with unknown type of SCT, because these patients were unknown in the DCOG registry.
Note that analyses are performed on cohort 1. In case of missing data for specific characteristics, percentages were calculated without "unknown". Percentages may not add to 100% due to rounding.
AML acute myeloid leukaemia; *APL* acute promyelocytic leukaemia; *CBF* core binding factor; *NOS* not otherwise specified; *CT* chemotherapy; *DCOG* Dutch Childhood Oncology Group; *FAB* French-American-British classification for AML subtypes; *ML-DS* myeloid leukaemia associated with Down Syndrome; *(allo/auto)SCT*, (allogenic/autologous) stem cell transplantation.

Table 5.2. Incidence for children, aged <18 years and diagnosed with AML in the Netherlands between 1990 and 2015

		AAPC									
Incidence		**1990-94**	**1995-99**	**2000-04**	**2005-09**	**2010-15**	**1990-2015**	**SE**	**95% CI low**	**95% CI high**	**p-value**
Total	Average number of new cases/ year	22	23	25	27	26					
	Age adjusted incidence rate (per 10^6)	6.6	6.9	7.2	8	8.1	1	0.5	0	2	0.05
Age (years)											
0	Average number of new cases/ year	3	2	2	4	4					
	Incidence rate (per 10^6)	16.4	12.4	11.9	23.8	19.9	2.5	1.5	-0.6	5.5	0.11
1-4	Average number of new cases/ year	6	8	9	9	9					
	Incidence rate (per 10^6)	7.8	9.7	10.8	11	12.9	2.2	0.7	0.8	3.5	<0.01
5-9	Average number of new cases/ year	3	4	3	4	4					
	Incidence rate (per 10^6)	3.8	3.7	3	4.2	3.6	1.4	1.5	-1.7	4.4	0.37
10-14	Average number of new cases/ year	5	5	7	6	6					
	Incidence rate (per 10^6)	6	5.8	7	5.9	6.3	0.2	1	-1.9	2.4	0.83
15-17	Average number of new cases/ year	4	4	4	4	4					
	Incidence rate (per 10^6)	6.3	6.9	6.3	6.7	5.9	-0.7	1.2	-3.2	1.8	0.57

Note that the average numbers calculated by age groups or sex may not be equal to the total average numbers due to rounding. Analyses are performed on Cohort 1.
AAPC average annual percentage change; *CI* confidence interval; *SE* standard error.

Trends in incidence rates

On average, 25 patients (range, 18–36) were diagnosed with pAML annually (cohort 1, including APL and ML-DS), increasing from 22 in 1990–94 to 26 patients in 2010–15, all ages combined. This corresponds with an increased world standardized rate from 6.6 to 8.1 per million person-years and an AAPC of +1.0% per year (p =0.05) (**table 5.2**). Incidence rates by age group showed a significant increase in incidence for 1 to 4 year olds only, AAPC +2.2% (p <0.01) (**table 5.2** and **supplementary figure S5.4**). Age-adjusted incidence rates by sex were stable (**figure 5.2**). Incidence of pAML patients for age 0–14 years increased over time with 1.2% per year (p =0.02). Age and sex-specific incidence rates for this age group (0–14 years) are shown in **supplementary table S5.5**.

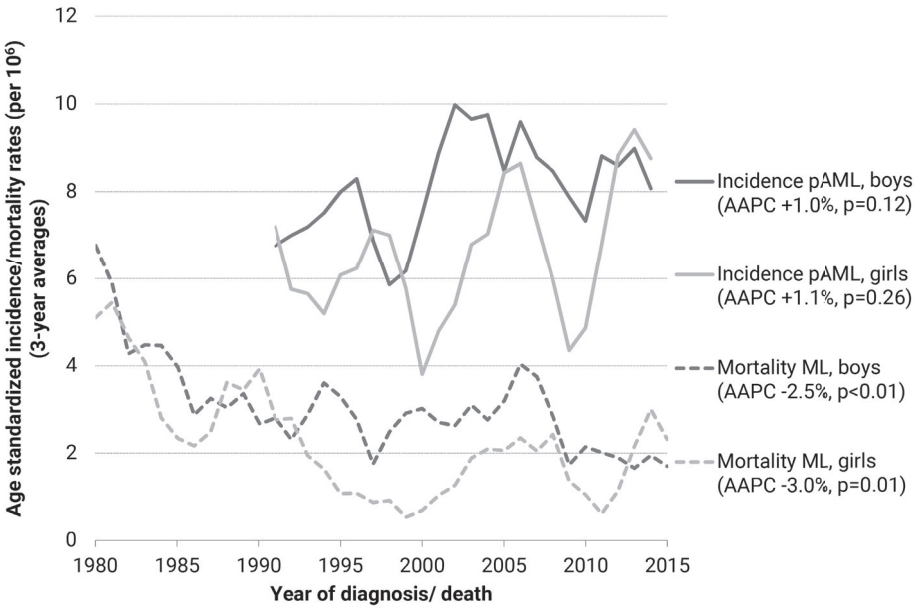

Figure 5.2. Age standardized incidence rates of paediatric AML and age standardized mortality rates of myeloid leukaemia. Age standardized incidence and mortality rates by sex according to the World Standard Rate. Three-year moving averages are shown. The average annual percentage change (AAPC) was calculated for each year of diagnosis/ death with linear regression analyses. Incidence analyses performed on cohort 1, age <18 years. Mortality analyses performed on data from Statistics Netherlands, age at death 0-19 years, cohort 2.
pAML paediatric acute myeloid leukaemia; *ML* myeloid leukaemia.

Trends in overall survival

The 5-year OS increased from 40% in 1990–94 to 57% in 1995–99 (p =0.04) and finally to 74% in 2010–15 (p <0.01) (**figure 5.3a**, cohort 1a). The 5-year OS significantly improved over time for 1–9 year olds, with the most evident increase during the last period (5-year OS 84%, p <0.01]. The 5-year OS for other age groups, FAB types and CBF leukaemia are shown in **table 5.3**.

Table 5.3. Five-year overall survival of patients aged <18 years and diagnosed with AML in the Netherlands, 1990-2015

	1990-2015			1990-1994			1995-1999			2000-2004			2005-2009			2010-2015[1]			
	n at risk	5y OS (%)	SE (%)	n at risk	5y OS (%)	SE (%)	*n* at risk	5y OS (%)	SE (%)	*n* at risk	5yOS (%)	SE (%)	*n* at risk	5y OS (%)	SE (%)	*n* at risk	5y OS (%)	SE (%)	p at 5-yr OS
	543	**57**	**2.1**	**93**	**40**	**5.1**	**100**	**57**	**5**	**103**	**55**	**4.9**	**112**	**52**	**4.7**	**135**	**73.8**	**3.9**	**<0.01**
Age groups																			
0	73	47	5.8	15	33	12.2	12	33	13.6	11	55	15	17	47	12.1	18	60	11.7	0.55
1-9	243	60	3.2	39	41	7.9	45	60	7.3	48	60	7.1	49	45	7.1	62	84	4.7	<0.01
10-17	227	57	3.3	39	41	7.9	43	60	7.5	44	50	7.5	46	61	7.2	55	66	6.8	0.09
Sex																			
male	305	54	2.9	51	39	6.8	53	53	6.9	68	54	6	64	45	6.2	69	75	5.3	<0.01
female	238	60	3.2	42	41	7.6	47	61	7.2	35	57	8.4	48	60	7.1	66	73	5.8	0.03
AML FAB types																			
FAB M0	36	29	7.8		ND														
FAB M1	49	58	7.2		ND														
FAB M2	95	62	5	20	30	10.3	14	70	12.6	26	62	9.5	18	72	10.6	17	88	8.1	<0.01
FAB M4	139	67	4	21	38	10.3	27	63	9.3	19	68	10.7	24	67	9.6	30	79	7.7	<0.01
FAB M5	131	55	4.4	23	48	10.4	25	52	10	20	65	10.7	27	48	9.6	24	49	11.2	0.67
FAB M6	11	36	14.5		ND														
FAB M7	36	44	8.3		ND														
Unknown	46	54	7.4		ND														
Subtype																			
CBF leukaemia: t(8;21) or inv(16)[2]	97	81	4	8	ND		19	84	8.4	23	78	8.6	18	83	8.9	29	89	6	0.01
AML other[3]	446	51	2.4	85	38	5.3	81	50	5.6	80	49	5.6	94	46	5.1	106	70	4.6	<0.01

[1] 6y period.

[2] CBF includes t(8;21) or inv(16); Tested more structurally from 2001 onwards and tested in structural manner from 2010 onwards.

[3] AML other; non-CBF leukaemia, contains 159 patients for whom it is unknown if they were tested on CBF abnormality.

NOTE. p=log rank tested if the 5-yr survival for a factor significantly increased over time. Analyses performed on Cohort 1a.

AML, acute myeloid leukaemia; *CBF*, core binding factor; *NOS* not otherwise specified; *CT*, chemotherapy; *DCOG*, Dutch Childhood Oncology Group; *FAB*, French-American-British classification for AML subtypes; *ND*, no survival analyses done;

(allo/auto)SCT, (allogenic/autologous) stem cell transplantation; *OS* overall survival; *SE*, standard error.

Table 5.4. Patient characteristics according to treatment protocol for the 393 pAML patients aged < 18 years

	ANLL87	ANLL92/94	MRC12/ANLL97	AML15	DB-AML01	
	(*n* [%])	(*n* [%])	(*n* [%])	(*n* [%])	(*n* [%])	**p-value**
Total	41 (10)	74 (19)	151 (38)	56 (14)	71 (18)	
Age groups (years)						0.59
0	6 (15)	13 (18)	14 (9)	9 (16)	9 (13)	
1-4	11 (27)	21 (28)	50 (33)	12 (21)	20 (28)	
5-9	9 (22)	15 (20)	26 (17)	14 (25)	14 (20)	
10-14	13 (32)	24 (32)	45 (30)	15 (27)	20 (28)	
15-17	2 (5)	1 (1)	16 (11)	6 (11)	8 (11)	
Sex						0.47
male	20 (49)	42 (57)	93 (62)	32 (57)	36 (51)	
female	21 (51)	32 (43)	58 (38)	24 (43)	35 (49)	
AML FAB types						*
M0	2 (5)	4 (6)	13 (9)	6 (11)	4 (6)	
M1	4 (10)	5 (7)	18 (12)	4 (8)	7 (11)	
M2	9 (23)	11 (15)	29 (20)	12 (23)	9 (14)	
M4	11 (28)	25 (35)	39 (27)	11 (21)	22 (33)	
M5	9 (23)	21 (30)	33 (22)	14 (26)	18 (28)	
M6	3 (8)	1 (1)	2 (1)	1 (2)	0 (0)	
M7	1 (3)	4 (6)	13 (9)	5 (9)	4 (6)	
Unknown (4.8% of total)	*2*	*3*	*4*	*3*	*7*	
Subtype						0.16
CBF leukaemia†	2 (100)	14 (23)	32 (23)	12 (22)	16 (23)	
No CBF leukaemia	0	46 (77)	107 (77)	42 (78)	55 (77)	
Not tested (17% of total)	39	14	12	2	0	
Initial therapy						<0.01
CT only	26 (63)	33 (45)	129 (85)	52 (93)	68 (96)	
CT+autoSCT	7 (17)	22 (30)	0	0	0	
CT+alloSCT	8 (20)	19 (26)	22 (15)	4 (7)	3 (4)	
CT+alloSCT RD&	0	1	8	2	2	
CR achieved	36 (88)	60 (81)	132 (88)	48 (86)	64 (90)	
Median follow-up time pts in CCR [range]	26.6 [25.3-29.0]	21.6 [4.3-25.3]	15.5 [11.4-19.4]	10.1 [8.2-12.2]	5.5 [1.2-7.6]	

† CBF includes t(8;21) and inv(16)/t(16;16). From 2010 onwards, CBF diagnostics were part of standard diagnostics.
& The number of patients from the CT and alloSCT groep that initially had refractory disease but received the alloSCT in first complete remission.
* Not applicable to calculate differences because many cells have < 5 observations.
Abbreviations : ANLL, acute non-lymphoblastic leukaemia; AML, acute myeloid leukaemia; CBF, core binding factor; CCR continuous complete remission; CT, chemotherapy; EFS, event-free survival; FAB, French-American-British classification;
pAML, paediatric AML; OS, overall survival; RD, refractory disease; (allo/auto)SCT, (allogenic/autologous) stem cell transplantation; SE, standard error.
NOTE. Analyses performed on Cohort 1c. Percentages may not add to 100% due to rounding.

The 5-year OS were 78 and 80% for patients with APL (n = 32) and ML-DS (n = 60), respectively (**supplementary figure S5.6**, cohort 1b). The 5-year OS for patients below age 15 years are shown in **supplementary table S5.5**.

Trends in mortality rates

The average number of ML deaths among patients below age 20 years decreased from 22 per year in 1980–84 to 6 in 2010–16 (Supplementary Table S7). The largest decrease was observed before the 1990s. Time trend analyses over 1980–2016 revealed an AAPC for boys −2.5 % per year (p <0.01) and AAPC for girls −3.0% (p =0.01) (**figure 5.2**).

Trends for DCOG protocol patients

For 393 patients with a diagnosis confirmed by the DCOG, we were able to report about the allocated treatment protocol (cohort 1c). Another 57 had their diagnosis confirmed by the DCOG but were not included in the protocol or were not eligible. Patient characteristics did not differ between the protocols (**table 5.4**). In total, 76 of the 326 patients who were tested cytogenetically had CBF leukaemia (23%) which remained stable during the last 20 years (19–23%). The proportion of patients treated with upfront alloSCT decreased over time, 20% in the ANLL87 protocol and 4% in the DB-AML 01 protocol, which is in line with the findings for all pAML patients in the Netherlands (**table 5.1**). The percentage of patients achieving CR was lowest for the ANLL92/94 protocol (81%) (**table 5.4**).

The 5-year OS for the ANLL92/94 protocol was the lowest with 47%, as compared with the DB-AML 01 protocol that had the best outcome with a 5-year OS of 70% (p <0.01; **figure 5.3b**). A multivariable analysis, adjusted for follow-up time, sex and age, demonstrated a significant decrease in the hazard rate (HR) of dying with increasing year of diagnosis, HR 0.96, p <0.01. Addition of protocol in the model attenuated the HR for year of diagnosis. This suggests that improvements in survival over time were mainly due to the treatment protocol. Patients treated according to the DB-AML 01 protocol had an estimated 49% reduction in risk of death (p =0.03) compared with those treated according to the ANLL87 protocol (**table 5.5**).

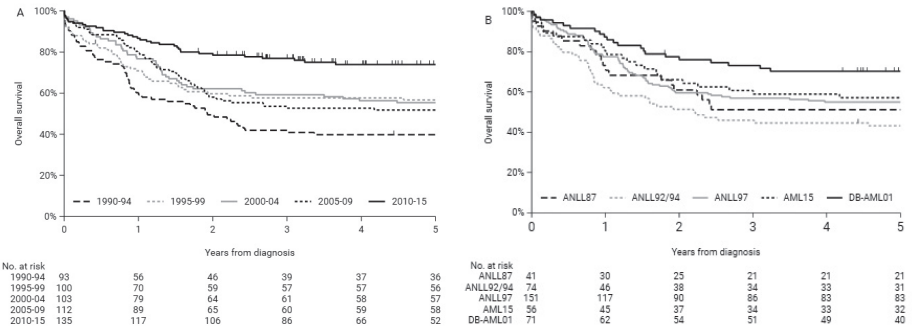

Figure 5.3. The 5-year overall survival of paediatric AML patients. A) according to period of diagnosis. B) according to treatment protocol. Analyses performed on cohort 1a, n = 543 (A) and cohort 1c, n = 393 (B)
AML, acute myeloid leukaemia; *OS* overall survival

Table 5.5. Multivariable analysis to identify patient and treatment characteristics that improved survival over time

	HR	95%CI	p-value
Age groups (years)			
0	Ref.		
1-4	0.59	0.37-0.95	0.03
5-9	0.53	0.32-0.86	0.02
10-14	0.67	0.42-1.06	0.09
15-17	0.82	0.44-1.54	0.55
Sex			
Male	Ref.		
Female	0.73	0.54-1.00	0.05
Treatment protocol			
ANLL87	Ref.		
ANLL92/94	1.28	0.75-2.19	0.36
ANLL97	0.87	0.53-1.43	0.59
AML15	0.81	0.44-1.47	0.49
DB-AML 01	0.51	0.28-0.95	0.03

The analysis is performed on cohort 1c and adjusted for follow-up time. Deaths within 5 years from diagnosis are considered here.
HR Hazard rate, *CI* confidence interval

DISCUSSION

To our knowledge, this is the first comprehensive, nationwide, population-based study reporting on incidence and outcome among newly diagnosed pAML patients <18 years old. The 5- year OS increased from 40% during the early 1990s to more than 70% in the most recent period, 2010–15. Of interest, a modest, albeit significant, increase in the incidence was observed for pAML patients aged 1 to 4 years.

The improved OS over time is in line with other developed countries.[5,15-18] There was a significant increase in survival between 1990–94 and 1995–99 as well as between 2005–09 and 2010–15. A clinically relevant reduction in risk of death was found for patients treated according to the DB-AML 01 protocol compared to the ANLL87 protocol. Preliminary data on event-free survival (EFS) for DB-AML 01 protocol show that the relapse rate is around 40% (our study and *de Moerloose et al*.[19]). However, 53% of the patients with a relapse, initially diagnosed in 2010–13, are still alive 3 years after their relapse diagnosis (unpublished data). We therefore cautiously endorse the conclusion from the BFM-AML colleagues[4] as well as from the NOPHO colleagues[20] that the efficacy of salvage therapy mainly contributed to the recent better outcome in pAML. The survival improvement in the 1990s is more difficult to interpret as subtle changes in therapy had taken place. Overall, we believe that the impact on survival is the result of a combination of improved diagnostics (resulting in early treatment), improved use of classic chemotherapeutic agents and combinations thereof, improved supportive care and improved salvage therapy.[2-4,20]

The modest increase in the incidence rate (+1% per year) was also reported by the American Cancer Society, +1.1% per year between 1975 and 2010.[1] However, from 1990s onwards the incidence was stable, AAPC +0.3% per year in the period 1990–2011.[16] This was also seen for pAML patients aged 0–14 years in Sweden[21] and Italy[18]. The increase in incidence could be explained by either improved access or refined diagnostics, including a better distinction between ALL and AML. The role of environmental factors in the aetiology of pAML still remains largely unknown.[22] Lastly, the relatively higher number of children with Down syndrome in the Netherlands, as compared with other European countries[23], might have resulted in a higher ML-DS incidence and increased overall incidence, although only comprising 9% of all patients.

The decrease in mortality rate is most prominent in the 1980s (2.8% per year), and confirmed by others.[24] We could not report about incidence and survival in that era, because this was before initiation of the NCR. During the 1980s, the intensity of AML treatment increased and

the advancements in supportive care (especially reduction of bleeding complications and leukostasis) must have contributed to the improvement of outcome in pAML in the 1980s.[4]

Subgroup analyses

Some groups, like infants and adolescents or patients with FAB M5, showed no significant increase in OS. Infants often harbour poor-risk aberrations, like 11q23/KMT2A rearrangements (formerly known as MLL-rearrangements)[25,26], and are at higher risk for toxicity and inappropriate dosing.[27] On the other hand, spontaneous remissions can also occur in neonates with t(8;16)(p11;p13).[28] Future studies should focus on how to improve outcome for these heterogenic subgroups.

In total, 87% of all Dutch pAML patients are treated within a clinical trial, whereas this is only 68% of adults aged 18–40 years.[29] In our study, 57 pAML patients below age 18 years were not treated in a paediatric oncology centre and not registered in the DCOG registry. These "NCR only" patients were older, were more often diagnosed with APL and less often with CBF leukaemia. The outcome of this small subgroup (n = 47) excluding APL and ML-DS was inferior to that of the total cohort of patients ascertained in the DCOG registry (5-year OS 1990–2015 was 42%), but similar to those of the 18–40 year olds.[29] Information on the applied treatment protocol was unknown in this subgroup. The number of pAML patients not treated by a paediatric oncologist decreased over time.

The proportion of patients who underwent alloSCT in CR1 decreased over time. Due to good results internationally with chemotherapy alone[30-33], upfront alloSCT was completely omitted in the DB-AML 01 protocol. In the current NOPHO-DBH AML 2012 protocol a subgroup of patients with FLT3-ITD-positive/NPM1 wildtype pAML are eligible for alloSCT in CR1 after three courses of chemotherapy. This will result in an increase in alloSCT in CR1 in these years.

Study limitations

The retrospective and descriptive design of this study implies the following: the ML mortality data do not distinguish between the different subgroups. However, the contribution of other forms than AML is low. Furthermore, this data also included 18- and 19-year-old patients at the time of death. This could be patients who were diagnosed at an earlier age or newly diagnosed at age 18 or 19 years with a short survival time. Patients who died after the age of 19 years were not included. Using the progress model proposed in this study, it is not possible to observe the final effect of the incidence–survival combination on mortality. It takes some time before changes in incidence and survival are reflected in the mortality statistics.[9] With

the improvement in OS from 2010 onwards, we expect mortality to decrease again in the near future. We did not use the period approach to predict 5-year survival for leukaemias diagnosed more recently (2010–15). This approach allows for the prediction of survival where 5 years of follow-up are not yet available.[34] Therefore, the survival estimate for the last period could be even underestimated. In June 2018, all Dutch paediatric oncology care has been centralized in the Princess Máxima Center for paediatric oncology. The centralization will hopefully further improve the very complex care of children and adolescents with AML and lead to further outcome improvements. Collaborations with international study groups remain necessary to enable high-quality research in respect to the genomic landscape of paediatric AML, better risk stratification and novel therapies in the future.[2]

CONCLUSION

In summary, we are the first to provide a comprehensive overview combining population-based epidemiological data of the NCR and clinical data of the DCOG of pAML during the last 26 years in the Netherlands. Overall, there was a slight increase in the incidence of pAML. Survival significantly improved over the past 26 years and nearly doubled from 40% in the early 1990s to 74% in 2010–15. Mortality rates especially decreased before the 1990s. In conclusion, recent progress in the treatment of pAML has been made in the Netherlands.

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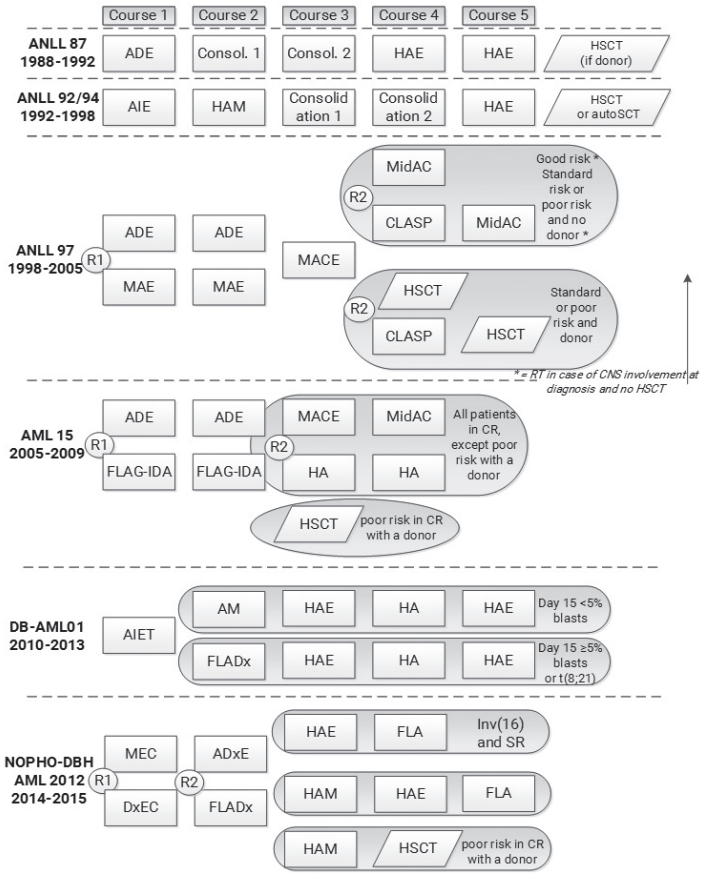
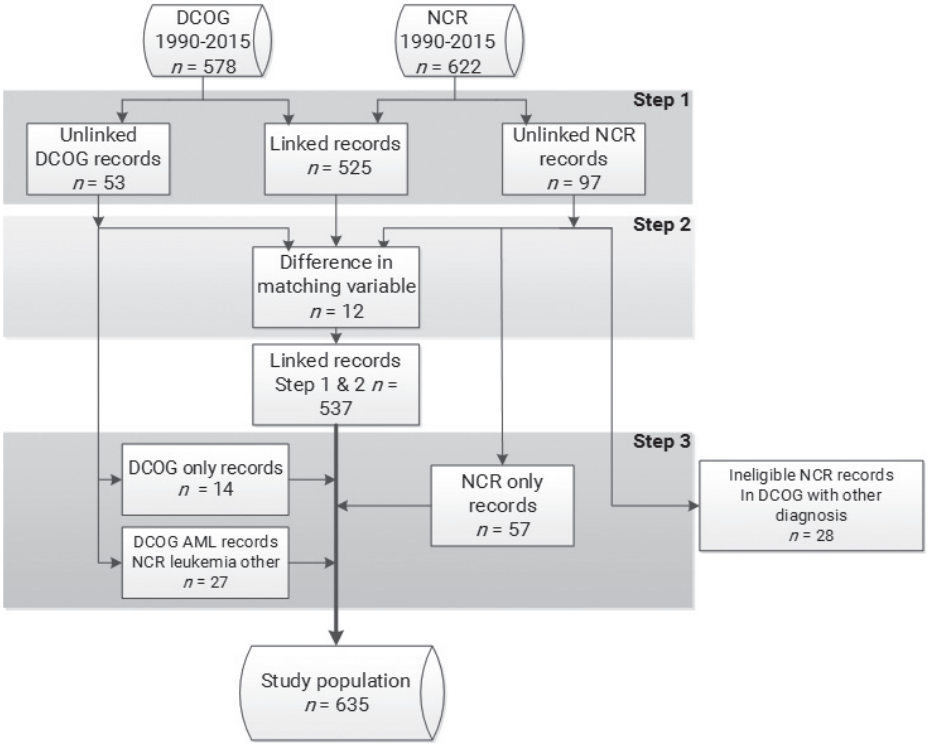
Supplementary figure S5.1. Overview of the DCOG treatment protocols active during the study period



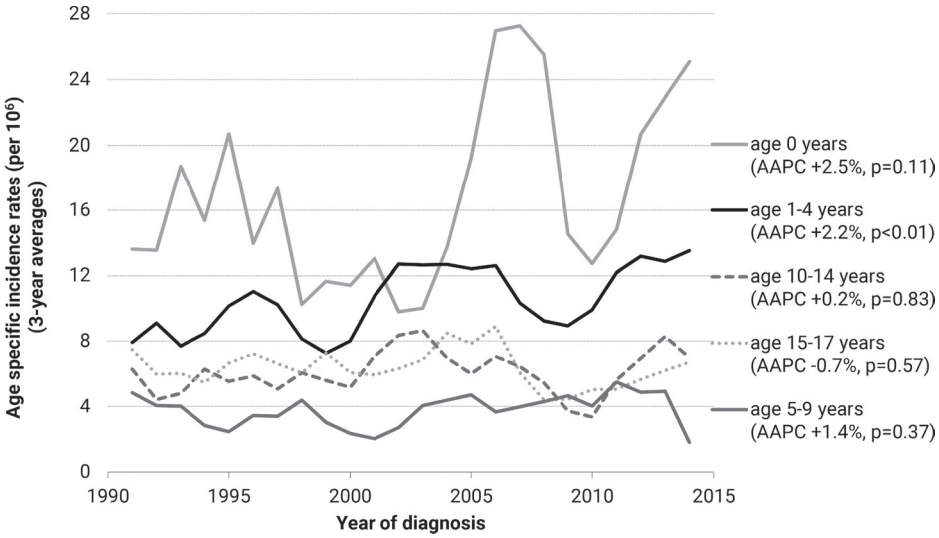
Dutch AML treatment protocols are based on treatment schemes used by other (international) study groups. The ANLL 87 and ANLL92/94 are derived from the BFM group, ANLL 97 and AML15 from the MRC group and DB-AML01 and NOPHO-DBH AML 2012 from the NOPHO group. For three protocols adaptions were made; in the ANLL87 and 92/94 maintenance and CNS irradiation were omitted. In DB-AML01 the first consolidation course with high dose cytosine arabinoside (HD Ara-C) and mitoxantrone was omitted. Stratifications were introduced from ANLL 97 onwards and are displayed in grey circles. Good risk patients have favourable cytogenetics, t(15;17), t(8;21) or inv(16). Poor risk patients have adverse cytogenetics; complex karyotype, -7, abn(3q), del(5q) or -5. Standard risk patients have other abnormalities or normal karyotype. From 2006 onwards, patients with ML-DS were treated in a separate protocol. In protocol ANLL92/94, all-trans retinoic acid was implemented as standard treatment modality for paediatric patients with APL (pAPL). Since 2010, pAPL patients are treated in a separate protocol.
Abbreviations: **ADE**, cytosine arabinoside (Ara-C), daunorubicin, etoposide; **ADxE**, Ara-C, liposomal daunorubicin, etoposide; **AIE**, Ara-C, Idarubicin, etoposide; **AIET**, Ara-C, idarubicin, etoposide, 6-thioguanine; **AM**, Ara-C, mitoxantrone; **auto-SCT**, autologous stem cell transplantation; **BFM** Berlin-Frankfurt-Munster study group; **CLASP**, HD-AraC 3 g/m^2, L-asparaginase; **consolidation 1**, prednisolone, 6-thioguanine, vincristine, Adriamycin, Ara-C; **consolidation 2**, 6-thioguanine, Ara-C, cyclophosphamide; **DxEC**, liposomal daunorubicin, etoposide, Ara-C; **FLA**, fludarabine, high dose (HD) Ara-C; **FLADx**, fludarabine, HD Ara-C, liposomal daunorubicin; **FLAG-Ida**, fludarabine, HD Ara-C, granulocyte colony stimulating factor, idarubicin; **HAE**, HD Ara-C, etoposide; **HA**, HD Ara-C; **HAM**, HD Ara-C and mitoxantrone **HSCT**, hematopoietic allogenic stem cell transplantation; **MACE**, amsacrine, Ara-C, etoposide; **MAE**, mitoxantrone, Ara-C, etoposide; **MidAC**, mitoxantrone, HD Ara-C; **MRC** Medical Research Council; **NOPHO**, Nordic Society of Paediatric Haematology and Oncology; **R1**: first randomization; **R2**, second randomization; **RT**, radiotherapy.

Supplementary figure S5.2. Linkage between the Dutch Childhood Oncology Group and Netherlands Cancer Registry data



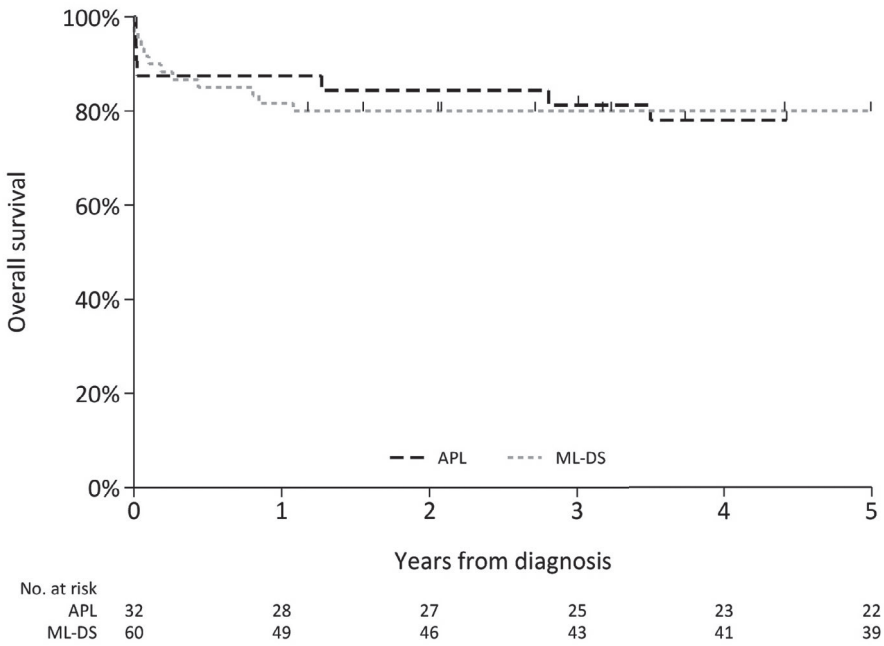
In order to check for completeness all children below age 18 and diagnosed with acute myeloid leukaemia (AML) between 1 January 1990 and 31 December 2015 were selected from both databases. Linkage between the data files from the Dutch Childhood Oncology Group (DCOG) and Netherlands Cancer Registry (NCR) was performed in three steps. First, data files were merged by date of birth, gender and year of diagnosis which resulted in 525 linked records. Twelve of the remaining records had an inconsistency in one of the three merging variables of step 1, but could be added to the linked records. After step 2, 537 records were linked. In the third step remaining unlinked records were checked in the other registry by date of birth only. Fourteen records were present in the DCOG registry, but could not be identified in the NCR. Another 27 records were also registered in the NCR, but with another diagnosis; acute lymphoblastic leukaemia (ALL, *n*=8), leukaemia not otherwise specified (n=10), mixed phenotype leukaemia (*n*=1), myelodysplastic syndrome or juvenile myelomonocytic leukaemia (*n*=7) and malignant mastocytosis (*n*=1). With respect to the unlinked NCR records, 57 records were not in the DCOG registry. These patients were included, but additional clinical information and treatment specifics were missing for them. Twenty-eight records were registered by the NCR as acute myeloid leukaemia (AML), but with another diagnosis by the DCOG, i.e., acute unspecified or mixed phenotype leukaemia (*n*=5), ALL (*n*=6), chronic myeloid leukaemia (*n*=1), and myelodysplastic syndrome (*n*=16). These records were excluded, because the diagnosis by the DCOG was assumed to be most reliable, since they function as a reference laboratory. After the final step, 635 patients could be included in the study.

