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Register-based studies on childhood cancer

Relapsed childhood acute lymphoblastic leukemia and skeletal adverse events in childhood cancer survivors in the Nordic countries

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Stockholm 2022

Published by Karolinska Institutet
Printed by Universitetsservice US-AB
Cover photo: Trausti Óskarsson

ISBN 978-91-8016-492-4

Register-based studies on childhood cancer - relapsed childhood acute lymphoblastic leukemia and skeletal adverse events in childhood cancer survivors in the Nordic countries

THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

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This thesis will be defended in the public at the Torsten N Wiesel lecture hall J3:04, BioClinicum, Karolinska Institutet, on **Friday 18th of February 2022 at 09:00 a.m**.

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To my family and friends

PREFACE

Before moving to Sweden in 2009 for my residency in pediatrics I was determined to become a pediatric oncologist. During my years of medical training, I was always drawn to the field of oncology and hematology and I found that cancer patients that I met at the clinic resonated with me. After my pediatric rotations at the Children´s Hospital (Barnaspítali Hringsins) in Reykjavík, I was convinced that I wanted to pursue a career in pediatric oncology. I soon became interested in studying childhood cancer and with great support from Ásgeir Haraldsson, professor in pediatrics and Ólafur Gísli Jónsson, pediatric oncologist/hematologist, we initiated epidemiological studies on childhood cancer in Iceland. Reading through the patient journals and collecting clinical data was an intensive but highly educative process for me as a junior physician. This work evolved into the Icelandic childhood cancer registry which is now also used as a clinical tool for the outpatient and follow-up care at Barnaspítali Hringsins.

In Sweden I wanted to continue my research on childhood cancer. After meeting with Mats Heyman, at that time, the supervisor of the Childhood Cancer Epidemiology Group at Karolinska Institutet, we decided to start an epidemiological PhD project where he would be my main supervisor. That turned out to be a great decision. We set up a study on relapses of childhood acute lymphoblastic leukemia (ALL) by using data from the NOPHO ALL registry. This I found very interesting both from the clinical and methodological standpoint. Survival analyses and regression analyses were quite new to me then. Since this study did not involve all the aspects necessary to complete a PhD training within childhood cancer epidemiology, we wanted to add other studies to the PhD project. At that time Arja Harila-Saari, a pediatric oncologist from Oulu had started working at our clinic. She had been studying osteonecrosis in childhood acute lymphoblastic leukemia with her PhD student, Riitta Niinimäki. The Adult Life after Childhood Cancer in Scandinavia (ALiCCS) project was at that time recruiting PhD students and with Arja´s help we started a collaboration study on skeletal adverse events. This study used data from various public health and population registries and included a very large number of study participants. For me this was a great opportunity to learn new aspects and methods and a very positive step for me as an evolving PhD student. In addition to Arja, Cecilia Petersen and Scott Montgomery accepted the invitation on co-supervising the project and I got accepted to the

PhD program at Karolinska Institutet in February 2013. Most of the PhD courses I took were a part of a training program initiated by Stockholm community, Research School for Clinician in Epidemiology. This was an excellent research school and I feel very fortunate that I got accepted for participation.

In parallel to the work on my PhD project I finished my residency in pediatrics and my fellowship training in pediatric oncology and hematology. There are many advantages in combining clinical work with epidemiological research. You get a better understanding on how to interpret the data and you see potential clinical applications of your results. Clinical pediatric oncologists with a cancer epidemiology profile are a rare species.

Over the last five years I have been involved in establishing a follow-up clinic for childhood cancer survivors at Karolinska University Hospital. At the follow-up clinic I have had very interesting and meaningful discussions with patients and their families on the cancer treatment and its side effects. This has inspired me to find ways to minimize treatment toxicities and maximize the health of childhood cancer survivors.

This PhD project has been a great experience and has taught me immensely. I feel very thankful for the guidance from my supervisors and collaborators as well as the generous funding from Barncancerfonden. I hope I will have the opportunity to continue my research in the future, to purse the truth and drive improvements for my patients and their families.

Winter 2022, Stockholm,

Trausti Óskarsson

“Declare the past, diagnose the present, foretell the future”
Hippocrates of Kos approximately 460-370 BC.

ABSTRACT

Background: Although cancer is a rare disease in children, it is the leading disease-related cause of death in children and adolescents in developed countries. Currently 80% of patients become long-time survivors but if a relapse occurs the outcome for most patients is still poor. Childhood cancer survivors are also at increased risk of chronic health conditions caused by the cancer treatment. The skeletal system is vulnerable to the toxic effects of cancer treatment during childhood and adolescence. Skeletal adverse events are not life-threatening events but may have a large impact on the quality of life and daily functions of childhood cancer survivors.

Aims: The overall aim of this thesis is to explore the use of the unique Nordic registry data to find ways to improve outcomes in childhood cancer. In *studies I and II* we identified a cohort of patients with relapsed acute lymphoblastic leukemia (ALL) within the NOPHO ALL registry and searched for factors associated with overall survival and treatment-related mortality (TRM). In *studies III and IV*, we used both the Nordic public health data registries and arthroplasty quality registries to explore the life-time pattern of skeletal late adverse events in a large cohort of childhood cancer survivors and to identify vulnerable subgroups.

Results: In *study I*, we observed an improvement in the 5-year overall survival after relapse of ALL between 1992-2001 and 2002-2011. We identified risk factors independently associated with death: short duration in first remission, bone marrow relapse, age ≥10 years at primary diagnosis, unfavorable cytogenetics and Down syndrome. Our findings indicate that the currently used risk stratification underestimates the risk of second relapses in patients with combined B-precursor relapses. In *study II,* we identified 52 patients who met criteria for TRM but we did not observe a reduction of TRM over time. Infections, predominantly bacterial infections, were the most common cause of death. Factors associated with TRM were high-risk stratification at relapse, unfavorable cytogenetics and allogeneic HSCT. In *study III*, we observed a 35% increased hospitalization risk for skeletal adverse events among childhood cancer survivors compared to population comparison subjects. For most of the skeletal adverse events the risk was highest in the years close to the treatment, but an excess risk extended for decades for some of the events. The relative risk was particularly high for osteonecrosis, especially among patients with hematological malignancies and patients diagnosed with cancer between 10-19 years of age. In *study IV*, we observed an increased risk for hip arthroplasties among survivors of leukemia and lymphoma and for knee arthroplasties among survivors of malignant bone tumors. The rate of arthroplasty operations was highest in early adulthood.

Conclusions: Finding ways to balance the treatment intention of inducing and maintaining long-term remission against the potential risk of life-threatening or long-term treatment complications is becoming more difficult. Individualized treatment approaches and novel strategies are therefore needed both to increase survival and improve health in patients with childhood cancer. Despite different study designs and end-points, *studies I-IV* provide evidence that the Nordic registry data can be used as excellent research tools to increase our knowledge on childhood cancer. The Nordic countries are in a unique position to conduct registry studies on childhood cancer by combining data from public health registries and different quality registries. The design of the registries and the regulatory framework should aim to facilitate research using this valuable source of information.

POPULÄRVETENSKAPLIG SAMMANFATTNING

Cancer hos barn är ovanligt, men trots det är barncancer den vanligaste sjukdomsrelaterade dödsorsaken hos barn efter nyföddhetsperioden. Överlevnaden för barn med cancer förbättrades dramatiskt under 60- och 70-talet, men även om överlevnaden sakta blivit bättre sedan 80-talet dör ca 20% fortfarande av sin cancersjukdom. Återfall är den vanligaste orsaken till död. Detta beror på att patienter med återfall generellt har mycket dålig prognos både på grund av sjukdomen i sig, men också att de har stor risk för livshotande behandlingsbiverkningar. För dessa patienter blir balansen mellan hög behandlingsintensitet och risken för behandlingsbiverkningar svår att hålla. För att öka överlevnaden för barn med cancer är det därför av yttersta vikt både att förebygga återfall och hitta förbättrade behandlingsstrategier mot återfall, när de inträffar.

De första generationerna långtids överlevare har nu uppnått hög ålder. Detta har medfört ökad kunskap om det förväntade livsförloppet och har lett till att ökad uppmärksamhet givits åt långvariga biverkningar av cancersjukdom och behandling, så kallade seneffekter. Under barn-och ungdomsåren har skelettet hög aktivitet. Mängden benmassa i skelettet byggs upp under tillväxten och blir maximal i ungdomsåren. Störningar i denna dynamiska process kan bland annat leda till benvävnadsskador, sänkt benmassa och sämre benkvalitet senare i livet. I svåra fall, kan inoperation av ledprotes krävas för att återställa ledfunktion och bli av med långvariga smärtor.

Den största utmaningen med epidemiologiska studier inom barncancerområdet är att få patienter diagnosticeras och den långa uppföljningstiden som krävs för att hitta sena återfall och sena behandlingsbiverkningar. Målet med detta doktorandprojekt var att använda de unika data som finns i nordiska (NOPHO) ALL registret, olika offentliga hälso-och befolkningsregister samt ledprotesregister i de nordiska länderna för att bättre förstå hur registerdata kan användas för att förbättra överlevnad och hälsa hos barn med cancer.

I studie I, identifierade vi en stor kohort av barn med återfall av akut lymfatisk leukemi (ALL) i det nordiska ALL registret och identifierade kliniska och genetiska faktorer som var associerade med sämre överlevnad. Kort tid från första diagnos till återfall, benmärgsengagemang vid återfall, ålder ≥10 vid första diagnos, ogynnsamma genetiska förändringar i ALL-cellerna och Down syndrom var faktorer som var associerade med ökad

risk för död efter återfall. Även om överlevnaden efter återfall av ALL var generellt dålig, blev den bättre med tiden. I studie II, letade vi efter riskfaktorer för behandlingsrelaterad död hos barn med återfall av ALL. Patienter med återfall som uppfyllde hög-risk kriterier, de som hade ogynnsamma genetiska förändringar i leukemicellerna och patienter som behandlades med stamcellstransplantation hade högst risk för behandlingsrelaterad död. Infektioner var den vanligaste dödsorsaken. Studier I och II, visar att även om överlevnaden för barn med återfall av ALL har blivit successivt bättre, är den fortfarande dålig, speciellt för barn med hög-risk återfall. För att förbättra behandlingsresultaten för patienter med återfall av ALL krävs ytterligare utveckling av strategier för bättre individanpassning av cancerbehandlingen.

I studie III och IV, använde vi olika offentliga hälsodata- och populationsregister samt ledproteskvalitetsregister för att beskriva skelettsjuklighet över hela livet hos barncanceröverlevare och för att identifiera speciellt känsliga subgrupper. Barncanceröverlevare hade en ökad risk för sjukhusinläggning för osteonekros, låg bentäthet, frakturer, artros och osteokondropatier. Risken var störst första åren efter cancerdiagnosen men den generellt ökade risken fortsatte fram tills 60 års ålder jämfört med kontrollpersoner som inte haft barncancer. Risken var störst för osteonekros hos barncanceröverlevare, speciellt bland före detta leukemi- och lymfompatienter samt de som var mer än 10 år vid diagnos av barncancer. I studie IV, hittade vi en ökad risk för behov av höftprotesoperation hos barncanceröverlevare som hade haft leukemi och lymfom och ökad risk för operation med knäprotes bland överlevare efter behandling för maligna bentumörer. Riskökningen för behov av ledprotes var högst första åren efter cancerdiagnosen. Skelettsjuklighet kan påverka livskvalitet och begränsa mobilitet. För att minska sjuklighet i skelettet hos barncanceröverlevare krävs anpassad behandling för dem som löper högst risk samt evidensbaserade uppföljningsrekommendationer för tidig diagnos och förbyggande åtgärder för alla barncanceröverlevare.

Sammanfattningsvis, har vi visat att nordiska registerdata är en viktig resurs för epidemiologiska studier av barncancer. Det stora antalet patienter som vi inkluderade samt den långa uppföljningstiden kompenserar till viss del för de svårigheter som är begränsande vid epidemiologiska studier av barncancer. Det är viktigt att det finns ett regelverk och struktur kring registerstudier som både underlättar registerforskning och ökar förtroendet för denna typ av studier i samhället.

LIST OF SCIENTIFIC PAPERS

I. **Oskarsson T**, Söderhäll S, Arvidson J, Forestier E, Montgomery S, Bottai M, Lausen B, Carlsen N, Hellebostad M, Lähteenmäki P, Pihkala U, Jonsson OG, Heyman M. *Relapsed childhood acute lymphoblastic leukemia in the Nordic countries – prognostic factors, treatment and outcome.* Haematologica. 2016; 101: 68-76.

II. **Oskarsson T**, Söderhäll S, Arvidson J, Forestier E, Frandsen TL, Hellebostad M, Lähteenmäki P, Jónsson ÓG, Myrberg IH, Heyman M. *Treatment-related death in relpased childhood acute lymphoblastic leukemia*.
Pediatric Blood and Cancer. 2018; 65(4): e26909.

III. **Oskarsson T**, Duun-Henriksen AK, Bautz A, Boschini C, Montgomery S, Harila-Saari A, Petersen C, Niinimäki R, Madanat-Harjuoja L, Tryggvadóttir L, Holmqvist AS, Hasle H, Heyman M*, Falck Winther J*. *Shared last authorship. *Skeletal adverse events in childhood cancer survivors: An Adult Life after Childhood Cancer in Scandinavia (ALiCCS) cohort study*.
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IV. **Oskarsson T**, Dehlendorff C, Krøyer A, Montgomery S, Harila-Saari A, Petersen C, Niinimäki R, Madanat-Harjuoja L, Wesenberg F, Garellick G, Dale H, Holmqvist AS, Hasle H, Falck Winther J, Heyman M. *Total hip and knee arthroplasties in childhood cancer survivors – a population-based cohort study*. Manuscript.

RELATED PUBLICATIONS

i. Taskinen MH*, **Oskarsson T***, Levinsen M, Bottai M, Hellebostad M, Jonsson OG, Lähteenmäki P, Schmiegelow K, Heyman M. *The effect of central nervous system involvement and irradiation in childhood ALL: Lessons from the NOPHO ALL-92 and ALL-2000 protocols.* Pediatric Blood and Cancer. 2017; 64: 242-249. *shared first authorship.

ii. **Oskarsson T**, Heyman M. *New concepts in acute lymphoblastic leukemia frontline trials.* HemaSphere. 2018; 2:8-10.

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iv. Jensen KS, **Oskarsson T**, Lähteenmäki P, Flaegstad T, Jonsson OG, Svenberg P, Heyman M, Norén-Nyström U, Schrøder H, Schmiegelow K*, Albertsen BK*. *Temporal changes in the incidence of relapse and in outcome after relapse of childhood acute lymphoblastic leukemia over three decades: a Nordic population-based cohort study*. *shared last authorship. Submitted for publication.

v. Lähteenmäki T, **Oskarsson T**, Heyman M, Lund B, Lepik K, Vaitkevisiene G, Jonsson OG, Häbel H, Norén-Nyström U, Lähteenmäki P, Schmiegelow K. *Age but not sex has effect on survival in patients younger than 18 years at diagnosis of acute lymphoblastic leukemia in the NOPHO-ALL2008 trial***.** Manuscript.