Supplementary figure S5.3. Age standardised incidence rates of paediatric AML by age group in the Netherlands between 1990 and 2015



Legend: Age standardised according to the World Standard Rate. Three-year moving averages are shown. The average annual percentage change (AAPC) was calculated for each year of incidence with linear regression analyses. Analyses performed on Cohort 1.

Supplementary figure S5.4. Survival curves of patients with APL and ML-DS diagnosed between 1990 and 2015



Abbreviations: APL, acute promyelocytic leukaemia; ML-DS, myeloid leukaemia associated with Down syndrome
Analyses performed for APL and ML-DS patients only (Cohort 1b).

Supplementary table S5.1. Selected morphology codes for acute myeloid leukaemia

AML subtype	ICD-O-3 code	ICCC-3 subgroup
AML with recurrent cytogenetic abnormalities		
Acute promyelocytic leukaemia, t(15;17)(q22;q11-12)	9866	Ib
AML with abnormal marrow eosinophils, inv(16) or t(16;16)	9871	Ib
AML, t(8;21)(q22;q22)	9896	Ib
AML, 11q23 abnormalities	9897	Ib
AML with multilineage dysplasia	9895	Ib
AML, other		
Acute erythroid leukaemia (FAB M6)	9840	Ib
Acute myelomonocytic leukaemia (FAB M4)	9867	Ib
AML, minimal differentiation (FAB M0)	9872	Ib
AML, without maturation (FAB M1)	9873	Ib
AML, with maturation (FAB M2, NOS)	9874	Ib
Acute monocytic leukaemia (FAB M5)	9891	Ib
Acute megakaryoblastic leukaemia (FAB M7)	9910	Ib
Myeloid sarcoma	9930	Ie
AML, NOS	9861	Ib
ML-DS	9898	Not in ICCC-3
Excluded AML subtype		
Therapy related myeloid neoplasm	9920	Ib

Legend: Selected morphology codes for acute myeloid leukaemia according to the International Classification of Diseases for Oncology, third edition (ICD-O-3) and subsequent subgroups of the International Classification of Childhood Cancer, third edition (ICCC-3) (1)

Before 2001, AML used to be classified according to the French-American-British (FAB) classification based on cytomorphology and immunophenotype.(2-4) Since 2001, the FAB classification has been replaced by the World Health Organization (WHO) classifications 2008 and 2017 that incorporates recurrent cytogenetic and molecular abnormalities (5, 6), of which many are associated with outcome. For example, core-binding factor (CBF) AML that is, t(8;21)(q22;q22); RUNX1-RUNX1T1 [t(8;21)] and inv(16)(p13.1q22)/t(16;16)(p13.1;q22); CBFB-MYH11 [inv(16)/t(16;16)], are associated with good outcome. (7-10) On the other hand, abnormalities such as monosomy 5 (-5) or del(5q), t(6;9)(p23;q34) [t(6;9)] and monosomy 7 (-7) have been identified over the past few years and are associated with poor outcome. (8, 9, 11, 12)

Abbreviations: AML, acute myeloid leukaemia: FAB, French-American-British classification: ML-DS, Myeloid leukaemia associated with Down Syndrome: NOS, not otherwise specified.

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Supplementary table S5.2. Incidence and survival for children, aged <15 years, diagnosed with AML in the Netherlands between 1990 and 2015

Incidence		**1990-94**	**1995-99**	**2000-04**	**2005-09**	**2010-15**	**AAPC 1990-2015**	**SE**	**95% CI low**	**95% CI high**	***p*-value**
Total	Average number of new cases/ year	18	19	21	23	23					
	Age specific incidence rate (per 1 million)	6.6	6.8	7.3	8.3	8.5	1.2	0.5	0.2	2.3	0.02
Boys	Average number of new cases/ year	9	10	13	13	12					
	Age specific incidence rate (per 1 million)	7.4	7.5	9.0	9.3	9.1	1.4	0. 7	-0.0	2.7	0.06
Girls	Average number of new cases/ year	9	9	8	10	11					
	Age specific incidence rate (per 1 million)	6.8	7.1	6.3	6.8	7.6	1.2	1.0	-1.0	3.31	0.27
Survival		**1990-94**	**1995-99**	**2000-04**	**2005-09**	**2010-15**	*p*-value improvement in time				
Total	5-y OS (SE)	41% (5.6%)	58% (5.4%)	56% (5.3%)	50% (5.2%)	73% (4.4%)	<0.01				
Boys	5-y OS (SE)	41% (7.6%)	57% (7.5%)	58% (6.5%)	43% (6.6%)	71% (6.1%)	0.02				
Girls	5-y OS (SE)	42% (8.2%)	59% (8.6%)	53% (8.8%)	60% (8.1%)	74 % (6.5%)	0.03				

Abbreviations: AAPC, average annual percentage change; CI, confidence interval; OS, overall survival; SE, standard error.
Incidence analyses performed on Cohort 1 and survival analyses on Cohort 1a.

Supplementary table S5.3. Mortality for children, aged 0-19 years at death, dying from myeloid leukaemia in the Netherlands between 1980 and 2016

Mortality		1980-84	1985-89	1990-94	1995-99	2000-04	2005-09	2010-16	AAPC 1980-2016	SE	95% CI low	95% CI high	*p*-value
Total	Average number of deaths/ year	22	12	10	7	8	10	6					
	Age adjusted mortality rate (per 10^6)	5.1	2.9	2.7	1.8	2.2	2.6	1.7	-2.8	0.6	-4.1	-1.5	<0.01
Boys	Average number of deaths/ year	12	6	6	5	6	6	4					
	Age adjusted mortality rate (per 10^6)	5.6	2.9	2.9	2.8	2.9	3.0	1.9	-2.5	0.6	-3.8	-1.2	<0.01
Girls	Average number of deaths/ year	10	6	5	2	3	4	3					
	Age adjusted mortality rate (per 10^6)	4.6	3.0	2.4	0.9	1.4	2.1	1.6	-3.0	1.1	-5.3	-0.7	0.01

Abbreviations: AAPC, average annual percentage change; CI, confidence interval; SE, standard error.

Note: The average numbers calculated by gender may not be equal to the total average numbers due to rounding. Analyses performed on cohort 2.

CHAPTER 6

Improved survival for adolescents and young adults with Hodgkin lymphoma and continued high survival for children in the Netherlands: a population-based study during 1990–2015

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ABSTRACT

Population-based studies that assess long-term patterns of incidence, major aspects of treatment and survival are virtually lacking for Hodgkin lymphoma (HL) at a younger age. This study assessed the progress made for young patients with HL (<25 years at diagnosis) in the Netherlands during 1990–2015.

Patient and tumour characteristics were extracted from the population-based Netherlands Cancer Registry. Time trends in incidence and mortality rates were evaluated with average annual percentage change (AAPC) analyses. Stage at diagnosis, initial treatments and site of treatment were studied in relation to observed overall survival (OS).

A total of 2,619 patients with HL were diagnosed between 1990 and 2015. Incidence rates increased for 18–24-year-old patients (AAPC + 1%, p =0.01) only. Treatment regimens changed into less radiotherapy and more 'chemotherapy only', different for age group and stage. Patients aged 15–17 years were increasingly treated at a paediatric oncology centre. The 5-year OS for children was already high in the early 1990s (93%). For patients aged 15–17 and 18–24 years the 5-year OS improved from 84% and 90% in 1990–94 to 96% and 97% in 2010–15, respectively. Survival for patients aged 15–17 years was not affected by site of treatment.

Our present data demonstrate that significant progress in HL treatment has been made in the Netherlands since 1990.

INTRODUCTION

In Western countries Hodgkin lymphoma (HL) is the most common type of cancer in late childhood and early adulthood. Among patients with cancer aged 15–19 years, 15% are diagnosed with HL compared to 4% of the patients aged <15 years.[1,2] In patients with cancer aged 20–24 years, 13% are diagnosed with HL.[1]

Since the end of the 1970s, patients with HL of all ages were treated with combined modality treatment approaches of chemotherapy and radiotherapy (RT), resulting in improved prognosis. The 5-year overall survival (OS) was excellent compared to other cancers in these age groups; 90% for children and 84% for adolescents and young adults (aged 15–44 years) in Europe during the late 1980s.[3,4] The other side of the coin was long-term adverse effects of therapy among survivors of HL treated before the 1990s, including second primary malignancies, cardiac toxicity, and impaired fertility.[5,6] Since the late 1990s, clinical trials for HL have focussed on a stepwise reduction of RT, while maintaining high OS rates and minimising the risk of long-term toxicity.[7-10] Today, the outcome of these clinical trials has resulted in risk-stratified and response-adapted strategies, in which the number of cycles of chemotherapy and the use of RT depends on initial staging and several anatomical and metabolic response criteria.[10,11] RT remains an essential component of treatment for patients who do not respond sufficiently to initial chemotherapy (20 Gy in paediatrics and 36 Gy in adults), for patients with bulky disease, and for adult patients with early-stage disease (20–30 Gy involved node RT).[11] Furthermore, the diagnostic strategies have changed as well. The availability of computed tomography (CT) dramatically changed diagnostics in the 1990s and made staging splenectomy obsolete. Pathological analysis using immunohistochemistry was implemented in the mid- 1990s. The positron emission tomography (PET)-CT scan gradually became a diagnostic method from 2000 onwards.

Besides changes in diagnostics and treatment regimens over time, the upper age limit for a referral to a paediatric oncology centre for HL shifted from 14 to 17 years in the Netherlands since 2004. Moreover, treatment regimens differ between paediatric and adult oncology centres. In Dutch paediatric oncology centres, national treatment protocols were implemented by the Dutch Childhood Oncology Group (DCOG) from 2007 onwards[12]; first in collaboration with the Children's Oncology Group (COG) in some centres, and, since 2011, in collaboration with the European Network for Paediatric Hodgkin Lymphoma (EuroNet-PHL) consortium in all paediatric oncology centres.[13] In the (young) adult setting, clinical trials within the European Organisation for Research and Treatment of Cancer (EORTC) consortium started in the 1960s, with an inclusion rate of 30% for patients aged 15–49 years diagnosed between 1986 and 2004.[14] Patients who did

not participate in clinical trials also benefitted: HL treatment in the non-trial population followed the same trend as in trials, as did survival, just with some lag time.[14] Where and how to treat adolescent (or even young adult) patients with HL is a difficult question. Two American studies demonstrated better outcomes when treated according to a paediatric treatment protocol.[15,16]

Population-based epidemiological studies for HL in children, adolescents, and young adults are limited in the literature and hitherto lacking for the Netherlands. The main aim of the present study was to evaluate the progress made for young HL patients (<25 years) diagnosed between 1990 and 2015, by describing trends in incidence, survival and mortality using data from the Netherlands Cancer Registry (NCR). Changes in treatment regimens over time and the shift of treatment for adolescents towards a paediatric oncology centre were also studied in relation to these trends, using young adults (18–24 years) as a comparative group. This group represents the youngest patients treated in adult oncology centres.

PATIENTS AND METHODS

Data sources

Data on incidence, treatment and survival of HL were derived from the NCR, which is maintained and hosted by the Netherlands Comprehensive Cancer Organisation (IKNL) since 1989. The NCR comprises nationwide population-based data on newly diagnosed malignancies[17], and currently covers 17 million inhabitants, of whom 28% are aged <25 years.[18] The NCR is notified by the Nationwide Network and Registry of Histopathology and Cytopathology, and the National Registry of Hospital Discharge Diagnoses (i.e. inpatient and outpatient discharges). Retrospectively, data are extracted on patient, tumour and primary treatment characteristics. Tumour characteristics also include data on Ann Arbor stage[19] (hereafter referred to as stage) and B symptoms (i.e., >10% weight loss over a period of 6 months, drenching night sweats, and unexplained fever). B symptoms were standardly registered in the NCR as from 2005. Primary treatment modalities are registered in broad categories (i.e., surgery, RT and systemic chemotherapy). Information on vital status (i.e., alive, dead or emigration) was obtained by annual linkage of the NCR with the Nationwide Population Registries Network that holds vital statistics on all residents in the Netherlands. The most recent linkage was performed on 1 February 2018.

Mortality data on HL [International Classification of Diseases (ICD)-9 code 201, ICD-10 code C81] for the period 1980–2016 were obtained from Statistics Netherlands.[20] Mortality data were presented in 5-year age groups, in which age represented age at death.

Patient and data selection

All patients aged <25 years and diagnosed with HL between 1 January 1990 and 31 December 2015 were extracted from the NCR using the definition of subgroup IIa of the International Classification of Childhood Cancer (ICCC), third edition[21], which is based on the ICD for Oncology third edition (ICD-O-3) morphology codes (referred to as ICD-O-3M).[22] Within this subgroup IIa, two diagnostic groups can be distinguished: (a) classical HL (cHL) and (b) nodular lymphocyte-predominant HL (NLPHL). NLPHL (ICD-O-3M-9659) has been a distinct entity since ICD-O-2, which was used by the NCR from 1993 onwards. The cHL cases are further classified in five histological categories: (i) nodular sclerosis (ICD-O-3M-9663-9667), (ii) mixed cellularity (ICD-O-3M-9652), (iii) lymphocyte rich (ICD-O-3M-9651, ICD-O-3M-9657, ICD-O-3M-9658), (iv) lymphocyte depleted (ICD-O-3M-9653), and (v) HL, not otherwise specified (ICD-O-3M-9650).

During this study period eight university medical centres (UMCs) were situated in the Netherlands and all had a paediatric oncology centre. Non-academic hospitals may also have treated patients with HL. For the period 2004–15, it was possible to specify the site of treatment: treatment in a paediatric oncology centre (within a UMC), treatment at an adult UMC oncology centre or in a non-academic hospital. These data obtained via a linkage between the NCR and the registry of the Dutch Childhood Oncology Group were used from previously published work by Reedijk et al.[23], with data update for the diagnostic years 2014 and 2015.

For patients with cHL, treatment was defined as 'chemotherapy only', 'chemotherapy plus RT', and 'RT only'. Patients without treatment (n = 22; 1%) or unknown treatment (n = 7; 0.3%), as well as patients who received surgery (± RT) (n = 5; 0.2%) were excluded from treatment analysis, due to probable under-registration of therapy.

Statistical analyses

Characteristics of the two histological entities, cHL and NLPHL, were described by age groups as percentages and tested with chi-squared tests. Incidence and survival analyses were performed for the age groups <15, 15–17, and 18–24 years, and by histological subtype and according to cHL stage. The study period was divided into five periods, namely 1990–94, 1995–99, 2000–04, 2005–09, and 2010–15. However, for NLPHL, the first two periods were merged into 1993–99. Different age and period groupings were used for mortality analyses, namely age groups <15, 15–19, and 20–24 years and periods 1980–84, 1985–89, 1990–94, 1995–99, 2000–04, 2005–09, and 2010–16.

Incidence and mortality rates were calculated as the average annual number of cases/deaths per million person-years, using the annual mid-year population size as obtained from Statistics Netherlands. Rates were age-standardised using the age structure of the World standard population for the age group <15 years.[24] Changes over time were evaluated by calculating the average annual percentage change (AAPC) for the whole study period (i.e., 1990–2015 for incidence and 1980–2016 for mortality). AAPC was derived from linear regression modelling, including the calendar year as a continuous variable.[24]

Changes in therapy modalities over time were tested by age group and stage with logistic regression with period as a continuous variable. The difference in the proportion of chemotherapy by stage between the age groups for the last period was tested with the chi-squared test. Survival time was calculated as the time elapsed between the date of diagnosis and the date of death due to any cause (event) or date at last follow-up (i.e., alive or censored). Traditional actuarial survival analysis was used to calculate OS at 5 and 10 years after diagnosis. Changes in 5-year OS for the different age groups and stages were evaluated by using parametric survival models (*streg*).[25] These models were used to estimate the risk of dying for the five periods of diagnosis and were adjusted for follow-up time (years). The variables gender, stage, treatment modality and site of treatment were entered in the model to evaluate the effect on the period of diagnosis.

An overview of the analyses performed and the selected patient cohorts are provided in **supplementary figure S6.1**. A p <0.05 was considered statistically significant. All statistical analyses were performed with STATA/SE 14.2 (StataCorp LP, College Station, TX, USA).

Ethical consideration

According to the Central Committee on Research involving Human Subjects (CCMO), this observational study does not require approval from an ethics committee in the Netherlands. Use of the anonymous data for this study was approved by the Privacy Review Board of the NCR, following the principles of the Code of Good conduct of the Federa (https://www.federa.org/codes-conduct).

RESULTS

Patient and tumour characteristics

During 1990–2015, data from 436 children (aged <15 years), 490 adolescents (15–17 years), and 1,693 young adults (18–24 years) with HL were registered in the NCR; 2,619 patients in total. Of all HL cases, 94% were diagnosed with cHL and 6% with NLPHL. Children were significantly more often diagnosed with NLPHL compared to young adults (12% vs. 4%; p <0.01).

Patient and tumour characteristics are presented by histological group, cHL (n = 2,470) and NLPHL (n = 149), in **table 6.1**. The median age at diagnosis was 19 (range 2–24) years for patients with cHL. Slightly more girls/females were diagnosed with cHL than boys/males, except in children aged <15 years. The most common histological subgroup was nodular sclerosis (79%). Two-thirds of the patients with cHL had early-stage HL (i.e., Stage I or II), followed by 20% with Stage III, and 12% Stage IV. B symptoms in cHL increased with age from 25% in the youngest age group to 38% at 18–24 years. The median age at diagnosis was 18 (range 4–24) years for across all studied age groups, 77% being a boy/male. Only 11 patients with NLPHL (7%) were classified with Stage III or Stage IV.

Trends in incidence

On average, for all age groups combined, 100 patients (range 83–129) were annually diagnosed with HL (94 with cHL and six with NLPHL). The overall age-standardised incidence rate of HL (WSR 0–24) significantly increased over time (AAPC +0.8%, p =0.01), as did the age-specific incidence rate for patients aged 18–24 years (AAPC +1.0%, p <0.01; **supplementary table S6.1**).

Age-specific incidence rates for cHL and NLPHL remained virtually unchanged over time, except for a significant increase in cHL in young adults (AAPC +0.9%, p =0.01; **figure 6.1a**). Stage-specific incidence rates decreased for Stage I cHL (AAPC -5.2%, p <0.01) and increased for Stage IV over time (AAPC +5.1%, p <0.01) (**figure 6.1b**). Incidence rates and AAPCs by age, histological group, gender and stage are provided in **supplementary table S6.1**. There were no other significant incidence changes over time.

Table 6.1. Characteristics of patients aged <25 years and diagnosed with Hodgkin lymphoma (HL) in the Netherlands between 1990 and 2015 by age group and histologic subtype of HL

	Age groups (at HL diagnosis)								
	<15 years		15-17 years		18-24 years		Total		
Characteristic	n	%	n	%	n	%	n	%	p-Chi²
cHL type	383		477		1610		2470		
Gender									0.01
Male	206	*54%*	209	*44%*	786	*49%*	1201	*49%*	
Female	177	*46%*	268	*56%*	824	*51%*	1269	*51%*	
Time period of diagnosis									0.70
1990-94	70	*18%*	83	*17%*	315	*20%*	468	*19%*	
1995-99	74	*19%*	90	*19%*	284	*18%*	446	*18%*	
2000-04	83	*22%*	102	*21%*	301	*19%*	486	*20%*	
2005-09	69	*18%*	83	*17%*	314	*20%*	464	*19%*	
2010-2015*	87	*23%*	119	*25%*	396	*25%*	595	*24%*	
Histologic category									0.01
Nodular sclerosis	278	*73%*	376	*79%*	1290	*80%*	1944	*79%*	
Mixed cellularity	38	*10%*	22	*5%*	103	*6%*	163	*7%*	
Lymphocyte rich	11	*3%*	13	*3%*	25	*2%*	49	*2%*	
Lymphocyte depleted	0	*0%*	4	*1%*	8	*0%*	12	*0%*	
Hodgkin, not otherwise specified	56	*15%*	62	*13%*	184	*11%*	302	*12%*	
Ann Arbor stage									0.22
I	50	*13%*	45	*10%*	177	*11%*	272	*11%*	
II	192	*51%*	275	*59%*	911	*57%*	1378	*56%*	
III	89	*23%*	89	*19%*	317	*20%*	495	*20%*	
IV	49	*13%*	61	*13%*	188	*12%*	298	*12%*	
Unknown (1% of total)	3		7		17		27		
B-symptoms [$]									<0.01
Absent	115	*75%*	133	*68%*	438	*63%*	686	*65%*	
Present, at least 1	38	*25%*	63	*32%*	262	*37%*	363	*35%*	
Unknown (1% of total)	3		5		10		18		
NLPHL type	53		13		83		149		
Gender									0.85
Male	41	*77%*	11	*85%*	65	*78%*	117	*79%*	
Female	12	*23%*	2	*15%*	18	*22%*	32	*21%*	
Time period of diagnosis									0.92
1993-99[#]	*7*	*13%*	*2*	*15%*	*18*	*22%*	*27*	*18%*	
2000-04	15	*28%*	3	*23%*	25	*30%*	43	*29%*	
2005-09	16	*30%*	4	*31%*	17	*20%*	37	*25%*	
2010-2015*	15	*28%*	4	*31%*	23	*28%*	42	*28%*	

Table 6.1. (continued)

	Age groups (at HL diagnosis)								
	<15 years		15-17 years		18-24 years		Total		
Characteristic	n	%	n	%	n	%	n	%	p-Chi²
Ann Arbor stage									0.15
I	32	*60%*	6	*46%*	50	*63%*	88	*61%*	
II	20	*38%*	7	*54%*	20	*25%*	47	*32%*	
III	1	*2%*	0	*0%*	5	*6%*	6	*4%*	
IV	0	*0%*	0	*0%*	4	*5%*	4	*3%*	
Unknown (4% of total)	0		0		4		4		
B-symptoms [$]									0.52
absent	27	*96%*	7	*88%*	33	*89%*	67	*92%*	
present, at least 1	1	*4%*	1	*13%*	4	*11%*	6	*8%*	
Unknown (4% of total)	3		0		3		6		

Note that the analyses are performed by classical Hodgkin lymphoma (cHL) and nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) separately. In case of missing data for specific characteristics, percentages were calculated without "unknown". Percentages may not add to 100% due to rounding.

* six-year period

[$] B-symptoms: weight loss (more than 10% within 6 months), fever without (other) cause or night sweat. B-symptoms were registered from 2005 onwards.

[#] NLPHL has a distinct morphology code which was used by the Netherlands Cancer Registry from 1-1-1993 onwards

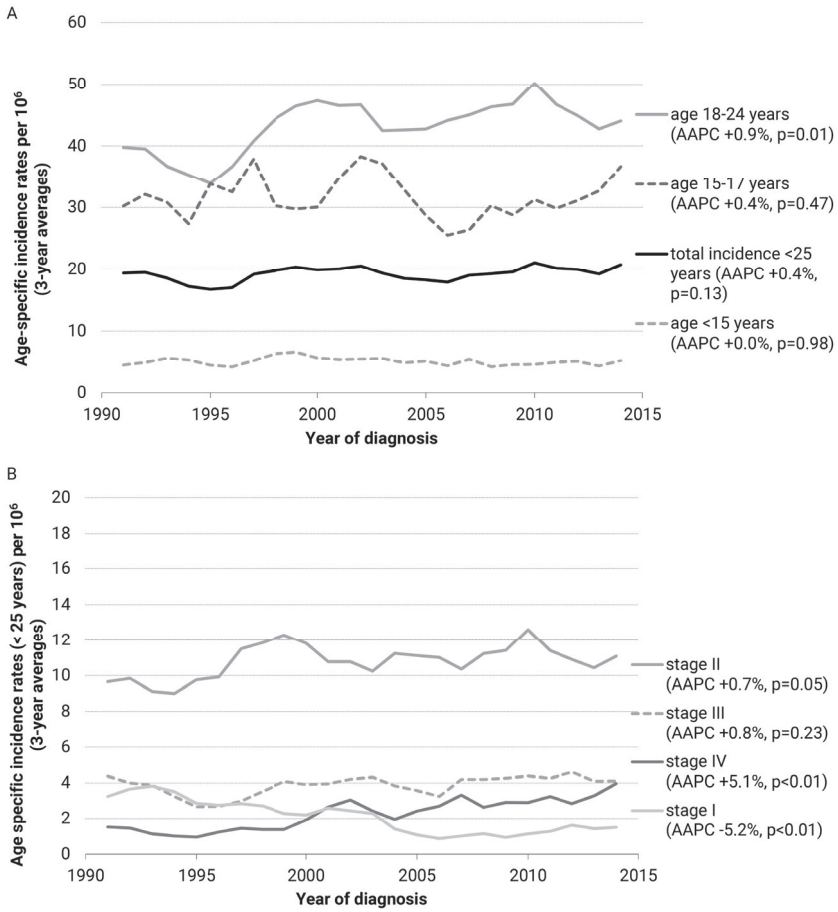

Figure 6.1. Age-specific incidence rates of patients aged <25 years and diagnosed with classical Hodgkin lymphoma in the Netherlands between 1990 and 2015. A) Incidence rates by age group. B) Incidence rates by stage. The 3-year moving averages are shown. The average annual percentage change (AAPC) was calculated for each year of diagnosis with linear regression analyses.

Trends in treatment for patients with cHL

The proportion of patients treated in a UMC (either paediatric or adult oncology centre) significantly increased over time for all age groups as presented in **figure 6.2**. Since 2004, virtually all patients aged <15 years (168/170) were treated in a UMC, of whom 99% in a paediatric oncology centre. The proportion of patients aged 15–17 years who were treated in a UMC was <50% before 1998 and increased to 62% in 2003, followed by a steep rise to 85% in 2007 and remained stable after that. However, these adolescent patients were often not treated in a paediatric oncology centre (27% in 2004), but this proportion increased to 81% in 2015 (**figure 6.2**). The proportion of patients aged 18–24 years who were treated in a UMC was <40% before 1996 and remained between 40% and 50% after 1996 (**figure 6.2**).

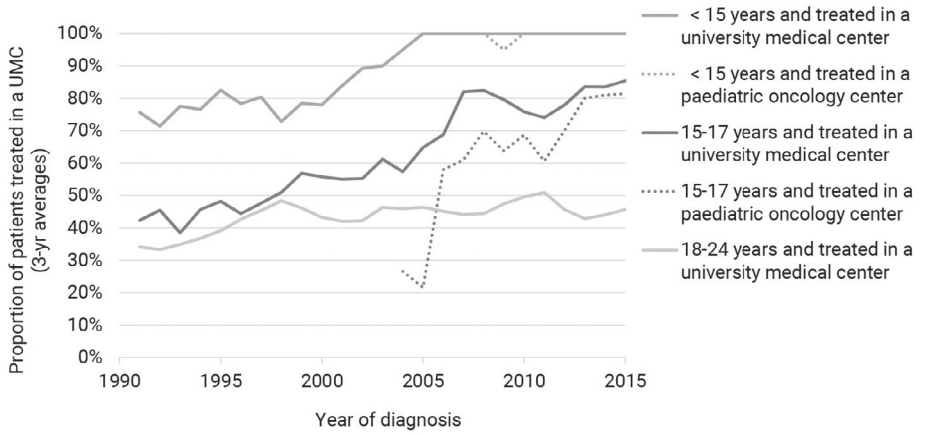

Figure 6.2. Patients aged <25 years and diagnosed with Hodgkin lymphoma in the Netherlands between 1990 and 2015 and site of treatment. The proportion of patients treated in a University Medical Centre (UMC) by age group is depicted by solid lines. From 2004 onwards, a distinction between UMC and Paediatric oncology centre was possible for patients aged <18 years and this is depicted by dashed lines.

Trends in initial treatment modalities are shown in **figure 6.3**. The percentage of patients receiving 'chemotherapy only' increased over time for early stage patients aged <15 years, from 55% in 1990–94 to 68% in 2010–15 (p =0.05). The percentage increased also for patients aged 15–17 years with Stage II, from 44% in 1990–94 to 60% in 2010–15 (p =0.01), and 80% of the patients with Stage III received 'chemotherapy only' in 2010–15 (p =0.03). The percentage of 'chemotherapy only' increased for patients aged 18–24 years with Stage III from 63% in 1995–99 to 92% in 2010–15, and for Stage IV from 60% in 1995–99 to 96% in 2010–15 (both p <0.01). The proportion of patients receiving 'chemotherapy only' was higher for patients aged <15 years with Stage I/II cHL compared to patients aged 15–17 years and patients aged 18–24 years with the same stage in the most recent period, 2010–15 (68% for <15 years, 55% for 15–17 years and 25% for 18–24 years; p <0.01). The opposite was true for Stage III and IV cHL, here the proportion of patients receiving 'chemotherapy only' was higher for patients aged 18–24 years compared to those aged 15–17 years (p <0.01) (**figure 6.3**). Treatment modality 'RT only' disappeared for all age groups after 2004.

Patients aged 15–17 years with cHL treated outside a paediatric oncology centre more often received a combined treatment modality 'chemotherapy + RT' than patients treated in a paediatric oncology centre (56% vs. 35%, p <0.01), who received 'chemotherapy only' more often. This was mainly observed for patients with Stage II (67% vs. 35%, p <0.01) (**supplementary table S6.2**).

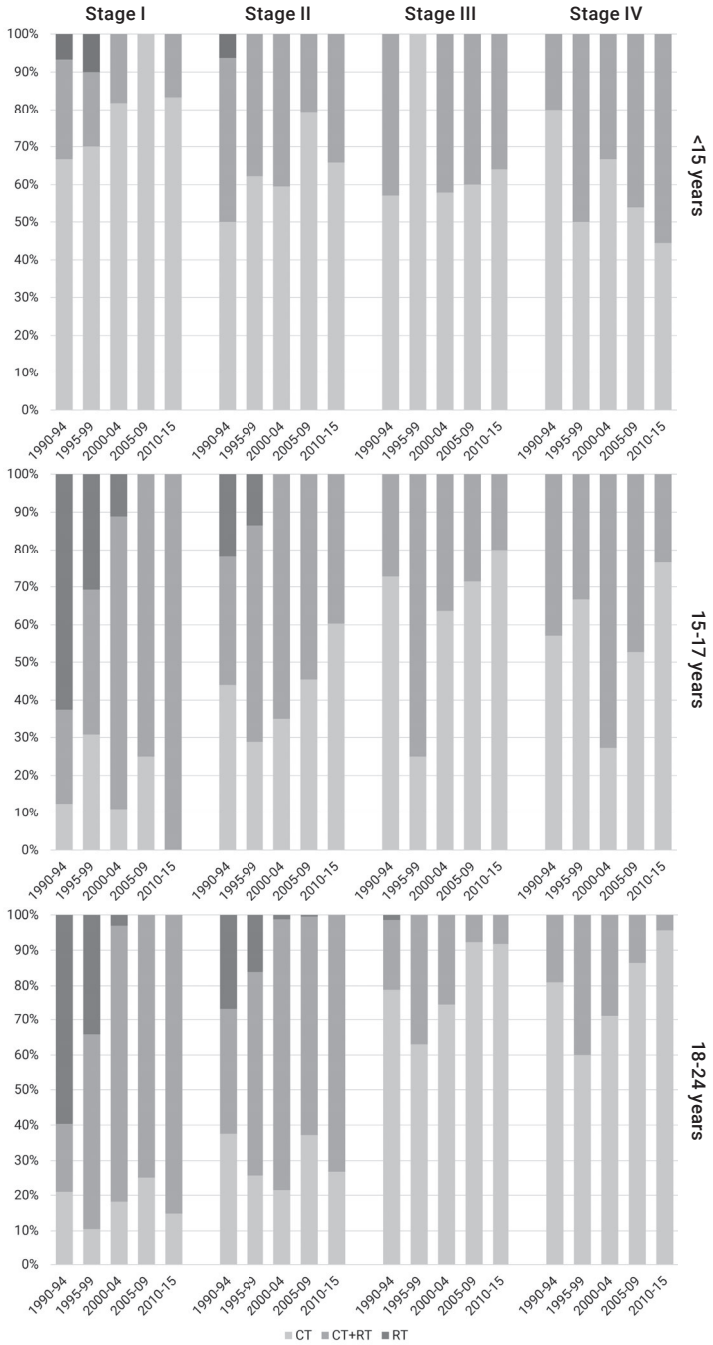

Figure 6.3. Trends in initial treatment modalities for patients aged <25 years and diagnosed with classical Hodgkin lymphoma in the Netherlands over time, 1990-2015, by age group and Ann Arbor stage. *CT* chemotherapy only; *CT+RT* chemotherapy plus radiotherapy, *RT* radiotherapy only.

Trends in survival for patients with cHL

The median (range) follow-up was 12.7 (0–28) years. For patients with cHL aged <15 years, the 5-year OS was already high in 1990–94 with 93% (SE 3%) and improved further to 98% (SE 2%) in 2010–15 (although not statistical significant, p =0.38) (**figure 6.4a**). For the age groups 15–17 and 18–24 years, the 5-year OS significantly increased from 84% (SE 4%) and 90% (SE 2%) in 1990–94 to 96% (SE 2%) and 98% (SE 1%) in 2010–15, respectively (both p <0.01). The 10-year OS for patients aged 15–17 years showed the most remarkable improvement over time, namely an increase from 80% (SE 4%) in 1990–94 to 95% (SE 2%) in 2005–09 (p <0.01) (**figure 6.4b**). Also, for patients aged 18–24 years, the 10-year OS increased from 88% (SE 2%) to 94% (SE 1%) between 1990 and 1994 and 2005–09 (p =0.02).

For patients with Stage II cHL, the 5-year OS significantly increased from 91% (SE 2%) in 1990–94 to 99% (SE 1%) in the period 2010–15 (p <0.01) (**figure 6.4c**). Also, for Stage III and IV the 5-year OS improved, 90% (SE 3%) and 79% (SE 7%) in 1990–94 to 96% (SE 2%) and 95% (SE 3%) in the period 2010–15 (p =0.04 and p =0.01, respectively). The 10-year OS significantly improved over time for patients with Stage I and Stage II (10-year OS for Stage I 100% (SE 0%) and for Stage II 95% (SE 1%) in the period 2005–09 (p =0.01) (**figure 6.4d**). The 5- and 10-year OS rates for cHL over time and by age, gender, histological category, stage and treatment modalities are summarised in **supplementary table S6.3**.

The multivariable survival models by age showed that the survival improvement over time remained significant for patients aged 15–17 and 18–24 years after adjusting for follow-up time, gender, stage, treatment modalities and site of treatment (UMC, yes/no) (**table 6.2**). For patients aged 15–17 years and diagnosed between 2004 and 2015, site of treatment did not influence the 5-year OS (p =0.16) (**figure 6.5**). In a multivariable survival model for this subgroup, the site of treatment did not have an effect on the 5-year OS after adjusting for follow-up time, gender, stage and treatment modalities (results not shown).

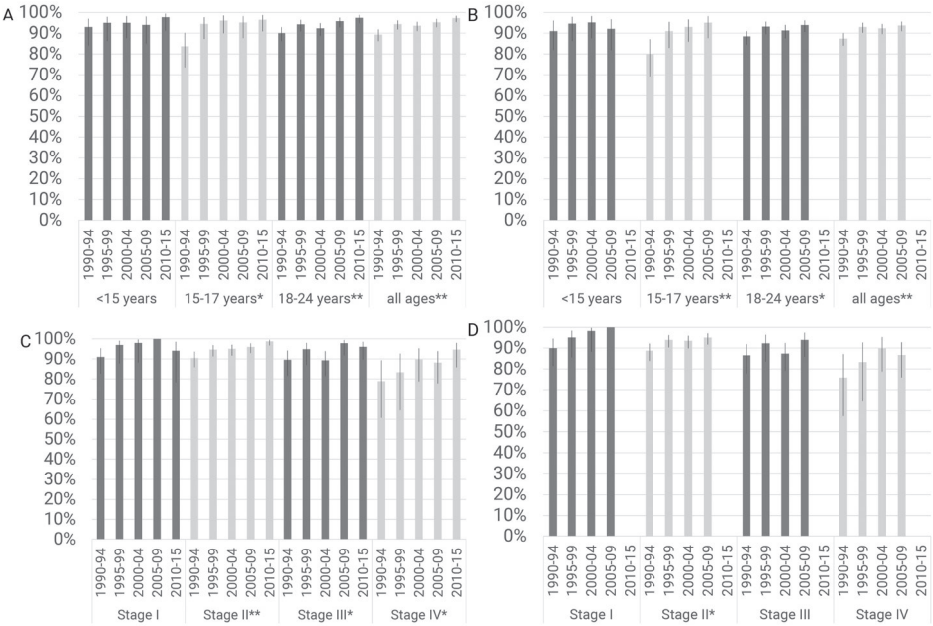

Figure 6.4. The 5- and 10-year overall survival (OS) for patients aged <25 years and diagnosed with classical Hodgkin lymphoma in the Netherlands by period of diagnosis. A) 5-year OS by age group. B) 10-year OS by age group. C) 5-year OS by stage. D) 10-year OS by stage. The *p* for trend was tested with *streg* and corrected for follow-up time. The 10-year OS for the period 2010-15 is not applicable. *p <0.05; **p <0.01.

Table 6.2. The adjusted risk of mortality within five years after diagnosis of classical Hodgkin lymphoma according to age group

	<15 years				15-17 years				18-24 years			
	N at risk	HR	95%CI	*p-value*	N at risk	HR	95%CI	*p-value*	N at risk	HR	95%CI	*p-value*
gender												
male	200	Ref.			202	Ref.			770	Ref.		
female	176	2.0	0.7-5.1	0.17	258	0.8	0.4-1.8	0.63	803	0.8	0.5-1.3	0.36
period of diagnosis												
1990-1994	66	Ref.			76	Ref.			298	Ref.		
1995-1999	74	0.6	0.1-2.2	0.44	87	0.4	0.1-1.0	0.06	272	0.6	0.3-1.2	0.17
2000-2004	81	0.5	0.1-2.0	0.36	99	0.2	0.0-0.6	0.01	296	0.7	0.4-1.3	0.30
2005-2009	68	0.5	0.1-2.1	0.37	81	0.2	0.0-0.6	0.01	313	0.4	0.2-0.8	0.01
2010-2015	87	0.2	0.0-1.3	0.11	117	0.1	0.0-0.5	<0.01	394	0.2	0.1-0.4	<0.01
Stage												
I	48	Ref.			41	Ref.			172	Ref.		
II	191	2.7	0.3-21	0.38	271	0.8	0.2-3.8	0.79	899	0.8	0.4-1.8	0.64
III	88	2.3	0.3-20	0.46	88	0.4	0.1-2.9	0.40	317	1.2	0.5-2.8	0.65
IV	49	4.0	0.4-36	0.27	60	2.6	0.5-14	0.27	185	1.9	0.8-4.6	0.16
UMC*												
no	48	Ref.			165	Ref.			910	Ref.		
yes	328	1.6	0.3-7.3	0.58	295	0.7	0.3-1.5	0.33	663	0.8	0.5-1.2	0.25
Initial therapy												
CT only	244	Ref.			217	Ref.			707	Ref.		
CT+RT	128	0.8	0.3-2.2	0.65	218	0.4	0.2-1.0	0.04	746	0.8	0.5-1.4	0.47
RT only	4	ND			29	0.2	0.0-1.6	0.12	120	0.4	0.1-1.2	0.12

Multivariable analyses were stratified by age. All HRs were adjusted for follow-up time, period of diagnosis, gender, stage, UMC and initial therapy. The risk of mortality within 5 years after diagnosis was significantly lower over time in patients aged 15-17 and 18-24 years. This finding was independent of gender, stage, site of treatment, and initial therapy. Chemotherapy combined with radiotherapy resulted in a significantly lower risk of mortality in patients aged 15-17 years only. *CI* confidence interval; *CT* chemotherapy; *CT+RT* chemotherapy and radiotherapy; *HR* hazard ratio; *RT* radiotherapy; *UMC* university medical centre.

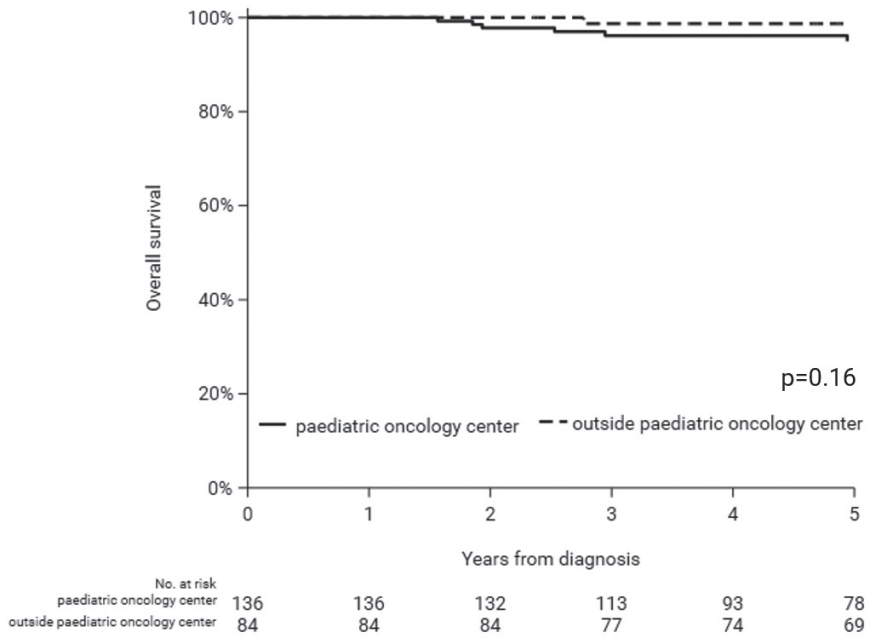

Figure 6.5. The 5-year overall survival (OS) of classical Hodgkin lymphoma patients aged 15-17 years at diagnosis according to site of treatment. The 5-year OS for treatment in a paediatric oncology centre was 95% (95% CI 89-98%). The 5-year OS for treatment outside a paediatric oncology centre was 99% (95% CI 92-100%), *p*-log rank was 0.16

Trends in treatment and survival for patients with NLPHL

For the 149 patients with NLPHL, it was not possible to describe trends in initial treatment modalities in detail due to low numbers per period. A notable change was observed for patients treated in the paediatric oncology setting; watchful waiting was increasingly used for those patients who received a complete resection with or after a diagnostic biopsy. The 10-year OS for patients with NLPHL appeared to be excellent (100%, data not shown).

Trends in mortality

In the early 1980s, approximately nine patients aged <25 years died from HL annually, while during 2010–15, about two patients died from HL per year. Mortality rates for HL significantly decreased for the age groups 15–19 and 20–24 years during 1980–2016 as presented in **figure 6.6** (15–19 years AAPC -6.3%, p <0.01; 20–24 years AAPC -3.0%, p <0.01).

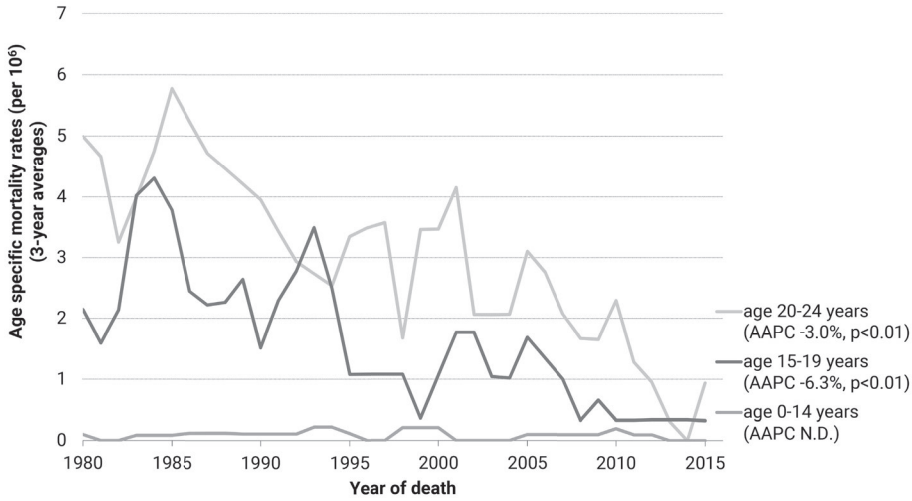

Figure 6.6. Age-specific mortality rates for deceased Hodgkin lymphoma patients aged <25 years at death and cause of death, in the Netherlands between 1980 and 2016. The 3-year moving averages are shown for three age groups, <15 years at death, 15-19 years at death and 20-24 years at death. The average annual percentage change (AAPC) was calculated for each year of diagnosis with linear regression analyses. AAPC analysis for the age group <15 years was not possible due to many years with zero deaths.

DISCUSSION

This is the first comprehensive population-based study on trends in incidence, treatment, survival and mortality among children (<15 years), adolescents (15–17 years) and young adults (18–24 years) with HL in the Netherlands. For children, incidence and survival trends remained stable, for adolescents incidence remained stable while survival increased and both incidence and survival increased for young adults. Treatment regimens changed into less RT and more 'chemotherapy only'. Children with Stage I and II cHL received more 'chemotherapy only' over time. The older age groups received more 'chemotherapy only' for Stage II (15–17 years) and III (15–17 years and 18–24 years), and for Stage IV (18–24 years). RT as a sole treatment modality was abandoned.

The increased incidence rates for patients aged 18–24 years, was also observed in other studies, showing an increase in incidence in patients aged 15–19 and/or 20–24 years.[26-28] We have no reason to assume that improved diagnostic procedures, such as the introduction of CT in the early 1990s and PET-CT in the early 2000s or an increase in Epstein-Barr virus and human immunodeficiency virus infection in the Dutch population have primarily driven the increase in HL incidence.[2] The increased incidence rate is in line with the overall increase of cancer in general, but the reason(s) remains unclear.

While the overall incidence rates of HL remained stable during the entire study period, a significant decline in Stage I disease was seen and a significant increase in Stage IV disease was observed since the diagnostic year 2000. This phenomenon is known as stage migration and is probably caused by improved imaging techniques. For example, improved imaging led to previously Stage II tumours to be classified as Stage III or IV, which, in turn, artificially increased survival in both groups (i.e., the Will Rogers phenomenon).[29] Stage migration in our present study could, in part, explain the improved survival by stage.

Treatment regimens changed into less RT and more 'chemotherapy only', but differed by age group, stage and site of treatment. Patients aged 15–17 years were increasingly treated at a paediatric oncology centre, rising to 81% in 2015. Because of the awareness of long-term adverse effects (e.g., second tumours and cardiotoxicities)[5,6,30,31], RT has changed over time from high-dose extended field RT via involved field RT[32] to involved node RT with lower doses[33], which substantially reduce cardiovascular disease risks for patients.[34] Chemotherapy regimens also changed over time, both combinations of anti-cancer drugs and dose reductions; however, anthracyclines (like doxorubicine) and cyclophosphamide, which are also related to long-term adverse effects, are currently still being used.[35,36] Furthermore, patients aged 15–17 years with early stage HL more often received a combined treatment modality when treated outside a paediatric oncology centre. Protocolised treatment of HL is very common in both the paediatric and adult setting and is constantly focussing on decreasing the burden of late adverse effects and increasing quality of life. However, monitoring long-term adverse effects of RT and chemotherapy and quality of life remains needed in the future.

Hodgkin lymphoma is one of the few malignancies with a comparatively favourable prognosis. NLPHL survival is excellent (100%) and currently, reduction of treatment is implemented for the patients treated in the paediatric oncology setting.[37,38] The 5-year OS for patients with cHL has exceeded 95% across all age groups (<25 years) during the most recent period, 2010–2015. These results were congruent with other industrialised countries. Most recent population-based studies from the USA, Australia, and Europe showed survival rates of approximately 95% for both children and young adults.[2,39-42] We investigated whether the observed changes in stage at diagnosis, site of treatment and treatment modalities contributed to improved survival. However, after adjustment for these changes over time, 'period of diagnosis' remained as an independent predictor for improved survival in the older age groups. The impact on survival might be the result of a combination of improved diagnostics (stage migration), improved use of combinations of classic chemotherapeutic agents, response-adapted use of RT and lastly, improved protocolised treatment.

Survival for patients aged 15–17 years was not influenced by the site of treatment. On the contrary, two American studies showed a better 5-year survival outcome for patients with HL when treated at a Children's Oncology Group centre for patients aged 15–19 years[16] or treated according to a paediatric trial (17–21 years).[15] Several explanations are worth mentioning as to why we could not confirm this benefit. Our population is more homogenous than the Northern American populations. Moreover, in the Netherlands health insurance is free and obligatory for all residents aged <18 years, resulting in equal access to care. Furthermore, in both the paediatric and adult setting there are multidisciplinary teams with representatives of all relevant care givers and protocolised treatments for HL treatment.

In agreement with several European studies, the mortality rates amongst patients aged 15–19 and 20–24 years declined over time.[43,44] We could not report on the incidence and survival in the 1980s, because this was before initiation of the NCR. During the 1980s and before, the focus of HL treatment was mainly on improving survival, while by the late 1980s the focus changed to decreasing treatment toxicity.[45-47]

Some limitations of the present study require consideration. Detailed information on treatment schemes (initial as well as relapse treatment) and trial inclusion are lacking in the NCR for individual patients. Moreover, analyses according to risk group or response status and late effects of treatment were not possible. Nevertheless, cancer registries remain the 'gold standard' for ascertaining trends in incidence, treatment and survival in the general patient population.[48] There was no central review of pathological specimens, we used the morphology code and defined the cHL subtype by how it was entered in the NCR database according to the then existing classification rules. We noticed a decrease in nodular sclerosis and an increase in unclassified HL. The increase in unclassified HL is in line with the review of pathology reports performed by Glaser *et al*.[49] They provided evidence that both changing surgical practices, with prevalent use of needle biopsies instead of excisional biopsies of a lymph node, lead to insufficient biopsy specimens for complete histological diagnosis, as well as the lack of prognostic significance for the different cHL subtypes contribute to an increase in unclassified HL. Mortality data included patients who died from HL up to age of 24 years at the time of death. Patients who died after this age were not included. A strength of the present study is the inclusion of the different age groups <15, 15–17 and 18–24 years, which raises awareness regarding differences in HL types, differences in treatment and site of treatment over time, especially for patients aged 15–17 years.

CONCLUSION

By combining the three epidemiological outcomes (i.e., incidence, mortality and survival) with year of diagnosis, Ann Arbor Stage and initial treatment modalities, we achieved a comprehensive assessment of HL treatment results in the present population-based study. Despite the increase in incidence for the age group 18–24 years, the survival for adolescents and young adults with HL improved and mortality decreased for these age groups. Survival for children aged <15 years was already >90% in the early 1990s. Currently, treatment protocols are more aware of improving quality of life and on decreasing the early and late effects of treatment. The differences in treatment between the paediatric and adult setting, as observed in the present study, could be studied in future treatment protocols, including long-term adverse effects.

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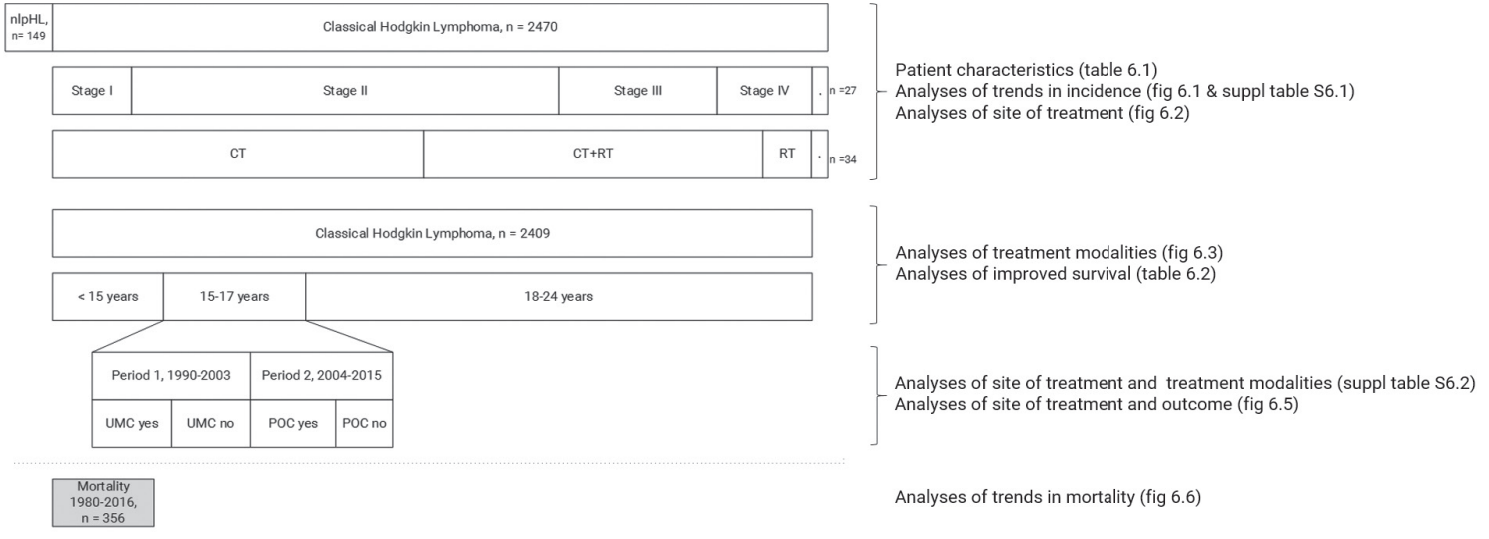
Supplementary figure S6.1 Inclusion of patients with Hodgkin lymphoma for the different analyses performed



In total 2619 patients aged <25 years with a Hodgkin lymphoma were extracted from the Netherlands Cancer Registry between 1990 and 2015. Nodular lymphocyte predominant HL (NLPHL) was registered as a distinct entity from 1993 onwards, n=149. Data from NLPHL and classical Hodgkin (cHL) patients were used to describe patient characteristics (table 6.1), to make incidence analyses overall and by gender, type and age group (supplementary table 1) and to determine site of treatment for the different age groups (figure 6.2). Data from cHL patients were used to make incidence analyses by age group and stage (figure 6.1) and for survival analyses (figure 6.4 and supplementary table 6.2). For cHL patients with known stage at diagnosis and treatment received, n=2409, the analyses of treatment modalities over time (figure 6.3) and the analyses of improvement over time (table 6.2) were performed. For cHL patients aged 15-17 years and diagnosed in time period 2004-2015, n=220, site of treatment and treatment modalities and outcome according to site of treatment were analysed (suppl table 6.2 and figure 6.5). For the mortality analyses the mortality data from Statistics Netherlands were used. All deceased patients with cause of death Hodgkin lymphoma (no histologic subtype available) during 1980-2016 were used, n=356 (figure 6.6).

Supplementary table S6.1 Incidence for children, adolescents and young adults, aged <25 years and diagnosed with Hodgkin lymphoma in the Netherlands between 1990 and 2015

Incidence cHL and NLPHL combined, ICCC group IIa		1990-94	1995-99	2000-04	2005-09	2010-15	AAPC 1990-2015	SE	95% CI low	95% CI high	p-value
	Average number of new cases/ year	95	93	106	101	107					
	Age standardized incidence rate (per 10^6) [a]	*15.8*	*17.2*	*19.7*	*18.2*	*18.7*	*0.8*	*0.3*	*0.2*	*1.4*	*0.01*
Age (years)											
0-14	Average number of new cases/ year	14	16	20	17	17					
	Age standardized incidence rate (per 10^6) [b]	*4.8*	*5.1*	*6.0*	*5.2*	*5.1*	*0.5*	*0.8*	*-1.2*	*2.2*	*0.57*
15-17	Average number of new cases/ year	17	18	21	17	21					
	Age specific incidence rate (per 10^6)	*29.8*	*33.0*	*36.6*	*28.9*	*34.4*	*0.6*	*0.6*	*-0.6*	*1.8*	*0.31*
18-24	Average number of new cases/ year	64	59	65	66	70					
	Age specific incidence rate (per 10^6)	*38.5*	*42.6*	*48.5*	*48.0*	*48.0*	*1.0*	*0.3*	*0.4*	*1.7*	*< 0.01*

Incidence NLPHL [#]		1993-99	2000-04	2005-09	2010-15	AAPC 1993-2015	SE	95% CI low	95% CI high	p-value
	Average number of new cases/ year	4	9	7	7					
	Age standardized incidence rate (per 10^6) [a]	*0.7*	*1.7*	*1.4*	*1.2*	*6.2*	*3.3*	*-0.6*	*12.9*	*0.08*
Age (years)										
0-14	*Average number of new cases/ year*	1	3	3	3					
	Age standardized incidence rate (per 10^6) [b]	*0.3*	*1.0*	*1.0*	*0.7*	*NA [c]*				
15-17	Average number of new cases/ year	0	1	1	1					
	Age specific incidence rate (per 10^6)	*0.5*	*1.0*	*1.3*	*1.1*	*NA [c]*				
18-24	Average number of new cases/ year	3	5	3	4					
	Age specific incidence rate (per 10^6)	*1.8*	*3.7*	*2.5*	*2.6*	*5.2*	*3.9*	*-3.0*	*13.1*	*0.21*

Incidence cHL		1990-94	1995-99	2000-04	2005-09	2010-15	AAPC 1990-2015	SE	95% CI low	95% CI high	p-value
	Average number of new cases/ year	94	90	97	93	100					
	Age standardized incidence rate (per 10^6) [a]	*15.5*	*16.6*	*18.0*	*16.8*	*17.4*	*0.5*	*0.3*	*-0.1*	*1.1*	*0.08*

Supplementary table S6.1 (continued)

Age (years)											
0-14	*Average number of new cases/ year*	14	15	17	14	15					
	Age standardized incidence rate (per 10⁶) [b]	*4.6*	*4.7*	*5.0*	*4.2*	*4.3*	*-0.3*	*0.9*	*-2.2*	*1.5*	*0.71*
15-17	Average number of new cases/ year	17	18	20	17	20					
	Age specific incidence rate (per 10⁶)	*29.4*	*32.6*	*35.5*	*27.5*	*33.2*	*0.4*	*0.6*	*-0.8*	*1.7*	*0.47*
18-24	Average number of new cases/ year	63	57	60	63	66					
	Age specific incidence rate (per 10 ⁶)	*37.8*	*40.9*	*44.7*	*45.6*	*45.4*	*0.9*	*0.3*	*0.2*	*1.5*	*0.01*
Incidence cHL Males		**1990-94**	**1995-99**	**2000-04**	**2005-09**	**2010-15**	**AAPC 1990-2015**	**SE**	**95% CI low**	**95% CI high**	**p-value**
	Average number of new cases/ year	45	42	51	44	49					
	Age standardized incidence rate (per 10⁶) [a]	*14.7*	*15.2*	*18.5*	*15.5*	*16.8*	*0.7*	*0.4*	*-0.2*	*1.6*	*0.10*
Age (years)											
0-14	*Average number of new cases/ year*	8	7	9	7	8					
	Age standardized incidence rate (per 10⁶) [b]	*5.5*	*4.6*	*5.4*	*4.0*	*4.8*	*-0.2*	*1.0*	*-2.3*	*1.8*	*0.82*
15-17	Average number of new cases/ year	6	7	11	7	9					
	Age specific incidence rate (per 10⁶)	*22.2*	*24.8*	*35.9*	*24.0*	*28.4*	*1.1*	*0.9*	*-0.7*	*3.0*	*0.22*
18-24	Average number of new cases/ year	31	28	31	30	32					
	Age specific incidence rate (per 10⁶)	*36.0*	*39.1*	*45.1*	*42.3*	*43.6*	*0.9*	*0.5*	*0.0*	*1.9*	*0.06*
Incidence cHL Females		**1990-94**	**1995-99**	**2000-04**	**2005-09**	**2010-15**	**AAPC 1990-2015**	**SE**	**95% CI low**	**95% CI high**	**p-value**
	Average number of new cases/ year	48	48	47	50	51					
	Age standardized incidence rate (per 10⁶) [a]	*16.3*	*18.0*	*17.5*	*18.2*	*18.2*	*0.3*	*0.4*	*-0.6*	*1.1*	*0.51*
Age (years)											
0-14	*Average number of new cases/ year*	6	8	7	7	6					
	Age standardized incidence rate (per 10⁶) [b]	*3.7*	*5.0*	*4.5*	*4.4*	*3.8*	*-0.6*	*1.4*	*-3.4*	*2.3*	*0.69*

Supplementary table S6.1 (continued)

15-17	Average number of new cases/ year	10	11	10	9	11					
	Age specific incidence rate (per 10^6)	*37.0*	*40.8*	*35.1*	*31.2*	*38.4*	*-0.1*	*0.9*	*-2.0*	*1.8*	*0.92*
18-24	Average number of new cases/ year	32	29	29	33	34					
	Age specific incidence rate (per 10^6)	*39.6*	*42.7*	*44.4*	*48.9*	*47.2*	*0.7*	*0.4*	*-0.2*	*1.6*	*0.12*
Incidence cHL by stage		**1990-94**	**1995-99**	**2000-04**	**2005-09**	**2010-15**	**AAPC 1990-2015**	**SE**	**95% CI low**	**95% CI high**	**p-value**
I	*Average number of new cases/ year*	18	12	11	5	7					
	Age standardized incidence rate (per 10^6) [a]	*2.9*	*2.3*	*2.1*	*0.9*	*1.2*	*-4.9*	*1.1*	*-7.2*	*-2.7*	*<0.01*
II	Average number of new cases/ year	47	54	53	56	55					
	Age standardized incidence rate (per 10^6) [a]	*7.8*	*9.9*	*9.8*	*10.0*	*9.6*	*0.8*	*0.4*	*0.0*	*1.6*	*0.05*
III	Average number of new cases/ year	19	16	21	19	21					
	Age standardized incidence rate (per 10^6) [a]	*3.2*	*2.9*	*3.8*	*3.4*	*3.6*	*0.9*	*0.6*	*-0.4*	*2.2*	*0.16*
IV	Average number of new cases/ year	7	6	12	14	18					
	Age standardized incidence rate (per 10^6) [a]	*1.1*	*1.1*	*2.2*	*2.5*	*3.0*	*5.3*	*1.0*	*3.2*	*7.3*	*<0.01*

Note that the average numbers calculated by age groups or stage may not be equal to the total average numbers due to rounding.
[a] age standardization according to the World Standard population 0-24 years
[b] age standardization according to the World Standard population 0-14 years
[c] AAPC analysis for this age group was not possible due to years with zero incidences.
[#] NLPHL has a distinct morphology code which was used by the Netherlands Cancer Registry from 1-1-1993 onwards

AAPC average annual percentage change, *cHL* classical Hodgkin lymphoma, *CI* confidence interval, *NLPHL* nodular lymphocyte predominant Hodgkin lymphoma, *SE* standard error

Supplementary table S6.2 Site of treatment according to stage for patients aged 15-17 years and diagnosed with classical Hodgkin lymphoma in the Netherlands between 2004-2015

	stage I		stage II		stage III		stage IV		Total	
	CT	CT+RT	CT	CT+RT	CT	CT+RT	CT	CT+RT	CT	CT+RT
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Pediatric oncology center	0 (0)	3 (100)	50 (65)	27 (35)	20 (77)	6 (23)	18 (60)	12 (40)	88 (65)	48 (35)
Outside pediatric oncology center	1 (10)	9 (90)	15 (31)	33 (67)	15 (83)	3 (17)	6 (75)	2 (25)	37 (44)	47 (56)
p-chi2	0.57		<0.01		0.60		0.44		<0.01	

Used abbreviations *CT* chemotherapy *CT+RT* chemotherapy plus radiotherapy

Supplementary table S6.3 Age specific 5- and 10-year overall survival (OS) for Hodgkin lymphoma patients over time and by age groups (next pages)

Table legend:
Note that if <20 patients per period were at risk the results of the survival analyses were not presented.
[1] 6y period
[2] p for trend in observed 5 and 10 year observed survival (OS) by using parametric survival model adjusted for follow-up time
* Patients with missing stage were not considered here
** UMC: treatment at an university medical center

	1990-2015					1990-1994					1995-1999				
	n at risk	5-yr OS	*SE*	10-yr OS	*SE*	n at risk	5-yr OS	*SE*	10-yr OS	*SE*	n at risk	5-yr OS	*SE*	10-yr OS	*SE*
Total cohort	**2470**	**94%**	***0%***	**93%**	***1%***	**468**	**89%**	***1%***	**87%**	***2%***	**448**	**94%**	***1%***	**93%**	***1%***
Gender															
Male	**1201**	94%	*1%*	92%	*1%*	**227**	89%	*2%*	87%	*2%*	**209**	94%	*2%*	92%	*2%*
Female	**1269**	94%	*1%*	93%	*1%*	**241**	90%	*2%*	88%	*2%*	**239**	95%	*1%*	94%	*2%*
Histologic category															
Nodular sclerosis	**1944**	94%	*1%*	93%	*1%*	**399**	89%	*2%*	88%	*2%*	**372**	95%	*1%*	94%	*1%*
Mixed cellularity	**163**	96%	*2%*	95%	*2%*	**33**	97%	*3%*	97%	*3%*	**40**	95%	*3%*	90%	*5%*
Lymphocyte rich	**49**	100%	*0%*	100%	*0%*										
Lymphocyte depleted	**12**	83%	*11%*												
Hodgkin, not otherwise specified	**302**	92%	*2%*	91%	*2%*	**23**	77%	*10%*	67%	*10%*	**24**	88%	*7%*	88%	*7%*
Ann Arbor stage *															
I	**272**	95%	*1%*	94%	*1%*	**89**	91%	*3%*	90%	*3%*	**62**	97%	*2%*	95%	*3%*
II	**1378**	95%	*1%*	94%	*1%*	**235**	91%	*2%*	89%	*2%*	**269**	95%	*1%*	94%	*1%*
III	**495**	93%	*1%*	91%	*1%*	**97**	90%	*3%*	87%	*3%*	**78**	95%	*3%*	92%	*3%*
IV	**298**	89%	*2%*	88%	*2%*	**34**	79%	*7%*	76%	*7%*	**30**	83%	*7%*	83%	*7%*
Initial therapy *															
chemotherapy only	**1177**	93%	*1%*	91%	*1%*	**215**	87%	*2%*	85%	*3%*	**172**	91%	*2%*	91%	*2%*
combined treatment modality	**1097**	96%	*1%*	94%	*1%*	**137**	90%	*3%*	89%	*3%*	**216**	96%	*1%*	94%	*2%*
radiotherapy only	**157**	97%	*1%*	95%	*2%*	**99**	95%	*2%*	93%	*3%*	**53**	100%	*0%*	98%	*2%*
UMC**															
No	**1167**	93%	*1%*	92%	*1%*	**275**	88%	*2%*	86%	*2%*	**227**	94%	*2%*	92%	*2%*
Yes	**1303**	95%	*1%*	94%	*1%*	**193**	92%	*2%*	90%	*2%*	**221**	95%	*1%*	94%	*2%*