CONTENTS

LIST OF ABBREVIATIONS

ALiCCS	Adult Life after Childhood Cancer in Scandinavia
ALL	Acute lymphoblastic leukemia
AML	Acute myeloid leukemia
BCP	B-cell precursor
BCR-ABL1	Fusion gene resulting from translocation t(9;22) fusing the *BCR* (breakpoint cluster region) gene with the *ABL1* gene
BFM	Berlin Frankfurt Münster
BM	Bone marrow
BMD	Bone mineral density
CAR T-cells	Chimeric Antigen Receptor T-cells
CCLG	British Children´s Cancer and Leukemia Group
CCSS	Childhood Cancer Survivor Study
COG	Children´s Oncology Group
CI	Confidence interval
CNS	Central nervous system
CR1	First complete remission
CR2	Second complete remission
DCOG	Dutch Children´s Oncology Group
DS	Down syndrome
DS-ALL	Acute lymphoblastic leukemia in Down syndrome
EFS	Event-free survival
EOI	End of induction
GDPR	General Data Protection Regulation
GVHD	Graft versus host disease
HeH	High hyperdiploidy
HR	Hazard ratio
HR relapse	High-Risk relapse
HSCT	Hematopoietic Stem Cell Transplantation
iBM relapse	Isolated bone marrow relapse
ICCC-3	International Classification of Childhood Cancer, third edition

ID	Induction Death
iEM relapse	Isolated extramedullary relapse
IGHG	International Guideline Harmonization Group
InReALL	International study for treatment of childhood Relapsed ALL
IR relapse	Intermediate-Risk relapse
ITT	Intention to treat
KM	Kaplan Meier
KMT2A	Lysine N-methyltransferase 2A (formerly known as *MLL*)
MDS	Myelodysplastic syndrome/myelodysplasia
MRD	Minimal residual disease
NAR	National arthroplasty registry
NARA	Nordic Arthroplasty Registry Association
NOPHO	Nordic Society of Paediatric Haematology and Oncology
NPR	National patient registry
OS	Overall survival
PanCare	Pan-European Network for Care of Survivors after Childhood and Adolescent Cancer
RALLE pilot	Finnish Relapse in Acute Lymphoblastic Leukemia pilot
RD	Resistant/Refractory Disease
SALUB	Svenska Arbetsgruppen för LångtidsUppföljning efter Barncancer
SIGN	Scottish Intercollegiate Guidelines Network
SMN	Second malignant neoplasm
SR relapse	Standard-Risk relapse
THA	Total Hip Arthroplasty
TKA	Total Knee Arthroplasty
TRM	Treatment-related mortality
WBC	White blood cell count

1 INTRODUCTION

Cancer is a rare disease in children but it is the most common disease-related cause of death in children past infancy in Western countries.[1] In Northern Europe the incidence rate for children <15 years was 131.5 per 1.000.000 person-years between 1991-2010 and for the period 1999-2007 the five-year survival was 78.4 to 81.2%.[2, 3] The most common cancer types are leukemia and central nervous system (CNS) tumors followed by lymphoma and different types of solid tumors (Figure 1). During the 1960s and 1970s the survival of patients with childhood cancer improved dramatically but over the last 30 years, only modest survival improvements have been achieved for most cancer types (Figure 2).[3, 4] Increased remission rates and decreased relapse rates have mainly been driven by the intensification of chemotherapy, more aggressive local treatment, adaptation of multimodal therapy and improvements in diagnostics and risk stratification. If relapse occurs the outcome for most patients continues to be poor.[5-8]

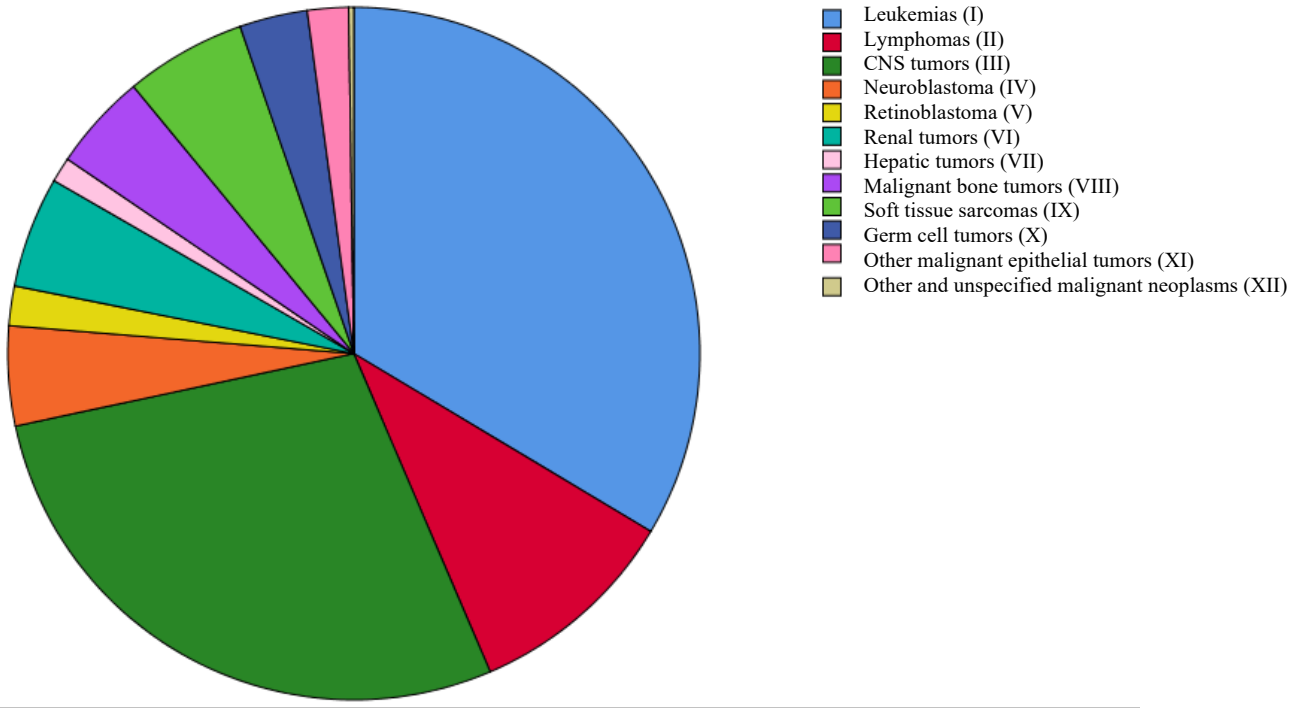

Figure 1. Distribution of childhood cancer types diagnosed in Sweden from 1951-2015, by the ICCC-3 classification system (groups I-XII). *Source*: The Swedish Childhood Cancer Registry; 2019; Oskarsson T, Lähteenmäki P, Heyman M, Gustafsson G.

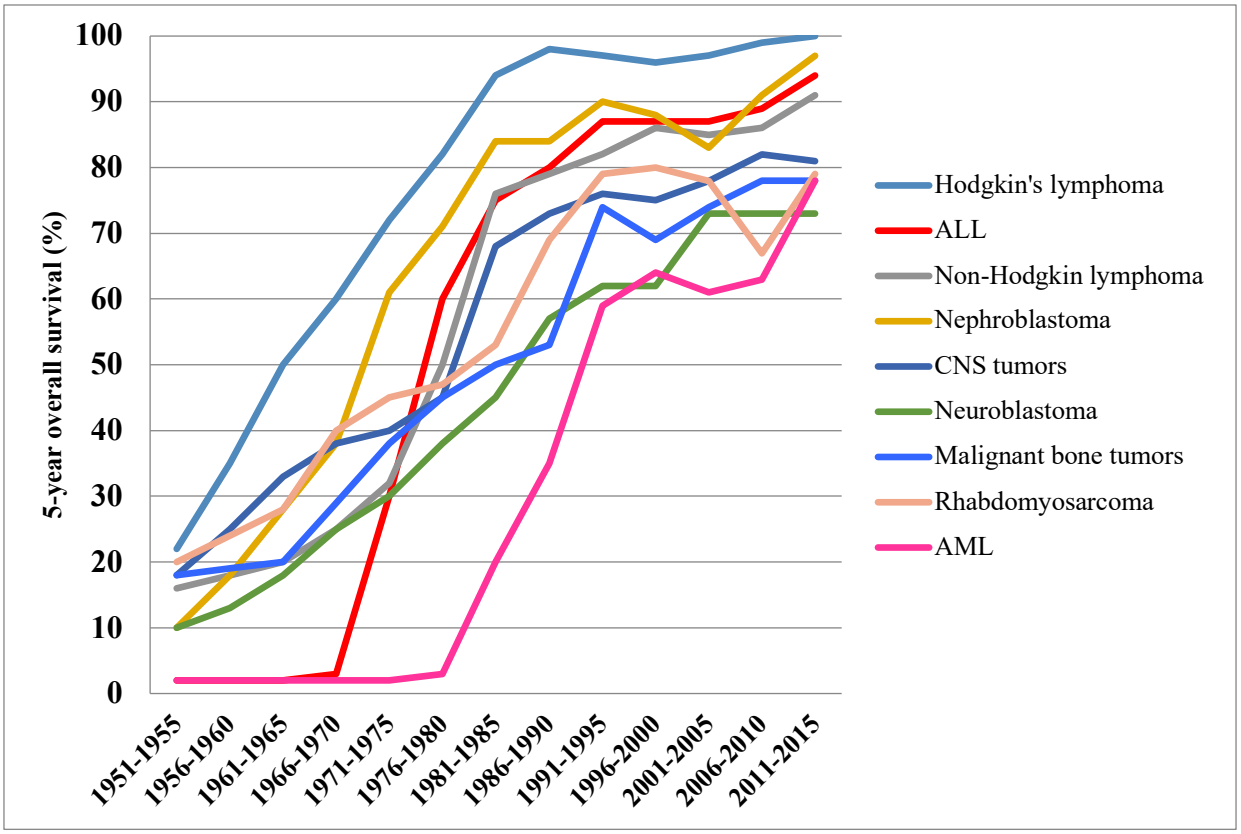

Figure 2. Temporal trends of overall survival of the most common childhood cancer types diagnosed in Sweden 1951-2015. *Source*: The Swedish Childhood Cancer Registry; 2019; Oskarsson T, Lähteenmäki P, Heyman M, Gustafsson G.

Risk-adapted treatment strategies are the cornerstone of modern cancer therapy. Treatment intensity has to be balanced against potential toxicity and the risk of insufficient treatment response and relapse. At relapse, this balance becomes even more difficult to maintain due to the high intensity needed to overcome potential treatment resistance mechanisms and the accumulated organ toxicity from previous treatment.

Unfortunately, despite advances in diagnostics, antimicrobial treatment and supportive care, treatment-related deaths still occur, especially among children with hematological malignancies and following allogeneic hematopoietic stem cell transplantation (HSCT).[9] During the cancer treatment, invasive infections are the most common cause of death but organ toxicities and second malignant neoplasm (SMN) may cause death years or decades after completion of treatment.[10, 11] The life expectancy of adult childhood cancer survivors is therefore shorter.[12]

To decrease the risk of serious treatment toxicity, treatment modifications and de-escalation of treatment have been implemented for subgroups of cancer patients without compromising the survival outcomes.[13, 14] For example, the reduction of anthracycline exposure and more restrictive use of radiotherapy have led to a reduction in cardiotoxicity and the incidence of SMN; nevertheless, cardiovascular and pulmonary diseases and SMN still account for most of the excess late mortality risk.[15-18] For children who need high intensity treatment such as patients with ALL requiring allogeneic HSCT in first remission, patients with high-risk solid tumors, or patients who have experienced a relapse, there has been very limited improvement in health-related late mortality, the rate of chronic health problems or the incidence of SMN. [19-21]

Treatment-related complications may develop into chronic health conditions that either present early or become symptomatic years after completion of cancer treatment.[22, 23] With the growing number of childhood cancer survivors, the awareness of late adverse effects of treatment is increasing. Approximately three-fourths of childhood cancer survivors are expected to suffer at least one health problem that can be directly related to the cancer treatment.[24, 25] This is a growing concern from a public health perspective. The identification of patients, who suffer from long-term adverse health outcomes make it possible to identify factors influencing these complications, such as different modalities of treatment as well as other contributing circumstances. Once the relevant factors have been identified, the various treatment modalities may be re-evaluated, the adverse consequences can be balanced against the beneficial effect on the cancer and the therapy may then hopefully be modified to optimize the treatment. Furthermore, development of screening guidelines for specific risk groups could enable early detection of adverse health outcomes and prevent serious consequences by the implementation of appropriate interventions and life-style recommendations.

During childhood and adolescence, the growing skeleton is particularly vulnerable to factors that interfere with its natural growth and development. The risk of treatment-related adverse effects in the skeletal system is highest during the treatment and the following years but the excess risk may continue for decades.[26-28] Although skeletal toxicity is not fatal it may lead to immobility and chronic pain. In the most severe cases where the cancer treatment directly or indirectly causes joint destruction or serious fractures, joint replacement is the definite treatment. Survivors of hematological malignancies are at particularly high risk for severe skeletal morbidity.[19, 29]

1.1 EPIDEMIOLOGICAL STUDIES ON CHILDHOOD CANCER

For rare and heterogenous diseases such as childhood cancer, the small population size makes it challenging to conduct clinical and epidemiological studies, due to the lack of statistical power to detect differences between groups and to capture rare outcomes. The issue of statistical power can be overcome by including large study populations and in the cases of rare outcomes occurring late, a long follow-up time. This has resulted in multiple national and international collaborations. Treatment standardizations and multicenter/multinational clinical trials and studies are major factors that have driven the progress observed in pediatric oncology.[30] The lessons from these cooperative studies have been applied to improve survival and reduce morbidity in childhood cancer survivors.

1.2 NORDIC COLLABORATION IN PEDIATRIC ONCOLOGY

In the Nordic countries, the Nordic Society of Paediatric Haematology and Oncology (NOPHO) was formally established in 1984. This collaboration has been very fruitful and long-lasting, initially focusing on the harmonization of leukemia treatment. The first unified clinical trial NOPHO started was the NOPHO AML-84 trial. ALL-therapy had been partially harmonized during the 1980s, but it was not until 1992, when the ALL-92 trial was opened that an all-Nordic ALL protocol was created. Since then, the Baltic countries have joined NOPHO as associated members and in the NOPHO ALL-2008 trial adults up to the age of 45 were also included as study participants. The Nordic collaboration has resulted in a broad range of research, including both clinical, basic and translational studies as well as clinical and population epidemiology. The NOPHO registries are very detailed and highly reliable sources of information. These registries have also proved to be very valuable for research purposes.

1.3 NORDIC POPULATION AND HEALTH REGISTRIES

The Nordic central population registries have been operational for over five decades (Table 1). These registries contain basic information on the citizens of each country that can be used for planning of public services, judicial administration and generation of statistics for policy making and research. In the Nordic countries, newborn citizens are automatically assigned a unique personal identification number. Subjects not born in the country may apply for a personal identification number after living in the country for six to twelve months. Before that time people are given a coordination number that is later replaced by

the personal identification number. Information available in the central population registries is for example, resident region, civil status, vital status, sex, immigration/emigration and various family and household variables. In Sweden for example, the central population registry is updated once a month.

Table 1. The start of recruitment in each of the registries used in the thesis, by country

	NOPHO ALL registry	**National Cancer registries**	**National Population registries**	**National Hospital registries**	**National Arthroplasty registries**	
Country					Hip	Knee
Denmark	1981	1943	1968	1977[1]	1995	1997
Finland	1981	1953	1969	1975	1981	1989
Iceland	1981	1955	1952	1999	N/A	N/A
Norway	1981	1953	1960	2008	1987	1994
Sweden	1981	1958	1968	1964[1,2]	1979[3]	1975

[1]Since 1995 in Denmark and 2001 in Sweden, diagnostic codes used in hospital-based outpatient clinics are available in the national hospital registries. [2]Established in 1964, reaching complete nationwide coverage in 1987. [3]The Swedish hip arthroplasty registry was established 1979 but the registrations began on an individual level in 1992 (linked to the social security number). Prior to that time hospitals delivered aggregated numbers on an annual basis.

Access to the Nordic public health care system is universal and independent on income. In the Nordic countries there are numerous nationwide registries, both public mandatory registries managed by regional or national authorities and quality registries managed by the medical profession compiling data on various aspects of health and socio-economic status of patients with a specific condition.[31] Health registries are an important tool to monitor diseases and health related factors in the population. The Nordic health registries are very reliable, extensive, well maintained and accessible. Along with the unique personal identification number, which enables cross-linkage between registries, this makes it possible for researchers to track individuals through different population and quality registries over the lifetime.[32] Cross-linking data from different health registries,

representing various exposures and outcomes is now used extensively by researchers in the Nordic countries.[33-37] This is particularly useful when examining rare diseases and rare outcomes because of the large size and long follow-up time.[38] The population demographics, health care and registry resources and childhood cancer epidemiology are very similar in the Nordic countries which makes it possible to, use data from health registries across the Nordic countries to create and follow extensive study cohorts also across the borders.

1.4 NATIONAL CANCER REGISTRIES

The Nordic cancer registries were established between 1943 and 1958 (Table 1) and since then have provided information on patterns and trends in cancer incidence and survival. In all countries, the registration is mandatory and is collected from public hospitals, private clinicians, pathology laboratories and radiology units. The coverage of the registries is nearly 100%.[39] Common variables are cancer topography and morphology codes, date of diagnosis, date of birth, sex and vital status. Since 2004 information on tumor stage (TNM Classification of Malignant Tumours staging) has been available in the Danish and Swedish cancer registries but for the other Nordic countries this data is still incomplete. Furthermore, no data is available on recurrences in any of the Nordic cancer registries.[40] The Nordic cancer registries have collaborated for decades and through the years have developed ways to ensure comparability between the registries. In 2002, the Association of Nordic Cancer Registries established the first version of the NORDCAN database.[35] NORDCAN is an open-access database, where basic epidemiological data and descriptive analyses are made easily available (www.ancr.nu).

1.5 NATIONAL PATIENT REGISTRIES

All of the Nordic countries also operate national patient registries, established at different time points in the Nordic countries, spanning the period from 1964 to 2008 (Table 1). Registrations are compulsory for all in-hospital stays at public hospitals and the coverage is now excellent. Currently, primary care visits are not registered in the national patient registries and only in Denmark (from 1995) and Sweden (from 2001) data on hospital-based outpatient visit are available. For in-hospital patients, discharge diagnoses by the International Classification of Diseases (ICD) system are made by the physician in-charge of the patient. Different versions of the ICD classification system have been used through

the years to code medical diagnoses and procedures; ICD-7: 1955-1968, ICD-8:1969-1986, ICD-9:1987-1995, ICD-10:1996-2020. Data available in-patient registries may differ between countries but can be divided into four categories: personal data, geographical data, medical data, and administrative data. The medical data normally includes both the main and secondary diagnoses.

1.6 NORDIC ARTHROPLASTY REGISTRIES

Since as early as 1970s data on hip and knee arthroplasties have been collected for quality control and research purposes in all of the Nordic countries except Iceland.[41-44] These registries operate as separate quality registries in each country but provide a population-based coverage of all hip and knee arthroplasties performed both at public hospitals and in the private sector.[44] The coverage is nearly complete for all primary operations but slightly lower for revisions.[45] Although, the registration of different parameters is not harmonized between registries, combining data from different registries has been done successfully within The Nordic Arthroplasty Registry Association (NARA) collaboration.[46] However, due to anonymization of patient data in the NARA database cross-linkage with data from other registries is not possible.

1.7 ADULT LIFE AFTER CHILDHOOD CANCER IN SCANDINAVIA

The Adult Life after Childhood Cancer in Scandinavia (ALiCCS) project was initiated in 2010 by the initiative of the Danish Research Council (www.cancer.dk/aliccs/). The aims of the project are to study adverse health outcomes in a large inter-Nordic cohort of childhood cancer survivors by comparing morbidity-specific incidences and cause-specific mortality with a randomized sample from the general population. The survivor cohort was identified in the national cancer registries and the population cohort in the national civil registration systems. Data on different end-points was collected from national hospital registries, cause of death registries, prescription registries, medical birth registries and psychiatric in-patient registries.[47] The ALiCCS collaboration has now resulted in a number of PhD projects and published manuscripts.[48-58] The large number of childhood cancer survivors included, the nationwide coverage and the long follow-up time in the Nordic health and population registries are the major strengths of the ALiCCS study design. In the original cohort study design, detailed information on the treatment administered was not included. To counter this, case-cohort studies are on-going where treatment data is being collected from medical

records.[47] Several other childhood cancer survivor cohorts exist both in Europe and in North-America. Each of these cohorts have their strengths and limitations but collectively they complement each other well for the purpose of mapping the risks and life patterns of adverse health outcomes in childhood cancer survivors (Table 2).[59-61]

1.8 SURVIVORSHIP CARE AND GUIDELINES

Apart from decreasing treatment exposure that may result in long-term adverse health outcomes, access to survivorship care and implementation of evidence-based survivorship guidelines is highly important to improve health and the quality of life in childhood cancer survivors. Screening programs, early diagnosis and specific interventions may decrease the risk and severity of chronic health conditions. Despite this, there is still a lack of harmonized survivorship care in the European countries.[62] The Pan-European Network for Care of Survivors after Childhood and Adolescent Cancer (PanCare) was founded in 2008 by representatives of 13 European countries (www.pancare.eu). This collaboration is the largest international platform for survivorship research and has resulted in two major EU funded projects, PanCare Life and PanCare SurFup.[63, 64] National survivorship guidelines are for example available in Sweden (SALUB), United Kingdom (CCLG and SIGN), the Netherlands (DCOG) and USA (COG) and by the initiative of PanCare the International Guidelines Harmonization Group (IGHG) was established (www.ighg.org) in 2010. Several risk-based guidelines by IGHG have been published and are now available for health care providers involved in the long-term follow up of childhood cancer survivors.

Table 2. Comparison between seven large childhood cancer cohorts

	Nordic ALiCCS	North-American CCSS	British CCSS	Dutch (DCOG) LATER	St. Jude LIFE	PanCare LIFE	PanCare SurFup
Years of diagnosis	1943-2008	1970-1986 (-1999 in extended cohort	1940-1991 (-2006 in extended cohort)	1963-2002	1962-2012	1940s-2000s	1940s-2000s
Age at diagnosis (years)	<20	<21	<15	<18	<25	<21	<21
Cancer types included	All types	Not all types[1]	All types	All types	All types	All types	All types
Cohort size (extended)	33,160	14,357 (37,593)	17,981 (34,490)	6,165	8,192[4]	~14,000[5]	~100,000
Start of study	2010	1994	1998	2006	2007	2013	2011
Survival (years) at cohort entry	≥1 year	≥5 years	≥5 years	≥5 years	≥10 years but ≥5 year since 2015	≥5 years	≥5 years
Coverage	Population-based 5 countries	Initially 26 institutions within USA and Canada (currently 31)	Population-based 3 countries	Nationwide hospital-based	Single institution	Population-and hospital-based 8 countries	Population-and hospital-based 12 countries
Identification of childhood cancer survivors	National cancer registries	Institutional/hospital registries	National cancer registration	Registry based on nationwide hospital-based cohorts	Hospital registry	Cancer registries and local databases	National cancer and hospital registries
Identification of adverse events	Registry data linkage	Periodic self-reported surveys, medical records	One-time self-reported survey	Periodic surveys, medical evaluations and medical records	Periodic surveys, medical evaluations and medical records	National registries and local databases	National registries and medical records
Adverse events included	Somatic and psychiatric outcomes	Somatic, psychological and social outcomes. Health-related QoL	Somatic, psychological and social outcomes. Health-related QoL	Somatic, psychological and social outcomes. Health-related QoL	Somatic, psychological and social outcomes. Health-related QoL	Female fertility, ototoxicity, health-related QoL	Cardiac disease, SMN[3], late mortality
Loss to follow-up	<1%	~15%	~1.5%	<1% for registry data	<1%	N/A	N/A
Response rate (surveys)	N/A	69%	71%	N/A	69.9%	N/A	N/A
Comparison population	Matched population comparisons	Siblings. General population in some studies	General population[2]	Siblings and matched population controls	Frequency matched community controls	Population comparisons in some of the studies	None for the cohort studies
Biomaterial/ germline DNA	No	Yes (limited number)	Yes (limited number)	Yes	Yes	Yes (limited to sub-studies)	No
Intervention trials	No	Yes	No	No	Yes	Yes	No
Lifestyle variables	No	Yes	Yes	Yes	Yes	Limited	No
Comorbidities	Data linkage	Self-reported	Self-reported	Self-reported, medical examination, medical records	Self-reported, medical examination, medical records	Yes (not in all studies)	Limited
Study design	Retrospective cohort and case-cohort studies	Retrospective cohort studies with prospective follow-up	Retrospective cohort and case-control studies	Retrospective cohort and case-control studies	Retrospective cohort studies with prospective follow-up	Retrospective cohort and nested case-control studies and molecular/genetic studies	Retrospective cohort and nested case-control studies
Treatment data	Only in case-cohort studies	Yes	Yes	Yes	Yes	Limited	Only in case-control studies

Adapted from publications by Winther et.al. 2015 and Norsker et.al. 2020

[1]Only leukemia, CNS tumors (meningioma and craniopharyngioma excluded), Hodgkin disease, non-Hodgkin lymphoma, neuroblastoma, soft tissue sarcoma, malignant kidney tumors and malignant bone tumors. [2]Population-based mortality and cancer incidence rates, Hospital Episode Statistics database. [3]Second sarcomas and second genito-urinary and digestive system carcinomas. [4] 60% of eligible survivors completed at least one visit. [5]The initial goal was 12,000.

2 AIMS OF THE THESIS

Childhood cancer is an uncommon group of diseases where specific outcomes are difficult to evaluate in small study populations. Patients with relapsed childhood cancer generally have a very poor outcome, are at higher risk of treatment toxicities and are hard to identify in public health registries. The Nordic collaboration and the use of inter-registry data-linkage are powerful tools and offer a unique opportunity for studying long-term outcomes in patients with childhood cancer. The general aim of the PhD project was to utilize data from the Nordic quality and public health registries to find ways to improve outcomes for patients with childhood cancer.

Specific aims:

Papers I and II: To improve outcome of future patients with relapsed childhood ALL by validating the current risk stratification, identifying risk factors for overall survival and treatment-related mortality and comparing outcomes between different treatment strategies.

Papers III and IV: To describe the lifetime pattern of skeletal adverse events in childhood cancer survivors and to identify patient groups that may need treatment modifications, early interventions and long-term surveillance.

3 ETHICAL CONSIDERATIONS

In this project we used registry data in all of the studies, both public registries and quality registries. Although the project did not involve direct contact with the study participants, several ethical issued need to be addressed:

3.1 INFORMED CONSENT

Registrations in national health registries such as cancer registries and hospital registries are generally performed without informed consent. Registration of individually identifiable health information is legally mandated to enable compilation of necessary health information for the public health system. Informing all patients regarding every registration would be both costly and time consuming. Furthermore, a mandatory informed consent for this type of registration could introduce a selection bias if people would refuse participation. In general, the benefits for the wider community of collecting such data are considered greater than maintaining the privacy of individual information. Furthermore, when such data are used it is exceedingly rare that individuals can be identified, since most such uses involve statistical analyses on group level. Therefore, omitting informed consent is generally thought to be justifiable. In contrast to public health registries the registered subjects have the right to withdraw personal information from quality registries without any personal cost or consequences. In the ethics application process for the ALiCCS project in Sweden an announcement on the project was published in the Swedish daily newspaper Dagens Nyheter with information on the opt-out possibility from the ALiCCS project.

The NOPHO database consists of a compilation of several treatment-study databases. Informed consent for this registration has been obtained, but the wording and form (oral or written) has varied over time and between the participating countries. Importantly, in contrast to the mandatory registration in the public health registries, the patients and their families have been informed about the purpose of the registration: to improve the basis for adequate treatment of all current and future patients. Even if they realize that the gains derived from the registration will mostly benefit future patients, the future use of this data to improve the management of the patients is what is generally expected. In clinical practice, families often express a wish that their hardship may be used to improve the lot of future patients and there is an expectation that their data is used for this purpose. It may still be seen as an ethical problem not informing the study participants about the study and the use of their personal data. However, apart from the considerations raised above, contacting

patients or their families for the approval of further study participation would not only be time consuming and expensive, but it could also be a unpleasant reminder of memories that these families have left behind, especially for bereaved families. For these reasons, we consider not contacting the study participants for a new informed consent in our project ethically acceptable.

3.2 DATA SAFETY/VIOLATION OF PRIVACY

Protection of the person´s privacy is a central focus when handling registry information. All study participants are assigned a research number (pseudo anonymization) and the data is exported for statistical purposes and analyzed. The registries are hosted at certified sites and have been approved by data safety authorities in each of the participating countries. Results from the project are presented on group level, with special consideration to small subgroups, taking care that tracing results to a specific study participant is impossible. It can additionally be argued that, also regarding the risk of violation of privacy, the benefit of the study outweighs the potential risk for breach of confidentiality.

3.3 BENEFITS/RISKS FOR STUDY PARTICIPANTS

Since we are looking retrospectively at factors related to the treatment of childhood cancer, study participants will in most cases not benefit directly from the results from the study, but the quality-registration in itself and the host of experience harbored in the registry may from time to time actually benefit also single patients in that it helps in treatment-decisions, for which the statistical basis is weak in the published literature. Increased knowledge of relapsed childhood ALL and late skeletal adverse events could lead to improved survival and decreased morbidity for future patients and this knowledge may be seen as a benefit even for the participating patients. A potentially more worrying scenario would be that families or patients themselves in hindsight, when the studies have been published, experience that the received treatments were suboptimal, However, for others new knowledge could have the opposite effect, reassuring patients with optimal therapy.

3.4 THE ROLE OF HEALTH REGISTRIES

To maintain the best available quality of data, regular surveys and analysis of data are important. Trends and patterns, both expected and unexpected may be identified and reported, errors and incomplete registrations can be corrected. One of the main roles of health registries is to provide continuing learning potential and improvements both in the quality of the health services and in the management of specific conditions. Using data

from health registries is therefore an important tool to improve health care and promote equality.

3.5 CONFLICTS OF INTEREST

Trust is one of the most integral factors when conducting research projects. Researchers should be objective and present their data honestly and without being influenced by their personal interest or agenda. Both academic and financial conflicts of interest can lead to a bias of judgment and manipulation of data. Lack of trust can therefore interfere with the interpretation of study results data. We declare no competing interests in this research project and have no relationships to disclose.

3.6 THE GENERAL DATA PROTECTION REGULATION

In May 2018, the General Data Protection Regulation (GDPR) went into effect in the European Union.[65] This regulation was implemented to further increase data safety and secure the autonomy of the subjects. The GDPR has added a new level of complexity to registry and epidemiological research. One of the beneficial effects of the GDPR is increased public trust towards registries, research and cross-border data sharing.[66] How local authorities interpret the GDPR is not homogenous and for many researchers this regulation might be perceived as inhibitive rather than enabling. Since informed consent is not required for registration in the Nordic public health registries, a strict interpretation of the GDPR by local or national authorities could restrict the use of population-based epidemiological studies. This is worrisome considering the fact that studies based on registry data are an important source of new knowledge that drives improvements within the health care system. The structure of the public health systems in the participating countries and the close similarities between the legal and ethical regulatory bodies makes cross-national data sharing possible. However, the administrative burden and bureaucracy is enormous and it may take years to complete the whole process, from application to receiving all data. To enable registry-based studies within the Nordic countries an multinational agreement on data sharing and a harmonized and a simplified application process would be extremely helpful.[67] At the same time registries should work on variable standardization and harmonize variable definitions to facilitate data linkage.

3.7 APPROVALS FROM NATIONAL ETHICS COMMITTEES

Studies I and II: EPN 2012/2179-31/3

Study III: Denmark (2010–41–4334), Finland (THL/1284/5.05.00/2013), Iceland (VSN 10–041-afg, VSN 10-041-V2), Sweden (EPN Ö 10-2010, 2010/66)

Study IV: Denmark (2010–41–4334, 2014-41-3032), Finland (THL/1284/5.05.00/2013, THL/1342/5.05.00/2015), Norway (2011/884/REK nord), Sweden (EPN Ö 10-2010, 2010/66, 2014/699)

4 BACKGROUND

4.1 STUDIES I AND II

Acute lymphoblastic leukemia (ALL) is the most common cancer type in children with an annual incidence of 21.6 (20.3-22.9) per million person-years in Northern Europe[2]. Before the early 1960s the outcome of childhood ALL was nearly universally fatal but with advances in chemotherapy, allogeneic hematopoietic stem cell transplantation (HSCT) and supportive care together with uniform treatment designed by collaborative groups, long-term survival in ALL is now up to 85-90% in children.[68-71]

Since 1992 all patients with childhood ALL in the Nordic countries have been treated according to the three consecutive NOPHO trials: ALL-92, ALL-2000 and ALL-2008. The successor, ALLTogether (EudraCT number 2018-001795-38 and NCT04307576), was launched initially as a pilot in 2018 and 2019 but is now open in all of the Nordic countries with active randomizations at most sites. The 5-year overall survival for patients 1-14.9 years with BCP and T-ALL has successively increased from 89% for NOPHO ALL-92 to 91% for ALL-2000 and 93% for ALL-2008 (Figure 3).

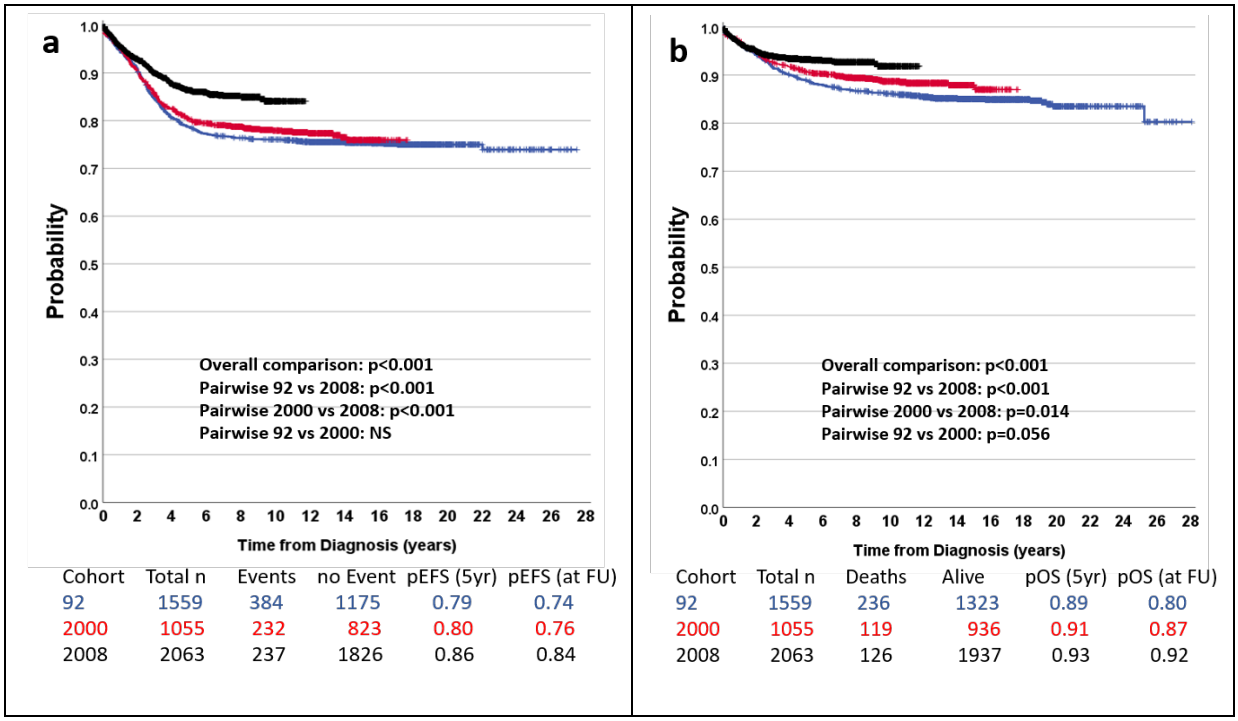

Figure 3. Outcome for children 1-14.9 years in the NOPHO ALL-92, ALL-2000 and ALL-2008 trials. a) Event-free survival b) Overall survival. *Source: Annual report from the ALL registration working group - NOPHO Annual Report 2019. Heyman M, Oskarsson T.*

Despite most patients now achieving prolonged complete remission, a significant fraction of patients still relapses. In the Nordic countries the relapse rate was close to 40% between 1981 and 1993 and out of the relapsed patients only 30% remained in long-term second remission.[72] Over the last three decades the reported relapse rates have been 8-20% in high-income countries and the overall survival rate after relapse is approximately 40-70%.[68, 73-79]

The varying treatment strategies for relapsed childhood ALL across different cooperative groups, different types of study designs and small cohorts, make comparisons between different studies and trials very difficult. Furthermore, patients with relapsed ALL are a more heterogenous group than at primary diagnosis, both clinically and biologically. In contrast to the primary treatment, relapse treatment has not been standardized across the Nordic countries. Nevertheless, most countries have used similar strategies with intensive chemotherapy and allogeneic HSCT in high-risk situations. Historically, the most common treatment protocols used during the last three decades have been the German Berlin-Frankfurt-Münster (BFM) ALL-REZ protocols, NOPHO ALL high-risk arms, the Finnish RALLE pilot and the British Children's Cancer and Leukemia Group (CCLG) ALL R3 protocol. In recent years, an attempt to implement a more uniform approach was made by the IntReALL collaboration (IntReALL 2010, SR trial: EudraCT 2012-000793-30 and NCT01802814 and HR trial: EudraCT 2012-000810-12 and NCT03590171) which most centers in the Nordic countries participated in either formally or by using it as best available treatment.