	2000-2004					2005-2009					2010-2015[1]				
	n at risk	5-yr OS	*SE*	10-yr OS	*SE*	n at risk	5-yr OS	*SE*	10-yr OS	*SE*	n at risk	5-yr OS	*SE*	p-value[2] 5-yr OS	p-value[2] 10-yr OS
Total cohort	**486**	**94%**	***1%***	**92%**	***1%***	**466**	**95%**	***1%***	**94%**	***1%***	**602**	**97%**	***1%***	<0.01	<0.01
Gender															
Male	**253**	93%	*2%*	92%	*2%*	**218**	94%	*2%*	93%	*2%*	**294**	98%	*1%*	<0.01	0.10
Female	**233**	94%	*2%*	93%	*2%*	**248**	96%	*1%*	94%	*2%*	**308**	97%	*1%*	<0.01	0.03
Histologic category															
Nodular sclerosis	**405**	94%	*1%*	93%	*1%*	**360**	94%	*1%*	92%	*1%*	**408**	98%	*1%*	<0.01	0.01
Mixed cellularity	**23**	91%	*6%*	91%	*6%*	**26**	100%	*0%*	100%	*0%*	**41**	96%	*4%*	0.64	0.31
Lymphocyte rich															
Lymphocyte depleted															
Hodgkin, not otherwise specified	**44**	86%	*5%*	86%	*5%*	**72**	97%	*2%*	97%	*2%*	**139**	94%	*2%*	<0.01	<0.01
Ann Arbor stage *															
I	**57**	98%	*2%*	98%	*2%*	**23**	100%	*0%*	100%	*0%*	**41**	94%	*4%*	0.15	0.09
II	**265**	95%	*1%*	94%	*2%*	**278**	96%	*1%*	95%	*1%*	**331**	99%	*1%*	<0.01	0.05
III	**103**	89%	*3%*	87%	*3%*	**94**	98%	*1%*	94%	*3%*	**123**	96%	*2%*	0.04	0.19
IV	**59**	90%	*4%*	90%	*4%*	**69**	88%	*4%*	87%	*4%*	**106**	95%	*3%*	0.01	0.31
Initial therapy *															
chemotherapy only	**205**	90%	*2%*	89%	*2%*	**259**	95%	*1%*	93%	*2%*	**326**	97%	*1%*	<0.01	0.02
combined treatment modality	**269**	97%	*1%*	95%	*1%*	**202**	96%	*1%*	96%	*2%*	**273**	98%	*1%*	<0.01	0.05
radiotherapy only	**<10**					**<10**					**<10**				
UMC**															
No	**231**	91%	*2%*	90%	*2%*	**195**	96%	*1%*	94%	*2%*	**239**	98%	*1%*	<0.01	0.01
Yes	**255**	96%	*1%*	94%	*1%*	**271**	95%	*1%*	93%	*2%*	**363**	97%	*1%*	0.03	0.31

	1990-2015					1990-1994					1995-1999				
	n at risk	5-yr OS	*SE*	10-yr OS	*SE*	n at risk	5-yr OS	*SE*	10-yr OS	*SE*	n at risk	5-yr OS	*SE*	10-yr OS	*SE*
< 15 years	**383**	**95%**	***1%***	**94%**	***1%***	**70**	**93%**	***3%***	**91%**	***3%***	**74**	**95%**	***3%***	**95%**	***3%***
Gender															
Male	**206**	96%	*1%*	96%	*1%*	**42**	95%	*3%*	93%	*4%*	**36**	97%	*3%*	97%	*3%*
Female	**177**	93%	*2%*	92%	*2%*	**28**	89%	*6%*	89%	*6%*	**38**	92%	*4%*	92%	*4%*
Histologic category															
Nodular sclerosis	**278**	95%	*1%*	89%	*4%*	**62**	94%	*3%*	94%	*3%*	**52**	98%	*2%*	98%	*2%*
Mixed cellularity	**38**	92%	*4%*	92%	*4%*										
Lymphocyte rich	**11**	100%	*0%*	100%	*0%*										
Lymphocyte depleted	**-**	-		-											
Hodgkin, not otherwise specified	**56**	96%	*3%*	93%	*4%*										
Ann Arbor Stage*															
I	**50**	98%	*2%*	98%	*2%*										
II	**192**	94%	*2%*	93%	*2%*	**33**	88%	*6%*	88%	*6%*	**45**	91%	*4%*	91%	*4%*
III	**89**	95%	*2%*	95%	*2%*										
IV	**49**	94%	*3%*	91%	*4%*										
Initial therapy *															
chemotherapy only	**244**	95%	*2%*	94%	*2%*	**38**	89%	*5%*	87%	*6%*	**52**	96%	*3%*	96%	*3%*
combined treatment modality	**129**	95%	*2%*	94%	*2%*										
radiotherapy only	**10**														
UMC**															
No	**50**	93%	*4%*	93%	*4%*										
Yes	**333**	95%	*1%*	94%	*1%*	**53**	91%	*4%*	89%	*4%*	**53**	96%	*3%*	96%	*3%*

	2000-2004					2005-2009					2010-2015[1]				
	n at risk	5-yr OS	*SE*	10-yr OS	*SE*	n at risk	5-yr OS	*SE*	10-yr OS	*SE*	n at risk	5-yr OS	*SE*	p-value[2] 5-yr OS	p-value[2] 10-yr OS
< 15 years	**83**	**95%**	***2%***	**95%**	***2%***	**69**	**94%**	***3%***	**92%**	***4%***	**87**	**98%**	***2%***	0.38	0.99
Gender															
Male	**46**	98%	*2%*	98%	*2%*	**33**	94%	*4%*	94%	*4%*	**49**	98%	*2%*	0.79	0.70
Female	**37**	92%	*5%*	92%	*5%*	**36**	92%	*5%*	88%	*6%*	**38**	97%	*3%*	0.34	0.90
Histologic category															
Nodular sclerosis	***67***	96%	*3%*	96%	*3%*	**44**	89%	*5%*	86%	*5%*	**53**	96%	*3%*	0.71	0.18
Mixed cellularity															
Lymphocyte rich															
Lymphocyte depleted															
Hodgkin, not otherwise specified															
Ann Arbor Stage*															
I															
II	***42***	98%	*2%*	98%	*2%*	**34**	97%	*3%*	93%	*5%*	**38**	97%	*3%*	0.07	0.18
III															
IV															
Initial therapy *															
chemotherapy only	**51**	96%	*3%*	96%	*3%*	**49**	94%	*3%*	92%	*4%*	**54**	98%	*2%*	0.28	0.48
combined treatment modality														0.58	0.88
radiotherapy only															
UMC**															
No															
Yes	***71***	94%	*3%*	94%	*3%*	**69**	93%	*3%*	91%	*4%*	**87**	98%	*2%*	0.25	0.77

	1990-2015					1990-1994					1995-1999				
	n at risk	5-yr OS	*SE*	10-yr OS	*SE*	n at risk	5-yr OS	*SE*	10-yr OS	*SE*	n at risk	5-yr OS	*SE*	10-yr OS	*SE*
15-17 years	**477**	**93%**	***1%***	**91%**	***2%***	**83**	**84%**	***4%***	**80%**	***4%***	**90**	**94%**	***2%***	**91%**	***3%***
Gender															
Male	**209**	93%	*2%*	89%	*2%*	**32**	83%	*7%*	77%	*8%*	**35**	94%	*4%*	89%	*5%*
Female	**268**	94%	*2%*	92%	*2%*	**51**	84%	*5%*	82%	*5%*	**55**	95%	*3%*	93%	*4%*
Histologic category															
Nodular sclerosis	**376**	94%	*1%*	90%	*2%*	**73**	82%	*5%*	78%	*5%*	**78**	96%	*2%*	92%	*3%*
Mixed cellularity	**22**	95%	*4%*	95%	*4%*										
Lymphocyte rich	**13**	100%	*0%*	100%	*0%*										
Lymphocyte depleted	**4**	100%	*0%*	100%	*0%*										
Hodgkin, not otherwise specified	**62**	89%	*4%*	89%	*4%*										
Ann Arbor Stage*															
I	**45**	93%	*4%*	88%	*5%*										
II	**275**	94%	*2%*	91%	*2%*	**52**	88%	*5%*	84%	*5%*	**52**	92%	*4%*	90%	*4%*
III	**89**	96%	*2%*	94%	*3%*										
IV	**61**	86%	*5%*	86%	*5%*										
Initial therapy *															
chemotherapy only	**217**	91%	*2%*	89%	*2%*	**36**	78%	*7%*	75%	*7%*	**27**	85%	*7%*	85%	*7%*
combined treatment modality	**218**	97%	*1%*	94%	*2%*	**26**	87%	*7%*	83%	*8%*	**49**	98%	*2%*	94%	*3%*
radiotherapy only	**30**	97%	*3%*	89%	*6%*										
UMC**															
No	**174**	92%	*2%*	87%	*3%*	**48**	79%	*6%*	72%	*7%*	**46**	93%	*4%*	87%	*5%*
Yes	**302**	94%	*1%*	93%	*2%*	**35**	91%	*5%*	91%	*5%*	**44**	95%	*3%*	95%	*3%*

	2000-2004					2005-2009					2010-2015[1]				
	n at risk	5-yr OS	*SE*	10-yr OS	*SE*	n at risk	5-yr OS	*SE*	10-yr OS	*SE*	n at risk	5-yr OS	*SE*	p-value[2] 5-yr OS	p-value[2] 10-yr OS
15-17 years	**102**	**96%**	***2%***	**93%**	***3%***	**83**	**95%**	***2%***	**95%**	***2%***	**119**	**96%**	***2%***	0.01	<0.01
Gender															
Male	**53**	92%	*4%*	90%	*4%*	**37**	92%	*4%*	92%	*4%*	**52**	100%	*0%*	0.03	0.09
Female	**49**	100%	*0%*	96%	*3%*	**46**	98%	*2%*	98%	*2%*	**67**	94%	*3%*	0.06	0.01
Histologic category															
Nodular sclerosis	***81***	98%	*2%*	94%	*3%*	**66**	94%	*3%*	91%	*3%*	**78**	99%	*2%*	<0.01	<0.01
Mixed cellularity															
Lymphocyte rich															
Lymphocyte depleted															
Hodgkin, not otherwise specified															
Ann Arbor Stage*															
I															
II	***58***	95%	*3%*	91%	*4%*	**45**	96%	*3%*	96%	*3%*	**68**	99%	*2%*	0.03	0.08
III															
IV															
Initial therapy *															
chemotherapy only	**39**	92%	*4%*	87%	*6%*	**41**	95%	*3%*	95%	*3%*	**74**	98%	*2%*	<0.01	0.02
combined treatment modality	**60**	100%	*0%*	98%	*2%*	**40**	98%	*3%*	98%	*3%*	**43**	95%	*3%*	0.40	0.02
radiotherapy only															
UMC**															
No	***43***	98%	*2%*	95%	*3%*										
Yes	***59***	95%	*3%*	91%	*4%*	**66**	94%	*3%*	94%	*3%*	**98**	96%	*2%*	0.54	0.86

	1990-2015					1990-1994					1995-1999				
	n at risk	5-yr OS	*SE*	10-yr OS	*SE*	n at risk	5-yr OS	*SE*	10-yr OS	*SE*	n at risk	5-yr OS	*SE*	10-yr OS	*SE*
18-24 years	**1610**	**94%**	***1%***	**93%**	***1%***	**315**	**90%**	***2%***	**88%**	***2%***	**284**	**94%**	***1%***	**93%**	***2%***
Gender															
Male	**786**	93%	*1%*	92%	*1%*	**153**	88%	*3%*	87%	*3%*	**138**	93%	*2%*	92%	*2%*
Female	**824**	95%	*1%*	94%	*1%*	**162**	*92%*	*2%*	90%	*2%*	**146**	*95%*	*2%*	94%	*5%*
Histologic category															
Nodular sclerosis	**1290**	94%	*1%*	93%	*1%*	**264**	91%	*2%*	89%	*2%*	**242**	94%	*2%*	93%	*2%*
Mixed cellularity	**103**	99%	*1%*	96%	*2%*										
Lymphocyte rich	**25**	*100%*	*0%*	100%	*0%*										
Lymphocyte depleted	**8**	75%	*15%*	75%	*###*										
Hodgkin, not otherwise specified	**184**	92%	*2%*	91%	*2%*										
Ann Arbor Stage*															
I	**177**	95%	*2%*	95%	*2%*	**65**	91%	*4%*	91%	*4%*					
II	**911**	96%	*1%*	95%	*1%*	**150**	92%	*2%*	91%	*2%*	**172**	96%	*1%*	96%	*2%*
III	**317**	92%	*2%*	89%	*2%*	**71**	89%	*4%*	85%	*4%*	**46**	91%	*4%*	87%	*5%*
IV	**188**	90%	*2%*	90%	*2%*	**22**	86%	*8%*	86%	*8%*	**20**	90%	*7%*	80%	*9%*
Initial therapy *															
chemotherapy only	**716**	93%	*1%*	91%	*1%*	**141**	89%	*3%*	86%	*3%*	**93**	90%	*3%*	89%	*3%*
combined treatment modality	**750**	96%	*1%*	95%	*1%*	**85**	88%	*4%*	88%	*4%*	**146**	96%	*2%*	94%	*2%*
radiotherapy only	**123**	97%	*2%*	96%	*2%*										
UMC**															
No	**942**	93%	*1%*	93%	*1%*	**210**	*89%*	*2%*	88%	*2%*	**160**	*94%*	*2%*	94%	*2%*
Yes	**668**	95%	*1%*	93%	*1%*	**105**	92%	*3%*	90%	*3%*	**124**	94%	*2%*	92%	*3%*

	2000-2004					2005-2009					2010-2015[1]				
	n at risk	5-yr OS	*SE*	10-yr OS	*SE*	n at risk	5-yr OS	*SE*	10-yr OS	*SE*	n at risk	5-yr OS	*SE*	p-value[2] 5-yr OS	p-value[2] 10-yr OS
18-24 years	**301**	**92%**	***2%***	**91%**	***2%***	**314**	**96%**	***1%***	**94%**	***1%***	**396**	**98%**	***1%***	<0.01	0.03
Gender															
Male	**154**	92%	*2%*	91%	*2%*	**148**	95%	*2%*	93%	*2%*	**193**	97%	*1%*	<0.01	0.09
Female	**147**	*93%*	*2%*	92%	*2%*	**166**	*97%*	*1%*	95%	*2%*	**203**	98%	*1%*	0.01	0.17
Histologic category															
Nodular sclerosis	***257***	93%	*2%*	92%	*2%*	**250**	96%	*1%*	93%	*2%*	**277**	99%	*1%*	<0.01	0.11
Mixed cellularity															
Lymphocyte rich															
Lymphocyte depleted															
Hodgkin, not otherwise specified														0.01	<0.01
Ann Arbor Stage*															
I														0.13	0.07
II	***165***	95%	*2%*	93%	*2%*	**199**	96%	*1%*	95%	*2%*	**225**	99%	*1%*	0.01	0.17
III	***62***	87%	*4%*	85%	*5%*	**65**	98%	*2%*	93%	*4%*	**73**	95%	*3%*	0.06	0.16
IV	***39***	85%	*6%*	85%	*6%*	**37**	89%	*5%*	86%	*6%*	**70**	95%	*3%*	0.03	0.80
Initial therapy *															
chemotherapy only	**115**	87%	*3%*	87%	*3%*	**169**	96%	*1%*	93%	*2%*	**198**	96%	*2%*	<0.01	0.09
combined treatment modality	**179**	96%	*2%*	94%	*2%*	**143**	95%	*2%*	95%	*2%*	**197**	98%	*1%*	0.01	0.08
radiotherapy only															
UMC**															
No	***176***	*89%*	*2%*	89%	*2%*	**178**	*95%*	*2%*	94%	*2%*	**218**	98%	*1%*	<0.01	0.14
Yes	***125***	67%	*2%*	95%	*2%*	**136**	96%	*2%*	94%	*2%*	**178**	97%	*2%*	0.07	0.13

CHAPTER 7

Stable incidence and improved survival in childhood and young adolescent non-Hodgkin lymphoma; a Dutch study on incidence, survival and mortality

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ABSTRACT

Outcome for childhood and young adolescent non-Hodgkin lymphoma (NHL) depends on type of NHL. With epidemiologic analyses of population-based trends in incidence, mortality and survival we aimed to provide insight in the progress made against childhood and young adolescent NHL in the Netherlands. Furthermore, trends in stage at diagnosis, site of treatment, and type of treatment were studied for the most common NHL subtypes.

Patient and tumour characteristics were extracted from the population-based Netherlands Cancer Registry for patients aged <18 years. Time trends in incidence and mortality rates were evaluated with average annual percentage change (AAPC) analyses. Stage at diagnosis and site of treatment were studied in relation to observed overall survival (OS). NHL subtypes considered were lymphoblastic lymphoma (LL), Burkitt lymphoma (BL), diffuse large B-cell lymphoma (DLBCL) and anaplastic large cell lymphoma (ALCL).

A total of 1,001 NHL were diagnosed between 1990 and 2015. The overall NHL incidence rate remained stable over time at 11 per million person-years (AAPC -0.2, p =0.68). A decrease was seen for 5-9 year-old patients (AAPC -2.6%, p <0.01) only. Treatment regimens changed into less radiotherapy and more 'chemotherapy only' for different NHL subtypes. Five-year OS increased from 71% in 1990-1994 to 87% in 2010-2015 (p <0.01). For patients with DLBCL and ALCL 5-year OS improved from 60% and 73% in 1990–1994, respectively, to 90% in 2010–2015. Five-year OS was already high for LL and BL in the 1990s. Since 2004 most of the 15-17 year old patients with NHL were treated at a paediatric oncology centre.

This population-based study demonstrated significant progress against childhood and young adolescent NHL, the incidence rates remained stable, survival increased substantially compared with the 1990s and mortality rates steadily decreased.

INTRODUCTION

Non-Hodgkin lymphoma (NHL) can be divided in immature and mature B- or T- cell NHL. Mature B-cell NHL (B-NHL) such as Burkitt lymphoma (BL) and diffuse large B-cell lymphoma (DLBCL) together with lymphoblastic lymphoma (LBL, precursor T-cell and precursor B-cell taken together as immature NHL) and anaplastic large cell lymphoma (ALCL, a mature T-NHL)) are the major subtypes of NHL in children and young adolescents.[1] These types account for approximately 90% of NHL cases, the remaining 10% comprise adult type lymphomas. Incidence rates for NHL in western countries are 5-6 per million children aged below 15 years and 10-17 per million persons aged 0-19 years.[2-4] Prognosis for NHL depends on subtype, stage of disease and somatic genetic aberrations.[5,6] Often, trends in incidence, survival and mortality are not described simultaneously and upper age limits differ in paediatric NHL epidemiological studies.

In the Netherlands, children (age <15 years) and adolescents (age 15-17 years) diagnosed with NHL were mainly treated in six specialized centres for paediatric oncology and since the early 1990s with similar treatment schemes in all centres.[7] Since 2018, therapy has been centralised in one national centre for childhood cancer, the Princess Máxima Center in Utrecht. Treatment of NHL depends on the cell type involved. For LBL, the application of acute lymphoblastic leukaemia (ALL)-based regimens turned out to be most effective, which has been initiated in the 1970s.[8,9] At that time, a four-drug regimen was more effective for mature B-NHL compared to the 10-drug ALL regimen, including cyclophosphamide, vincristine, doxorubicin and corticosteroids. In the 1980s, high-dose methotrexate and high dose cytarabine were incorporated into treatment regimens for B-cell NHL, as exemplified by the "Total B" regimen.[10,11] Treatment for ALCL consisted of mature B cell-like treatment protocols, with a duration of 4-6 months. In 1999 the ALCL99 protocol was implemented.[12,13]

The population-based Netherlands Cancer Registry (NCR) registers all tumours in the Netherlands, irrespective of patients' age or hospital diagnosed. To study the clinical progress made against childhood and young adolescent NHL in the Netherlands, we performed epidemiologic analyses on trends in incidence, mortality and survival. Furthermore, trends in stage at diagnosis, site of treatment, type of treatment and survival were studied for NHL subtypes LBL, BL, DLBCL and ALCL.

PATIENTS AND METHODS

Patient selection and data sources

Patients aged <18 years and diagnosed with NHL between 1990 to 2015 were extracted from the NCR. The NCR relies on comprehensive case notification through the Nationwide Network and Registry of Histopathology and Cytopathology, and the National Registry of Hospital Discharges (inpatient and outpatient discharges). After notification, trained registrars of the NCR extract data on patient and tumour characteristics, and primary therapy through medical records review. Information on vital status (that is, alive, dead, or emigration) is obtained by annual linkage of the NCR with the Nationwide Population Registries Network that holds vital statistics on all residents in the Netherlands. Last linkage was at February 1st 2019.

Disease specific mortality data from 1980 to 2016 were derived from Statistics Netherlands.[14] The NHL specific ICD-9 codes 200 and 202 and ICD-10 codes C82-C85 were used. Mortality data were obtained in 5-year age groups in which age represents age at death.

Defining subgroups

Clinically, four NHL subgroups exist in paediatric haemato-oncology; immature B- and T-LBL, mature B-NHL and mature T (T-NHL). The most common NHL subtypes LBL, the mature B-NHL: BL and DLBCL and ALCL (mature T-NHL) in paediatric NHL, were studied in more detail. Lymphoid malignancy subtypes were defined using the 2008 WHO classification scheme, its terminology is also incorporated into the third edition of the International Classification of Diseases for Oncology (ICD-O).[15,16] The histological categories used in this study are provided in **supplementary table S7.1**. NCR data further included Murphy/St Jude's stage (referred to as Stage)[17] and therapy codes which differentiate between treatment modalities (i.e., surgery, radiotherapy and systemic chemotherapy).

Incidence and survival analyses were performed for the age groups 0-4, 5-9, 10-14 and 15-17, and by most common NHL subtype. Mortality analyses used the age groups 0-14 and 15-19. Period of diagnosis was defined in five periods: 1990-94, 1995-99, 2000-04, 2005-09 and 2010-15. Treatment in a university medical centre (UMC) was defined positive if patients' hospital of diagnosis or hospital of treatment was a UMC. From 2004 onwards, it was also possible to split this group of UMC treated patients in those treated at a paediatric oncology ward or adult haematology ward within the UMC. (data used from previously published work by Reedijk et al.[7] and updated with the diagnostic years 2014 and 2015). Treatment was defined as chemotherapy (CT) only or CT + radiotherapy (RT) (CT + RT). Patients without treatment or unknown treatment

(n = 12, 1%) were excluded from this treatment analysis. Autologous stem cell transplantations (ASCTs) were uncommon, only 22 patients (2%) went for ASCT and were included in the CT group. The addition of Rituximab for $CD20^+$ lymphoma to a selected group of patients started off protocol in 2004 for paediatric patients.[18,19] Rituximab has been implemented in a standard protocol for paediatric patients from 2010 onwards. Rituximab is considered as immunotherapy (IT), and was included in the CT group (n=46).

Statistical analyses

Characteristics of the study population in relation to age groups or NHL subtypes were described as percentages and tested with $\chi 2$ tests. Differences in median ages by subgroup were tested with Kruskall-Wallis.

Annual age group specific incidence and mortality rates were calculated per 1 million person-years, using the annual mid-year population size as obtained from Statistics Netherlands. Rates were age-standardized using the age structure of the World standard population for age range 0-14 and 0-17 for estimation of incidence rates, and 0-19 year for mortality rates.[20] Average annual percent changes (AAPC) of incidence rates over the total period 1990-2015 were estimated from linear regression modelling including calendar year as a continuous variable.[20] AAPC analyses also provides a corresponding 95% confidence interval (CI) and p-values. Rates and average numbers were also calculated for the five time periods. AAPC of mortality rates were analysed from 1980 onwards per five year periods. The last period was 7 years, 2015-2016 were also included.

Survival time was calculated as the time elapsed between the date of diagnosis and the date of death of any cause (event) or date at last follow-up (alive, censored). Two patients with a NHL diagnosis found at autopsy were excluded from survival analyses (0.2%). Traditional cohort-based survival analysis was used to calculate observed survival at 5 and 10 years after diagnosis. Observed survival was used instead of relative survival because competing causes of death are rare among childhood and young adolescent cancer patients in developed countries such as the Netherlands.[21] Time trends in observed 5- and 10-year survival were evaluated by using parametric survival models (*streg*). To estimate the improvement over time, risk of dying by period of diagnosis was modelled, adjusted for follow-up time (in years). The variables age, gender, stage and therapy were entered in the model to evaluate the effect on the period of diagnosis. A *p*-value <0.05 was considered statistically significant. All statistical analyses were performed with STATA/SE 16.1 (StataCorp LP).

Ethical consideration

According to the Central Committee on Research involving Human Subjects (CCMO), this type of study does not require approval from an ethics committee in the Netherlands. Use of data for this study was approved by the Privacy Review Board of the NCR and the principles of the Code of Good conduct of the Federa. www.federa.org.

RESULTS

Patient and tumour characteristics

Between 1990 and 2015, 1,001 NHL in children and young adolescents aged <18 years were diagnosed in the Netherlands and included in this study. Mature B-NHL is the most common NHL subgroup, with 599 included patients (60%). BL and DLBCL comprised 350 (58%) and 180 (30%) of the B-NHL patients, respectively. The other mature B-NHL diagnoses comprised 69 patients (12%). Immature NHL (LBL) accounted for 241 patients (24%), with immature T-LBL being most predominant (80%) within the LBL. Mature T-NHL accounted for 161 patients (10%), with ALCL being the most frequent type (61%) and all other mature T-NHL accounted for 39%. Characteristics of NHL subtype are shown in **table 7.1**. Further details of the subtypes in the mature B-cell other and mature T-cell other lymphomas are provided in **supplementary table S7.1**.

Eleven infants (aged <1 year) were diagnosed with NHL during this 26-year diagnostic period (3x LBL, 1x BL, 2x DLBCL, 1x ALCL and 3x T other). Patients with LBL were significantly younger than patients with mature B-NHL or mature T-NHL (both p <0.01) (**table 7.1**). Patients with mature T-NHL were significantly older than patients with mature B-NHL (p =0.01). The distribution of different NHL subtypes by age group is presented in **figure 7.1**. Overall, 70% of the NHL patients were boys (p <0.01). No differences in stage distribution were observed between different NHL subtypes (**table 7.1**).

Table 7.1: Characteristics of non-Hodgkin lymphoma (NHL) patients aged <18 years diagnosed between 1990 and 2015 in the Netherlands

	all lymphomas		average per year	immature NHL		mature B-NHL		mature T-NHL		
	n	%		n	%	n	%	n	%	p-value#
	1001	**100%**	**38**	**241**	**24%**	**599**	**60%**	**161**	**16%**	
age groups										
0-4	173	17%	6	59	24%	93	16%	21	13%	<0.01
5-9	291	29%	11	75	31%	181	30%	35	22%	
10-14	311	31%	12	79	33%	177	30%	55	34%	
15-17	226	23%	9	28	12%	148	25%	50	31%	
median age (IQR)				*9 (5-12)*		*10 (6-14)*		*12 (8-15)*		<0.01
gender										<0.01
male	702	70%	27	162	67%	443	74%	97	60%	
female	299	30%	11	79	33%	156	26%	64	40%	
time period										0.10
1990-94	199	20%	40	63	26%	103	17%	33	20%	
1995-99	190	19%	38	42	17%	124	21%	24	15%	
2000-04	177	18%	35	32	13%	113	19%	32	20%	
2005-09	196	20%	39	45	19%	119	20%	32	20%	
2010-15*	239	24%	40	59	24%	140	23%	40	25%	
stage										0.61
I	205	22%	8	44	20%	138	24%	23	17%	
II	217	24%	8	51	24%	130	23%	36	27%	
III	189	21%	7	45	21%	113	20%	31	23%	
IV	307	33%	12	76	35%	186	33%	45	33%	
Unknown (N=84 --> 8%)	82			25		31		26		
Treatment in UMC										0.08
no	110	11%	4	18	8 %	76	13 %	16	10 %	
yes	891	89%	34	223	92 %	523	87 %	145	90 %	
histologic category				**241**		**599**		**161**		
precursor B-cell LBL	49	5%	2	49	20%					
precursor T-cell LBL	192	19%	7	192	80%					
Burkitt lymphoma	350	35%	13			350	58%			
DLBCL	180	18%	7			180	30%			
other mature B-cell lymphoma**	69	7%	3			69	12%			
ALCL	98	10%	4					98	61%	
other mature T-cell lymphoma**	63	6%	2					63	39%	

NOTE: Due to rounding off average numbers may differ from total average numbers

* 6-year period

** Other occurring types of mature lymphomas are in supplementary table S7.1

p-values based on chi-square test and kruskall wallis for age

Used abbreviations: LBL lymphoblastic lymphoma, DLBCL diffuse large B-cell lymphoma, NHL non-Hodgkin lymphoma, ALCL anaplastic large cell lymphoma, UMC university medical centre

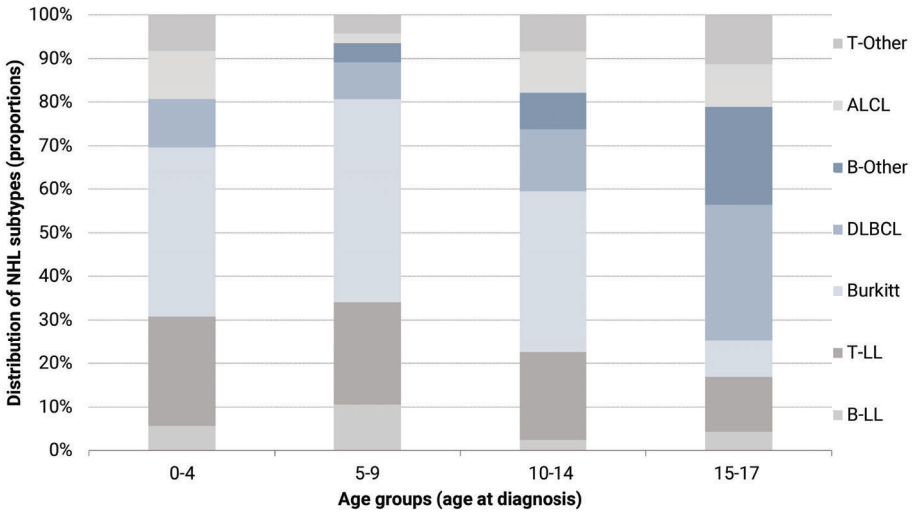

Figure 7.1 Distribution of the different non-Hodgkin lymphoma subtypes by age group in the Netherlands, during 2010-15. Used abbreviations: *B-LBL* B-cell lymphoblastic lymphoma, *T-LBL* T-cell lymphoblastic lymphoma, *Burkitt* Burkitt lymphoma, *DLBCL* diffuse large B-cell lymphoma, *B-Other* other mature B-cell non-Hodgkin lymphoma morphologies, *ALCL* anaplastic large cell lymphoma, *T-Other* other mature T-cell non-Hodgkin lymphoma morphologies

Trends in incidence rates

On average, 39 children and young adolescents were diagnosed with NHL annually, range 28-48. The overall NHL world standardized rate (WSR 0-17 years) and the incidence rates for the subtypes remained stable over time at 11 per million person-years (**supplementary table S7.2**, **figure 7.2**). Age-specific incidence rates showed a significant decrease in incidence for patients aged 5 to 9 year from 15 per million person-years in 1990-94 to 8 per million person-years in 2010-15 (AAPC -2.6% [*p* <0.01]; **supplementary table S7.2**). This decrease was also seen for 5-9 year old male patients, AAPC -2.7% [p =0.01] and 5-9 year old patients with BL, AAPC -3.2% [p =0.01]. Stage specific incidence rates showed a decrease in stage I lymphomas, from 2 per million person-years to 1 per million person-years, AAPC -2.6% [p =0.03]. Age, sex and stage specific incidence rates are shown in **supplementary table S7.2**.

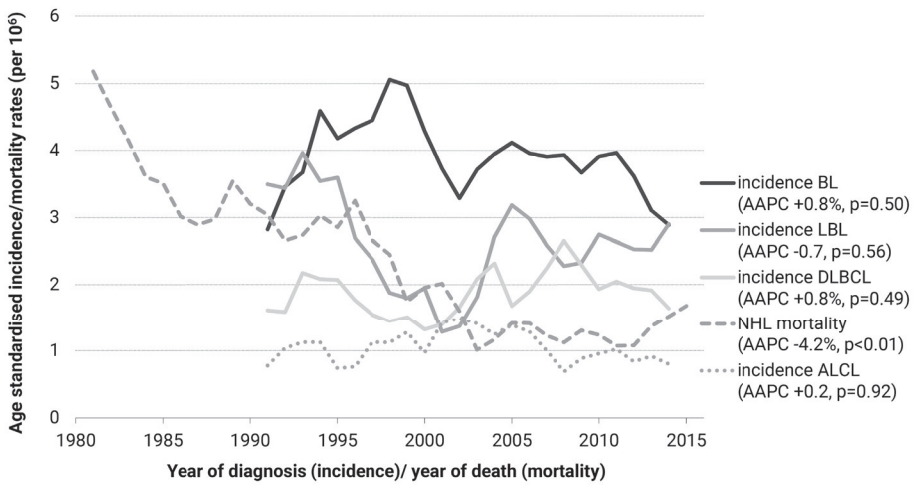

Figure 7.2 Time trends in age-standardized incidence (0-17 years) and mortality (0-19 years) rates of non-Hodgkin lymphoma (by subtype) in the Netherlands, 1990-2015.
Three year moving averages are shown for both incidence and mortality rates. Incidence rates for BL, LBL, DLBCL and ALCL for patients aged 0-17 year in the Netherlands. Mortality analyses performed on data from Statistics Netherlands, age at death 0-19 years. Standardization according to the World Standard Rate (WSR). Used abbreviations: *AAPC* average annual percentage change, *NHL* non-Hodgkin lymphoma, *LBL* lymphoblastic lymphoma, *BL* Burkitt lymphoma, *DLBCL* diffuse large B-cell lymphoma, *ALCL* anaplastic large cell lymphoma.

Trends in treatment and site of treatment

For patients with LBL, BL, DLBCL and ALCL (n = 867) trends in treatment were studied. The most frequently used treatment regimen for these patients was chemotherapy only (CT only). The proportion of patients receiving CT only significantly increased over time for patients with LBL (from 89% in 1990-94 to 98% in 2010-15) and patients with BL (from 93% in 1990-94 to 98% in 2010-15, [*p* for trend =0.01] (**figure 7.3**). In 2004 immunotherapy was introduced and since then the proportion of patients with BL and DLBCL receiving CT+IT substantially increased. The proportion of patients with DLBCL receiving CT (+/- IT) increased to 95% in the last period, although not significant. The proportion of patients with ALCL and receiving CT only fluctuated over time, probably due to the low numbers of patients (i.e., about 20 patients per diagnostic period). The proportion of ALCL patients receiving CT + RT was overall less than 5%.