4.1.1 Primary and secondary events in childhood ALL: Balancing the treatment intensity

Even though most children with ALL reach and remain in first complete remission (CR1), there are still patients who fail to reach CR1 due to refractory disease or treatment-related death during induction (induction death) and patients who die in CR1 (Figure 4).[80, 81] Invasive infections during periods of prolonged neutropenia, most of them treatment-related, account for most of these treatment failures.[82, 83] Another type of adverse events related to treatment toxicities, are SMNs. These occur at higher frequencies in childhood cancer survivors exposed to craniospinal and/or total body irradiation but SMNs have also been associated with exposures to cyclophosphamide, type II topoisomerase inhibitors and the duration and intensity of oral maintenance treatment for ALL.[84-86]

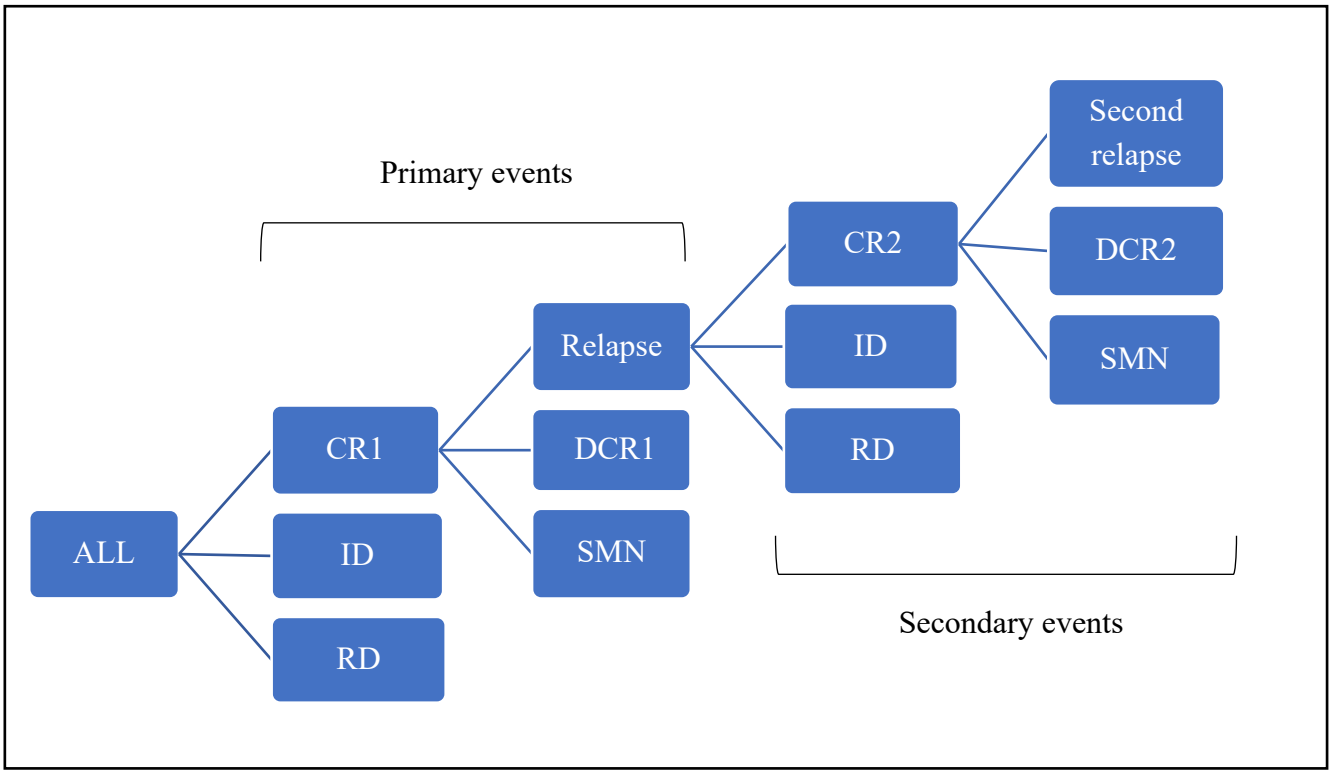

Figure 4. Primary and secondary events in ALL

First complete remission (CR1), induction death (ID), refractory/resistant disease (RD), death in first complete remission (DCR1), second complete remission (CR2), death in second complete remission (DCR2), second malignant neoplasm (SMN)

Of all primary events, relapse is the most common cause of treatment failure in childhood ALL. Patients who relapse may have received inadequate treatment due to toxicity and/or treatment delays but in most cases, relapses occurs when drug-resistant leukemic clones emerge.[87] Relapses may occur during treatment or years after completion of leukemia treatment. This highlights the core problem when choosing the most appropriate treatment intensity for each patient. With high treatment intensity, the risk of treatment-related mortality and SMN increases but with low treatment intensity, the risk of refractory disease and relapse increases. This delicate balance becomes even more difficult to maintain treating relapsed ALL, when previous treatment renders patients more susceptible to treatment toxicities and a high treatment intensity is needed to induce long lasting second remission.

4.1.2 The idea of risk stratification: Lessons from the past, predictors of the future

Modern risk-adapted treatment of childhood ALL is the result of continuous efforts to refine risk assessments and adjustments to multiagent chemotherapy. Initially, clinical characteristics such as sex, age, immunophenotype, white blood cell count and extramedullary involvement were the only factors used to assign patients to risk groups.[88] In recent decades treatment response assessed by measurable residual disease (MRD) monitoring has gained a leading role in determining the treatment intensity and with advances in genetic research a number of ALL subtypes with distinct biological characteristics have emerged.[89, 90] Most current ALL trials use risk stratifications based on baseline characteristics (age, immunophenotype, white blood cell count), genetic aberrations in the leukemic cells and MRD assessments at the end of induction and early in the consolidation phase.[90] Based on these factors, patients are allocated to separate treatment arms designed to allocate the patient to the most appropriate treatment intensity according to the risk of relapse.

Patients with relapsed ALL need higher treatment intensity to overcome potential acquired drug resistance. As previously mentioned, this may be problematic since patients who relapse have accumulated organ toxicities from the previous treatment and the high intensity of the relapse treatment makes them particularly vulnerable to serious treatment complications. The backbone of the chemotherapy offered to patients with relapsed ALL is similar to the high-risk arms of primary ALL treatment.[76, 91] During the induction period patients are very vulnerable to invasive infections due to the prolonged neutropenia. After the induction phase, second remission is consolidated either with continuing chemotherapy or with allogeneic HSCT. Only a very selected group of poor responders undergo allogeneic HSCT during the primary treatment, whereas a high fraction of relapse patients, are allocated to remission consolidation with allogeneic HSCT. Since allogeneic HSCT is associated with a variety of serious toxicities such as invasive infections and graft-versus-host disease (GVHD) it is important to select these patients well to avoid over-treatment.

Table 3. Risk stratification of relapsed childhood acute lymphoblastic leukemia by ALL-REZ BFM, CCLG ALL R3 and IntReALL

ALL-REZ BFM

	BCP			T-cell		
	iEm	**Combined**	**iBm**	**iEm**	**Combined**	**iBm**
Very early	S2	S4	S4	S2	S4	S4
Early	S2	S2	S3	S2	S4	S4
Late	S1	S2	S2	S1	S4	S4

CCLG ALL R3

	BCP			T-cell		
	iEm	**Combined**	**iBm**	**iEm**	**Combined**	**iBm**
Very early	HR	HR	HR	HR	HR	HR
Early	IR	IR	HR	IR	HR	HR
Late	SR	IR	IR	SR	HR	HR

IntReALL

	BCP			T-cell		
	iEm	**Combined**	**iBm**	**iEm**	**Combined**	**iBm**
Very early	HR	HR	HR	HR	HR	HR
Early	SR	SR	HR	SR	HR	HR
Late	SR	SR	SR	SR	HR	HR

Standard-risk (SR) group (white boxes), Intermediate-risk (IR) group (light grey boxes) and high-risk (HR) group (dark grey boxes) according to the IntReALL risk classification. *Isolated extramedullary relapses (iEM)*: relapses not involving the bone marrow, such as the CNS, testis, lymph nodes, mediastinum and skin. *Combined relapses*: coexistent bone marrow and extramedullary involvement. *Isolated bone marrow relapses (iBM)*: bone marrow relapses without detectable extramedullary involvement. *Very early relapses*: occurring <18 months from primary diagnosis. *Early relapses*: occurring ≥18 months from diagnosis and <6 months after completion of primary therapy. *Late relapses*: occurring ≥6 months after completion of primary therapy.

The risk stratification strategies commonly used in ALL relapse differs significantly from the ones used during the primary diagnosis. It includes fewer variables and unlike the primary treatment, age, white blood cell count and cytogenetics are currently not used to stratify patients between different risk groups. The risk stratification used by BFM, CCLG and InReALL is based on three baseline factors, immunophenotype, the time from diagnosis to relapse and the site of relapse (Table 3). This strategy is based on clinical experiences showing that short time in first remission, bone marrow involvement and T-cell immunophenotype is associated with worse chance of salvage. The IntReALL protocol stratifies patients into Standard-Risk (SR) and High-Risk (HR) relapses. This risk stratification is very similar to the one developed by BFM where patients were assigned to 4 strategic groups S1-S4 and CCLG which included three groups, SR, Intermediate-Risk (IR) and HR in the ALL R3 trial (Table 3).[76, 92] The North American Children´s Oncology Group (COG) classifies all T-ALL relapses and all relapses occurring <18 months from diagnosis as HR but uses MRD response to stratify patients with BCP relapses occurring ≥18 months from diagnosis to either SR or IR groups.[93]

Historically allogeneic HSCT has been recommended for S3/S4/HR relapses if second morphological remission is achieved but the use of allogeneic HSCT for patients with S1/S2/SR relapse has been more controversial and has generally not been recommended. However, in recent years poor post-induction MRD response has been used more commonly to select patients initially stratified as SR/IR for allogeneic HSCT. This strategy was used in the ALL R3 trial for IR relapses and by IntReALL for SR relapses.

4.1.3 Factors predicting outcome in relapsed ALL

4.1.3.1 Duration of first remission

The strongest risk factor for poor overall survival after ALL relapse is a short duration of first complete remission.[68, 75, 94, 95] Traditionally relapses occurring <18 months from primary diagnosis are classified as “very early”, relapses occurring ≥18 months from diagnosis and <6 months from the end of treatment as “early” and relapses occurring ≥6 months from the end of treatment are classified as “late”. All very early relapses occur on-treatment but all late relapses occur after cessation of treatment. During the primary leukemia treatment drug resistant subclones might emerge in the bone marrow and/or in the extramedullary compartments which respond poorly to further chemotherapy. Second relapses are common in patients with very early relapses if only chemotherapy is used,

therefore allogeneic HSCT has been the recommended choice of treatment to achieve long lasting second remission in such patients. Late occurring relapses generally respond better to salvage treatments and may have different biological features than on-therapy relapses.[96] In some cases, late relapses could represent new leukemia masquerading as relapse.[97, 98]

4.1.3.2 Site of relapse

Bone marrow involvement at relapse is associated with poor overall survival, especially in T-ALL. Patients with early iBM BCP relapses are stratified as HR but all other BCP relapses as SR if they occur early or late. All early and late iEM T-ALL relapses are classified as non-HR. Extramedullary involvement, particularly in the CNS, is more common at relapse than at primary diagnosis. Although testicular involvement is rare among males with childhood ALL it is more common at relapse than at primary diagnosis.[99] There is a debate whether bone marrow and CNS disease are in fact two separate entities and whether the ability to infiltrate the CNS is based on distinct molecular features of the leukemia clone.[100] One hypothesis is that in cases of extramedullary involvement the primary treatment may not have been sufficient in reaching all sanctuary sites with limited penetration of some chemotherapeutic drugs, such as CNS and testicles. Therefore, instead of the relapse emerging from drug resistant leukemic clones in the bone marrow, the untreated and/or quiescent leukemic cells at sanctuary sites expand and successively seed to the bone marrow. This could be both because of the above-mentioned hypothesis and the development of leukemic clones with more invasive abilities. Generally, iEM relapses have better outcome than combined and iBM relapses. However, very early iEM have poor prognosis.[101, 102]

4.1.3.3 Immunophenotype

Historically, the outcome at primary diagnosis of T-cell ALL has been worse than for BCP ALL but with risk adjustments in contemporary primary ALL treatment the outcome is now similar.[103] However, the outcome for relapsed T-cell ALL is still very poor.[7, 104] A subgroup of T-ALL, early T-cell precursor ALL, has been associated with inferior outcomes, but although the early MRD response is worse it is still debatable whether the overall survival is worse than for other subgroups of T-ALL.[105, 106] Thus, relapse of T-ALL is generally associated with a dismal outcome with the possible exception of early/late iEM relapses.[7]

4.1.3.4 Cytogenetics

In the NOPHO ALL-92 trial two chromosomal aberrations (t(9;22)(q34;q11) and t(4;11)(q21;q23) rearrangements) were implemented as high risk features in the risk assignment. In the NOPHO ALL-2000 trial, t(1;19)(q23;p13)/*TCF3-PBX1*, hypodiploidy (<45 chromosomes) and KMT2A-rearrangements (formerly *MLL*-rearrangements) were included as additional high risk cytogenetic features.[68] In the successor NOPHO ALL-2008 trial, dic(9;20)(p13;q11) and iAMP21 were added to the baseline risk group stratification, both stratifying to at least IR therapy.[107] Patients with *BCR-ABL1*-positive BCP ALL have been treated according separate primary protocols, including tyrosine-kinase inhibitors, since the early 2000´s, mostly the EsPhALL protocol. In the current ALLTogether trial, t(17;19)(q22;p13)/*TCF3-HLF* fusion, ABL-class fusions (other than *BCR-ABL1*) and poor risk copy number alteration in BCP ALL have been added as high-risk features. On the contrary, cytogenetic aberrations in T-ALL have generally not been used to identify patients at higher risk for treatment failure, despite that some genetic alterations have been associated with inferior outcome, such as PIK3 pathway mutation status.[106]

Since cytogenetics has been an integral factor in the primary risk stratification for a long time, it is surprising that cytogenetic findings have not been used to guide the treatment of relapsed ALL. Normally, key genetic abnormalities present at primary diagnosis are maintained at relapse. However, leukemia subclones that emerge during or after the primary treatment may accumulate additional mutations that drive chemoresistance, some of which are chemotherapy-induced.[108] In a study by Irving J. et.al, data from the ALLR3 trial on relapsed ALL in children, suggest that integration of clinical risk factors and cytogenetic risk groups could improve the risk stratification for BCP ALL relapses.[109] Patients stratified as SR but with a high-risk genetic profile had worse outcome than SR patients with good risk genetic profile. Interestingly, the outcome for patients stratified as HR relapse was very similar between the genetic risk groups. In the ALLR3 study, patients with t(1;19) and iAMP21 had a very poor outcome after relapse. In a recent study where combined data from the ALLR3 and the ALL-REZ BFM 2002 trials was analyzed, high-risk genetics were associated with poor overall survival in patients with HR relapse.[110]

4.1.3.5 Down syndrome

Constitutional trisomy 21 (Down syndrome) is defined as a cancer predisposition syndrome due to the elevated risk of childhood leukemias.[111] Historically, survival outcomes for children with Down syndrome and ALL (DS-ALL) has been inferior to non-DS-ALL, both due to increased treatment-related mortality and higher relapse risk.[11, 83, 112] The risk stratification strategies used for patients with DS-ALL are normally the same as for non-DS-AL but patients with DS-ALL now receive modified ALL treatment where the exposure to anthracyclines and high-dose methotrexate has been decreased.[113] This strategy has resulted in survival outcomes similar to non-DS-ALL in some protocols.[114, 115]

4.1.3.6 Age

Patients ≥10 years of age with ALL generally have worse outcome than patients 1-9 years of age.[79-81, 116] Although older patients more often have disease characteristics associated with worse overall outcome such as T-cell ALL and BCP ALL with poor risk cytogenetics, most studies have shown that age is an independent risk factor for survival.[80, 116, 117] In the NOPHO ALL-92 and ALL-2000 trials age was used in the primary risk stratification, but in the NOPHO ALL-2008 trial, where patients up to 45 years old were included, age was not in itself stratifying. In the NOPHO ALL-92 and ALL-2000 trials, patients ≥10 years had worse EFS and OS compared to patients 1-9 years but age was not an independent risk factor for TRM.[68, 83] In the NOPHO ALL-2008 trial the risk for both DCR1 and relapse was higher among patients 10-17 years compared to 1-9 years.[79] The reason behind this age effect is unknown but most likely reflects both pharmacokinetic and immunological differences between different age groups. External factors such as treatment compliance and life style factors could contribute as well. Age is not used as a stratifying factor at relapse in childhood ALL, but the prognosis for adults with ALL relapse is very poor.[118]

4.1.3.7 White blood cell count

High white blood cell count (WBC) at diagnosis is generally regarded as a high-risk feature since it is associated with inferior remission rates, worse MRD response and a higher relapse risk.[119] White blood cell counts ≥100 x10^9/l (also called hyperleukocytosis) at initial diagnosis have been associated with worse outcome in patients with ALL relapse.[7]

4.1.3.8 Treatment response and Minimal Residual Disease

Before the implementation of MRD twenty years ago, morphologic response was the only tool available for treatment response assessment. Patients with ≥25% lymphoblasts in the

bone marrow at the end of induction (EOI) have a very poor outcome and patients with ≥5% at EOI are generally recommended to undergo allogeneic HSCT.[107, 120] Treatment response monitoring with MRD is now a central tool in the modern risk-adapted primary ALL treatment and is a very reliable predictor of outcome.[121] Although MRD is not a part of the risk group allocation at relapse, it is as strong predictor of outcome at relapse as well. Poor EOI MRD response is very predictive for poor outcome after relapse.[77, 101, 110, 122, 123] Furthermore, it has been shown that outcome after allogeneic HSCT in CR2 is better if MRD levels are low prior to the start of HSCT conditioning therapy.[110, 124]

4.1.4 Treatment related mortality

Infants, patients with hematological malignancies, advanced disease, relapse and patients undergoing allogeneic HSCT experience profound and often prolonged immunosuppression and consequently experience an excess risk of TRM.[125] Treatment-related mortality occurs in 3-5% of patients with primary childhood ALL and is most commonly caused by infectious complications.[76, 81-83] Factors reported to be associated with TRM during the primary treatment of childhood ALL are age < 1 year and age ≥10 years, female gender, Down syndrome, WBC ≥200 x 10^9/l at diagnosis, T-cell immunophenotype and allogeneic HSCT.[11, 80-83] Patients with relapsed childhood acute lymphoblastic leukemia are more susceptible to the adverse effects of chemotherapy because of the cumulative effect of organ toxicities and the high intensity of the relapse treatment. Furthermore a higher proportion of patients undergo allogeneic HSCT in second complete remission, where prolonged severe immunosuppression and graft versus host disease (GVHD) are additional risk factors for life threatening events.[126] Careful selection of patients for the most appropriate treatment intensity is highly important since “over-treatment” increases the risk of TRM and SMN but “under-treatment” increases the risk of poor treatment response and subsequent relapse.

To decrease the risk of invasive infections, antimicrobial prophylaxis is commonly prescribed in childhood cancer patients at highest risk for invasive infections. The etiological spectrum of infectious agents is different between treatment phases and treatment modalities.[11] Antifungal prophylaxis is standard of care for children undergoing allogeneic HSCT and is often prescribed for patients with relapsed ALL undergoing intensive chemotherapy phases, even though the evidence for its benefit is not strong.[127] Prophylaxis with antiviral drugs is also a routine procedure in children undergoing allogeneic HSCT but is not recommended in patients undergoing chemotherapy alone.[128]

There are no universal definitions of TRM or disease progression available.[129] This is a very important issue, since without standardized definitions study comparisons are biased and inaccurate. The International Pediatric Oncology Mortality Classification Group defines TRM as any death occurring as the first event if there was an ongoing treatment with a curative intent irrespective of remission status and all deaths occurring as a first event in second complete remission (CR2).[130]

4.2 STUDIES III AND IV

With the growing number of long-time survivors of childhood cancer, increasing focus is now placed on the health and wellbeing of this vulnerable population.[3, 25, 131] Evidence is accumulating on treatment-related chronic health conditions, late occurring treatment-related adverse events and the burden of common health problems among survivors compared to the general population.[10, 24, 132, 133] The main focus of research has been on endocrine disorders and fertility[48, 53, 134-136], cardiovascular diseases[49, 137, 138] and second malignant neoplasm[85, 139, 140] but data on other health-related outcomes is growing. Most adverse events are highly dependent on the therapeutic regimen that patients receive but the individual variability is large, which makes the prediction of the exposure effect more complicated.[23, 141, 142]

Treatment-related adverse events in the skeletal system, such as osteonecrosis, low bone mineral density (BMD) and fractures have been described both at diagnosis, during treatment and after cessation of treatment for childhood cancer.[28, 143, 144] Skeletal morbidity may cause chronic pain, impaired mobility and poor quality of life and in severe cases may require major surgical interventions to alleviate symptoms and restore joint function.[29, 145, 146] Reduced mobility may potentiate other late adverse events and increase the mortality risk.[147-149] Bone development is a highly dynamic process during childhood and adolescence. Interruptions in the normal bone development and injuries to the bone tissues may have long-term effects on the skeletal system (Figure 5).[150, 151]

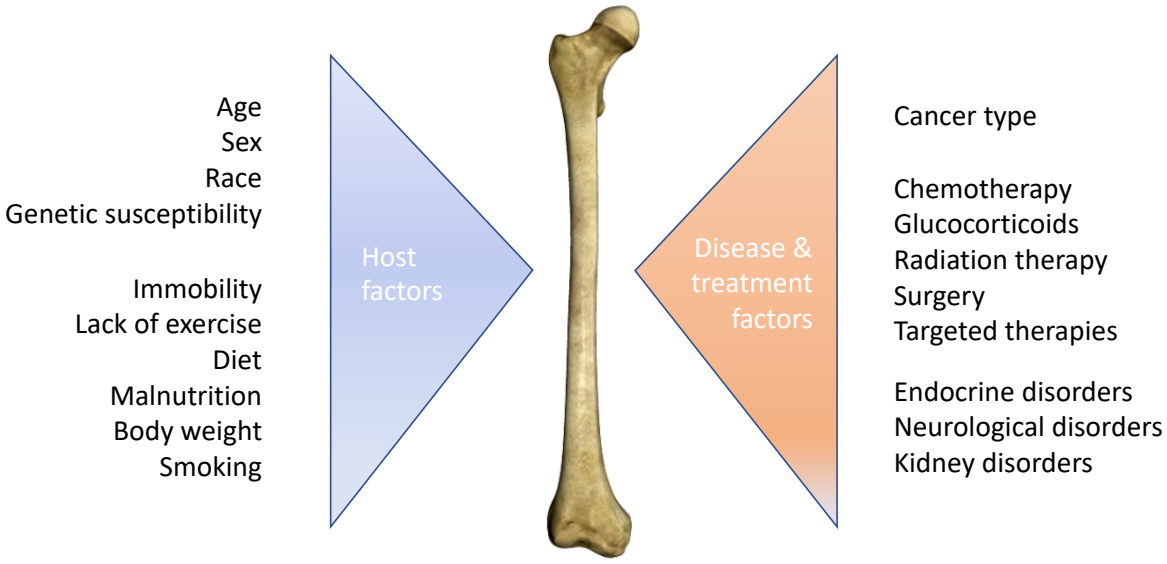

Figure 5. Risk factors for skeletal morbidity in childhood cancer survivors

4.2.1 Osteonecrosis

Osteonecrosis or avascular necrosis is a well-known complication of childhood cancer, especially in adolescents with hematological malignancies.[26, 144, 152-155] Patients may have mild or negligible symptoms but some experience severe symptoms that may have a large impact on their daily life and function.[146, 156, 157] Most commonly, osteonecrosis presents during cancer treatment but less is known about late-occurring presentations and the long-term effects of osteonecrosis.

The pathogenesis of osteonecrosis in childhood cancer is multifactorial but it is hypothesized that reduced blood flow to bone tissues is mainly caused by treatment-induced vasculopathy and increased intraosseous pressure.[158, 159] The most common sites of osteonecrosis are long and weight bearing bones, but frequently osteonecrosis involves multiple sites simultaneously.[160] The anatomical structure of the femoral head renders it especially vulnerable to comprised blood flow and osteonecrosis in this part of the bone may ultimately lead to weakened bone structures and joint collapse.[161]

In the North American Childhood Cancer Survivor Study, the 20-year cumulative incidence of osteonecrosis was 0.4% among the 9,261 5-year survivors diagnosed with cancer from

1970 to 1986, generating a RR of 6.2 (95% CI 2.3-17.2) compared to their siblings.[26] The highest risk of osteonecrosis was among survivors of hematological malignancies and survivors ≥10 years at diagnosis.

Most published studies on osteonecrosis have focused on patients with ALL, lymphoma and patients undergoing allogeneic HSCT.[159] The frequency of osteonecrosis among patients with ALL and lymphoma varies greatly, depending on the detection methods, definitions/grading, timing, type of treatment and the subgroup of patients the estimates apply to. The reported cumulative incidence of symptomatic osteonecrosis in patients with childhood ALL varies between 1.0% and 28% but in prospective studies using magnetic resonance imaging (MRI), even higher frequencies (15-38%) of ON have been found.[26, 157, 160, 162-166] Treatment-related factors associated with osteonecrosis include high cumulative doses glucocorticoids, irradiation and allogeneic HSCT.[26, 167-171] In recent years, treatment de-escalations among patients with low-risk childhood ALL have been successful with regard to event-free survival but osteonecrosis remains as one of the most serious treatment-related toxicities.[172] The high exposure to glucocorticoids is most likely the main culprit.[165, 173] Although osteonecrosis has a strong association with glucocorticoids the median time from ALL diagnosis to symptomatic osteonecrosis is approximately one year, when the patient has entered the maintenance phase of the ALL treatment and the glucocorticoid exposure is limited or has ceased.[160, 174, 175] The risk of osteonecrosis in patients with ALL is however not associated with the metabolite levels of 6-mercaptopurine or methotrexate.[176] Previous studies have shown that patients undergoing allogeneic HSCT have an increased risk of osteonecrosis.[177-179] This could be caused by multiple factor such as high cumulative doses of chemotherapies and glucocorticoids, TBI, GVHD and the immunosuppressive therapy.[180, 181] A common finding in studies on osteonecrosis in patients with childhood ALL is the excess risk among patients ≥10 years compared to patients <10 years but there is a controversy regarding whether females are at higher risk than males.[144, 153, 160, 175, 182] Rapid growth of the skeletal system, hormonal effects and pharmacodynamic factors likely explain why osteonecrosis is more common among older children and adolescents.[159] Genome-wide association studies have identified inherited gene variants associated with an increased risk of osteonecrosis in patients with ALL but implementations of specific treatment modifications have not been attempted to this point.[183]

Whether osteonecrosis presents with symptoms or is detected with radiological imaging in asymptomatic patients, there are no treatment alternatives available that can reverse the bone damage or prevent further progression. If osteonecrosis is detected during treatment, treatment modifications are often chosen but no prospective studies have evaluated the effect of these measures.[184] Bisphosphonates have been used to alleviate symptoms in patients with osteonecrosis but whether it prevents the progression of joint destruction has yet to been proven.[167, 185, 186] Surgical interventions have been used but the effectiveness is unclear at this point.[182, 186] Follow-up recommendations for patients with MRI confirmed osteonecrosis are based on symptoms and the severity grade.[187]

4.2.2 Osteoporosis and fractures

The peak bone mass is normally attained during the childhood and adolescence years.[188, 189] Compromised bone growth and accrual of bone mass during this period may have long-term effects on the BMD and the quality of the bone. Low BMD is relatively common in the general population.[190, 191] The frequency of low BMD increases with age, especially in post-menopausal women and the compromised bone strength increases the risk of fractures.[192, 193] Bone mass is usually measured with dual-energy X-ray absorptiometry (DXA scan) which reports values with standard deviations from the expected mean, so called Z-scores (t-scores are preferred in postmenopausal women). Z-scores lower than -1 are defined as low BMD and Z-scores lower than -2 as very low BMD, indicating a presence of osteoporosis.[194]

Low BMD and osteoporosis have been described in children with cancer and adult survivors of childhood cancer, most commonly in patients and survivors of ALL and after allogeneic HSCT.[28, 150, 177, 195-200] Low BMD has been observed at diagnosis, during cancer treatment and in the period close to the completion of treatment but less is known on how bone mineral deficits evolve over time.[143, 174, 201-203] The prevalence of low BMD varies greatly between studies, depending cancer diagnosis, treatment exposure, age and the outcome definition.[204]

The underlying factors that cause low BMD and osteoporosis in childhood cancer survivors are multifactorial. Apart from underlying genetic susceptibility, drugs such as glucocorticoids and methotrexate, irradiation, GVHD, gonadal insufficiency, smoking, immobilization, calcium and vitamin D deficiencies and malnutrition are all factors associated with the development of osteoporosis.[180, 203, 205-210]

Pathologic fractures are more common among patients with malignant bone tumors and an increased fracture risk have been reported at diagnosis and during treatment of ALL.[207, 211, 212] Less is known about the long-time risk of fractures among childhood cancer survivors. In the North American CCSS a generally increased risk of fracture was not observed, except among female survivor ≥50 years.[213] In a prospective study on patients with childhood ALL the estimated three-year cumulative fracture incidence was 17.8% and a higher fracture risk was observed among patients with low BMD at cancer diagnosis and during treatment.[214]

It has been shown that pharmacological interventions may decrease the risk of fractures in individuals with osteoporosis.[215] Since BMD and Z-scores correlate strongly with the risk of fractures, identifying childhood cancer survivors with impaired BMD may decrease future fracture risk if early interventions are initiated.[216-218] However, in the absence of randomized trials and due to insufficient evidence from previous studies, it is unknown whether early identification of low BMD and early treatment reduces the risk of fractures among adult survivors of childhood cancer.[218]

4.2.3 Osteochondropathies and osteoarthrosis

Osteochondropathies are a group of diseases and disorders that affect the growth centers and osteochondral parts of bones and most often are self-limiting.[219, 220] Osteoarthrosis results from degenerative cartilage changes that may at advanced stages require total joint arthroplasty.[221] Osteochondropathies are a disease of the childhood and adolescence, in contrast to osteoarthrosis, the incidence of which increases greatly with older age.

Osteochondropathies and osteoarthritis have been poorly investigated in childhood cancer survivors but other musculoskeletal late adverse events have been described.[222] Growth impairment and growth abnormalities may be seen after radiotherapy, where epiphyseal plates are involved in the radiation field.[223] Since glucocorticoids, chemotherapy, irradiation and treatment-induced endocrinopathies have negative effects on the bone metabolism, bone metabolism and bone vascularization, it is possible that these negative effects extend also to the articular cartilage.

4.2.4 Total joint arthroplasties

The only definitive treatment available for impaired joint function and chronic pain due to severe joint damage is surgical joint replacement (total joint arthroplasty). Total joint arthroplasty is a surgical intervention in which the whole joint surface is replaced with an endoprosthetic implant. The most common joints replaced are the hip and knee joints and the most common age at operation is between 60 and 70 years.[224] Osteoarthrosis is the most common indication for both total hip- and total knee arthroplasty.[225, 226] Other indications are for example fractures, inflammatory arthritis, osteonecrosis and malignancy.[224] Among children and young adults, inflammatory arthritis and osteonecrosis are the most common operation indications.[227] Other indications for total joint arthroplasty during childhood and adolescence are congenital hip disorders, Legg-Calvé-Perthes disease, slipped capital femoral epiphysis and posttraumatic arthritis.[204] Patients with malignant bone tumors commonly undergo total joint arthroplasty, but most commonly these operations occur within the first months of the cancer treatment.