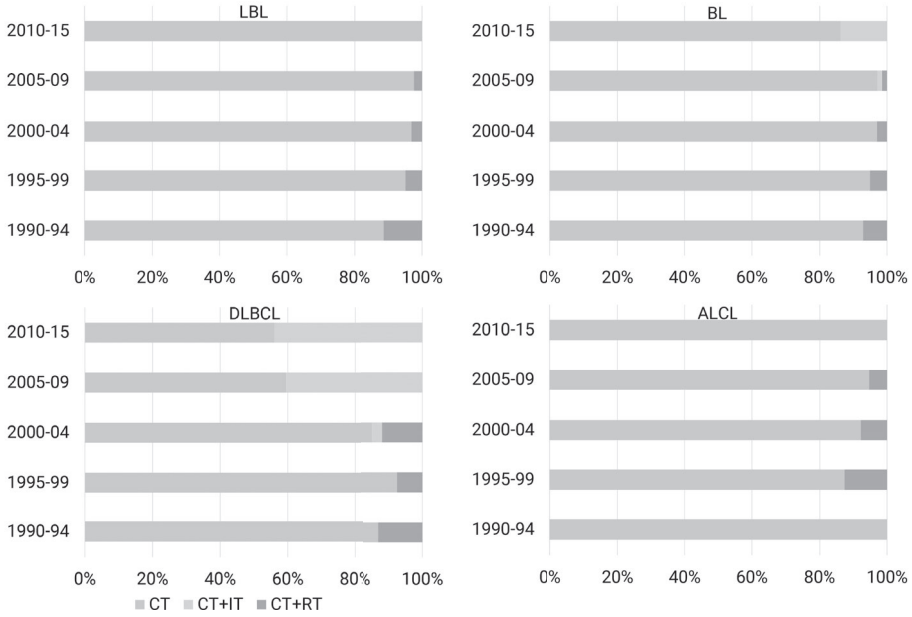

Figure 7.3 Time trends in treatment of non-Hodgkin lymphoma according to subtype for patients aged <18 years, diagnosed 1990-2015. Used abbreviations: *LBL* lymphoblastic lymphoma, *BL* Burkitt lymphoma, *DLBCL* diffuse large B-cell lymphoma, *ALCL* anaplastic large cell lymphoma. *CT* chemotherapy, *CT+IT* chemotherapy and immunotherapy , *CT+RT* chemotherapy and radiotherapy

The proportion of patients treated in a UMC increased over time from 74% in 1990 to 99% after 2010 (**figure 7.4**). After 2003, most patients were treated at a paediatric oncology centre within the UMC (95%). For example, in the last two years of this study only four patients were not treated at a paediatric oncology centre, all four aged 17 years at diagnosis.

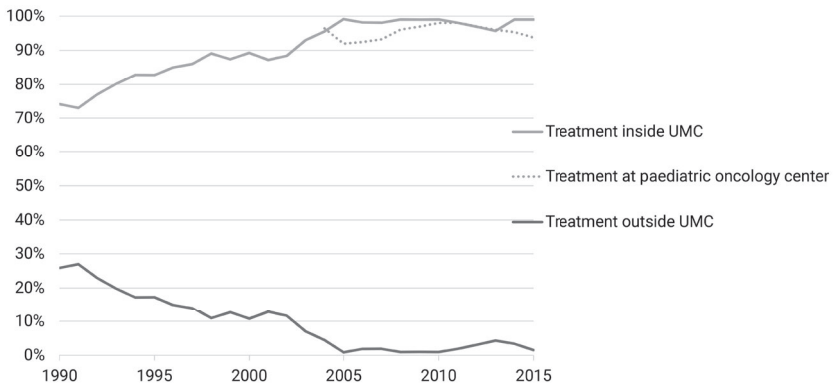

Figure 7.4 Time trend in site of treatment for patients newly diagnosed with non-Hodgkin lymphoma aged <18 years, 1990-2015 In 2014-15 4 patients of 17 years old at diagnosis were treated outside a paediatric oncology center. *UMC* = University Medical Center

Trends in overall survival

Five-year OS improved from 71% in 1990-94 to 87% in 2010-15 (p <0.01) (**table 7.2**). Median follow-up time was 11.1 years (range 0 – 28 years). For patients with LBL, BL, DLBCL and ALCL trends in survival were studied in more detail (n = 867). The 5-year OS improved over time for patients with DLBCL (5-year OS 60% in 1990-94 versus 5-year OS 90% in 2010-15, p <0.01) and for patients with ALCL (5-year OS 73% in 1990-94 versus 5-year OS 90% in 2010-15 p =0.03) (**figure 7.5** and **table 7.2**). The 5-year OS for LBL non-significantly improved over time to 83% in 2010-15 (p =0.10), no difference between immature B- and T-cell type. The 5-yr OS for BL was already above 80% in 1990-94 and slightly improved to 89% in 2010-15 (p =0.20). Age-specific increases in survival over time were only significant for patients aged 15-17 years and diagnosed with subtypes BL and DLBCL (p for trend 0.046 and <0.01 respectively). Gender specific improvements in 5-year OS were only seen for both male and female patients with DLBCL (**table 7.2**). Stage specific improvements in 5-year OS over time were again only seen for patients diagnosed with DLBCL, stage II and higher improved over time (**table 7.2**).

Determinants for risk of death

The multivariable analysis for the risk of dying from DLBCL subtype within 5-years after diagnosis demonstrated a significant decrease in the hazard ratio (HR) during the periods 2005-09 and 2010-15 (HR 0.3, p =0.01, HR 0.1, p <0.01) relative to the period 1990-94, adjusted for follow-up time, age groups, gender, stage and site of treatment (**table 7.3**). Female patients with DLBCL had an increased risk of death compared to male patients (HR 2.0, p =0.03). Patients with stage III or stage IV B-NHL were at higher risk of dying compared to patients with stage I B-NHL (HR 5.2, p =0.01 and HR 5.5, p <0.01) (**table 7.3**). Patients treated outside a UMC had a borderline significant higher risk of dying compared to patients treated at a UMC (HR 2.6, p =0.05).

No significant changes over time in the risk of dying were observed for subtypes LBL, BL and ALCL.

Table 7.2 Five-year overall survival for non-Hodgkin lymphoma patients aged <18 years, diagnosed in the Netherlands between 1990 and 2015

		n at risk	5-yr OS (%)	*SE (%)*	p value[a]											
all patients		**1002**	**81**	***1***	**< 0.01**											
period	1990-94	**198**	71	*3.3*												
	1995-99	**190**	77	*3.1*												
	2000-04	**176**	85	*2.7*												
	2005-09	**195**	85	*2.6*												
	2010-15	**243**	87	*2.2*												
by NHL subtype		**LBL**				**BL**				**DLBCL**				**ALCL**			
		n at risk	5-yr OS (%)	*SE (%)*	p value[a]	n at risk	5-yr OS (%)	*SE (%)*	p value[a]	n at risk	5-yr OS (%)	*SE (%)*	p value[a]	n at risk	5-yr OS (%)	*SE (%)*	p value[a]
		240	**78**	***3***	0.10	**350**	**86**	***2***	0.20	**180**	**76**	***3***	**<0.01**	**97**	**78**	***4***	**0.03**
period	1990-94	**63**	68	*6*		**58**	83	*5*		**33**	60	*9*		**15**	73	*11*	
	1995-99	**42**	81	*6*		**82**	83	*4*		**28**	64	*9*		**17**	65	*12*	
	2000-04	**32**	88	*6*		**68**	90	*4*		**34**	73	*8*		**26**	73	*9*	
	2005-09	**44**	77	*6*		**69**	87	*4*		**43**	86	*5*		**19**	95	*5*	
	2010-15	**59**	83	*5*		**73**	89	*4*		**42**	90	*5*		**20**	90	*7*	
age groups	0-4	**59**	78	*5*	0.32	**72**	90	*4*	0.54	**14**	ND			**11**	ND		
	5-9	**74**	85	*4*	0.94	**138**	87	*3*	0.91	**26**	77	*8*	0.05	**24**	83	*8*	0.70
	10-14	**79**	77	*5*	0.41	**104**	85	*3*	0.22	**61**	80	*5*	0.94	**36**	75	*7*	0.13
	15-17	**28**	65	*9*	0.07	**36**	**77**	***7***	**0.05**	**79**	**75**	***5***	**<0.01**	**26**	72	*9*	0.25
gender	male	**161**	79	*3*	0.32	**290**	86	*2*	0.27	**118**	**80**	***4***	**0.02**	**54**	81	*5*	0.15
	female	**79**	86	*5*	0.17	**60**	85	*5*	0.51	**62**	**69**	***6***	**<0.01**	**43**	74	*7*	0.08

Table 7.2 (continued)

by NHL subtype		LBL				BL				DLBCL				ALCL			
		n at risk	5-yr OS (%)	*SE (%)*	p value[a]	n at risk	5-yr OS (%)	*SE (%)*	p value[a]	n at risk	5-yr OS (%)	*SE (%)*	p value[a]	n at risk	5-yr OS (%)	*SE (%)*	p value[a]
stage	I	**44**	79	*6*	0.60	**58**	91	*4*	0.35	**55**	87	*5*	0.28	**9**			
	II	**51**	80	*6*	0.43	**73**	89	*4*	0.63	**43**	**81**	***6***	**0.02**	**32**	78	*7*	0.08
	III	**45**	89	*5*	0.71	**76**	86	*4*	0.82	**22**	**64**	***10***	**0.03**	**24**	78	*9*	0.11
	IV	**76**	67	*5*	0.55	**123**	85	*3*	0.32	**51**	**64**	***7***	**<0.01**	**31**	74	*8*	0.24
	missing	***24***				***20***				***9***				***1***			
Treatment in UMC	no	**17**	82	*8*		**30**	83	*7*		**27**	67	*9*		**8**	ND		
	yes	**223**	78	*3*	0.08	**320**	86	*2*	0.32	**153**	**78**	***3***	**<0.01**	**89**	79	*4*	0.05

[a] p-values per category for improvements in 5-year OS by period were derived from parametric survival models adjusted for follow-up time. Used abbreviations: *LBL* lymphoblastic lymphoma, *BL* Burkitt lymphoma, *DLBCL* diffuse large B-cell lymphoma, *NHL* non-Hodgkin lymphoma, *ALCL* anaplastic large cell lymphoma, *UMC* university medical centre, *ND* 5-year OS not determined, <15 patients in a category

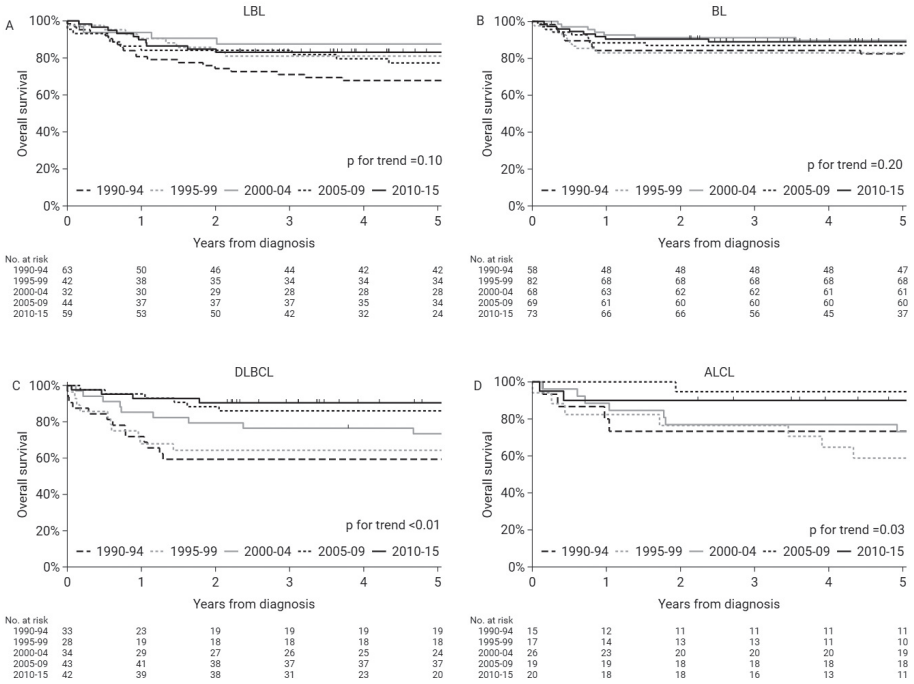

Figure 7.5 Five year overall survival for patients aged <18 years, diagnosed with a non-Hodgkin lymphoma in the Netherlands, between 1990 and 2015, by period and subtype. Used abbreviations: *LBL* lymphoblastic lymphoma, *BL* Burkitt lymphoma, *DLBCL* diffuse large B-cell lymphoma, *ALCL* anaplastic large cell lymphoma

Table 7.3 The adjusted risk of death within five years after DLBCL

NHL subtype		DLBCL						
			Univariate analysis			Multivariable analysis		
		n at risk	HR	*95% CI*	P	HR	*95% CI*	p-value
period	1990-94	**32**	Ref.			Ref.		
	1995-99	**26**	0.9	*0.4-2.1*	0.80	1.3	*0.5-3.2*	0.62
	2000-04	**32**	0.6	*0.2-1.3*	0.19	0.5	*0.2-1.4*	0.20
	2005-09	**42**	0.3	*0.1-0.7*	0.01	0.3	*0.1-0.8*	0.01
	2010-15	**39**	0.1	*0.0-0.5*	<0.01	0.1	*0.0-0.5*	<0.01
age groups	0-4	**11**	Ref.			Ref.		
	5-9	**25**	0.6	*0.2-2.2*	0.48	0.5	*0.1-1.7*	0.25
	10-14	**59**	0.5	*0.2-1.5*	0.21	0.4	*0.1-1.4*	0.16
	15-17	**76**	0.6	*0.2-1.8*	0.38	0.5	*0.1-1.6*	0.23
gender	male	**115**	Ref.			Ref.		
	female	**56**	1.7	*0.9-3.1*	0.11	2.0	*1.0-3.9*	0.04
Stage	I	**55**	Ref.			Ref.		
	II	**43**	0.5	*0.6-4.2*	0.42	2.1	*0.7-6.0*	0.18
	III	**22**	3.2	*1.2-8.9*	0.02	5.2	*1.6-16*	0.01
	IV	**51**	3.4	*1.4-8.1*	0.01	5.5	*2.1-14*	<0.01
Treatment in UMC	yes	**144**	Ref.			Ref.		
	no	**27**	1.6	*0.8-3.4*	0.20	2.6	*1.0-6.5*	0.05

Multivariable analyses for NHL subtype DLBCL only. In this multivariable analysis, each covariate is simultaneously adjusted for all other covariates and follow-up time. Hazard ratios represent risk of death within 5 years from diagnosis compared to the reference category. Patients with missing Murphy stage (n=9; 5%) in total, were excluded. Used abbreviations: HR Hazard Ratio, DLBCL diffuse large B-cell lymphoma, UMC university medical centre

Trends in mortality rates

The average number of NHL deaths among patients aged below 20 years decreased from 21 per year in 1980-84 to 6 in 2010-16 (**supplementary table S7.3**). The largest decrease was observed before the 1990s. Time trend analyses over 1980-2016 revealed an AAPC -4.2% per year (p <0.01) (**figure 7.1**). Also for the period 1990-2016 the AAPC trend analysis remained significant.

DISCUSSION

This is the first comprehensive population-based study on trends in incidence, treatment, survival and mortality among children and adolescents with NHL in the Netherlands. Incidence rates remained stable, overall and type specific. Treatment regimens for LBL and BL changed into less combined chemotherapy plus radiotherapy and more chemotherapy only. For age-specific incidence rates we observed a decrease in incidence for age group 5-9 years. Survival improved over time, mostly for subtypes DLBCL and ALCL. The observed progress against childhood and young adolescent NHL is supported by steadily decreasing, independently assessed mortality rates for this young patient group.

The stable incidence rate of NHL, 11 per million person-years, is comparable with findings and rates in other Western countries.[2-4,22-24] Within our study we also performed incidence trend analyses for the main clinical subgroups of paediatric NHL, being LBL, BL, DLBCL and ALCL. The type-specific incidence rates remained stable over the period 1990-2015. For age-specific incidence rates we observed a marked decrease in the incidence rate for patients aged 5-9 years. For this age group, the decreasing trend was also visible for boys and patients with BL. This trend is, to our knowledge, not reported before. Because of the arbitrary distinction between acute lymphoblastic leukaemia (ALL) and LBL, we have compared the NHL incidence time trends with the ALL incidence trends in the Dutch population.[25] However, no age specific in- or decreases in ALL were found. EBV infection is one of the known risk factors for NHL. One could speculate that less young children encountered an EBV infection in the Netherlands. Unfortunately, there is no information on the prevalence for this kind of infections in the Netherlands, so the reason for this decreasing trend remains unknown.

Treatment for the four common types of paediatric NHL changed into more chemotherapy only. Chemotherapy regimens changed over time, both combinations of anti-cancer drugs and dose reductions; however, monitoring long-term adverse effects and quality of life remains needed in the future for this patient group. Chemotherapeutic drugs, anthracyclines (such as doxorubicine) and cyclophosphamide and cytarabine, are related to long-term adverse effects like secondary malignancies, cardiotoxicity, and gonadal damage.[26-29] Patients with NHL were almost all treated in an UMC, at the paediatric oncology centre of the UMC. Treatment at a UMC resulted in a (borderline) decreased risk of dying. Also, patients aged 15-17 years were treated at the paediatric setting, which was different compared to similarly aged patients with acute lymphoblastic leukaemia or Hodgkin lymphoma in the Netherlands, 13% and 25% were not treated at a paediatric oncology centre during 2010-15, respectively.[25,30]

Survival for NHL increased over time, currently being 87% for patients diagnosed in 2010-2015. Improvements over time were mainly seen for patients with DLBCL and ALCL. Probably due to more protocolized treatment schemes by the end of the 1990s, survival rates improved for these two types. The addition of Rituximab for high-risk DLBCL patients might have improved survival for these patients as well. Five-year observed survival (OS) rates for BL and LBL were already above 80% at the end of the 1990s. Five-year OS rates for NHL from our study were comparable with the corresponding rates in Australia (82% for ICCC-3 group IIb NHL, without BL and 91% for ICCC-3 group IIc Burkitt lymphoma, diagnostic period considered 1997-2006), Europe (84% for ICCC-3 group IIb NHL, without BL and 90% for ICCC-3 group IIc BL, diagnostic period considered 2000-2006) and US (84%, diagnostic period 2003-2009), respectively.[31-33] For DLBCL we found that girls and higher staged tumours had worse outcome. Burkhardt et al. described inferior outcome for female adolescent DLBCL patients compared to younger female patients in univariate analysis, although after adding high serum lactate dehydrogenase (LDH) concentration (as surrogate for tumour mass) in a multivariate analysis, this effect did not remain significant.[34] We did not see that female patients were diagnosed with higher stages or older ages in our study. Current treatment protocols do stratify according to stage. Gender differences in survival needs further investigation.

In agreement with other studies, mortality rates declined constantly over time at each age group.[35,36] Increased intensity of induction and reinduction therapy were the first important components of successful NHL treatment protocols at the end of the 1970s and 1980s.[10] We could not report on the incidence and survival in the 1980s because this was before initiation of the NCR. Improvements in protocolized chemotherapy schemes and risk stratifications, together with monoclonal antibody therapy, further improved NHL outcome in this young patient group.[9]

Some limitations of this study require consideration. Detailed information on treatment schemes (initial as well as relapse treatment) and trial inclusion are lacking in the NCR for individual patients. Moreover, analyses according to risk group or response status and late effects of treatment were not possible. Nevertheless, cancer registries remain the gold standard for ascertaining trends in incidence, treatment, and survival in the general patient population.[37] There was no central review of pathological specimens, we used the morphology code and defined NHL subtype as how it was entered in the NCR database according to the then existing classification rules. However, we cross-checked the morphology codes for NHL patients from one of the largest paediatric oncology centres with the NCR and the coded morphologies matched >95%. Mortality data included patients who died from NHL up to age 19 at time of death. Patients who died after this age were not included. A strength of this study are the epidemiological trend analyses according to clinical relevant subtypes of NHL, which raises awareness regarding differences in NHL types.

CONCLUSION

By combining the three epidemiological outcomes (i.e. incidence, mortality, and survival) with year of diagnosis, NHL subtype, stage and initial treatment modalities, we achieved a comprehensive assessment of progress against NHL in children and young adolescents in the Netherlands. We showed stable incidence rates and improved survival, supported by steadily declining mortality rates.

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Supplementary table S7.1 Non-Hodgkin lymphoma numbers, subtypes and morphology codes used

NHL Subgroup	SUBTYPE†	ICD-O-3 CODES	Exclusion:	Treatment scheme (protocol)	number of cases included in the study
Lymphoblastic lymphoma					**241**
	Precursor B-cell lymphoblastic leukemia/ lymphoma, NOS	9727(B), 9728, 9811, 9835(B), 9836	C42.1	ALL-like	47
	Precursor B-cell lymphoblastic leukemia/ lymphoma, with recurrent genetic abnormalities	9812-9818	C42.1	ALL-like	<5
	Precursor T/NK-cell lymphoblastic leukemia/ lymphoma, NOS	9727(T,NK), 9729, 9835(T,NK), 9837	C42.1	ALL-like	192
Mature B-cell lymphoma					**599**
	Burkitt lymphoma/leukemia	9687, 9826		B-NHL	350
	Diffuse large B-cell lymphoma	9678, 9680, 9684(B), 9688, 9712, 9731, 9734, 9735, 9737-9738, 9765-9766, 9769, 9970		B-NHL	180
	Primary mediastinal (thymic) large B-cell lymphoma	9679		B-NHL	14
	Follicular lymphoma	9597, 9690-9698		other	15
	Marginal zone lymphoma	9689, 9699, 9764		other	11
	Grey zone lymphoma	9596		Hodgkin or mature B-NHL	<5
	B-cell lymphoid neoplasms, NOS	9590(B), 9591(B), 9675(B), 9820(B)	for 9591 C42.1		25
Mature T- cell lymphoma					**161**
	Anaplastic large cell lymphoma ALK-positive	9714		ALCL	98
	Mycosis fungoides	9700			9
	Peripheral T/NK-cell lymphoma, NOS	9702			33

Supplementary table S7.1 (continued)

NHL Subgroup	SUBTYPE†	ICD-O-3 CODES	Exclusion:	Treatment scheme (protocol)	number of cases included in the study
	Angioimmunoblastic T/NK-cell lymphoma	9705			<5
	Subcutaneous panniculitis-like T-cell lymphoma	9708			<5
	Primary cutaneous T-cell lymphoma, NOS	9709			<5
	Hepatosplenic T-cell lymphoma	9716			<5
	Primary cutaneous CD30 1 lymphoproliferative disorders	9718			9
	Extranodal NK/T-cell lymphoma, nasal type	9719			<5
	Primary cutaneous gamma-delta T-cell lymphoma	9726			<5
	Systemic EBV-positive lymphoproliferative disease	9724			<5

Abbreviations: B = B cell; NK = natural killer cell; NOS = not otherwise specified; T= T-cell
† Subtypes according to World Health Organization (WHO) Classification of Tumours of Haematopoietic and Lymphoid Tissues (ref 16)
Arbitrary distinction between precursor lymphoblastic leukemia and LBL is based on percentage of blasts in the bone marrow: LBL = <25% blasts the bone marrow (topography C42.1) the record was excluded. (ref 15)

If coded as originating from

Supplementary table S7.2: Incidence for children and young adolescents, aged <18 years and diagnosed with non-Hodgkin lymphoma in the Netherlands between 1990 and 2015

Incidence total NHL, ICCC group IIb + IIc		1990-94	1995-99	2000-04	2005-09	2010-15	AAPC 1990-2015	95% CI low	95% CI high	p-value
	Average number of new cases/ year	40	38	35	39	40				
	Age standardized incidence rate (per 10^6) [a]	*11.6*	*10.8*	*9.6*	*10.8*	*10.9*	*-0.2*	*-0.9*	*0.6*	*0.68*
Age (years)										
0-4	Average number of new cases/ year	7	7	5	9	6				
	Age specific incidence rate (per 10^6)	*7.0*	*6.8*	*5.1*	*9.1*	*6.6*	*0.1*	*-2.0*	*2.3*	*0.90*
5-9	Average number of new cases/ year	13	13	11	11	7				
	Age specific incidence rate (per 10^6)	*14.7*	*13.3*	*11.5*	*10.8*	*8.4*	*-2.6*	*-4.3*	*-0.9*	*<0.01*
10-14	Average number of new cases/ year	12	11	10	12	15				
	Age specific incidence rate (per 10^6)	*13.0*	*12.1*	*10.3*	*12.3*	*14.0*	*0.3*	*-0.9*	*1.4*	*0.64*
15-17	Average number of new cases/ year	8	7	9	7	12				
	Age specific incidence rate (per 10^6)	*13.8*	*13.0*	*15.0*	*12.3*	*19.9*	*2.0*	*-0.6*	*4.6*	*0.12*
Incidence NHL males		**1990-94**	**1995-99**	**2000-04**	**2005-09**	**2010-15**	**AAPC 1990-2015**	**95% CI low**	**95% CI high**	**p-value**
	Average number of new cases/ year	28	27	27	26	26				
	Age standardized incidence rate (per 10^6) [a]	*16.2*	*14.8*	*14.3*	*14.2*	*11.8*	*-0.8*	*-1.7*	*0.2*	*0.10*
Age (years)										
0-4	Average number of new cases/ year	5	4	5	5	4				
	Age specific incidence rate (per 10^6)	*10.0*	*8.4*	*8.9*	*11.2*	*6.9*	*-0.4*	*-3.3*	*2.5*	*0.75*
5-9	Average number of new cases/ year	10	10	10	7	6				
	Age specific incidence rate (per 10^6)	*20.8*	*19.4*	*19.4*	*13.6*	*10.7*	*-2.7*	*-4.5*	*-0.8*	*0.01*
10-14	Average number of new cases/ year	8	8	8	8	9				
	Age specific incidence rate (per 10^6)	*17.7*	*16.3*	*15.2*	*16.6*	*14.0*	*0.1*	*-1.5*	*1.6*	*0.95*
15-17	Average number of new cases/ year	5	5	5	6	8				

Supplementary table S7.2: (continued)

	Age specific incidence rate (per 10^6)	*19.1*	*18.4*	*15.4*	*18.1*	*21.3*	*1.4*	*-1.4*	*4.2*	*0.31*
Incidence NHL females		**1990-94**	**1995-99**	**2000-04**	**2005-09**	**2010-15**	**AAPC 1990-2015**	**95% CI low**	**95% CI high**	**p-value**
	Average number of new cases/ year	11	12	9	12	13				
	Age standardized incidence rate (per 10^6) [a]	*6.7*	*6.7*	*5.1*	*7.1*	*6.0*	*-0.2*	*-2.1*	*1.7*	*0.79*
Age (years)										
0-4	Average number of new cases/ year	2	2	2	3	1				
	Age specific incidence rate (per 10^6) [b]	*4.6*	*4.6*	*3.6*	*6.9*	*2.6*				
5-9	Average number of new cases/ year	4	2	2	2	3				
	Age specific incidence rate (per 10^6) [b]	*9.3*	*5.0*	*4.1*	*3.7*	*4.7*				
10-14	Average number of new cases/ year	3	4	3	5	5				
	Age specific incidence rate (per 10^6)	*6.8*	*8.3*	*6.1*	*9.6*	*7.8*	*0.6*	*-1.5*	*2.7*	*0.58*
15-17	Average number of new cases/ year	2	3	2	3	4				
	Age specific incidence rate (per 10^6)	*6.7*	*11.9*	*8.5*	*9.5*	*12.6*	*6.0*	*-4.5*	*17.7*	*0.26*
Incidence LBL		**1990-94**	**1995-99**	**2000-04**	**2005-09**	**2010-15**	**AAPC 1990-2015**	**95% CI low**	**95% CI high**	**p-value**
	Average number of new cases/ year	13	8	6	9	10				
	Age standardized incidence rate (per 10^6) [a]	*3.8*	*2.4*	*1.8*	*2.6*	*2.8*	*-0.7*	*-3.2*	*1.8*	*0.56*
Age (years)										
0-4	Average number of new cases/ year	3	2	1	3	2				
	Age specific incidence rate (per 10^6) [b]	*3.3*	*1.6*	*1.4*	*3.5*	*2.0*				
5-9	Average number of new cases/ year	4	3	2	3	3				
	Age specific incidence rate (per 10^6) [b]	*4.2*	*3.1*	*2.0*	*2.8*	*3.0*				
10-14	Average number of new cases/ year	4	3	3	3	4				

Supplementary table S7.2: (continued)

	Age specific incidence rate (per 10^6) [b]	*4.6*	*2.8*	*2.6*	*2.6*	*3.2*				
15-17	Average number of new cases/ year	1	1	0	0	2				
	Age specific incidence rate (per 10^6) [b]	*2.4*	*2.2*	*0.7*	*0.3*	*3.3*				
Incidence Burkitt lymphoma		**1990-94**	**1995-99**	**2000-04**	**2005-09**	**2010-15**	**AAPC 1990-2015**	**95% CI low**	**95% CI high**	**p-value**
	Average number of new cases/ year	12	16	14	14	12				
	Age standardized incidence rate (per 10^6) [a]	*3.4*	*4.7*	*3.8*	*3.9*	*3.4*	*0.8*	*-1.8*	*3.5*	*0.50*
Age (years)										
0-4	Average number of new cases/ year	2	3	3	4	2				
	Age specific incidence rate (per 10^6) [b]	*1.8*	*3.1*	*3.2*	*3.7*	*2.6*				
5-9	Average number of new cases/ year	5	8	5	5	4				
	Age specific incidence rate (per 10^6)	*5.9*	*8.2*	*5.2*	*4.6*	*3.8*	*-3.2*	*-5.5*	*-0.8*	*0.01*
10-14	Average number of new cases/ year	3	4	4	4	5				
	Age specific incidence rate (per 10^6) [b]	*3.1*	*4.3*	*3.6*	*4.2*	*5.2*				
15-17	Average number of new cases/ year	2	1	2	1	1				
	Age specific incidence rate (per 10^6) [b]	*2.8*	*2.5*	*2.8*	*2.3*	*1.7*				
Incidence DLBCL		**1990-94**	**1995-99**	**2000-04**	**2005-09**	**2010-15**	**AAPC 1990-2015**	**95% CI low**	**95% CI high**	**p-value**
	Average number of new cases/ year	7	6	7	9	7				
	Age standardized incidence rate (per 10^6) [a]	*1.9*	*1.5*	*1.8*	*2.2*	*1.8*	*0.8*	*-1.5*	*3.0*	*0.49*
Age (years)										
0-4	Average number of new cases/ year	1	0	0	1	1				
	Age specific incidence rate (per 10^6) [b]	*0.6*	*0.4*	*0.2*	*0.8*	*0.7*				
5-9	Average number of new cases/ year	1	1	1	1	1				

Supplementary table S7.2: (continued)

	Age specific incidence rate (per 10^6) [b]	*1.5*	*0.8*	*1.0*	*1.2*	*0.7*				
10-14	Average number of new cases/ year	2	2	2	4	2				
	Age specific incidence rate (per 10^6) [b]	*2.7*	*2.4*	*1.6*	*3.6*	*2.0*				
15-17	Average number of new cases/ year	2	2	4	3	4				
	Age specific incidence rate (per 10^6) [b]	*4.0*	*4.0*	*7.0*	*5.0*	*6.2*				
Incidence ALCL		**1990-94**	**1995-99**	**2000-04**	**2005-09**	**2010-15**	**AAPC 1990-2015**	**95% CI low**	**95% CI high**	**p-value**
	Average number of new cases/ year	3	3	5	4	3				
	Age standardized incidence rate (per 10^6) [a]	*0.9*	*1.0*	*1.4*	*1.0*	*0.9*	*0.2*	*-3.0*	*3.4*	*0.92*
Age (years)										
0-4	Average number of new cases/ year	0	0	0	1	1				
	Age specific incidence rate (per 10^6) [b]	*0.4*	*0.4*	*0.2*	*0.6*	*0.7*				
5-9	Average number of new cases/ year	1	1	2	1	0				
	Age specific incidence rate (per 10^6) [b]	*0.7*	*1.0*	*1.6*	*1.4*	*0.2*				
10-14	Average number of new cases/ year	1	1	2	1	2				
	Age specific incidence rate (per 10^6) [b]	*1.5*	*1.5*	*2.0*	*0.8*	*1.3*				
15-17	Average number of new cases/ year	1	1	1	1	1				
	Age specific incidence rate (per 10^6) [b]	*1.5*	*1.1*	*2.4*	*1.7*	*2.0*				
Incidence NHL by stage [c]		**1990-94**	**1995-99**	**2000-04**	**2005-09**	**2010-15**	**AAPC 1990-2015**	**95% CI low**	**95% CI high**	**p-value**
	Average number of new cases/ year	33	32	31	34	29				
	Age standardized incidence rate (per 10^6) [a]	*7.6*	*7.3*	*6.7*	*7.5*	*6.4*	*-0.7*	*-1.5*	*0.1*	*0.10*
Stage										
I	Average number of new cases/ year	9	6	6	7	5				
	Age specific incidence rate (per 10^6)	*2.0*	*1.5*	*1.2*	*1.6*	*1.0*	*-2.6*	*-5.0*	*-0.2*	*0.03*

Supplementary table S7.2: (continued)

II	Average number of new cases/ year	8	8	8	7	7				
	Age specific incidence rate (per 10^6)	*1.9*	*1.9*	*1.8*	*1.6*	*1.5*	*-1.3*	*-3.2*	*0.6*	*0.17*
III	Average number of new cases/ year	5	6	6	8	7				
	Age specific incidence rate (per 10^6)	*1.1*	*1.5*	*1.3*	*1.8*	*1.6*	*5.6*	*0.0*	*11.6*	*0.05*
IV	Average number of new cases/ year	11	11	11	11	10				
	Age specific incidence rate (per 10^6)	*2.6*	*2.5*	*2.4*	*2.5*	*2.2*	*-0.5*	*-2.0*	*1.0*	*0.50*

Note that the average numbers calculated by age groups or stage may not be equal to the total average numbers due to rounding.
[a] age standardization according to the World Standard population 0-17 years
[b] AAPC analysis for this age group was not possible due to years with zero incidences.
[c] only calculated for patients with a known stage and diagnosed with LBL, BL, DLBCL or ALCL
Used abbreviations: AAPC average annual percentage change, CI confidence interval, *ICCC* international classification of childhood cancers, *NHL* non-Hodgkin lymphoma, *LBL* lymphoblastic lymphoma, *BL* Burkitt lymphoma, *DLBCL* diffuse large B-cell lymphoma, *ALCL* anaplastic large cell lymphoma

Supplementary table S7.3: Mortality rates for children, aged <20 years at death, dying from NHL in the Netherlands between 1980 and 2016

mortality males & females		1980-84	1985-89	1990-94	1995-99	2000-04	2005-09	2010-16	1980-2016 AAPC	SE	95% CI low	95% CI high	p-value
	Average number of deaths/ year	20	13	11	10	6	5	6					
	Age adjusted mortality rate (per 10^6)[a]	*4.5*	*3.2*	*2.9*	*2.6*	*1.5*	*1.4*	*1.4*	*-4.2*	*0.6*	*-5.3*	*-3.1*	*<0.01*
Age (years)													
0-4	Average number of deaths/ year	3	3	1	1	0	2	1					
	mortality rate (per 10^6)[b]	*2.8*	*3.1*	*1.8*	*1.3*	*0.3*	*2.3*	*1.2*					
5-9	Average number of deaths/ year	5	3	3	2	1	1	0					
	mortality rate (per 10^6)[b]	*5.1*	*3.2*	*3.1*	*2.1*	*1.2*	*1.0*	*0.3*					
10-14	Average number of deaths/ year	5	2	2	3	1	2	1					
	mortality rate (per 10^6)[b]	*4.2*	*2.3*	*2.4*	*3.5*	*1.2*	*1.6*	*1.4*					
15-19	Average number of deaths/ year	8	5	5	4	4	1	3					
	mortality rate (per 10^6)[b]	*6.1*	*4.2*	*4.6*	*3.9*	*3.8*	*1.0*	*3.0*					

mortality males		1980-84	1985-89	1990-94	1995-99	2000-04	2005-09	2010-16	1980-2016 AAPC	SE	95% CI low	95% CI high	p-value
	Average number of deaths/ year	14	9	7	6	3	4	4					
	Age adjusted mortality rate (per 10^6)[a]	*6.4*	*4.2*	*3.7*	*2.9*	*1.5*	*2.2*	*1.7*	*-4.3*	*0.7*	*-5.7*	*-2.8*	*<0.01*

mortality females		1980-84	1985-89	1990-94	1995-99	2000-04	2005-09	2010-16	1980-2016 AAPC	SE	95% CI low	95% CI high	p-value
	Average number of deaths/ year	6	4	4	4	3	1	2					
	Age adjusted mortality rate (per 10^6)[a]	*2.4*	*2.1*	*2.1*	*2.3*	*1.4*	*0.5*	*1.0*	*-5.7*	*1.7*	*-9.1*	*-2.1*	*<0.01*

Note that the average numbers calculated by age groups or stage may not be equal to the total average numbers due to rounding.

[a] age standardization according to the World Standard population 0-19 years

[b] AAPC analysis for this age group was not possible due to years with zero incidences.

Used abbreviations: AAPC average annual percentage change, CI confidence interval

CHAPTER 8

Neuroblastoma between 1990 and 2014 in the Netherlands: Increased incidence and improved survival of high-risk neuroblastoma

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ABSTRACT

Long-term trends in neuroblastoma incidence and survival in unscreened populations are unknown. We explored trends in incidence, stage at diagnosis, treatment and survival of neuroblastoma in the Netherlands from 1990 to 2014.

The Netherlands Cancer Registry provided data on all patients aged <18 years diagnosed with a neuroblastoma. Trends in incidence and stage were evaluated by calculating the average annual percentage change (AAPC). Univariate and multivariable survival analyses were performed for stage 4 disease to test whether changes in treatment are associated with survival.

Of the 593 newly diagnosed neuroblastoma cases, 45% was <18 months of age at diagnosis and 52% had stage 4 disease. The age-standardized incidence rate for stage 4 disease increased at all ages from 3.2 to 5.3 per million children per year (AAPC +2.9%, p <0.01). This increase was solely for patients ≥18 months old (3.0-5.4; AAPC +3.3%, p =0.01). Five-year OS of all patients increased from 44 ± 5% to 61 ± 4% from 1990 to 2014 (p <0.01) and from 19 ± 6% to 44 ± 6% (p <0.01) for patients with stage 4 disease. Multivariable analysis revealed that high-dose chemotherapy followed by autologous stem cell rescue and anti-GD2-based immunotherapy were associated with this survival increase (HR 0.46, p <0.01 and HR 0.37, p <0.01, respectively).

Incidence of stage 4 neuroblastoma increased exclusively in patients aged ≥18 months since 1990, whereas the incidence of other stages remained stable. The 5-year OS of stage 4 patients improved, mostly due to the introduction of high-dose chemotherapy followed by stem cell rescue and immunotherapy.

INTRODUCTION

The incidence of neuroblastoma (NBL) in developed countries is 11-13 per million children aged <15 years and varies from 65 per million in children <1 year to 1 per million in children of 10-14 years.[1-3] NBL is a heterogeneous tumour entity with a variable clinical course. The long-term survival is good to excellent in low-risk disease (5-year overall survival (OS) of >85% in International Neuroblastoma Staging System (INSS) stage 1, 2, 4S[4], or International Neuroblastoma Risk Group Staging System stage L1,MS[5]), but poor in patients with high-risk disease (5-year OS of <50% in stage 4/M in patients ≥18 months old at diagnosis, and/or with MYCN (V-myc avian myelocytomatosis viral related oncogene, neuroblastoma derived) amplification).[6] Furthermore, patients with a more differentiated histology (ganglioneuroblastoma [GNBL]) fare a more favourable course of disease than patients with undifferentiated histology (NBL).[7,8] In the past decades, therapy for high-risk patients has been modified in several ways to increase survival. Induction chemotherapy was intensified, high-dose chemotherapy followed by autologous stem cell rescue and standard radiotherapy were introduced. Most recently, anti-GD2 immunotherapy has been added to the maintenance therapy; this monoclonal antibody is given in combination with alternating GM-CSF or IL-2 to stimulate the immune response.[9-12]

Improvements in cancer outcome are often analysed as improvements in survival, but cancer incidence analyses should also be used to monitor changes in outcome by changes in the prevalence of (unknown) risk factors.[13] While survival provides a measure of prognosis and improvement in the treatment, trends in cancer mortality are the result of trends in both incidence and survival. The three analyses together increase the comprehension of the total progress against cancer in a given area over time.[14-16]

These epidemiological analyses were used in the evaluations of the NBL screening programs, conducted between 1985 and 2000 in Japan and parts of Germany, France, Austria, Canada and the United Kingdom. The rationale behind the screening programs was that detection at an earlier stage of disease would lead to an improved prognosis. Although the screening studies identified more young patients with low-risk NBL, this had no effect on incidence of high-risk disease or overall mortality, suggesting overdiagnosis of low-risk patients.[13,16-22] This resulted in the termination of all screening programs. A disadvantage of these screening programs is that change in the incidence over time. In the Netherlands, no screening programs have been performed.

The purpose of this comprehensive, population-based study was to describe the trends in incidence, treatment modalities and survival in NBL patients aged <18 years, diagnosed between 1990 and 2014, and to study the effect of changes in treatment on the survival of patients with stage 4 NBL.

PATIENTS AND METHODS

Data sources

The Netherlands Cancer Registry (NCR) is a nationwide population-based registry, established in 1989, hosted by the Netherlands Comprehensive Cancer Organization (IKNL). The NCR only registers persons with the Dutch nationality, or people who have been living in the Netherlands for at least three months before diagnosis. Trained registrars of the NCR extracted data on patient and tumour characteristics, and given treatment by retrospective medical record review. Only first-line treatment modalities were registered.

The NCR registers morphology according to the International Classification of Diseased for Oncology (ICD-O-3)[23], currently the ICD-O-3.1 system.[24] Tumour stage was recorded using the TNM classification[25] until 2003 and subsequently according to the Extent of Disease[26] (EoD) classification. Localized disease (TNM/EoD) was converted to INSS stage 1/2, regional disease to stage 3 and metastatic disease to stage 4 or 4S. To validate stage and treatment modalities, hospital-based NBL databases were used to crosscheck these items and to identify patients with NBL stage 4S, according to the INSS staging system.[4] Information on risk stratification, MYCN status and other genetic prognostic factors was not available.

Patient and data selection

Clinical data from Dutch patients aged <18 years at diagnosis and diagnosed with a NBL or a GNBL between 1990 and 2014 were extracted from the NCR. Information on vital status (alive, dead, or emigration) was obtained by annual linkage with the Nationwide Population Registries Network that contains vital statistics on all Dutch residents. Last linkage was on February 1, 2018. Because of privacy regulations, no data on cause of death could be obtained. Nationwide disease-specific mortality data were not informative because NBL was non-consistently coded as a malignancy of the adrenal gland, the connective and soft-tissues, and the peripheral nervous system.[27]

Statistical analyses

For the NBL patient population, the following characteristics were described: age at diagnosis, gender, histology (NBL vs. GNBL), stage and location of the primary tumour. Differences in these characteristics were tested using $\chi 2$ tests. For analysis over time, five-year periods were defined: 1990-94, 1995-99, 2000-04, 2005-09 and 2010-14.

Overall incidence rates were calculated as the average annual number of cases per 1 million person-years, using annual midyear population sizes from Statistics Netherlands, these were provided for the age groups: 0, 1-4, 5-9, 10-14, and 15-17 years. Incidence rates were also calculated for age groups (<18 and ≥18 months), stage and stage per age group. The population at risk <18 months was calculated as the population aged 0 years plus 1/8th of the population aged 1-4 years. Similarly, the population at risk ≥18 months was calculated as the population aged 5-17 years plus 7/8th of the population aged 1-4 years. Rates were age-standardized using the age structure of the world standard population.[28] Changes in incidence over time were evaluated by calculating the average annual percentage change (AAPC). AAPC was derived from a regression line fitted to the natural logarithm of the rates, using the calendar year as regressor variable (i.e. $y = ax + b$ where $y = \ln(\text{rate})$ and x = calendar year; then AAPC = $100 \times (e^a - 1)$) and calculated for the whole study period 1990-2014.[28]

Traditional cohort-based survival analysis using Kaplan-Meier method with log-rank test was used to calculate overall survival (OS). Survival time was calculated as the time elapsed between the date of diagnosis and the date of death of any cause or date at last follow-up (alive, censored).

For analyses in patients with stage 4 NBL, treatment modalities were dichotomized to yes/no (see **table 8.2**). Differences in frequency of applied treatment modalities by period of diagnosis were tested using $\chi 2$ tests.

Time trends in observed 5-year OS were first evaluated by using a parametric survival model. The dichotomized treatment modalities were added to the model to investigate the effect of therapy on the hazard ratio (HR) of period of diagnosis. Age group (<18 and ≥18 months), a strong independent predictor of survival, was also entered in the multivariable models. All statistical analyses were two-sided and a *p*-value <0.05 was considered significant. Analyses were performed with STATA/SE 14.2 (StataCorp LP, College Station, TX, 2015).

RESULTS

Patient characteristics

Between 1990 and 2014, 509 newly diagnosed patients with NBL and 84 with GNBL were registered by the NCR, of which 583 (98%) were histologically confirmed. Patient and tumour characteristics are presented in **table 8.1**. Median age at diagnosis was 21 months (range 0-16 years), male sex was slightly predominant (54%; male/female ratio = 1.2:1). Seventy percent

of the patients had an adrenal or abdominal primary tumour. Most patients were diagnosed with stage 4 disease (52%), followed by stage-1/2 disease (28%), stage 3 (12%), and stage 4S (8%). For 8 patients, no data were available on stage of disease (**table 8.1**). In patients aged <18 months, stage 1/2 was the most common (41%), and stage 4 disease was observed in 26% of the patients. In patients aged ≥18 months, stage 4 dominated (73%; **figure 8.1**).

Table 8.1 Patient characteristics for patients diagnosed with a neuroblastoma before age 18 in the Netherlands, during 1990-2014 (n=593)

	1990-94 n (%)	1995-99 n (%)	2000-04 n (%)	2005-09 n (%)	2010-14 n (%)	total n (%)
Age groups						
<18 months	45 (45)	54 (48)	56 (45)	57 (46)	53 (41)	265 (45)
≥18 months	55 (55)	59 (52)	68 (55)	68 (54)	77 (59)	327 (55)
Gender						
male	53 (53)	61 (54)	76 (61)	65 (52)	67 (52)	322 (54)
female	47 (47)	52 (46)	48 (39)	60 (48)	63 (48)	270 (46)
Histology						
NB	90 (90)	89 (79)	106 (85)	106 (85)	117 (90)	508 (86)
GNB	10 (10)	24 (21)	18 (15)	19 (15)	13 (10)	84 (14)
Stage						
1/2	26 (27)	37 (33)	39 (32)	35 (28)	27 (21)	164 (28)
3	14 (15)	13 (12)	15 (12)	14 (11)	17 (13)	73 (13)
4	47 (49)	52 (46)	63 (52)	66 (53)	75 (58)	303 (52)
4S	9 (9)	10 (9)	5 (4)	9 (7)	11 (9)	44 (8)
Unknown	4	1	2	1	0	8
Location primary tumor						
Side chain	23 (23)	32 (28)	32 (26)	33 (26)	37 (28)	157 (27)
- thorax	*13 (13)*	*19 (17)*	*18 (15)*	*13 (10)*	*26 (20)*	*89 (15)*
-pelvis	*5 (5)*	*7 (6)*	*6 (5)*	*8 (6)*	*4 (3)*	*30 (5)*
- not otherwise specified [a]	*5 (5)*	*6 (5)*	*8 (7)*	*12 (10)*	*7 (5)*	*38 (6)*
Adrenal/abdominal	70 (70)	79 (70)	88 (71)	90 (72)	90 (69)	417 (70)
Unknown/no primary tumor	7 (7)	2 (2)	4 (3)	2 (2)	3 (2)	18 (3)

Bold fonts indicate characteristics categories, italic fonts indicate subgroups.

[a] Sympathetic side chain tumours, without specified location.

NB, neuroblastoma; *GNB*, ganglioneuroblastoma.

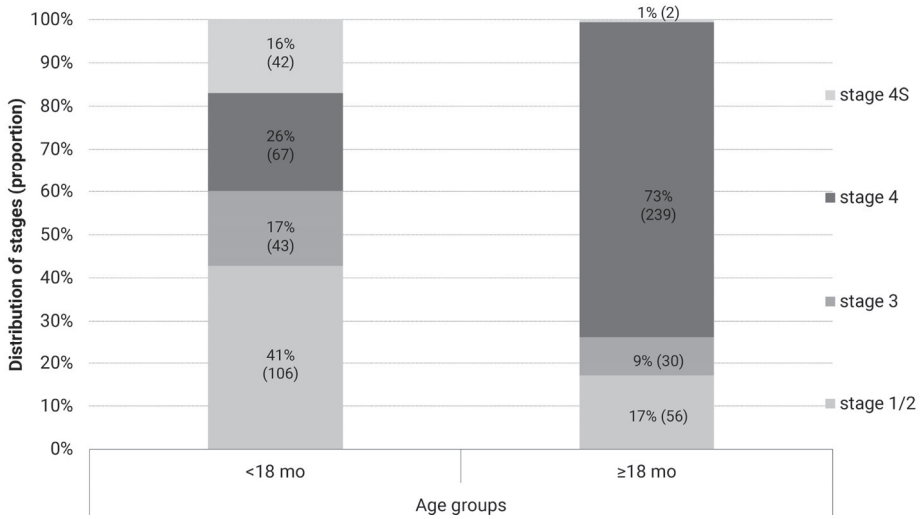

Figure 8.1 Stage distribution of neuroblastoma patients aged <18 and ≥18 months at diagnosis.
For patients <18 months and ≥18 months of age the percentage of each stage at diagnosis is given in the bars with the number of patients between parentheses. Two patients were diagnosed as stage 4S, while they were ≥18 months of age. Stage of disease was unknown in 8 patients, 7 of them aged <18 months and were not included in this graph.
Used abbreviation mo., months

Incidence

In the time period 1990-94, on average, 20 new patients per year were diagnosed with NBL; this increased to 26 patients per year between 2010 and 2014 (**figure 8.2a**). The overall incidence rate (all stages, <18 years) significantly increased by 1.6% per year from 6.4 to 9.1 per million between 1990 and 2014 (p =0.01; **figure 8.2b**). Stage 4 NBL increased with 2.9% per year (p <0.01), while the incidence of all other stages remained stable (**figure 8.2b**). Incidence rates by age, gender, histological type and stage, as well as the AAPC analyses for NBL patients aged <15 years are provided in **supplementary table S8.1**. No other significant changes in these rates were observed.

The age-specific incidence rates for patients aged <18 and ≥18 months by stage are shown in **figure 8.2c** and **d**. Incidence rates were stable for all stages in patients aged <18 months, whereas an increase in incidence of stage 4 NBL was seen in patients aged ≥18 months (AAPC +3.3%, p =0.01). For this age group, the number of stage 4 patients almost doubled from 7 patients per year in 1990-94 to 12 patients per year in 2010-14. The incidence rates for the other stages in patients aged ≥18 months remained stable.

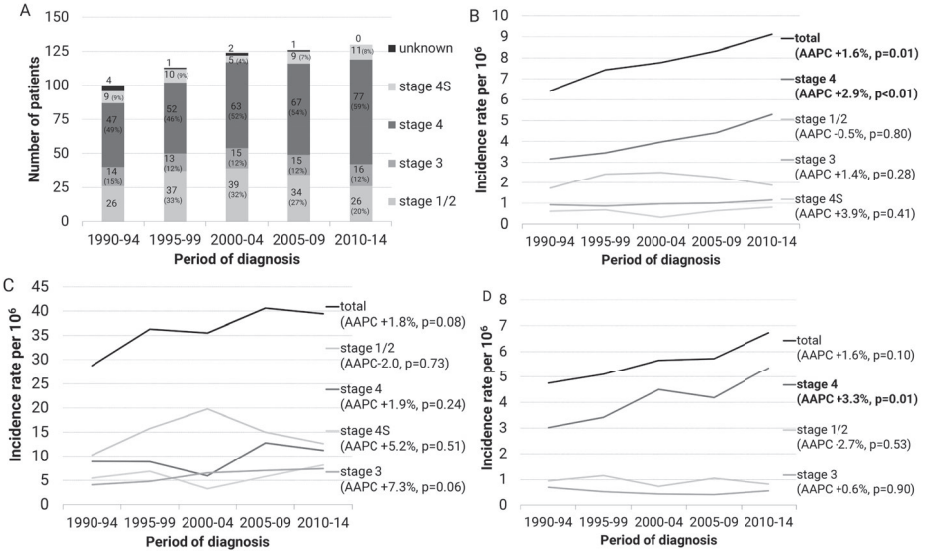

Figure 8.2 Time trends in neuroblastoma incidence per five year period.
Number of newly diagnosed patients (percentage in parentheses) are given by stage and diagnostic period (A). Time trends of incidence rates according to stage were calculated per million children aged 0-17 years (B); per million children aged 0-17 months (C); and per million children aged 18 months - 17 years (D). The Average Annual Percentage Change (AAPC) is given in the legends of B-D, bold fonts indicate significant changes over time.

Therapy and survival

The 5-year survival rates varied by stage: 93 ± 2% in stage 1/2 disease; 84 ± 6% in stage 4S; 70 ± 5% in stage 3 disease; 35 ± 3% in stage 4 disease (**figure 8.3a**). Five-year OS of all patients improved from 44 ± 5% in 1990-94 to 61 ± 4% in 2010-14 (p <0.01) (**figure 8.3b**).

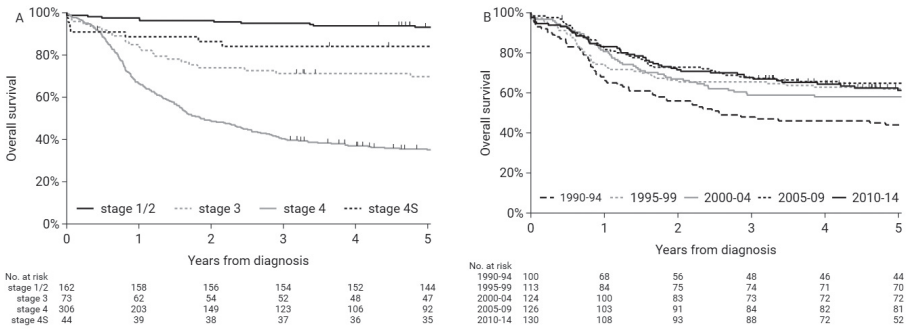

Figure 8.3 Five year overall survival (OS) for neuroblastoma patients.
Five year OS rates are given for different stages (A) and different time periods (B). Stage specific 5-yr OS was 93±2% for stage 1/2, 84±6% for stage 4S, 68±6% for stage 3 and 35±3% for stage 4 (A). Five-yr OS for all stages combined was 44±5% in 1990-94; 62±5% in 1995-99; 58±4% in 2000-04; 65±4% in 2005-09 and 61±4% in 2010-14 (B).

Five-year OS of patients with stage 4 NBL improved significantly from 19 ± 6% in 1990-94 to 44 ± 6% in 2010-14 (p <0.01; **figure 8.4a**). For patients with the poorest outcome (stage 4 and ≥18 months old), 5-year OS significantly improved from 6 ± 4% in 1990-94 to 43 ± 7% in 2010-14 (p <0.01; **figure 8.4b**). The 5- and 10- year OS rates over time for gender, age group, histologic type and stage are summarized in **supplementary table S8.2**.

Important changes in the treatment of patients with stage 4 disease were made between 1990 and 2014. High-dose chemotherapy with autologous stem cell transplantation was given in 21% of patients with stage 4 between 1990 and 1999 and in 69% between 2010 and 2014 (p <0.01); the frequency of primary tumour surgery increased from 58% to 84% (p <0.01); radiotherapy increased from 16% to 40% (p <0.01); immunotherapy increased from 0% in 1990-99 to 4% in 2005-09 and 53% in 2010-14 (p <0.01). The number of patients receiving ^{131}I-MIBG-therapy (39%) and chemotherapy (98%) did not change between 1990 and 2014.

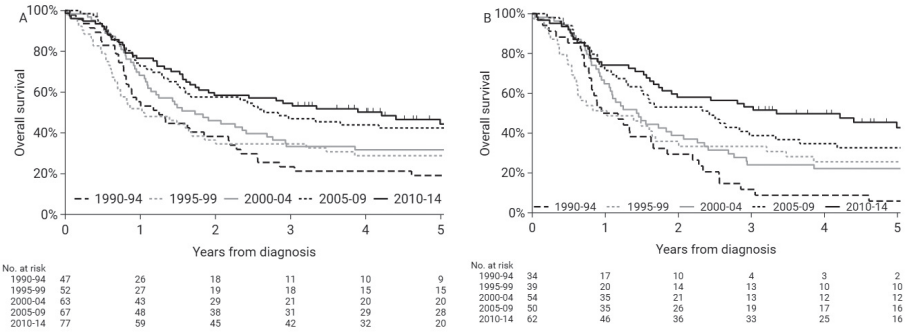

Figure 8.4 Time trends of five year overall survival (OS) for patients with a stage 4 neuroblastoma.
Five year OS rates are given by 5-year periods for all patients with stage 4 neuroblastoma (A), and for patients with stage 4 neuroblastoma ≥18 months at diagnosis (B).

Multivariable survival analysis for stage 4 neuroblastoma

In univariate analysis, the risk of dying (HR) from stage 4 NBL was significantly lower during the periods 2005-09 and 2010-14 compared with 1990-94 (HR 0.54, p =0.01 and HR 0.50, p <0.01, respectively). Patients aged ≥18 months had a poorer survival probability (HR 2.12, p <0.01) than patients aged <18 months (**table 8.2**). Other prognostic factors were the treatment modalities high-dose chemotherapy with stem cell rescue, immunotherapy and surgery. The first multivariable model contained age and period of diagnosis. In this model, the two most recent periods of diagnosis were associated with better outcome (HR 0.52 and 0.44, p =0.01 and p <0.01, respectively). Addition of the different treatment modalities to a second multivariable model resulted in the loss of significance for the HRs of these recent periods of diagnosis (HR

0.85 and 1.14, *p* =0.52 and *p* =0.60, respectively; **table 8.2**). Patients who received high-dose chemotherapy with stem cell rescue (HR 0.46, *p* <0.01) and patients who received immunotherapy (HR 0.37, *p* <0.01) had a significant reduction of the risk of dying. The changes in the treatment modalities were better discriminants for the changes in survival over time, than the periods of diagnosis (**table 8.2**).

Table 8.2 Uni- and multivariable analyses for 5-year overall survival for stage 4 neuroblastoma patients by age group, period of diagnosis and treatment modalities

		Univariate analysis			Multivariable analysis, model without treatment modalities			Multivariable analysis, model with treatment modalities		
	n	**HR**	**95% CI**	***p***	**HR**	**95% CI**	***p***	**HR**	**95% CI**	***p***
Age groups										
< 18 months	67	Ref.			Ref.			Ref.		
>= 18 months	239	2.16	1.44 - 3.25	<0.01	2.31	1.53 - 3.48	<0.01	3.21	2.10 - 4.91	<0.01
Period										
1990-1994	47	Ref.			Ref.			Ref.		
1995-1999	52	0.89	0.57 - 1.40	0.62	0.84	0.53 - 1.32	0.44	1.03	0.65 - 1.64	0.88
2000-2004	63	0.72	0.47 - 1.12	0.15	0.65	0.42 - 1.01	0.06	0.95	0.60 - 1.51	0.83
2005-2009	67	0.54	0.34 - 0.85	0.01	0.52	0.33 - 0.82	0.01	0.85	0.53 - 1.38	0.52
2010-2014	77	0.50	0.32 - 0.78	<0.01	0.44	0.28 - 0.69	<0.01	1.14	0.69 - 1.90	0.60
ASCT										
no	151	Ref.						Ref.		
yes	155	0.45	0.34 - 0.60	<0.01				0.46	0.32 - 0.64	<0.01
Surgery										
no	82	Ref.						Ref.		
yes	224	0.58	0.43 - 0.79	<0.01				0.75	0.54 - 1.04	0.09
Immunotherapy										
no	262	Ref.						Ref.		
yes	44	0.38	0.23 - 0.62	<0.01				0.37	0.19 - 0.72	<0.01
Radiotherapy										
no	214	Ref.						Ref.		
yes	92	0.76	0.55 - 1.03	0.08				1.21	0.84 - 1.74	0.30

HRs were corrected for follow-up time.

Bold fonts indicate characteristics categories.

ASCT, autologous stem cell transplantation after high-dose chemotherapy; *HR*, hazard ratio; *95% CI*, 95% confidence interval.

DISCUSSION

This is the first report on incidence and survival of children and adolescents with an NBL in the Netherlands. Over a 25-year period, we observed a significant increase in incidence of stage 4 disease in patients aged ≥18 months, while the incidence of other stages and ages remained stable. Five-year OS improved for all ages and stages, the most distinct for patients aged ≥18 months with stage 4 NBL, where an improvement of 37 percentage points was seen.

The age-standardized incidence rate of around 10.5 cases per million children in 2010-14 observed in this study is similar to other high-income countries as Canada, USA, and neighbouring European countries (WSR 0-14 years 10.1-15.0).[29,30] The overall increase in NBL incidence of 1.6% per year is in line with the increase in NBL incidence in older children (1-4 year) of 1.7% per year in Europe (1978-97), and of 1.6% per year in Canada (1992-2010).[2,3] However, in Denmark, NBL incidence has been stable between 1981 and 2000 for all stages and age categories[31], whereas in England, a slight decrease in incidence of 0.2% for all stages and age categories was seen between 1993 and 2000.[16] In Germany, analyses of both tumour stage and age were performed. They found a small (7% per 10 year) increase in overall incidence, but this was attributed to an increase in stage 1-3 and stage 4S and a decrease in stage 4, which is contradicting our data.[32] Etiological factors for NBL are largely unknown other than 'it is a developmental tumour of the sympathetic nervous system'. Genetic predisposition is rare (estimated at 1-2%)[33], and no environmental factors have been consistently associated with NBL.[34] Improved prenatal ultrasounds only contribute to an increase in patients aged <18 months at diagnosis. In fact, this has also been shown in NBL screening studies based on urinary catecholamine measurements in infants.[17,20,35] Higher registration rates caused by immigration for medical reasons can be ruled out because the Netherlands has a long-standing population-wide cancer registry, covering at least 95% of all newly diagnosed malignancies in Dutch inhabitants.[36]

The increase in overall incidence is caused by an increase in the incidence of stage 4 NBL in patients aged ≥18 months. In this group, the number of newly diagnosed patients almost doubled. The increase cannot be assigned to higher sensitivity of molecular markers (amplification of MYCN or loss of heterozygosity of chromosome 1p) because these influence risk stratification and not stage of disease. Improved sensitivity of diagnostics and upstaging of patients with lower stage disease can play a small role, but seems to be negligible because only a minimal (non-significant) decrease in lower stage disease was observed, while there was a significant increase in overall incidence and in stage 4 incidence. This leaves the cause of the

increased incidence for this subgroup unclear. The improved survival for patients with stage 4 disease is associated with changes in therapy.

Multivariable analysis showed that high-dose chemotherapy followed by autologous stem cell rescue and immunotherapy (HR 0.46, p <0.01 and HR 0.37, p <0.01) were the treatment modalities that more adequately predicted the survival improvement than the periods of diagnosis. Berthold *et al.* and Pinto *et al.*[9,37] reported previously of a survival benefit for high-dose chemotherapy in high-risk NBL, compared with maintenance therapy. Immunotherapy was introduced in 2009, and in this cohort, only 44 of the 306 patients with stage 4 disease received immunotherapy. Despite this very small number, we observed a significant effect on OS in both the univariate (HR 0.38, p <0.01) and multivariable analysis (HR 0.37, p <0.01). This cohort seems to confirm earlier studies demonstrating a benefit for maintenance therapy with immunotherapy.[12,38] In addition, we expect roles for the intensified induction chemotherapy and the improved supportive care over time, but the current data set did not allow these analyses.

The longstanding population-based Netherlands Cancer Registry follows international standards and coding practices, and has, also through its participation in international projects (Eurocare, ACCIS, CI 5), many quality checks. The NCR is one of the few registries that also register stage and initial treatment. A limitation of this study is the lack of data on prognostic markers such as MYCN amplification and on cause of death. However, because the paediatric population in this study is not suspected for other serious underlying diseases or competing causes of death, the observed survival, as reported here, is representative for the NBL-specific survival.[39] Another limitation is the relative small size of the Dutch population, resulting in a smaller cohort than the German, European, or American SEER databases.[1,32,39]

CONCLUSION

Our population-based study comprehensively analysed incidence, incidence changes over time, survival, and treatment of NBL during a 25-year period in the Netherlands. We observed an increase of 1.6% per year in total incidence and more particularly for patients with stage 4 disease who were ≥18 months of age. Survival for this group improved from 6 ± 4% in 1990-94 to 43 ± 7% in 2010-14. The improved survival of stage 4 patients is predominantly associated with the introduction of high-dose chemotherapy with autologous stem cell rescue and immunotherapy.