Surgical revision may be necessary if the joint replacement does not work as intended or if complications occur, but during the last decades the revision rate has decreased.[44] Young individuals in general are reported to have worse implant survival compared to older individuals but recent studies have shown that implant survival is improving in this population.[227-229] The most common indication for surgical revision among young individuals is aseptic loosening of the endoprosthesis.[228, 230] A higher level of physical activity, long time since arthroplasty and a higher proportion of underlying conditions that affect the implant survival, for example inflammatory arthritis, are more common among young individuals.[231] Studies have shown that young age at arthroplasty, male gender and underlying osteonecrosis increase the risk for surgical revision.[230, 232]

Very few studies have been published on arthroplasty in children and adults with cancer. In a registry-based study on Norwegian cancer patients 16-90 years at diagnosis, the risk for total hip arthroplasty (THA) was slightly higher among patients with hematologic malignancies and tumors in the pelvic region compared to the general population.[233] In a registry-based study on Finnish cancer patients (all ages included), patients diagnosed with hematologic and lymphoid malignancies <50 years of age were at eight-fold higher risk and patients <35 years of age were 45 times more likely to undergo TKA and THA compared to the general population.[146] The same authors published a registry-based study on THA and

TKA among Finnish and Danish leukemia and lymphoma patients <31 years of age. In that study THA were more common than TKA and age ≥10 years at cancer diagnosis and allogeneic hematopoietic stem cell transplantation were risk factor for total joint arthroplasty.[29] In a study from the North American CCSS, 5-survivors treated for high-risk ALL during the 1990s, patients with relapsed ALL and patients with ALL who underwent allogeneic HSCT were at higher risk of undergoing total joint arthroplasty compared to a sibling comparison group.[19]

5 PATIENTS AND METHODS

5.1 STUDIES I AND II

5.1.1 Data sources

The Childhood Cancer Research Unit at the Department of Women's and Children´s Health, Karolinska Institutet, hosts the NOPHO ALL registry. Data on childhood ALL in the Nordic countries has been collected in the NOPHO ALL registry since 1982. From 1992, the treatment has been harmonized into uniform treatment protocols, starting with NOPHO ALL-92. Initially, the protocols were treatment recommendations, but from NOPHO ALL-2000, the protocol also contained a randomized intervention and NOPHO ALL-2008 included three randomized elements. In the NOPHO ALL-92, ALL-2000 and ALL-2008 protocols a thorough registration of baseline variables, treatment- and follow-up data in the ALL registry was mandatory. After initial registration, requests for updates of the current follow-up status are sent out annually to the pediatric oncology clinics in the Nordic countries. Most registration is performed by pediatric oncologists or research nurses. The NOPHO ALL registry is well-maintained and is generally considered an excellent source of high-quality data. The main focus of the NOPHO ALL registry is on the primary disease but some data on relapsed ALL is also available, including relapse site involvement and therapy intention, administered treatment and follow-up status/events after relapse. Although the coverage of new cancer cases is excellent in the Nordic cancer registries, they do not routinely collect data on relapses.[39] In the ICD classification system, leukemias are the only childhood cancer type where specific coding for relapses exists. Therefore, it is possible to collect data on ALL relapses from hospital registries but how well ALL relapses are represented in hospital registries is unknown.

Despite the generally high data quality in the NOPHO ALL registry, detailed data review revealed some shortcomings, particularly pertaining to follow-up after primary events, such as variables concerning relapse treatment, the current follow-up status and details regarding the cause of death. To attain complete registration, we sent requests to participating clinics to supplement missing data on the total of 95 cases (of the 485 included). The response was excellent and most queries could thus be resolved and data amended.

5.1.2 Cohort description

In total 2668 patients with BCP and T-cell ALL, aged 1.0 – 14.9 years were eligible for the NOPHO ALL-92 and ALL-2000 protocols. The protocols were open from January 1992 to December 2007. From January to June 2008, an additional 67 patients meeting the inclusion criteria were treated according to the NOPHO ALL-2000 protocol as best available treatment until the NOPHO ALL 2008 trial was officially launched in July 2008. Among the 2735 patients treated according to the ALL-92 and ALL-2000 protocols, 516 relapsed in first complete morphological remission before 01.01.2012. Of these, 485 relapsed after receiving chemotherapy alone and 31 after undergoing HSCT in CR1 (Figure 6). For the purpose of our study, we excluded patients that had undergone HSCT in first complete remissions (n=130) since these patients are invariably excluded from relapse protocols and have an almost uniformly dismal prognosis. The final study cohort included 485 patients, 1.0-14.9 years at initial diagnosis, with first relapse of BCP and T-cell ALL. We used the same cohort for studies I and II except for two patients who only received palliative treatment and were excluded from study II. The follow-up time in the NOPHO ALL registry was until 01.01.2014 for study I and 01.01.2016 for study II. For the whole cohort the median time from the diagnosis of ALL to relapse was 31.3 months (1.8-143.8 months)/2.6 years (0.2-12.0 years). The median follow-up time for relapse patients who were alive at the last known follow-up was 12 years (2.2-19.7 years) for the ALL-92 relapse cohort and 4.9 years (0.6-9.9 years) for ALL-2000 patients. Only 10 patients were lost to follow-up, all in CR2 at the time of last contact and with a median follow-up time of 8.2 years (range 1.1-12.2 years). We retrospectively assigned relapse risk groups according to the criteria of the IntReALL 2010 relapse trial, the standard treatment for relapsed childhood ALL in the Nordic countries at the time of compilation of the material.

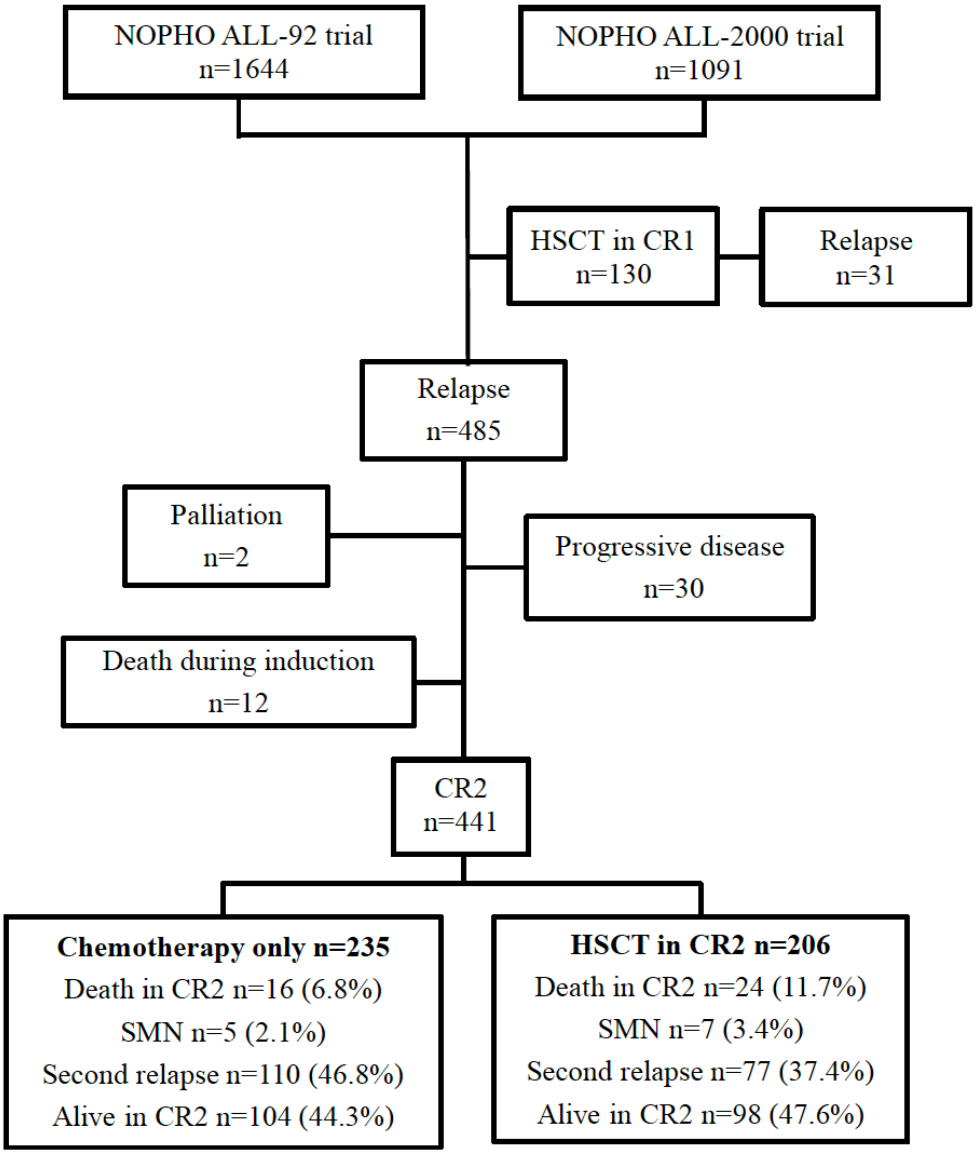

Figure 6. Flow chart of primary event among patients with relapsed childhood ALL
Modified from Oskarsson T et al. 2017

5.1.3 Definitions of terms used in studies I and II

Relapse: Conventionally, relapse occurring in the bone marrow is defined on a morphological basis as leukemic blasts ≥25% on a bone marrow examination. Since the treatment of relapsed ALL was not standardized in the Nordic countries during the research period, a uniform definition of bone marrow relapse did not exist. However, there has been a Nordic consensus to define bone marrow relapse as the reappearance of ≥5% of lymphoblasts in the bone marrow, confirmed by flow-cytometry and/or specific cytogenetic

findings. Central nervous system relapse was confirmed in the presence of ≥5 white blood cells per µL of cerebrospinal fluid identified as leukemic blasts after cytocentrifugation.

Second remission: Since data on MRD was only available for a very limited number of patients and no uniform criteria existed for second remission (CR2), we relied on the reported achievement of second remission which was likely identical to the currently used definition of remission during the primary treatment: M1 marrow status (<5% lymphoblasts in bone marrow) or MRD <5%, together with restoration of normal hematopoiesis.

Isolated bone marrow relapses (iBM): bone marrow relapses without any extramedullary involvement.
Isolated extramedullary relapses (iEM): relapses not involving the bone marrow, such as the CNS, testis, lymph nodes, mediastinum and skin.
Combined relapses: coexistent bone marrow and extramedullary involvement.

Very early relapses: relapses occurring <18 months from primary diagnosis.
Early relapses: relapses occurring ≥18 months from diagnosis and <6 months after completion of primary therapy.
Late relapses: relapses occurring ≥6 months after completion of primary therapy.

Unfavorable cytogenetics: hypodiploidy (modal chromosomal number <45), *KMT2A* (MLL) rearrangements, *BCR-ABL1* and t(1;19).
Favorable cytogenetics: high hyperdiploidy (modal chromosomal number >50, HeH) and t(12;21).
Other cytogenetics: iAMP21, dic(9;20), unspecified chromosomal abnormalities.
Normal/missing cytogenetics: 46XX/XY karyotype as only finding or missing values.

Treatment-related death (TRM): defined as any death occurring as the first event in the absence of progressive disease at the time of death.[130] All deaths after HSCT in CR2 were defined as TRM if second relapse or SMN had not occurred.
Disease progression: defined as death occurring as the first event if the patient was not in CR2 and if there were no serious treatment-related complications reported.
Primary cause of death: if a single event was reported by the clinician or if it was the main event causing death.

Secondary cause of death: when an underlying treatment-related condition existed, for example, GVHD.
Infectious death: When the clinical picture strongly indicating an infectious process and/or a microbiologically proven infection.

5.2 STUDIES III AND IV

5.2.1 Data sources

One-year childhood cancer survivors were identified in the nationwide cancer registries of Denmark, Finland, Iceland, Norway and Sweden (Table 4). From the cancer registries, we obtained the personal identification number, the type of cancer and the date of diagnosis. Childhood cancer survivors were then assigned to one of the 12 main diagnostic groups according to the International Classification of Childhood Cancer (ICCC-3).[234]

Comparison subjects who did not have cancer and were alive at the time of cancer diagnosis of corresponding patient (5:1 selection ratio) were selected from the national central population registries and matched by age, sex and country (Denmark, Iceland) or county/municipality of residence (Finland, Sweden). Fewer than five comparison subjects were available for a minority of childhood cancer survivors, where the matching criteria could not be met.

Study participants had to be alive or born after the start of complete centralized registration of residents, when all citizens were assigned a unique personal identification number that allows accurate linkage of data across registries (Iceland 1955, Denmark and Sweden 1968, Finland 1971). Information on emigration and vital status during the follow-up period was obtained from the central population registries.

In study III, the source of outcome data were the national patient registries (NPR) and in study IV the study outcomes were captured in the national arthroplasty registries. The coding of hospital visits in the NPRs allowed us to identify hospitalizations for skeletal diseases as markers for adverse events in the skeletal system. In the NPRs, discharge diagnoses were coded according to the successive revisions of the International Classification of Diseases (ICD) coding systems (ICD-7 – ICD-10). Since the coding of skeletal adverse events was not uniform between the different versions of the ICD coding systems, we adapted the coding to the newest and most detailed version (ICD-10) and

grouped skeletal adverse events into the following categories: osteonecrosis, osteoporosis, fractures, osteochondropathies and osteoarthritis. Although osteochondropathies are a heterogenous group of diseases they have a pathological condition of the cartilage and the articular surface in common. Bone or joint diseases with infectious (osteomyelitis, septic arthritis) or rheumatic (inflammatory arthritis) etiologies were excluded. The first record of hospitalization for each diagnosis of a skeletal adverse event was used, regardless of whether it was the main or a supplemental diagnosis. In the event that patients or comparison subjects were hospitalized for multiple skeletal diseases (simultaneously or separately), the first hospitalization for each skeletal adverse event was accounted for as an event when investigating the skeletal adverse events separately.

The follow-up period in the NPRs started one year after the date of cancer diagnosis or when the NPR started, whichever occurred later. The follow-up ended at the time of first hospitalization for a skeletal disease, the time of diagnosis of a new primary cancer, at the time of emigration or death or at the end of the study (Table 4), whichever occurred first.

Since 1995 in Denmark and since 2001 in Sweden, information about diagnostic codes used in hospital-based outpatient clinics have been available. We decided to use diagnostic codes from inpatient discharge records only to avoid discrepancies between time periods and the participating countries.

To take into account potential effect modification by other adverse events, we included endocrine disorders (adapted ICD-10 codes: E01-E35, E89) and neurological disorders (adapted ICD-10 codes: H53.0–H54.9, G40.0–G41.9, G50– G59.8, G80.0–G83.9) specifically, since both groups could theoretically modify the risk of being hospitalized for skeletal adverse events. We considered data on gastrointestinal and kidney disorders as well, but these groups did not contain sufficient numbers of cases to enable meaningful subgroup analyses.

In both the childhood cancer survivor cohort and the comparison subject cohort, we excluded individuals with constitutional chromosomal abnormalities (International Classification of Diseases – ICD codes: ICD-8: 759.3−759.5, ICD–9: 758 and ICD-10: Q90−Q99) as the main or supplemental discharge diagnosis in the NPRs to avoid potential confounding by genetic predisposition.

In study IV, the source of outcomes were the Nordic hip and knee arthroplasty registry data. By using the personal identifiers, data linkage allowed us to track study participants within both cohorts in the arthroplasty registries. The primary arthroplasty and first surgical revision for each joint were counted. We collected data on the date of primary arthroplasty, operation indication, laterality and the date of surgical revision. The registration of the operation indication was not uniform between the different arthroplasty registries. Therefore, we created nine groups containing the most common operation indications: osteoarthritis, fractures, rheumatic arthritis, osteonecrosis, malignancy, dysplasia, Perthes disease, other and missing.

The follow-up period started one year after cancer diagnosis for survivors and the matching date for comparison subjects, or at the start point of the respective arthroplasty registry, whichever occurred later (Table 4). The recruitment period for the national arthroplasty registries extended beyond the end of follow-up in the central population registries but since data on vital status and emigration was obtained from the central population registries the follow-up period in the arthroplasty registries was limited to the end of follow-up in the central population registries (Table 4). For the main analyses, the follow-up ended at the time of arthroplasty, a new primary cancer, death, emigration or at the end of the study.

Table 4. The recruitment period in the national registries used in studies III and IV

Country	[1]Cancer registries	Hospital registries	Population registries	Hip arthroplasty registries	Knee arthroplasty registries
Denmark	1943-2008	1977-2010	1968-2010	1995-2017	1997-2017
Finland	1971-2008	1975-2012	1969-2012	1981-2016	1989-2016
Iceland	1955-2008	1999-2008	1960-2010	1999-2008	1999-2008
Norway	1953-2008	2008-2010	1960-2010	1987-2016	1994-2016
Sweden	1958-2008	1964-2009	1967-2009	1992-2015	1975-2015

[1]Over time, cancers have been notified according to the International Classification of Diseases, 7th–10th revisions (ICD-7–10), or the ICD for Oncology, 1st–3rd editions (ICD-O1–O3).

5.2.2 Cohort description

The childhood cancer cohorts used in studies III and IV were sub-cohorts within the ALiCCS childhood cancer survivor cohort. In study III, the final study cohort included 26,334 survivors and 127,531 comparison subjects but in study IV the final study cohort included 33,172 and 161,541 comparison subjects. The main reasons for the discrepancies in the size of the study cohorts were different compositions with regards to which countries were included. We could not include Norway in study III due to lack of access to complete hospitalization histories needed for the study and since no arthroplasty registries exist in Iceland, we did not include Iceland in study IV. Descriptions of the cohort characteristics used in studies III and IV are described in papers III (supplementary appendix) and IV (main text).

5.3 STATISTICAL ANALYSES

5.3.1 Studies I and II

We exported pseudoanonymized data files from the NOPHO ALL registry and created a single dataset where we merged datafiles with information on inclusion variables from the NOPHO ALL-92 and ALL-2000 trials and a centralized review of cytogenetics by the NOPHO cytogenetics working group. We checked all key variables for potential errors and misclassifications. For most of the descriptive and statistical analyses we used the IBM SPSS statistics software.

Descriptive statistics were used to report the cohort characteristics and for tabular compilation of relapse treatments, secondary events, causes of death and the etiology of infectious deaths. To test the distribution within baseline variables among relapsed patients between the NOPHO ALL-92 and ALL-2000 trials we used non-parametric methods to generate p-values, where $p<0.05$ was defined as statistically significant. Pearson´s chi squared tests or Fisher´s exact tests (for small sample sizes) were used to compare proportions for data described in categorical variables and Mann-Whitney U tests comparison of continuous data.

For the survival analyses in study I, we chose overall survival (OS) as the main outcome variable. Due to the shortcomings in the NOPHO ALL registry regarding potential incomplete follow-up registrations, overall survival is a more robust end-point than event-

free survival (EFS) in second remission. Furthermore, since the outcome after relapse in CR≥2 is generally poor the EFS and OS estimates are very similar. We used the Kaplan-Meier method to estimate the likelihood of survival over time and to generate survival curves. The time from relapse diagnosis was used as the underlying time scale. Overall survival was defined as the time from relapse diagnosis to death by any cause and censoring occurred at the date of last known follow-up in CR2. Event-free survival was defined as the time from relapse diagnosis to the date of death (TRM or progressive disease), second relapse, SMN or the date of last follow-up in CR2. Events beyond second relapse and SMN were not analyzed further. We used the log-rank test to compare survival functions between groups with different baseline factors, risk stratifications, treatments and time period. Curves describing the likelihood of isolated second events and TRM were generated accounting for the competing nature of the alternative second events [235]. In the analyses where we estimated the cumulative incidence of TRM in patients who did not undergo HSCT, HSCT was added as a separate competing event.

Survival analyses where allogenic HSCT is included as a covariate are problematic. In the ALL registry, data is available on patients that have undergone allogenic HSCT in CR2. However, patients who died in the post-induction phase or during the HSCT conditioning phase were not coded as HSCT patients in the NOPHO ALL registry. This can cause overestimation of the effect of HSCT on survival since patients who fail before they reach HSCT will be allocated to the chemotherapy arm. Therefore, in study I, when we estimated the effect of HSCT on overall survival using the Kaplan-Meier method, we excluded patients that died before reaching CR2 since they were not eligible for HSCT at the time of death (n=44) and patients who only received chemotherapy but died in CR2 or developed second relapse before the median time from relapse diagnosis to HSCT (landmark day 162, n=15). Analyzing patients from the Intention to Treat (ITT) perspective would have been the method of choice but information on ITT in the NOPHO ALL registry was not reliable. Data was missing in a large number of patients and during the course of treatment the ITT is likely to have changed for some patients. In addition, since the criteria for HSCT in CR2 were not universal the decision on HSCT was often made on individual basis.

In study I, Cox proportional hazards regression models were used to generate estimates of hazard ratios (with 95% confidence intervals) for different independent variables (baseline risk factors) where death was the dependent variable. For the subgroup analysis including

only SR patients, we used a stratified Cox proportional hazards regression model and included HSCT in CR2 as a time-dependent covariate.

In study II, we used competing risks regression models to analyze risk factors for TRM, estimating sub-distribution hazard ratios with 95% confidence intervals.[236] To limit the number of variables and to demonstrate the effect of the risk stratification on TRM we used InReALL risk groups (SR and HR) in the adjusted regression models. Likewise, we compared high-risk stratification at primary diagnosis (combined Intensive, Very Intensive, Extra Intensive risk groups) to non-high-risk (combined Standard risk and Intermediate risk). Allogeneic HSCT was included as a time-dependent covariate. In regression models where we included only patients who did not undergo HSCT, HSCT was added as a competing event in addition to second relapse, SMN and death of disease progression.

Both STATA and R statistical analysis software were used for generating cumulative incidence estimates and hazard ratios where time-dependent variables were included as covariates and analyses in which adjustments were made for competing risks.

5.3.2 Studies III and IV

All data processing and statistical analyses were conducted by data managers and statisticians at the Danish Cancer Society Research Center, the host of the ALiCCS project.

5.3.2.1 Study III

Hospitalization rates per 100,000 person-years were used as the main measure of frequency and standardized hospitalization rate ratios (RRs) as the main relative risk estimate. The standardized hospitalization rate ratio represents the relative risk for skeletal adverse events among childhood cancer survivors by comparing the observed number of first hospitalizations to the expected number of hospitalizations among the matched comparison subjects. Absolute excess risks (AER) were used to estimate the absolute additional risk of hospitalization for a skeletal disease by calculating the difference between the observed and expected hospitalization rates per 100,000 person-years. The 95% CIs were computed from Fieller's theorem based on the assumption that the observed number of hospital admissions followed a Poisson distribution.[237] Rate ratios with 95% CIs not including 1.0 were considered significantly increased. Risk estimates were calculated for each type of skeletal adverse event and then stratified by sex, cancer type, age at cancer diagnosis and the

attained age. Cumulative excess hazards for each type of skeletal adverse events were calculated to illustrate how hospitalizations among survivors advanced over time.

Prentice-Williams-Peterson (PWP) models were used to estimate the hazard ratio of recurrent fractures (only first recurrence counted) but were performed on a restricted risk set that only included subjects with previous hospitalizations for fractures.

Cause-specific hazard ratios were estimated for all types of skeletal events combined with and without hospitalizations for endocrine and neurological disorders.

To validate the robustness of our study design, RRs for each type of skeletal adverse event were estimated by including different subsets of study participants in five sensitivity analyses to addressing the following issues:

1) The impact of malignant bone tumors on the risk estimates, by excluding patients with malignant bone tumors (ICD-10, C40-41, C76.0-76.8) and their comparison subjects.
2) The impact of late treatment failures due to the cancer, by only including 5-year survivors and their comparison subjects.
3) The influence of left truncation (since the study did not capture events that occurred prior to the start of NPR in each country), by including only survivors diagnosed maximum one year prior to the start of the NPR and their comparison subjects.
4) The effect of coding discrepancies between the earlier and later versions of the ICD coding systems, by only including discharge diagnoses coded by ICD-9 and ICD-10.
5) The impact of potential hospitalization/surveillance bias by searching for discrepancies in the outcome registration between the inpatient and outpatient hospital registries in Denmark and Sweden by including only outpatient visits.

5.3.2.2 Study IV

Incidence rates per 100,000 person-years were calculated and used to estimate incidence rate ratios (IRR) by comparing the incidences between the survivor- and comparison subject cohorts. The 95% confidence intervals were computed based on the assumption that the observed numbers of arthroplasties followed a Poisson distribution.[237] Cumulative incidence curves were generated for hip and knee arthroplasties calculated with the Aalen-Johansen estimator and stratified by cancer diagnosis. Death and diagnosis of a new cancer

were defined as competing events. To identify subgroups at excess risk for arthroplasty, we performed within-cohort (childhood cancer survivors only) Cox regression analyses to generate cause-specific hazard ratios by taking into account the effect of sex, age, country, year of diagnosis and cancer diagnosis. Attained age (age at cancer diagnosis plus the time since cancer diagnosis) was the underlying time-scale.

In studies III and IV, SAS and R statistical analysis software were used to for statistical calculations and modelling as well as generation of figures. In study III, Microsoft Excel software was used to generate figures illustrating the hospitalization rate for skeletal adverse events.

6 RESULTS AND DISCUSSION

6.1 STUDIES I AND II

The relapse rate for patients initially treated according to NOPHO ALL-92 was 19.7% and the corresponding figure for NOPHO ALL-2000 was 14.8%. The follow-up time for the ALL-2000 cohort was shorter and therefore our study did not capture all of the late occurring relapses. According to the current status of the NOPHO ALL registry, the relapse rate in the ALL-2000 cohort is now very similar to the ALL-92 cohort.

In contrast to the situation in primary ALL where approximately 2-3% of patients have CNS involvement at diagnosis, 28% had CNS involvement at relapse. Approximately half of the CNS involving relapses were isolated CNS relapses, of which the majority where on-treatment relapses. This is of concern and points out a well-known weakness in the upfront CNS-directed treatment and, in addition, also reflects the differences in disease biology between the primary diagnosis and relapse.[100]

6.1.1 Risk stratification

6.1.1.1 Duration of CR1 and site of relapse

We confirmed previous findings that short time in CR1 was the strongest prognostic factor for patients with ALL relapse. The main reasons for the strong predictive value of short duration of CR1 on survival are likely to be the underlying genetic alterations that mediate cell proliferation and treatment resistance.[108, 238] In study II, very early relapses were also a strong predictive factor for TRM.

The association between the timing of relapse and relapse site is illustrated in Figure 7. In approximately half (232 of 485) of patients, the relapse occurred ≥ 36 month from diagnosis. Late occurring relapses are generally associated with better outcome than early relapses. We identified 54 patients, who had their relapse ≥ 5 years from the primary diagnosis and seven of them relapsed ≥10 years from the primary diagnosis. The majority of these patients had an upfront favorable risk profile (nine initially stratified as ≥HR). Favorable cytogenetics were observed in 23 of the late relapsing patients and only one had unfavorable cytogenetics (*BCR-ABL1*). Of the 54 patients, 37 had iBM relapses, seven combined and 10 iEM relapses. The 5-year OS for patients with very late relapses was 63.8

± 6.7% (standard error). Patients with very late iBM relapses have been described as having better outcome than patients with very late combined and iEM relapses.[239] The pattern of relapse and the outcome for patients relapsing ≥ 5 years from primary diagnosis compared to those who relapse ≥10 years from primary diagnosis is reported to be very similar.[240] There is evidence that supports that in some cases, late occurring T-cell or late occurring t(12;21) positive BCP relapses may represent second leukemias instead of recurrence.[98, 241]

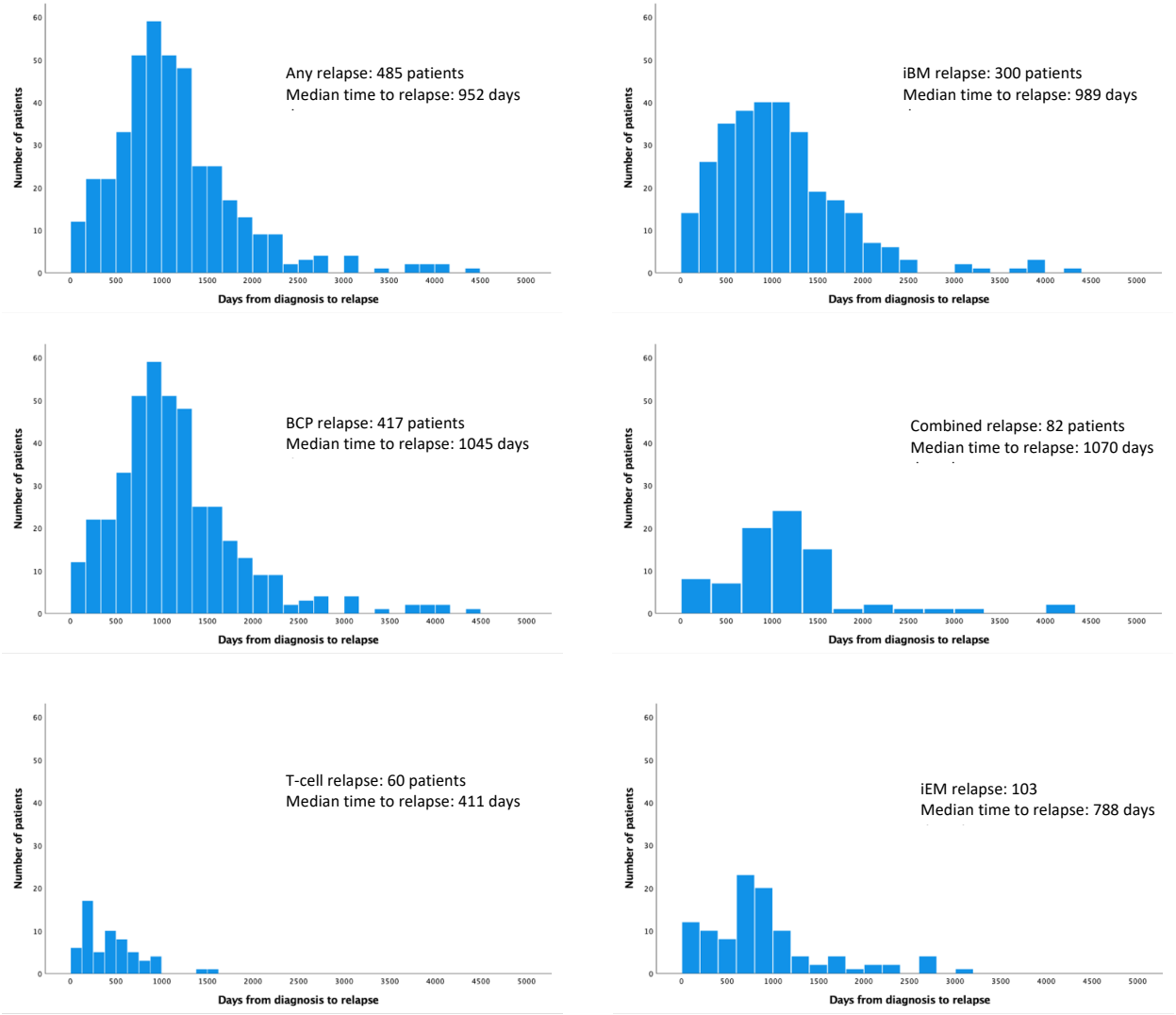

Figure 7. The time pattern of relapse, by immunophenotype and relapse site

Eight patients had an unknown immunophenotype

6.1.1.2 Immunophenotype

In study I, the 5-year OS for relapsed T-cell ALL was only 28.3 ± 5.8% compared to 55.1 ± 2.5% for BCP relapses. T-cell relapses occurred earlier than BCP relapses, median time 411 days (58-1584) compared to 1045 days (56-4374 days), respectively (Figure 7). Only 4 of the 60 T-ALL relapses were stratified as SR at relapse. T-cell ALL relapses are more chemo-resistant than their BCP counterparts.[242]

The strong correlation between T-cell immunophenotype and short duration in CR1 had as a result that T-cell immunophenotype lost its statistical significance as a risk factor for death after relapse after adjusting for the time to relapse, solely (data not shown) or in combination with different baseline variables (hazard ratio 1.43, 95% CI; 0.97-2.11). T-cell relapse occurred more often in the extramedullary compartment compared to BCP relapse ($p<0.001$) (Figure 8). In study II, immunophenotype was not a predictor for TRM.

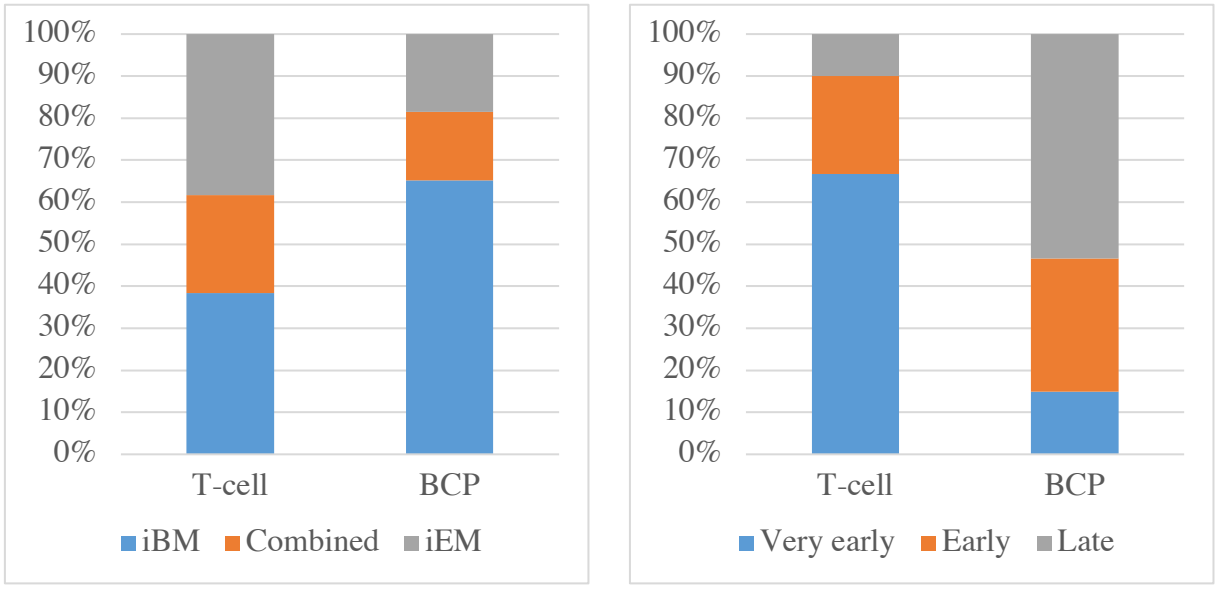

Figure 8. Site of relapse and time to relapse by immunophenotype

6.1.1.3 Cytogenetics

Although favorable cytogenetics, t(12;21) and HeH, are associated with good outcome for primary ALL, it is still the most common cytogenetic group at relapse. In study I, 35% of all relapses were initially classified with favorable cytogenetics, as opposed to approximately 50% at primary diagnosis. Patients with t(12;21) and HeH cytogenetics make up a heterogeneous group. Studies have shown that patients with HeH ALL can be

subdivided to good risk and poor risk profiles where HeH ALL with a poor risk profile have an intermediate prognosis.[243] Similarly it has been shown that patients with relapsed t(12;21) positive ALL may have copy number alterations associated with poor outcome.[244]

In studies I and II, we grouped the cytogenetic aberrations to gain power for subgroup analyses. Our classification of "unfavorable cytogenetics" was based on previous findings that *KMT2A* rearrangements, hypodiploidy, *BCR-ABL1* were associated with poor outcome at primary diagnosis and at that time, there were indications that the outcome in patients with t(1;19) positive ALL was very poor after relapse. During the ALL-92 and ALL-2000 trials the cytogenetic aberrations dic(9;20) and iAMP21 were not routinely detected or registered. In the ALL-2008 trial patients with these two aberrations were not eligible for the standard risk arm treatment.[245, 246] In our relapse cohort seven patients were registered with iAMP21 and six with dic(9;20), most from the ALL-2000 trial era. We grouped these patients into the cytogenetics group "other". In the ALLR3 trial, patients with iAMP21 and t(1;19) had poor outcome after relapse but outcomes for dic(9;20) were not reported. In our cohort, four of seven patient with iAMP21 were alive in CR2 at the last know follow-up, one of six with t(1;19) and three of eight with dic(9;20). Adding iAMP21 to the group "unfavorable cytogenetics" did not change the risk estimates for that group significantly (data not shown).