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Supplementary table S8.1 Incidence for children, aged <15 years, diagnosed with neuroblastoma in the Netherlands between 1990 and 2014

Incidence Males & Females		1990-94	1995-99	2000-04	2005-09	2010-14	AAPC 1990-2014	SE	95% CI low	95% CI high	p-value
	Average number of new cases/ year	20	23	25	25	25					
	Incidence rate (per 10^6)	*7.2*	*7.8*	*8.3*	*8.5*	*8.8*	*0.9*	*0.5*	*-0.2*	*2.0*	*0.10*
	Age-standardized incidence rate (per 10^6)[a]	*7.9*	*8.8*	*9.3*	*9.8*	*10.5*	*1.3*	*0.5*	*0.2*	*2.4*	*0.02*
Age (years)											
0	Average number of new cases/ year	7	8	9	9	8					
	Incidence rate (per 10^6)	*35.8*	*42.2*	*44.4*	*47.6*	*47.1*	*1.4*	*0.9*	*-0.5*	*3.2*	*0.14*
1-4	Average number of new cases/ year	10	12	13	12	14					
	Incidence rate (per 10^6)	*13.5*	*15.3*	*16.1*	*15.7*	*18.6*	*1.2*	*0.8*	*-0.5*	*2.9*	*0.17*
≥ 5	Average number of new cases/ year	3	3	3	4	3					
	Incidence rate (per 10^6)	*1.4*	*1.3*	*1.4*	*2.1*	*1.7*	*3.2*	*3.1*	*-3.3*	*9.6*	*0.32*
Age (months)											
< 18	Average number of new cases/ year	9	11	11	12	11					
	Incidence rate (per 10^6)	*30.8*	*37.0*	*36.8*	*41.3*	*39.4*	*1.4*	*0.9*	*-0.5*	*3.4*	*0.15*
≥ 18	Average number of new cases/ year	11	12	14	14	15					
	Incidence rate (per 10^6)	*4.8*	*5.1*	*5.7*	*5.7*	*6.7*	*1.4*	*1.0*	*-0.5*	*3.4*	*0.15*

Incidence Males		1990-94	1995-99	2000-04	2005-09	2010-14	AAPC 1990-2014	SE	95% CI low	95% CI high	p-value
	Average number of new cases/ year	11	12	15	13	13					
	Age-standardized incidence rate (per 10^6)[a]	*8.5*	*9.5*	*11.5*	*9.9*	*10.7*	*1.0*	*0.7*	*-0.4*	*2.4*	*0.16*
Age (months)											
< 18	Average number of new cases/ year	5	6	7	6	6					
	Incidence rate (per 10^6)	*30.9*	*37.4*	*42.5*	*41.7*	*43.7*	*5.2*	*4.7*	*-4.6*	*14.7*	*0.29*
≥ 18	Average number of new cases/ year	6	7	9	7	7					
	Incidence rate (per 10^6)	*5.2*	*5.6*	*7.0*	*6.0*	*6.3*	*0.6*	*1.4*	*-2.3*	*3.5*	*0.69*

Supplementary table S8.1(continued)

Incidence Females		1990-94	1995-99	2000-04	2005-09	2010-14	AAPC 1990-2014	SE	95% CI low	95% CI high	p-value
	Average number of new cases/ year	9	10	10	12	12					
	Age-standardized incidence rate (per 10^6)[a]	*7.5*	*8.3*	*7.4*	*9.5*	*10.5*	*1.3*	*1.0*	*-0.8*	*3.3*	*0.21*
Age (months)											
< 18	Average number of new cases/ year	4	5	5	6	5					
	Incidence rate (per 10^6)	*30.8*	*36.6*	*30.9*	*40.9*	*34.9*	*-0.2*	*1.3*	*-2.9*	*2.4*	*0.87*
≥ 18	Average number of new cases/ year	5	5	5	6	8					
	Incidence rate (per 10^6)	*4.5*	*4.6*	*4.3*	*5.4*	*7.2*	*2.5*	*1.6*	*-0.8*	*5.7*	*0.13*
Incidence neuroblastoma		**1990-94**	**1995-99**	**2000-04**	**2005-09**	**2010-14**	**AAPC 1990-2014**	**SE**	**95% CI low**	**95% CI high**	**p-value**
	Average number of new cases/ year	18	18	21	21	23					
	Age-standardized incidence rate (per 10^6)[a]	*7.1*	*7.0*	*7.9*	*8.5*	*9.5*	*1.5*	*0.6*	*0.3*	*2.7*	*0.01*
Age (months)											
< 18	Average number of new cases/ year	8	9	10	11	10					
	Incidence rate (per 10^6)	*28.1*	*31.6*	*32.9*	*37.8*	*37.2*	*1.9*	*1.1*	*-0.4*	*4.0*	*0.10*
≥ 18	Average number of new cases/ year	10	9	11	11	13					
	Incidence rate (per 10^6)	*4.3*	*3.8*	*4.6*	*4.6*	*5.8*	*1.6*	*1.0*	*-0.4*	*3.6*	*0.11*
Incidence ganglioneuroblastoma		**1990-94**	**1995-99**	**2000-04**	**2005-09**	**2010-14**	**AAPC 1990-2014**	**SE**	**95% CI low**	**95% CI high**	**p-value**
	Average number of new cases/ year	2	5	4	4	3					
	Age-standardized incidence rate (per 10^6)[a]	*0.8*	*1.8*	*1.4*	*1.4*	*1.1*	*2.4*	*3.1*	*-4.0*	*8.7*	*0.45*
Age (months)											
< 18	Average number of new cases/ year	1	2	1	1	1					
	Incidence rate (per 10^6)	*2.8*	*5.4*	*3.9*	*3.5*	*2.2*	*-9.5*	*8.1*	*-26.8*	*6.8*	*0.23*

Supplementary table S8.1(continued)

≥ 18	Average number of new cases/ year	1	3	2	3	2					
	Incidence rate (per 10^6)	*0.5*	*1.3*	*1.0*	*1.1*	*0.9*	*3.3*	*4.5*	*-6.1*	*12.6*	*0.48*
Incidence by stage[b]		**1990-94**	**1995-99**	**2000-04**	**2005-09**	**2010-14**	**AAPC 1990-2014**	**SE**	**95% CI low**	**95% CI high**	**p-value**
	Average number of new cases/ year	19	22	24	25	25					
	Age-standardized incidence rate (per 10^6)[a]	*7.5*	*8.7*	*9.1*	*9.7*	*10.5*	*1.5*	*0.5*	*0.4*	*2.6*	*0.01*
Stage											
1/2	*Average number of new cases/ year*	5	7	8	7	5					
	Age-standardized incidence rate (per 10^6)[a]	*2.0*	*2.9*	*2.9*	*2.7*	*2.2*	*-0.5*	*1.8*	*-4.2*	*3.3*	*0.80*
3	Average number of new cases/ year	3	3	3	3	3					
	Age-standardized incidence rate (per 10^6)[a]	*1.1*	*1.0*	*1.1*	*1.2*	*1.4*	*1.5*	*1.3*	*-1.3*	*4.2*	*0.28*
4	Average number of new cases/ year	9	10	13	13	15					
	Age-standardized incidence rate (per 10^6)[a]	*3.7*	*4.1*	*4.7*	*5.2*	*6.0*	*2.7*	*0.7*	*1.2*	*4.2*	*<0.01*
4S	Average number of new cases/ year	2	2	1	2	2					
	Age-standardized incidence rate (per 10^6)[a]	*0.7*	*0.8*	*0.4*	*0.8*	*0.9*	*4.0*	*4.7*	*-5.8*	*13.7*	*0.41*

[a] age standardization according to the World standard rate (0-14 years)

[b] calculated for patients with known stages (the unknown 8 were excluded)

In case of zero patients in a year, an incidence rate of 0.01 was assumed.

Abbreviations: AAPC: average annual percentage change; SE: standard error; 95% CI: 95% confidence interval

Supplementary table S8.2 Five-year and 10-year overall survival for neuroblastoma patients diagnosed and treated in the Netherlands over time.

	1990-2014					1990-1994					1995-1999				
	n at risk	5-yr OS	SE	10-yr OS	SE	n at risk	5-yr OS	SE	10-yr OS	SE	n at risk	5-yr OS	SE	10-yr OS	SE
Total	**593**	**59%**	**2%**	**56%**	**2%**	**100**	**44%**	**5%**	**44%**	**5%**	**113**	**62%**	**5%**	**55%**	**5%**
Gender															
Male	**323**	57%	3%	54%	3%	**53**	51%	7%	51%	7%	**61**	52%	6%	46%	7%
Female	**270**	60%	3%	58%	3%	**47**	36%	7%	36%	7%	**52**	73%	6%	66%	7%
Age groups															
<18 months	**265**	81%	2%	81%	2%	**45**	64%	7%	64%	7%	**54**	81%	5%	81%	5%
≥18 months	**328**	41%	3%	36%	3%	**55**	27%	6%	27%	6%	**59**	44%	6%	37%	6%
Histology															
NB	**509**	54%	2%	51%	2%	**90**	43%	5%	43%	5%	**89**	53%	5%	49%	5%
GNB	**84**	87%	4%	84%	4%										
Stage**															
1/2	**162**	93%	2%	92%	2%	**26**	77%	8%	77%	8%	**37**	97%	3%	95%	4%
3	**73**	70%	5%	70%	5%										
4	**306**	35%	3%	30%	3%	**47**	19%	6%	19%	6%	**52**	29%	6%	23%	6%
4S	**44**	84%	6%	84%	6%										

	2000-2004					2005-2009					2010-2014				
	n at risk	5-yr OS	SE	10-yr OS	SE	n at risk	5-yr OS	SE	10-yr OS	SE	n at risk	5-yr OS	SE	p-value* 5-yr	p-value* 10-yr
Total	**124**	**58%**	**4%**	**55%**	**5%**	**125**	**65%**	**4%**	**58%**	**5%**	**130**	**61%**	**4%**		
Gender															
Male	**76**	57%	6%	54%	6%	**66**	66%	6%	60%	6%	**67**	58%	6%	0.07	0.11
Female	**48**	60%	7%	56%	8%	**60**	63%	6%	60%	7%	**63**	65%	6%	0.03	0.04
Age groups															
<18 months	**56**	89%	4%	89%	4%	**57**	84%	5%	84%	5%	**53**	81%	5%	0.06	0.02
≥18 months	**68**	32%	6%	31%	6%	**69**	49%	6%	41%	6%	**77**	48%	6%	0.01	0.06
Histology															
NB	**106**	52%	5%	51%	5%	**107**	60%	5%	55%	5%	**117**	60%	5%	0.01	0.05
GNB															
Stage**															
1/2	**39**	95%	4%	95%	4%	**34**	100%	0%	100%	0%	**26**	92%	5%	0.04	<0.01
3															
4	**63**	32%	6%	30%	6%	**67**	43%	6%	33%	6%	**77**	45%	6%	<0.01	0.01
4S															

* p for trend in observed 5 and 10-year OS by using parametric survival model adjusted for follow-up time.

** Stage is missing for 8 patients.

The analysis per period was not performed when patient number at start of the interval was below 20. For the period 2010-2014, only 5-yr OS could be calculated. Abbreviations: n: number; SE: standard error; OS: overall survival; NB: neuroblastoma; GNB: ganglioneuroblastoma.

CHAPTER 9

General discussion and future perspectives

REGISTRIES FOR CHILDHOOD AND YOUNG ADOLESCENT CANCERS IN THE NETHERLANDS

In **chapter 2** we performed a methodological linkage study to confirm the diagnoses in the Netherlands Cancer Registry (NCR) with the diagnoses in the Dutch Childhood Oncology Group (DCOG) registry for children and young adolescents with cancer diagnosed during 2004-2013. The population-based NCR registers data on all cancer patients at a national level, regardless of age and hospital. The DCOG registry is a hospital based registry for patients treated at a paediatric oncology centre. In total 6,021 children and young adolescents with cancer aged ≤17 years were included in the 10 year period. The number of children and young adolescents diagnosed with cancer each year was substantially higher when NCR data was used compared to DCOG data. After linkage and several checks, 4,935 patients (82%) with cancer were classified as registered in both registries. In case of differences in the topography or morphology (~7% of the tumours in both registries) the NCR records were taken, because of the NCRs' prolonged registration history and international coding guidelines. Furthermore, 1,086 patients with cancer aged ≤17 years were registered in the NCR only; 68% of these patients were treated at a university medical centre, but not known at the paediatric oncology centre and 32% were treated outside a university medical centre.

Because this thesis is focused on population based studies and the NCR covers cancer diagnoses for the whole Dutch population since 1989, we used the NCR data as a basis for all analyses in this thesis. For the leukaemia and lymphoma papers, **chapters 4, 5, 6 and 7**, additional clinical data from the DCOG registry was used.

TRENDS IN INCIDENCE

The incidence of childhood cancer is modestly increasing worldwide.[1-7] Recent population-based incidence trends of cancer in children and young adolescents are not publicly available for the Netherlands. To fill this gap we aimed to get an answer on our first research question: **"What are the trends in incidence for cancer in children and young adolescents, in general and for five of the main cancers?"**

The overall incidence for all childhood cancers combined in the Netherlands did increase with 0.6% per year (**chapter 3**). A comparison with age-standardised incidence rates from other countries is provided in **table 9.1**. Considerable similarities in both incidence rates and reported changes over time can be seen between the different western countries.

Tumour-specific overall incidence rates did not change for ALL, AML, HL, NHL and NBL (**chapters 4-8**). However, in subgroup analyses some age group, type, or stage-specific changes in incidence were seen for specific tumours, listed in **table 9.2**.

Table 9.1 Age standardised incidence rates (per million person-years) for the Netherlands compared with several other countries with recently published rates and AAPC analyses

Main groups	The Netherlands[8] age 0-17 yrs 1990-2017	Canada[3] age 0-14 yrs 1992-2010	Piedmont (Italy)[4] age 0-14 yrs 1967-2011[#]	United Kingdom[5] age 0-14 yrs 1993-2010*	Japan[5] age 0-14 yrs 1993-2010*	Australia[6] age 0-14 yrs 1997-2006[&]	United States[7] age 0-19 yrs 2001-2009	Europe[2] age 0-14 yrs 1991-2010
I Leukaemias, myeloproliferative and myelodysplastic diseases	45 +0.7%, 0.3-1.2	51 +0.6%, 0.1-1.2	51 +0.6%, 0.0-1.2	47	43	53 +0.9%, 0.3-1.5	45	47 +0.7%, 0.5-0.8
lymphoblastic leukaemia[a]	35 +0.6%, 0.1-1.1	40 +0.6%, 0.1-1.1	37 +0.9%,0.3-1.4			41	33	
acute myeloid leukaemia (AML)	8	7	7			9	8	
II Lymphomas and reticuloendothelial neoplasms	20	17	19	15	11	15 +0.7%,0.0-1.3	25	16
Hodgkin Lymphoma (HL)	9	6	8			6	13	
Non-Hodgkin Lymphoma and Burkitt lymphoma (NHL)	11	8	10			9	11	
III CNS and miscellaneous intracranial and intraspinal neoplasms	30[b] +1.0%,0.5-1.5	34[b]	37[b] +1.8%, 0.9-2.7	23[c]	18[c]	36[b] +1.7%,0.6-2.8	30[b]	22[c] +0.5%, 0.2-0.8
IV Neuroblastoma and other peripheral nervous cell tumours (NBL)	8 +1.2%, 0.1-2.0	12	12 +1.2%, 0.2-2.1	9	9	10	8	
V Retinoblastoma	7	4	4	5	5	4	3	
VI Renal tumours	9	9	7	9	3	9	7	
VII Hepatic tumours	2	2	2	2	3	3 +3.3%, 0.8-5.9	2	
VIII Malignant bone tumours	9	7	9	6 +1.3%,0.1-2.5	4	7	9	

Table 9.1 (continued)

Main groups	The Netherlands[8] age 0-17 yrs 1990-2017	Canada[3] age 0-14 yrs 1992-2010	Piedmont (Italy)[4] age 0-14 yrs 1967-2011[#]	United Kingdom[5] age 0-14 yrs 1993-2010*	Japan[5] age 0-14 yrs 1993-2010*	Australia[6] age 0-14 yrs 1997-2006[&]	United States[7] age 0-19 yrs 2001-2009	Europe[2] age 0-14 yrs 1991-2010
IX Soft tissue and other extraosseous sarcomas	10	10	9	9	7	8	12	
X Germ cell tumours, trophoblastic tumours, and neoplasms of gonads	7	5	4	5 +1.6%, 0.1-3.1	9	6 +2.3%, 0.9-3.7	11	
XI Other malignant epithelial neoplasms and melanomas	9	6 +2.5%, 0.2-4.7	4	4	3	7	18 +0.8%,0.1-1.5	
XII Other and unspecified malignant neoplasms	0.4	3	1	2	1	0.4	1	

Trends were calculated by AAPC (average annual percentage change) analyses; + indicates significant increase in AAPC, - means significant decrease in AAPC. 95% confidence intervals are presented after the AAPC

[a] including acute lymphoblastic leukaemia (ALL)

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

[c] Excluding pilocytic astrocytomas

[#] AAPC trend analyses for period 1976-2011

[*] Incidence rates for period 2005-2010

[&] AAPC trend analyses for period 1983-2006

Table 9.2 Most important outcomes for the overall incidence and the five childhood and young adolescent cancers studied in more detail

	general descriptive		change in incidence	change in survival	change in mortality	change in cancer care
Overall incidence	total N	15,233	overall ↑			
	study period	1990-2017	patients aged 0 years ↑			
Chapter 3			patients aged 10-14 years ↑			
	average number/year in 2010-2015	579	patients aged 15-17 years ↑			
ALL	total n	2997	overall =	overall ↑	overall ↓	treatment by paediatric oncologist ↑ for patients aged 15-17 year
Chapter 4	study period	1990-2015	patients aged 10-14 years with BCP-ALL ↑			treatment by paediatric oncologist was already high for patients ≤14 years
	average number/year in 2010-2015	117	patients aged 15-17 years with T-ALL ↓			survival benefit for patients aged 15-17 year when treated according to a paediatric protocol treatment according to last treatment protocol led to better outcome compared with older treatment protocol
	5-yr overall survival 2010-2015	91%				
AML	total n	635	overall =	overall ↑	overall ↓	treatment by paediatric oncologist ↑ over time treatment according to last treatment protocol led to better outcome compared with older treatment protocol small subgroup analysis revealed lower survival probability for patients treated outside a paediatric oncology centre
Chapter 5	study period	1990-2015	patients aged 1-4 years ↑	main improvements for younger age groups and most recent treatment protocol		
	average number/year in 2010-2015	26				
	5-yr overall survival 2010-2015	74%				

Table 9.2 (continued)

	general descriptive		change in incidence	change in survival	change in mortality	change in cancer care
HL [$]	total n	926	overall =	patients aged 15-17 year ↑	overall ↓	treatment by paediatric oncologist ↑ for patients aged 15-17 year
Chapter 6	study period	1990-2015	stage I disease ↓ stage IV disease ↑			
	average number/year in 2010-2015	45				treatment differed between paediatric and adult protocols,; less radiotherapy for lower staged tumours in paediatric protocol.
	5-yr overall survival 2010-2015	97%				no difference in survival outcome for patients aged 15-17 year and treated according to a paediatric or adult protocol
NHL	total n	1004	overall =	overall ↑	overall ↓	treatment by paediatric oncologist was already high for patients ≤17 years since 2004 patients treated outside a UMC had a borderline significant worse survival outcome
Chapter 7	study period	1990-2015	patients aged 5-9 year ↓			
	average number/year in 2010-2015	41				
	5-yr overall survival 2010-2015	87%				
NBL	total n	592	overall =	overall ↑	data not available	all patients were treated by a paediatric oncologist.
Chapter 8	study period	1990-2014	patients aged ≥18 months ↑			improved survival of stage IV patients is predominantly associated with high dose chemotherapy and autologous stem cell rescue and immunotherapy
	average number/year in 2010-2014	33	stage IV disease ↑			
	5-yr overall survival 2010-2014	61%				

Symbol explanation: ↑ significant increase, ↓ significant decrease, = no significant trend

$ the original publication also concerned young adults aged 18-24 years, but were excluded in this table

Used abbreviations n = number of patients, *ALL* acute lymphoblastic leukaemia, *BCP-ALL* precursor B-cell ALL, *AML* acute myeloid leukaemia, *HL* Hodgkin lymphoma, *NHL* non-Hodgkin lymphoma, *NBL* neuroblastoma

Possible causes for variation in incidence

The increases in incidence, as reported above, might be interpreted as true increases. However, this might also be misleading. Possible causes that theoretically may influence the changing incidence rates over time are: 1. earlier diagnosis, 2. new or improved detection techniques, 3. risk factor prevalence and 4. changes in registry practices or referral patterns. This is presented in **figure 9.1**, a more detailed version of the cancer detection phase from **figure 1.2** in the introduction.

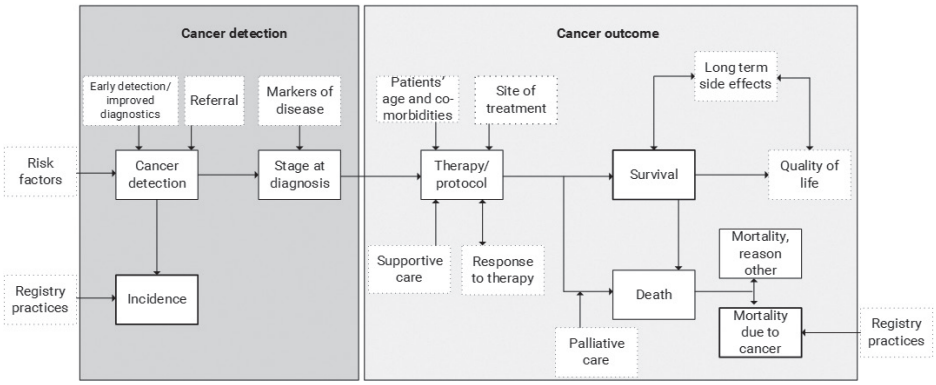

Figure 9.1 Extended schematic overview of the conceptual framework with the interplay between cancer detection and cancer outcome and the outcome measures used in thesis. Incidence, survival and mortality are the main parameters of interest. Inspired on figure 1.2 in the introduction of this thesis and figure 1 in the discussion of Mieke Aarts' thesis (2012).

Earlier detection

Earlier detection can be achieved by prevention campaigns and/or increased awareness among general practitioners, clinicians and the general population. An example is the melanoma prevention campaign which led to increased awareness of naevi among general practitioners, dermatologists and the general population[9] and probably resulted in an increased detection of early stage melanomas in our study (**chapter 3**). However, this relatively small number of patients with a melanoma could not have increased the overall incidence rate.

To detect tumours at an earlier stage with a screening programme for a specific part of the population is another instrument for earlier detection. Several countries implemented a screening for NBL by measuring urinary catecholamines in infants.[10,11] This screening did not take place in the Netherlands. Another type of screening, in sense of earlier detection, are prenatal ultrasounds, which are more frequently used during pregnancy (at 10, 20 and since ~2012 also at third trimester in midwifery care in the Netherlands.[12,13] Among the youngest children age <1

year, we observed increased incidences of leukaemias and CNS tumours (**chapter 3**). However, leukaemias and >98% of paediatric CNS tumours are not detectable by prenatal ultrasound.[14] Therefore, the increases among the youngest children do not seem to be caused by prenatal ultrasounds. For the five tumours studied in more detail in **chapters 4-8**, no increases in this youngest age group were seen. To conclude, early detection does not seem to contribute to the overall increase in incidence.

New or improved detection techniques

A new or improved diagnostic technique could lead to more tumours being diagnosed at an earlier stage or to diagnosis of tumours that otherwise remained undetected. Introduction of the MRI-scan (half-way 1990s in the Netherlands) led to better specification of astrocytomas, from unspecified into pilocytic astrocytomas and consequently an increased incidence of in this specific type (**chapter 3**). Probably, the rise in unspecified gliomas at the brain stem is partially also due to the increased use of MRI, resulting in more specific diagnosis. An example of earlier detection is the rise in early disease of testicular germ cell tumours which might partly be caused by the use of more sensitive imaging modalities. Moreover, diagnostic awareness of these testicular germ cell tumours among general practitioners might play a role as well.[15]

HL, soft tissue sarcomas and medullary thyroid carcinomas were detected more often at higher stages due to better imaging with the MRI or PET-CT (end 1990s), the incidence rates for these tumours overall, did not increase (**chapter 3**). For HL we observed a decrease in stage I HL and an increase in stage IV HL (**chapter 6**), this phenomenon is called stage migration.[16] For NHL no changes in stage distributions over time were noticed (**chapter 7**). The remarkable increase in incidence that was observed for stage 4 NBL patients aged ≥18 months (the number of patients almost doubled, from 7 per year in 1990-94 to 12 in 2010-14), could not be explained by better detection techniques, nor did we observe stage-migration, as the incidence trends for the other stages remained constant over time (**chapter 8**). This is probably a real increase.

Ultimately, we would like to compare the stage distributions per tumour with data from other countries, to observe the distribution of "worse prognosis patients"/ case-mix. Few population-based (childhood) cancer registries seem to register this. Recently, a proposal by Gupta et al. has been launched.[17] The Australian cancer registry has reported about the stage at diagnosis for children, 0-14 years, diagnosed with solid tumours.[18] Overall, the stage distribution at diagnosis for their neuroblastomas and the neuroblastomas in our **chapter 8**, seem comparable. However, their study included all solid tumours in childhood, and was therefore not as specific as ours. For example, incidence rates according to stage and/or age were not provided. Five-year

survival rates in this Australian study seem to be slightly higher for all stages than those in the Netherlands. It would be interesting to compare this data in more detail.

Incidence rates for early stage tumours did not increase for most tumours, therefore we have no reason to believe that improved diagnostic techniques did increase the number of children and young adolescents diagnosed with cancer. During the time frame considered in this thesis, many molecular markers were identified, which may influence risk stratification rather than detection rate or stage of disease.

Changes in risk factor prevalence

An overview of risk factors is given in **table 9.3**. The majority of risk factors reported in literature are related to factors influencing the pathogenesis of leukaemia in early life, before age 5. However, there was no increase in ALL incidence for patients aged <5 years but rather in the older age groups. No risk factors are reported for older ALL patients. Contrary, for AML we found an increase in incidence for patients aged 1-4 year. The relatively higher number of children with Down Syndrome in the Netherlands, as compared with other European countries[19], might have resulted in a higher ML-DS incidence and increased overall incidence, although only comprising 9% of all patients. The decrease in incidence for patients aged 5-9 year and diagnosed with NHL, was not found before. EBV infection is one of the known risk factors for NHL. The hypothesis that less young children encountered an EBV infection in the Netherlands could not be tested as there is no information on the prevalence for this infection in the Netherlands. For most solid tumours, including NBL, etiological factors are largely unknown. No environmental factors have been consistently associated with NBL and genetic predisposition is rare.[20,21]

Table 9.3 Reported risk factors (and evidence) in childhood cancer occurrence

	factor	reported association (evidence)*	Reference
ALL	High birth weight	increased risk (-)	Caughey et al. 2009[22]; GR Rapport 2012[23];Roman et al. 2013[24]
	Extremely low-frequency (ELF) magnetic fields	increased risk (-)	GR Rapport 2012[23]
	Inherited risk factors; Down syndrome, certain genetic syndromes (Bloom, Fanconi anemia and Nijmegen breakage syndrome), congenital immunodeficiency diseases	increased risk (+)	Bruwier et al 2012[25]; GR Rapport 2012[23]
	Pesticide exposure	increased risk (-)	GR Rapport 2012[23]
	Delayed infection hypothesis (Greaves) or 'population mixing hypothesis (Kinlen)	increased risk (?)	Kinlen et al 1993[26]; Greaves 2006[27]; GR Rapport 2012[23]
	Breast feeding	Decreased risk (-)	GR Rapport 2012[23]
AML	High birth weight	increased risk (-)	Caughey et al. 2009[22]; GR Rapport 2012[23]
	Inherited risk factor; Down syndrome	increased risk	Bruwier et al 2012[25]
	Breast feeding	Decreased risk (-)	GR Rapport 2012[23]
Leukaemia, not specified	Ionizing radiation in utero	increased risk (+)	Doll 1997[28]; GR Rapport 2012[23]
	Radiation exposure from CT scans in early life	increased risk (-)	Pearce et al 2012[29]; GR Rapport 2012[23]
	Parental smoking or alcohol consumption	increased risk (-)	Cogliano et al 2011[30]; GR Rapport 2012[23]
Hodgkin Lymphoma	EBV-infection or HIV infection	increased risk	Ward et al 2014[21]
	History of mononucleosis	increased risk	Ward et al 2014[21]
Non-Hodgkin Lymphoma	EBV infection	increased risk	Ward et al 2014[21]
	Immunosuppression (such as inherited immunodeficiency, HIV, post transplantation immunosuppression)	increased risk	Ward et al 2014[21]
Burkitt lymphoma	EBV infection	increased risk	Ward et al 2014[21]
Neuroblastoma	Family history of neuroblastoma or genetic predisposition (1-2% of cases)	increased risk	Matthay et al. 2016[20]

* Level of evidence for reported causal associations; -- unlikely/weak, - limited/possible, + strong, ? inadequate/uncertain, derived from GR Rapport 2012[23]

Changes in registry or referral practices

The decrease in NHL incidence for patients aged 5-9 years was not clearly related to a specific type of NHL. Lymphoblastic lymphomas (LL) are closely related to ALL. The percentage of blasts in the bone marrow defines the diagnosis to be a LL, blasts <25%, or ALL, blasts ≥25%. The decrease in NHL for 5-9 year old patients was not accompanied by an increase in ALL for this age group. Possible misclassification of NHL as leukaemia by the registration clerk of the NCR has been checked by a linkage with the diagnoses in the DCOG registry and no discrepancies were found. Furthermore, a case ascertainment study performed in the Netherlands for children diagnosed with leukaemia or lymphoma in the early 1990s, appeared to be very good.[31]

Another, hypothetical, change could be that more advanced tumours were missed by the NCR in the 1990s, compared with the more recent periods, because of early death before the diagnosis could be confirmed. For patients suspected for a leukaemia, this could be true if no bone marrow smear was sent to the DCOG. Pathological confirmation of severe NBL in very sick children could have been omitted, and therefore could have been missed by the registration personnel of the NCR. However, the number of patients included in the NBL study (**chapter 8**) was similar to the number of patients used in the hospital-based studies of Verly *et al*.[32]

These two somewhat theoretical examples make changing incidence patterns by changes in registry practice unlikely. Furthermore, changes in referral pattern are also less likely. Every Dutch inhabitant is registered in a general practice. The general practitioner acts as a gatekeeper for specialist care, so that specialised care is limited to those patients who are referred by their general practitioner.[33] Referral to a secondary care hospital will be arranged shortly after a child or young adolescent and his/her parents visit the general practitioner with complaints. Referral to paediatric oncology can be arranged quickly thereafter. Furthermore, over 90% of all children up to the age of 4 visit the free public service of child health clinics that monitor health and social development on a regular basis.[34] This has not changed during the 26 year period of these studies.

Some considerations for comparisons of incidence trends

The increase in incidence for the clinic results in about 3 more patients per year. The cumulative risk to develop cancer during childhood, is still about 0.3%. This to express the very rareness of cancer occurrence in the first 18 years of life.

Most studies consider childhood cancer only to occur in children aged 0-14 years, some consider the age group 0-19 years. The age range 0-17 is uncommon in epidemiological papers,

however, we choose to take this range since this is the age range treated at a paediatric oncology centre in the Netherlands. For the most recent period of diagnosis, 2010-2014/2017, not much epidemiologic literature was available to compare.

There are differences in the clinical practice and registration practice considering benign or malignant tumours. Registration of benign and borderline CNS tumours and myelodysplastic syndromes in the NCR became mandatory since diagnostic year 2001 and Langerhans cell histiocytosis since 2012 and carcinoid tumours of the appendix since 2013. The reported numbers and incidence rates therefore underestimate slightly the true rates. On the other hand, the NCR does not register for example anaplastic anaemia and Fanconi anaemia which entities are seen and treated by a paediatric oncologist. It is essential to know which "tumours" are included in a paper and which are not.

Concluding remarks on registries and incidence trends for children and young adolescents with cancer in the Netherlands

Not all children and young adolescents with cancer were seen and treated at a paediatric oncology centre and are therefore not registered in the DCOG registry, but included in the NCR. Overall, 82% of the patients were in both registries. The overall incidence study, with data from the NCR for diagnostic period 1990-2017, demonstrated a slight increase in the overall incidence, 0.6% per year. This increase could be related to increases in a few main groups. However, explanations for these increases are probably unknown. The age-specific increases in ALL and AML, the decrease in NHL together with the stage specific increase for NBL could be due to chance, or, related to changing risk factors that are still unknown.

THE IMPACT OF CHANGES IN CANCER MANAGEMENT ON FIVE PEDIATRIC AND YOUNG ADOLESCENT CANCER TRENDS

Despite the obvious relevance for clinical purposes, research and health-care policy making, a complete population-based overview of incidence, survival and mortality for paediatric and young adolescent cancer patients is not yet obtained for the Netherlands. We described the trends of five specific childhood and young adolescent cancers in more detail. Furthermore, after the linkage study performed in **chapter 2**, we were able to analyse the site of treatment for paediatric and young adolescent patients with cancer. With these studies we aimed to get an answer to our second research question: **"What is the impact of changes in cancer management on paediatric and young adolescent cancer trends?"**

Site of treatment

In total 82% of the children and young adolescents with cancer were treated at a paediatric oncology centre, with differences in gender, age group and tumour type. Over time, especially, more 15-17 year old patients were treated at a paediatric oncology centre in the Netherlands. However, we also found that 46% of these young adolescents were not yet treated in a paediatric oncology centre in 2013. Children and young adolescents, who were referred less often to a paediatric oncology centre, were:

1. Older aged,
2. More often diagnosed with (young) adult type tumours (for example CML, any epithelial carcinoma, chondrosarcoma and other bone sarcomas, and non-rhabdoid sarcoma),
3. More often diagnosed with localised tumours that only needed surgical resection of their tumour (for example pilocytic astrocytoma, thyroid carcinoma or melanoma).

Although the included upper age limits differed, the first two conclusions were also reported by six previously published studies that used data from population-based cancer registries. [35-40] The third point, related to stage at diagnosis, was a new finding in our results.

Where and how to treat younger patients with cancer (age 15-17 years) remains a clinical dilemma. The pathogenesis for the bone and soft tissue sarcomas, epithelial neoplasms and gonadal germ cell tumours is equal for adolescents and young adults (AYA).[41,42] From epidemiological studies in the Netherlands we know that these tumours become more frequent in the young adult age range (up to 40 years, NCR data).[9,43] For children and adolescents with osteosarcomas, Ewing tumours and rhabdomyosarcomas, multidisciplinary treatment protocols are followed at the paediatric oncology centres since the late 1990s. In these specific treatment

protocols, the upper age limit is 21 or 40 years for patients with rhabdomyosarcoma and osteosarcoma respectively, indicating that it will be the best available treatment for patients up to that age.[44,45] There are no specific paediatric treatment protocols for the tumours in the ICCC main group XI Other malignant epithelial neoplasms and melanomas/ carcinomas in children.

Paediatric treatment protocols are more intensive compared to (young) adult treatment protocols. Disparities in drug selection and dose intensity in treatment practices between paediatric and adult departments may cause the survival rate differences as was demonstrated in the early 2000s for ALL and Wilms tumours.[46,47] In the tumour specific chapters we were able to report about the site of treatment for patients aged 15-17 years and relate it to cancer outcome, as discussed below.

Cancer specific survival trends

Cancer outcome for children and young adolescents is influenced by several factors like incidence, stage at diagnosis, response to treatment, and patient characteristics like age and co-morbidities, as depicted in **figure 9.1**. In the tumour specific studies performed, we were able to report survival improvements according to stage at diagnosis, site of treatment and specifically relate the improvements to a protocol or a treatment modality. The main findings of the changes in survival and mortality trends for the paediatric and young adolescent tumours studied in this thesis, are shown in **table 9.2**. For each of the five cancers studied, significant progress was made over time. Survival outcomes were comparable with the most recent literature from other countries, as discussed in the tumour specific chapters.

Five-year overall survival (OS) for patients with ALL increased from 80% in 1990-94 to 92% for patients diagnosed in 2010-15 (**chapter 4**). As mentioned in the introduction the 5-year survival outcome for childhood AML diagnosed up to 2009 was 59% in the Netherlands.[48] This percentage seemed relatively low compared to other north-western European countries. In our paper (**chapter 5**) we demonstrated increasing improvement in survival outcome in the last period. Patients with AML and treated according to the treatment protocol, introduced in 2010, did have a 5-year OS probability of 74% and a lower death risk compared to the treatment protocol active in the first years of our study.

For patients with HL (**chapter 6**) and NHL (**chapter 7**), improvements in survival were seen both overall, and age, stage and subtype specific. Here the improvements are a result of improved diagnostics (for HL due to the stage migration), improved use of combinations of chemotherapeutics and response adapted treatment enhancements.

For NBL patients an increase in 5-year OS was observed over the 25-year period, overall, for the age groups, and for the different stages (**chapter 8**). Surgical resections and use of radiotherapy were more often applied for high stage NBL over time. The introduction of high-dose chemotherapy with autologous stem cell rescue (late 1990s) and immunotherapy (after 2009) were significantly associated with the improved survival of stage 4 NBL patients.

Subsequent improvements in treatment protocols resulted generally in increased survival and less cancer related mortality. The multivariable survival analyses per cancer type in this thesis were able to unravel the underlying protocol or specific treatment item that improved survival over time, especially for patients with AML and NBL. Improvements in supportive care[49,50] as well as improvements in second line therapies, for recurrent disease or relapses, might have occurred as well. However, confirmatory -event specific analyses- are not possible with data from the NCR.

Site of treatment and survival for young adolescent cancer patients

In both the paediatric and AYA cancer care setting, cancer treatment is increasingly protocolised by multidisciplinary teams of all relevant care givers. Lymphomas were the most frequent tumour for patients aged 15-17 years and HLs were treated more often at a paediatric oncology centre over time (**chapter 6**). We did not discern better outcomes when treated according to paediatric HL treatment protocols, unlike American colleagues.[36,51] However, less radiotherapy was given to lower staged HL patients when treated according to a paediatric HL treatment protocol. For patients with NHL and treated outside a UMC we saw a borderline significant worse survival outcome (**chapter 7**).

For ALL we demonstrated a survival disparity for young adolescents (**chapter 4**). The lower survival of this age group compared to younger patients is well known. We also showed that 15-17 year old patients had a 70% reduction in death rate when treated at a paediatric oncology centre. After the publication of significant difference in outcome for young adolescents with ALL treated on a paediatric versus adult protocol[46], ALL treatment for AYA patients until the age of 40 has been adapted to a paediatric inspired protocol.[52] Possibly, there are still differences in management of treatment-related toxicities and/or trial participation in adult versus paediatric centres.[53] Active collaboration between paediatric and (adolescent and young) adult units treating these relatively young patients with all kind of tumours is needed to have the best chances for cure and less side-effects at the long term.

Cancer specific mortality trends

Cancer mortality rates declined for the childhood and adolescents cancers studied in this thesis. With the performed AAPC analyses in the statistical package Joinpoint, we checked for trend transitions (joinpoints) during the study period. This was not the case in the trends for the tumours studied. The rates constantly decreased over time since the 1980s.

Declining mortality rates were a result of improved survival over time. However, we need to be aware that, despite better supportive care and second line treatments, patients live longer, but at a later point in time still may die as a consequence of cancer recurrences or long-term treatment-related adverse events.[54,55] Monitoring the current patient group is warranted, to detect long-term adverse events.

Concluding remarks on impact of changes in cancer management for the five tumour specific chapters

The linkage of the DCOG registry with the NCR enabled us to describe changes in the site of treatment for childhood and young adolescents with cancer in the Netherlands. Patients less often treated at a paediatric oncology centre were older, had more adult like tumours or lower staged tumours. The prognosis for childhood and young adolescent cancers in this thesis indeed improved substantially during 1990-2015. This progress was confirmed by decreasing mortality rates for the leukaemias and lymphomas. Patients aged 15-17 years and diagnosed with ALL should be treated at a paediatric oncology centre. For patients of the same age with HL no difference in survival was observed, although treatment regimens differed between adult and paediatric oncology centres, where less radiotherapy was administered.

Possible pitfalls when combining the trends to measure progress against cancer

In this thesis we implied the progress framework as proposed in the thesis of Karim-Kos[56], by reporting on childhood and young adolescent trends in cancer incidence, survival and mortality. With this approach we gained a more objective assessment of progress against childhood and young adolescent cancer achieved in the Netherlands, while avoiding over-interpreting findings from each of these measures only.

In **chapter 4** (ALL) and **chapter 8** (NBL), we reported slightly increasing incidence rates up to 2015 and 2014 respectively. In **chapter 3**, including diagnosis years 2016 and 2017, significant increases in incidence were observed for both tumour types. Childhood cancer occurrence is a very delicate subject in public, so just reporting about an increase needs a subtle approach, and monitoring of the increase for a substantial time. Temporary and spatial variations might occur, also called clustering, but hardly to be clarified due to small numbers.

For five of the most common childhood and adolescent cancer types, we performed survival analyses which resulted in up-to-date population-based survival rates for the Netherlands which were lacking. In addition, with multivariable survival analyses we analysed the main reasons for improvements. It would be interesting to make meaningful comparisons in the future at a population-based level, when, hopefully, other cancer registries will expand their registry with items like stage at diagnosis and treatments provided.

For most tumour specific analyses we checked the numbers obtained from Statistics Netherlands with the number of deceased patients among those diagnosed with that specific tumour type. The annual comparison between the aggregate number of deceased patients registered in the NCR by age at death and sex and those registered as cancer x death with Statistics Netherlands was checked for four tumours in this thesis, NBL excluded. The numbers were similar overall. Age at death and cause of death, cancer related or other, remain factors that do not imply one to one extraction of both methods. Changes in mortality do not necessarily reflect recent progress, as mortality in a given year reflects the risk of cancer death among patients diagnosed over the preceding years depending on the prognosis of the tumour (e.g. leukaemia mortality rate in a given year represents the current deaths within that year, but also reflects deaths from therapy given in the preceding 5-10 years).

Knowing the cause of death in a cancer registry might inform about whether children died from their cancer itself, or from a consequence of their intensive treatment or from other causes.[57,58]

Other clinically relevant items that are not routinely registered by the NCR are response to therapy and information on relapse(s) and an institutes' supportive care regimen. Linking with a registration or database that does contain that information, needs to be considered. Especially since childhood cancers are so relatively rare and much life-years will be lost.

Population-based cancer registries have a main purpose to provide statistics on the variation in time and place of incidence and survival of cancer as well as demographic, clinical and tumour characteristics.[59] The population-based studies in this thesis, with data from the NCR as basis, are descriptive, but combined with complete follow-up of vital status and independent aggregate cause of death information also enable assessment of real progress over time, in other words a lower burden of disease. The combination with results of long term surveillance as done in long term side effect (in Dutch LATER) studies will complete the the survivorship picture in the long run. The NCR is also an ideal sampling frame for in depth etiologic and prognostic research.[60] Taken into account four decades of intensive but inconclusive etiological, often clustering related, research of causes of childhood and young adolescent cancer in high income countries (**table 9.3**), it is perhaps not surprising to observe the minimal variation in incidence of these cancers across the world, but especially in areas with similar patterns of mortality and life-expectancy below age 30. This also distinguishes childhood and young adolescent cancers from cancers at middle and older age where lots of research has been done on prevention, followed by prevention campaigns.

OVERALL CONCLUSIONS

- Significant progress against childhood and young adolescent cancers considered in this thesis was observed for the Netherlands since 1990.
- The slightly increasing overall incidence rate of childhood and young adolescent cancer could not be explained by a rise in early diagnosis, improved diagnostics, nor by changing registry practices, thus leaves a variety of unknown risk factors as an explanation for the increase.
- For ALL, AML, HL, NHL and NBL we observed:
    - Incidence decreased for patients aged 5-9 years and diagnosed with NHL
    - Improved survival for all tumour types
    - A mortality decrease for each of these tumour types
- Progress in our terms was observed, because the prognosis for childhood and young adolescent cancers did improve substantially, mainly by improved effective combinations of treatments. Over time more patients aged 15-17 years were increasingly treated at a paediatric oncology centre. Specifically patients with ALL seemed to benefit.
- Incidence, survival and mortality rates were comparable with other north-western countries in Europe.

FUTURE PERSPECTIVES

In the Netherlands we now have the unique situation that childhood and young adolescent cancer care and research is centralized into one national centre. The mission of the Princess Máxima Center is to cure every child with cancer, with fewer adverse late effects in life. The paediatric oncologists have their treatment protocols, trials and cancer care databases, researchers have their biologic, genomic, and proteomic databases. The ultimate connection between these two pillars will be made by a very detailed paediatric cancer registry, which receives its data from within the hospital, but also by linking this to an objective, population-based registry like the NCR. This will enable measurement of expected continuation of progress, also for other childhood and young adolescent cancer types. And the registry will be the basis for many studies involved in cancer detection and patient outcome.

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CHAPTER 10

Summary

Samenvatting

SUMMARY

The general objective of this thesis is to assess and clarify epidemiologic progress against childhood cancers occurring during the last decades in the Netherlands (1990-2015). A minimal data set for every newly diagnosed cancer patient is collected by registrars of the Netherlands Cancer Registry. The Dutch Childhood Oncology Group (DCOG) registers data for all patients seen and treated by the paediatric oncologists in the seven paediatric oncology centres. The DCOG is the network organisation for the paediatric oncologists with a reference laboratory and an own basis clinical registry from 2003 onwards. National guidelines for diagnosis and treatment of childhood leukaemia started in 1972, and currently more than 40 multidisciplinary protocol committees exist. We performed a linkage study to confirm the diagnoses in the NCR with the diagnoses in the DCOG registry for children and young adolescents with cancer diagnosed during 2004-2013 (**chapter 2**). This study showed that 82% of the children and young adolescents (aged <18 years) diagnosed with cancer were known in both registries. Meaning that 18% of the patients were not treated in a paediatric oncology centre. To report about population-based trends in incidence, stage at diagnosis, treatment and survival patterns, irrespective of site of treatment, we used the NCR data as a basis for all other analyses in this thesis.

The first aim was to describe the trends in incidence for cancer in children and young adolescents, in general and for five of the main cancers. Over a 28-year period the annual overall cancer incidence slightly increased. In 1990-99 481 children and young adolescents were diagnosed with cancer yearly on average, in 2010-2017 542. The age standardised incidence rate increased from 144 per million person-years in 1990-99 to 162 in 2010-2017. This increase of 0.6% was comparable with changes in incidence in other western countries. The incidence of leukaemia, malignant CNS tumours including pilocytic astrocytomas, neuroblastoma and Ewing bone tumours significantly increased (**chapter 3**). In the following chapters we described the incidence for five of the main cancers in detail:

- The overall incidence for ALL patients <18 years at diagnosis remained stable at 37 per million children, despite increases for B-cell precursor ALL (BCP-ALL) at age 10-14 years and T-cell ALL at age 15-17 years (**chapter 4**).
- For children diagnosed with AML there was a slight increase in the incidence at age 1–4 years (**chapter 5**).
- The incidence for HL in children and young adolescents remained stable. In this study we also included young adults aged 18-24 year, here we observed a significant increase.

Furthermore, the incidence for advanced stage HL increased whereas the incidence of lower staged HL decreased (**chapter 6**).

- The overall incidence of NHL remained stable. For patients aged 5-9 years a decrease in incidence was seen (**chapter 7**).
- The incidence of NBL slightly increased (**chapter 3**) and the incidence of stage 4 NBL increased exclusively in patients aged ≥18 months since 1990, whereas the incidence of other stages remained stable (**chapter 8**).

Possible causes that influenced the changing incidence rates over time are: 1. earlier diagnosis, 2. new or improved detection techniques, 3. risk factor prevalence and 4. changes in registry practices of referral patterns. Earlier and new or improved diagnostic techniques can explain a small part of the number of diagnoses (testicular germ cell tumours, melanoma and some CNS tumours), although these could not have caused the overall slight increase in childhood cancers. Still, changing risk factors that are unknown might be considered as possible explanations. We did not study this in more detail in this thesis and further research in this field in needed.

The second aim was to describe the trends in survival and mortality of children and young adolescents with cancer and to study the impact of changes in cancer management on paediatric and young adolescent cancer trends. Again the NCR data was the basis, and to study the site of cancer treatment, the DCOG data was used. The mortality data were derived from Statistics Netherlands that holds a registration based on causes of death from all deceased persons registered in the Netherlands. The trends in site of treatment, survival and mortality for five of the main cancers were described in detail:

- A remarkable change was seen in the proportion of patients aged 15-17 that were treated in a paediatric oncology centre, this increased from 33% in 2004 to 54% in 2013. The children that were not treated in a paediatric oncology centre were older, diagnosed with tumours occurring more often in young adults or had lower-staged tumours at diagnosis (**chapter 2**).
- Five-year OS for patients with ALL improved from 80% in 1990-94 to 91% in 2010-15, and improved significantly for all age groups and BCP-ALL. Patients aged 15-17 years were increasingly treated in a paediatric oncology centre, from 35% in 1990-94 to 87% in 2010-15 and experienced a 70% reduction of risk of death compared to those treated outside such a centre. Simultaneously, mortality rates decreased significantly for all age groups (**chapter 4**).
- Overall, the 5-year survival for patients with AML significantly improved over the past 26 years and nearly doubled from 40% in the early 1990s to 74% in 2010–15. Multivariable analysis showed a 49% reduction in risk of death for AML patients treated according to

the latest DB-AML 01 protocol. Although the group of children with AML that were treated outside a paediatric oncology centre was small, their survival outcome was comparable with the survival outcome for young adults. The continuing decrease of mortality (AAPC −2.8% per year (95% CI −4.1 to −1.5)) supports the conclusion of true progress against AML in the Netherlands (**chapter 5**).

- The 5-year OS for children diagnosed with HL was already high in the early 1990s (93%). For patients aged 15–17 and 18–24 years the 5-year OS improved from 84% and 90% in 1990–94 to 96% and 97% in 2010–15, respectively. Patients aged 15–17 years were increasingly treated at a paediatric oncology centre. Survival for patients aged 15–17 years was not affected by site of treatment, although treatment regimens differed between adult and paediatric oncology centres, where less radiotherapy was administered (**chapter 6**).
- Five-year OS for children and young adolescents with NHL improved from 71% in 1990-1994 to 87% in 2010-2015. Since 2004 most of the 15-17 year old patients with NHL were treated at a paediatric oncology centre. Mortality rates steadily decreased from 20 patients in 1980-84 to 6 patients in 2010-16 on average (**chapter 7**).
- Five-year OS for children with NBL of all patients improved from 44% to 61% from 1990 to 2014. Patients aged ≥18 months and diagnosed with stage 4 disease have a worse prognosis, however their 5-year OS improved from 6% in 1990-94 to 43% in 2010-14. All children with NBL were treated at a paediatric oncology centre. Mortality rates from Statistics Netherlands were not specific enough for this tumour type (**chapter 8**).

The prognosis for the five childhood and young adolescent cancers studied in this thesis, indeed improved substantially during 1990-2015. This progress was confirmed by decreasing mortality rates for the leukaemias and lymphomas. The progress against the five childhood and adolescent cancers are the result of improvements effective combinations of treatments, as well as improvements in both supportive care and second line therapies. With the centralisation of childhood and young adolescent cancer care into one national centre, the Princess Máxima Center, it will remain important to measure the expected continuation of progress for the cancers studied, also for other childhood and young adolescent cancer types.

The results of this thesis may be used as starting point for further etiologic research, for evaluation of new treatments, and may be used by paediatric oncologists to inform patients and their parents with up-to-date information about incidence and prognosis.

SAMENVATTING

Met dit epidemiologisch beschrijvend onderzoek wilden we nagaan in welke mate vooruitgang is geboekt bij kinderen en jong adolescenten (0-17 jaar) met kanker sinds 1990. Hierbij hebben we gekeken naar de trends in incidentie (het vóórkomen) van kanker, de overleving (uitgedrukt in het percentage patiënten die 5 jaar na diagnose nog in leven zijn) en de sterfte aan kanker. Vooruitgang kan bestaan uit een dalende sterfte als gevolg van een afname in incidentie en/ of gunstiger overlevingskansen door verbeterde behandeling. Bij een stabiele of toenemende incidentie gecombineerd met beduidend hogere overlevingskansen waardoor de sterfte toch nog afneemt, spreken we ook van vooruitgang.

In Nederland worden sinds 1989 gegevens van alle patiënten met kanker, ongeacht hun leeftijd, geregistreerd vanuit de ziekenhuisdossiers door medewerkers van de Nederlandse Kankerregistratie (NKR). De Stichting Kinderoncologie Nederland (SKION) registreert de gegevens van kinderen met kanker die behandeld zijn in één van de kinderoncologische centra. SKION is het netwerk van kinderoncologen met een referentielaboratorium voor hematologische afwijkingen (sinds 1972) en een trial en datacentrum voor kinderoncologische behandelingen met een eigen registratie van ziektegegevens (sinds 2003). We hebben de gegevens van kinderen met kanker, die behandeld zijn in de periode 2004-13, uit beide registraties gekoppeld (**hoofdstuk 2**). Hieruit bleek dat 82% van de jonge patiënten in beide registraties bekend was en dat 18% niet behandeld werd in één van de kinderoncologische centra. Om uitspraken te kunnen doen over de mate van vooruitgang op populatieniveau hebben we voor alle studies in dit proefschrift gebruik gemaakt van de NKR als basis, omdat hierin alle kinderen en jong adolescenten zijn geregistreerd onafhankelijk van hun behandelingscentrum.

Ons eerste doel was om de trends in incidentie van alle vormen van kinderkanker te beschrijven, en voor 5 tumorsoorten in meer detail. In de afgelopen 28 jaar nam het aantal kinderen en jong adolescenten die de diagnose kanker kregen licht toe. In 1990-99 kregen gemiddeld per jaar 481 kinderen tot en met 17 jaar de diagnose kanker, in 2010-17 waren dit er 542. Het voor leeftijdsopbouw gestandaardiseerde incidentiecijfer steeg van 144 per 1 miljoen kinderen in de jaren '90 naar 162 in 2010-17. Deze lichte stijging van gemiddeld 0.6% per jaar was vergelijkbaar met incidentietrends in andere westerse landen en werd veroorzaakt door toenames in de incidentie van leukemie, hersentumoren, neuroblastomen en Ewing bottumoren (**hoofdstuk 3**). In de daarop volgende hoofdstukken beschrijven we de incidentie van vijf tumorsoorten in detail en vonden we het volgende:

- De incidentie van kinderen en adolescenten met acute lymfatische leukemie (ALL) bleef stabiel. Voor de subtypes B-voorloper ALL in de leeftijdsgroep 10-14 en T-cel ALL bij 15-17 jarigen zagen we een lichte toename in de incidentie (**hoofdstuk 4**).
- Voor kinderen met acute myeloïde leukemie (AML) vonden we een lichte toename in de incidentie van AML in de leeftijdsgroep van 1-4 jaar (**hoofdstuk 5**).
- Het voorkomen van Hodgkin lymfoom (HL) onder kinderen bleef relatief stabiel sinds 1990. Voor deze studie onderzochten we ook jongvolwassenen van 18-24 jaar, ter vergelijking. In die groep vonden we wel een significante stijging in de incidentie over de tijd. Ook nam de incidentie van laag stadium HL af, en nam hoog stadium HL toe (**hoofdstuk 6**).
- De overall incidentie van het non-Hodgkin lymfoom (NHL) bleef stabiel. Onder kinderen in de leeftijd van 5-9 jaar zagen we een significante afname in de incidentie (**hoofdstuk 7**).
- De incidentie van neuroblastoom (NBL) nam toe, met name onder kinderen van 18 maanden en ouder met stadium IV NBL. Bij hen zagen we een toename van gemiddeld 7 naar gemiddeld 12 kinderen per jaar met deze diagnose in respectievelijk 1990-94 en 2010-14 (**hoofdstuk 8**).

Verschillende factoren kunnen de veranderingen in de incidentietrends over de tijd mogelijk verklaren:

1) eerdere diagnose van tumoren (vroeg-detectie),
2) nieuwe of verbeterde diagnostische technieken,
3) een veranderend vóórkomen van risicofactoren in de populatie, maar ook
4) veranderingen in de verwijs patronen en/of registratie.

Vroeg-detectie en verbeterde diagnostische technieken hebben een relatief klein aantal diagnoses verklaard (in geval van zaadbalkanker, melanoom en enkele vormen van hersenkanker). Toch heeft dit niet geleid tot de algehele lichte stijging in incidentie. Over factoren die het risico op het krijgen van kanker bij kinderen vergroten is nog te teveel onbekend, waardoor het niet mogelijk is om een antwoord te geven op de vraag of toename van bepaalde risicofactoren de reden is achter de lichte incidentiestijging. In dit proefschrift hebben we dit niet onderzocht en verder onderzoek naar mogelijke risicofactoren van kinderkanker zou duidelijkheid kunnen bieden. Het Nederlandse verwijssysteem van huisarts naar de tweedelijns zorg is sinds de jaren ‘90 nauwelijks veranderd en heeft daarmee geen invloed gehad op de geobserveerde incidentietrends. Ook hebben we de invloed van veranderingen in de NKR registratie zo minimaal mogelijk gehouden door de vormen van kanker die in het verleden niet volledig werden geregistreerd, buiten de analyses te houden.

Het tweede doel was om de overleving en sterfte van kinderen met kanker in kaart te brengen en te relateren aan onderliggende veranderingen in de kinderoncologische zorg qua behandeling en type behandelcentrum (kinderoncologisch centrum ja/nee). Voor deze studies zijn data van de NKR aangevuld met gegevens uit de SKION registratie . De sterftecijfers komen uit het de doodsoorzakenregister van het Centraal Bureau voor de Statistiek (CBS), die gebaseerd zijn op doodsoorzaakverklaringen die worden ingevuld door de behandelend arts of schouwarts na overlijden.

Een duidelijke toename vond plaats in het percentage adolescenten (15-17 jarigen) dat werd behandeld in een kinderoncologisch centrum (KOC). Dit steeg van 33% in 2004 naar 54% in 2013. Van de totale groep kinderen (0-17 jaar) die niet in een KOC werden behandeld, waren ouder, hadden vormen van kanker die vaker bij jongvolwassenen voorkomen en hadden vaker lagere stadia bij diagnose waarvoor alleen een chirurgische behandeling voldoende was. De belangrijkste bevindingen voor de vijf soorten kinderkanker die we in detail bestudeerden, zijn:

- De overleving van kinderen met ALL verbeterde significant voor alle leeftijden en type B-voorloper ALL. De jong adolescenten werden over de tijd vaker behandeld in een KOC, 87% van de kinderen in 2010-2015 t.o.v. 35% van de kinderen in 1990-1994. De kans op sterfte in een KOC bleek bij 15-17 jarigen 70% lager wanneer behandelding plaats vond in een KOC. De CBS-sterftecijfers over de periode 1980-2016 lieten een significant dalende trend zien voor alle leeftijdsgroepen, dit wijst op een langlopende ontwikkeling van kleine verbeteringen.
- De prognose van kinderen met AML verbeterde vooral sterk in de laatste jaren. Waar in het begin van de jaren ’90 nog 40% in leven was 5 jaar na diagnose, bleek dit nu 74% te zijn. We concludeerden ook dat met het recente AML behandelprotocol een substantiële vermindering ontstond in de kans om te overlijden (-49%). Het percentage kinderen tot en met 17 jaar behandeld in een KOC nam significant toe over de tijd, van 85% in 1990-94 naar 97% in 2010-15. De overleving van kinderen behandeld buiten een KOC bleek lager dan bij behandeling binnen een KOC, maar vergelijkbaar met de overleving van jongvolwassenen met AML in Nederland. De continu dalende sterfte bevestigde de vooruitgang voor AML, bij min of meer gelijkblijvende incidentie.
- De prognose voor kinderen tot en met 14 jaar, gediagnosticeerd met HL, was al goed, in de laatste periode is 98% van deze kinderen 5 jaar na diagnose nog in leven. Dat is op dit moment ook het geval voor 15-17 jarige kinderen, waarbij de 5-jaars overleving 84% was in de begin jaren ’90. Het percentage 15-17 jarige kinderen die behandeld werden in een KOC nam significant toe over de tijd, van 27% in 2004 naar 81% in 2015. Ook vonden we een

verschil in behandelaanpak tussen de kinderoncologie en de volwassen hemato-oncologie; laag stadium HL krijgt vaker alleen chemotherapie bij behandeling op de kinderoncologie, en chemotherapie plus radiotherapie bij behandeling op de volwassenafdeling. De overleving is voor alle patiënten hoog, maar de uitkomsten op lange termijn, zoals mogelijke verschillen in lange termijneffecten van behandeling, moeten gemonitord worden.

- De 5-jaars overlevingskans voor kinderen tot en met 17 jaar met NHL steeg van 71% in 1990-94 naar 87% in 2010-15. Meer dan 95% van de kinderen met NHL werd in een KOC behandeld vanaf 2004. De sterfte aan NHL daalde ook over de gehele periode van gemiddeld 20 kinderen per jaar in 1980-84 naar gemiddeld 6 in 2010-16.
- De prognose voor kinderen met een NBL verbeterde van 44% in 1990-94 naar 61% in 2010-14. De overleving voor kinderen ≥18 maanden bij diagnose was slecht, maar verbeterde sterk. Waar begin jaren '90 nog 6% in leven was 5 jaar na diagnose, is dat nu 43% voor kinderen die gediagnosticeerd waren in 2010-2014. Alle kinderen met een NBL werden en worden in een KOC behandeld. Sterftecijfers van het CBS konden niet bestudeerd worden, deze worden niet specifiek/gedetailleerd genoeg vastgelegd voor dit type kanker.

Al met al kunnen we concluderen dat er vooruitgang geboekt is bij vijf van de meest voorkomende kankersoorten bij kinderen, bij sommige, AML en NBL, zijn zelfs grote stappen gemaakt. De verbeteringen in de overleving gingen ook gepaard met dalende sterftecijfers. Waarschijnlijk komt dit door verbeterd gebruik van cytostatica en combinaties hiervan, verbeterde "supportive" care en verbeterde recidief behandelingen. Nu de behandeling van kinderen met kanker sinds 2018 is gecentraliseerd in één kinderoncologisch centrum, het prinses Maxima Centrum, blijft het belangrijk om de incidentie en overlevingskansen van deze type kinderkankers in de gaten te houden en dit onderzoek uit te breiden naar de meer zeldzamere vormen van kinderkanker.

Deze resultaten van dit proefschrift kunnen gebruikt worden als opstap naar etiologisch onderzoek en evaluatie van nieuwe behandelingen. Omdat het populatiecijfers betreft, zijn ze bij uitstek geschikte om gebruikt worden door artsen om kinderen en hun ouders te informeren over up-to-date incidentie en prognose.

Appendices

List of abbreviations

Curriculum Vitae

PhD portfolio

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LIST OF (FREQUENTLY) USED ABBREVIATIONS

AAPC	average annual percentage change
ACCIS	the Automated Childhood Cancer Information System
ALL	acute lymphoblastic leukemia
alloSCT	allogenic hematopoietic stem cell transplantation
(p)AML	(paediatric) acute myeloid leukemia
ASCT	autologous stem cell transplantation
ASR	age-standardised incidence rates
BFM	Berlin-Frankfurt-Munster study group
CCMO	Central Committee on Research involving Human Subjects
cHL	classical Hodgkin lymphoma
CI 5	cancer incidence in 5 continents
CI	confidence interval
CML	chronic myelogenous leukaemia
CNS	central nervous system tumour
COG	Children's Oncology Group
CT	chemotherapy
CT+RT	chemotherapy plus radiotherapy
DCLSG	Dutch Childhood Leukemia Study Group
DCOG	Dutch Childhood Oncology Group
EBV	Epstein-bar virus
EORTC	European Organisation for Research and Treatment of Cancer
EpSSG	European Paediatric Soft Tissue Sarcoma Study Group
EUROCARE	European cancer registry based study on survival and care of cancer patients
EuroNet-PHL	European network for paediatric Hodgkin lymphoma
GM-CSF	granulocyte-macrophage colony-stimulating factor
GNBL	ganglioneuroblastoma
GPOH	Society for Paediatric Oncology and Haematology
Gy	gray
HL	Hodgkin lymphoma
IACR	International Association of Cancer Registries
ICCC-3	International classification of childhood cancers, third edition
ICD-O	International Classification of Diseases for Oncology
IKNL	Netherlands Comprehensive Cancer Organisation

IL-2	interleukine-2
INSS	International Neuroblastoma Staging System
KiKa	Stichting Kinderen Kankervrij
LMR	national registry of hospital discharge diagnoses
MTC	medullary thyroid carcinomas
MYCN	V-myc avian myelocytomatosis viral related oncogene, neuroblastoma derived) amplification
NBL	neuroblastoma
NCR	Netherlands Cancer Registry
NHL	non-Hodgkin lymphomas
NLPHL	nodular lymphocyte predominant Hodgkin lymphoma
NOS	not otherwise specified
OS	overall survival
OR	odds ratio
PALGA	nationwide network and registry of histopathology and cytopathology
PET-CT	combinatie van Positron Emissie Tomografie (PET) en Computer Tomografie (CT-scan).
RT	radiotherapy
SIOP	International Society of Paediatric Oncology
TNM	classification scheme for malignant tumours based on tumour size, lymph node involvement and metastasis
WHO	World Health Organisation

CURRICULUM VITAE

Ardine Reedijk was born in Maasdam, the Netherlands, on January 10th 1981. In 1999, she competed her secondary education (VWO) at Rijksscholengemeenschap in Oud-Beijerland. She then moved to Nijmegen to study Biomedical Sciences, direction Epidemiology, at the Radboud University. In 2001 she went to Lund for a minor internship at the Hematopoietic Stem Cell Laboratory & Lund Stem Cell Center at the Lund University (mentors: Lars Nilsson and Stein-Erik Jacobsen). Ardine did her major internship on describing trends in incidence, treatment and survival of childhood, adolescent and young adult cancers in the Southern part of the Netherlands at the research department of the Netherlands Comprehensive Cancer Organisation (IKNL), location Eindhoven (mentors: Maryska Janssen-Heijnen and Jan Willem Coebergh). She obtained her Master's degree certificate in 2003.

In 2003, Ardine started working as researcher at the Netherlands Comprehensive Cancer Organisation (IKNL), location Rotterdam where she worked mainly on breast, cervical and prostate cancer related projects together with postoperative complication projects. Childhood cancer research was a topic she had personal interest in and in 2009 she was asked to work for the Dutch Childhood Oncology Group (DCOG) in Den Haag. She worked as data manager and trial manager for acute myeloid leukemia protocols mainly. And together with Henrike Karim-Kos and Jan Willem Coebergh she initiated a research proposal on describing trends in incidence, survival and mortality of childhood and young adolescent cancer in the Netherlands. The proposal was further finalized in collaboration with Rob Pieters and Leontien Kremer. The project entitled "Epidemiological progress against childhood and young adolescent cancer in the Netherlands since 1989" was financially approved by Kika.

End 2015 she started working as junior researcher on this project at the Princess Máxima Center for pediatric oncology. In 2018 it became a PhD trajectory under supervision of prof. dr. Leontien Kremer (Princess Máxima Center for pediatric oncology, Utrecht and Department of Pediatrics, Amsterdam UMC), prof. dr. Rob Pieters (Princess Máxima Center for pediatric oncology), prof. dr. Jan Willem Coebergh (Department of Public Health, Erasmus MC University Medical Center Rotterdam) and dr.ir. Henrike Karim-Kos (Princess Máxima Center for Pediatric Oncology and Department of Research and Development, Netherlands Comprehensive Cancer Organisation (IKNL)). This thesis is the result of this PhD trajectory and the ideal combination of the work in her former jobs. Since 2019 she combines her work with data management tasks for several projects on survivorship research among childhood cancer survivors.

PHD PORTFOLIO

Name PhD student:	Ardine Reedijk
Institute:	Princess Máxima Center for pediatric oncology
PhD period:	December 2015 – May 2020
PhD programme:	Epidemiology
Promotors:	prof. dr. L.C. Kremer, prof. dr. R. Pieters and prof. dr. J.W.W. Coebergh
Copromotor:	dr. H.E. Karim-Kos

PhD training	Year
Courses within the PhD programme	
Clinical Epidemiology, Julius Center, UMCU	2019
Mixed Models, Julius Center, UMCU	2019
Applied economic modelling for the veterinary sciences, Julius Center, UMCU	2019
Prognostic research, Julius Center, UMCU	2020
General courses	
Endnote, Erasmus MC Rotterdam	2016
Statistical methods for population-based cancer survival analysis, in company training at the Netherlands Comprehensive Cancer Organisation (IKNL)	2016
Advanced medical writing, NIHES, Erasmus MC Rotterdam	2018
Presentation course in company training at the Princess Máxima Center for pediatric oncology	2019
Mindfulness and Stress Reduction, Graduate School of Life Sciences, UMCU	2019
Seminars and workshops	
Netherlands cancer registry research meetings & journal clubs	2016-17
Public health seminar Erasmus MC, oral presentation	2017
Kika site visit, oral presentation	2017
LATER research meetings & journal clubs	2016-20
Princess Máxima Research retreat	2017-19
Princess Máxima Research meetings & seminars	2017-20
(Inter)national conferences and meetings	
SKION dagen, Utrecht (oral presentation in 2017)	2016-18
38th Annual scientific meeting of the International Association of Cancer Registries (IACR), Marrakech (oral presentation)	2016
39th Annual scientific meeting of the International Association of Cancer Registries (IACR), Utrecht (poster presentation)	2017
51st International Society of Pediatric Oncology (SIOP), Lyon (poster presentation)	
Symposium of the Netherlands Cancer Registry	2017-18
Other activities	
Supervision of a master student (AMC, Epidemiology)	2018-19

LIST OF PUBLICATIONS

Publications in this thesis

Reedijk AMJ, van der Heiden-van der Loo M, Visser O, Karim-Kos HE, Lieverst JA, de Ridder-Sluiter JG, Coebergh JWW, Kremer LC**, Pieters R**. Site of childhood cancer care in the Netherlands. Eur J Cancer. 2017 Dec;87:38-46.

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Reedijk AMJ, Coebergh JWW, de Groot-Kruseman HA, van der Sluis IM, Kremer LC, Karim-Kos HE* Pieters R*. Progress against childhood and adolescent acute lymphoblastic leukaemia in the Netherlands, 1990-2015.
Leukemia. Accepted for publication

Reedijk AMJ, Beishuizen A, Coebergh JWW, Kremer LC, Pieters R, Karim-Kos HE**, Loeffen JLC**. Stable incidence and improved survival in childhood and young adolescent non-Hodgkin lymphoma; a Dutch study on incidence, survival and mortality. Manuscript in preparation

*Shared first authorship
**Shared last authorship

Other publications

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DANKWOORD

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