In study I, patients with unfavorable cytogenetics were at higher risk for second relapses and death due to TRM or disease progression. An interesting and puzzling finding in study II was the higher risk of TRM among patients with unfavorable cytogenetics also after adjusting for relapse risk group. Only five of 28 patients with unfavorable cytogenetics were alive in CR at the last follow-up.

6.1.1.4 Down syndrome

In study I, patients with relapsed DS-ALL had a dismal outcome. Of 17 patients with relapsed DS-ALL only three were alive in CR2 at the last known follow-up. Ten of these patients suffered a second relapse and two died of disease progression. One experienced a hematological SMN and one received treatment with palliative intent at relapse. In contrast to previous reports, no events of TRM occurred among the patients with relapsed DS-ALL. Our hypothesis is that patients with DS-ALL did not receive adequate treatment intensity due to concerns of TRM. In a study by Meyr et al. TRM was the main reason for treatment failure among DS patients with relapse of -ALL but with treatment modifications and better

supportive care, survival has improved with time.[247] Study I was underpowered to detect differences in survival over time.

6.1.1.5 Age

In study I, age ≥10 years at diagnosis was associated with worse overall survival after relapse, even after adjusting for factors used for relapse risk group allocation and cytogenetic risk groups. Second relapse was the most common adverse event. In study II, age ≥10 years was not a risk factor for TRM. The 5-year OS for patients ≥10 years who underwent allogeneic HSCT in CR2 was 46.7 ± 7.0% but 40.1 ± 9.5% for patients ≥ 10 years treated with chemotherapy alone (p=0.266). Among patients stratified as SR at relapse, 62% of patients ≥10 years at diagnosis underwent HSCT in CR2 compared to 34% of patients <10 years. The reason for this difference is not clear but for SR relapses the choice of proceeding to allogeneic HSCT in CR2 was made by the clinicians in charge of the patients and is likely to be the result of poor initial treatment response. This is further emphasized by our finding that age ≥10 years was a risk factor for death in univariable analysis of SR patients, but after adjusting for allogenic HSCT in CR2, sex, WBC at primary diagnosis and cytogenetics, age ≥10 years was not a statistically significant risk factor. Although our data suggests that patients ≥10 years at primary diagnosis had worse overall survival after relapse compared to patients <10 years, it is not clear how or whether age should guide the choice of relapse treatment.

6.1.1.6 White blood cell count

In study I, hyperleukocytosis at ALL diagnosis was a risk factor for death in the unadjusted risk regression but was not an independent risk factor for death in the adjusted regression analysis. However, we identified a subgroup of patients with T-ALL and hyperleukocytosis at diagnosis (n=27) with a very poor overall survival after relapse, only four survivors and adjusted hazard ratio was 2.4 (95% CI, 1.4-4.0). This subgroup of patients is in large need for new therapies. In the NOPHO ALL-92 and ALL-2000 trials, patients with BCP ALL and hyperleukocytosis had worse EFS compared to patient with WBC <100 x 10^9/L but interestingly, patients with T-ALL and hyperleukocytosis, did not have worse EFS.[119]

6.1.1.7 Treatment response

Measurements of MRD were not implemented in the Nordic countries until approximately 2002 and have not been systematically registered for relapsed patients and could thus unfortunately not be included in our analyses. However, MRD-response has mostly been used to identify patients with initial SR-characteristics at relapse with slow response for up-grading of therapy (to HSCT) and most patients have been stratified based on up-front criteria at relapse.

6.1.1.8 Validation of current risk stratification model

We validated the current risk stratification used in the Nordic countries by retrospectively allocating patients to the SR and HR relapse groups as defined by IntReALL and estimated the 5-year OS for the subclasses within each risk group (Table 5). The 5-year OS for patients stratified as SR was 65.6 ± 2.9% but only 30.5 ± 3.3% for patients stratified as HR at relapse. The largest group was late iBM BCP relapses. This group is stratified as SR and the 5-year OS was 60% ± 4.1%. The best OS was found for early and late iEM BCP and late combined BCP relapses whereas very early relapses (5-year OS 25.2% ± 4.3%) and T-cell ALL relapses (5-year OS 28.3 ± 5.8%) had dismal OS estimates. For patients with HR relapses the OS for T-cell ALL and BCP ALL was similar. This finding was also observed in the ALL-REZ BFM 2002 and ALLR3 trials.[110]

Interestingly, the OS for patients with early combined BCP relapses was surprisingly poor since these relapses are stratified as IntReALL-SR, but had very similar OS as early iBM BCP relapses, a group stratified as HR. Within the early combined BCP group (n=21), 10 patients had favorable cytogenetics, none had unfavorable cytogenetics and 19 were < 10 years at diagnosis. Five of the seven patients who underwent HSCT in CR2 were alive in CR2 at last known follow-up. The IntReALL 2010 protocol recommends that patients with early combined BCP relapses to undergo HSCT in CR2 if a matched donor is available. Both HR relapses and early combined BCP relapses need new therapeutic strategies to improve survival. This argument is strengthened by our findings in study II that HR relapse and HSCT in CR2 are strong risk factors for TRM. Since the main reasons for treatment failures in patients with HR profile at relapse are either second relapse or TRM, the task of maintaining the fine balance between overtreatment and undertreatment with conventional treatment strategies is very challenging.

Table 5. Risk stratification by immunophenotype, the time from diagnosis to relapse and the anatomic site of relapse.

Relapse risk groups	Number patients (HSCT in CR2) 5-year overall survival or number alive/total					
	BCP			T-cell		
	iEM	Combined	iBM	iEM	Combined	iBM
Very early	n=9 (2) 6/9	n=4 (3) 0/4	n=50* (24) 22.0 ± 5.9%	n =18 (9) 27.8 ± 10.6%	n =10 (4) 30.0 ± 14.5%	n =12 (4) 8.3 ± 8.0%
PD	0	2	12	1	1	4
TRM	1	0	9	3	3	2
2nd relapse	5	3	18	8	4	5
CR2	3	0	9	5	2	1
SMN	0	0	1	1	0	0
Early	n=44 (12) 76.0 ± 6.6%	n=21 (7) 38.0 ± 10.6%	n=67 (42) 36.6 ± 6.0%	n=3 (1) 1/3	n=3 (2) 0/3	n=8 (5) 4/8
PD	0	2	3	1	1	1
TRM	1	4	7	0	0	1
2nd relapse	13	8	35	1	2	4
CR2	29	6	19	1	0	2
SMN	1	1	3	0	0	0
Late	n=24 (1) 82.0 ± 8.3%	n=43 (10) 77.4 ± 6.7%	n=155 (65) 60.3 ± 4.1%	n=2 (1) 1/2	n=1(1) 1/1	n=3 (2) 1/3
PD	0	0	3[1]	1	0	0
TRM	2	2	15	0	0	1
2nd relapse	5	14	57	0	0	1
CR2	16	26	78	1	1	1
SMN	1	1	2	0	0	0

Modified from Oskarsson T et al. 2016

Standard-risk group (white boxes) and high-risk group (grey boxes) according to the IntReALL risk classification. The boxes include the total number of patients and the overall survival for each subgroup. For subgroups involving less than 10 patients, survival is presented as the proportion of patients alive within the subgroup at the end of the follow-up period instead of 5-year overall survival (± standard error). *Isolated extramedullary relapses (iEM)*: relapses not involving the bone marrow, such as the CNS, testis, lymph nodes, mediastinum and skin. *Combined relapses*: coexistent bone marrow and extramedullary involvement. *Isolated bone marrow relapses (iBM)*: bone marrow relapses without any extramedullary involvement. *Very early relapses*: occurring <18 months from primary diagnosis. *Early relapses*: occurring ≥18 months from diagnosis and <6 months after completion of primary therapy. *Late relapses*: occurring ≥6 months after completion of primary therapy. Eight patients with unknown immunophenotype were excluded from the survival analysis; very early iBM = 1, early iBM = 2, early iEM = 1, late iBM = 2, late iEM = 2. In one of the patients with an unknown immunophenotype TRM occurred. *12 patients with unfavorable cytogenetics, 12 with other cytogenetics, 13 with favorable cytogenetics.[1] Two patients received only palliation (one with Down syndrome)

6.1.2 Treatment and survival

During the study period, relapse treatment according to the BFM ALL-REZ protocols was the most common treatment used in the Nordic countries (60%). The overall second remission rate was 91% and the proportion of patients undergoing allogeneic HSCT in second remission was 43%. Despite this intensive therapy, second relapses occurred in 38% of the patients. As expected, overall survival for patients with HR relapses was significantly higher if HSCT was performed in second remission compared with patients that did not undergo allogeneic HSCT. On the contrary, mortality was higher for SR patients that underwent allogeneic HSCT compared to chemotherapy only; adjusted hazard ratio 2.8 (95% CI, 1.80-4.41). This could be due to the selection of patients to the HSCT groups with non-stratifying factors that are associated with worse overall survival (higher age, unfavorable cytogenetics) and poor MRD response after the re-induction therapy. However, in the adjusted Cox regression models (including HSCT as a time-dependent covariate) we did not identify other independent risk factors for overall survival in patients with SR relapses. Since we did not have information on MRD we could not ascertain if some of the patients with SR relapse underwent allogeneic HSCT due to poor MRD response to the induction phase of the relapse treatment (which is very likely). Although cytogenetic risk groups were included in the multivariable risk regression models, this study was under-powered to detect survival differences between the cytogenetic risk groups in patients with SR relapses.

The 5-year overall survival for the whole relapse cohort was 51.3 ± 2.3% but the 5-year EFS was 43.7 ± 2.3%. Since the OS and EFS estimates were similar, it indicates that the survival after second relapse was very poor. The 5-year OS and 5-year EFS estimates were very similar, indicating a very poor survival after second relapse. The 5-year overall survival for patients who relapsed 2002-2011 was 57.5 ± 3.4% and 44.7 ± 3.2% if the relapse occurred 1992-2001 ($p<0.001$). Most of the improvement was attributable to the lower incidence of second relapses in the later period and not to a lower TRM, which remained the same between the periods. We hypothesize that one of the explanations could be the introduction of MRD analyses during the latter period. Minimal residual disease is used to quantify initial treatment response and for the selection patients for the most appropriate treatment intensity. In addition, it has been shown that outcome after allogeneic HSCT is better if MRD levels are low prior to the start of HSCT conditioning therapy.[124] General improvements in the HSCT results and better supportive care are also likely to be contributing factors.[248]

6.1.3 Treatment-related mortality

Treatment-related deaths occurred in 52 patients (10.8%) who were treated for relapse with curative intention (n=483, two only received palliative treatment). Compared to the risk of TRM in the primary NOPHO ALL-92 and ALL-2000 protocols, the likelihood of TRM was approximately three times higher during treatment for relapse.[82, 83] Twelve patients died before achieving second remission, 16 died during chemotherapy in second remission and 24 patients after undergoing hematopoietic stem cell transplantation. Infections were the most common primary cause of death, 38 of 52 (73.1%) and GVHD the most common secondary cause of death. Independent risk factors for treatment-related mortality were high-risk stratification at relapse, hazard ratio 2.2 (95% CI: 1.3-3.9) and unfavorable cytogenetics, hazard ratio 3.4 (1.3-9.2) but in contrast to previous findings; we did not find any statistically significant sex- or age differences. As expected, hematopoietic stem cell transplantation was also strongly associated with TRM, hazard ratio 4.6 (2.2-9.9). Patients with on-treatment relapses and bone marrow involvement start the relapse treatment when the bone marrow is still under the effect of the primary treatment and the immune system is compromised. Therefore, it not surprising that infectious TRM was more common among patients stratified as HR at relapse. Interestingly, unfavorable cytogenetics were an independent risk factor for TRM also after adjusting for the relapse risk group. This is a novel finding but needs to be interpreted with caution due to the low number of events. On-treatment bone marrow involving relapses and BCP relapses with unfavorable cytogenetics could harbor genetic aberrations that interact with the host immune system and the bone marrow microenvironment differently than late occurring relapses.

In study II, bacterial infections were most common during intensive chemotherapy phases but viral infections were more common during or following HSCT. In recently published European guidelines (ECIL-8) on antibiotic prophylaxis for patients with childhood cancer and children undergoing allogeneic HSCT, routine antibacterial prophylaxis is not recommended.[249] The risk of drug toxicity and the emergence of antibiotic resistance outweighs the potential survival benefit. However, the guidelines also state that antibacterial prophylaxis might be justifiable after careful risk-benefit evaluation on case-to-case basis. Previous studies on antibiotic prophylaxis where patients with ALL relapse have been included have not stratified patients by risk group or other baseline factors. Based on the findings in study II, it would be interesting to design a prospective study where patients with HR ALL-relapses would be randomized to receive antibiotic prophylaxis.

6.1.4 Second malignant neoplasm

Second malignant neoplasm following treatment of childhood ALL are rare but are nevertheless a potential threat to the overall survival. The most common types of SMNs following treatment of primary ALL are myelodysplasia (MDS), acute myeloid leukemia (AML) and nonmeningioma brain tumors and the outcome is generally poor.[84] Treatment modalities associated with SMN such as CNS irradiation, allogeneic HSCT, particularly with total body irradiation are more commonly used for treatment of ALL relapse compared to the primary treatment. In our relapse cohort, we identified 12 patients with SMNs (2.5%) (Table 6). This is higher than reported in the NOPHO ALL-92 and ALL-2000 trials in which the 15-year cumulative incidence of SMN was 1.2% (95% CI 0.8-1.7) and the majority were hematological malignancies.[68] Only five of the 12 patients were stratified as HR relapses. Five of the SMN-cases occurred after completion of intensive chemotherapy and seven occurred post-HSCT. The median time from relapse diagnosis to SMN was 60 months (4-139 months). The four cases of post transplantation lymphoproliferative disease (PTLD) occurred early, between 4-9 months after relapse diagnosis and between 38-126 days from HSCT. All but one underwent either CNS irradiation or allogeneic-HSCT including total body irradiation. Only three patients with SMNs survived long-term (local treatment only). Our results indicate that SMNs are more common in patients with ALL relapse than in patients in CR1. In contrast to the primary treatment where hematological SMNs dominate, SMNs in relapsed ALL are predominantly solid and CNS tumors (or PTLD). Both CNS and total body irradiation are still important treatment modalities for relapsed ALL despite the risk of long-term toxicity and SMN. A recent study (FORUM) showed that total body irradiation plus etoposide prior to HSCT was superior to myeloablative chemotherapy.[250] Radiation induced SMN is therefore expected to be a continuing challenge over the next decades.

Table 6. Characteristics of patients with second malignant neoplasm after first relapse of childhood ALL.

Case	SMN	Immuno-phenotype	Cyto-genetics	Primary treatment/ risk group[2]	Months to SMN[3]	Age at relapse	Time to relapse	Site of relapse	Relapse protocol	HSCT in CR2	Irradiation for relapse[4]	Alive/ Dead
1	MDS	B-lineage	t(12;21)	ALL-2000/IR	24	<10 years	Late	iBM	RALLE	No	No	Dead
2	AML	B-lineage	other	ALL-92/≥HR	97	≥10 years	Early	iBM	NOPHO HR arm	Yes	CNS	Dead
3	Malignant melanoma	B-lineage	missing	ALL-92/IR	76	<10 years	Early	iBM	NOPHO HR arm	No	CNS	Alive
4	Mucoepidermoid carcinoma	B-lineage	t(12;21)	ALL-92/SR	49	<10 years	Late	iCNS	NOPHO HR arm	No	CNS	Alive
5	Synovial Sarcoma	B-lineage	normal	ALL-92/SR	90	≥ 10 years	Late	BM+CNS	Other	Yes	TBI	Alive
6	High-grade glioma	B-lineage	normal	ALL-92/SR	139	≥10 years	Early	BM+CNS	NOPHO HR arm	Yes[6]	CNS	Dead
7	High-grade glioma	B-lineage	other	ALL-2000/≥HR	72	<10 years	Late	BM+CNS	ALL-REZ BFM	No	CNS	Dead
8	High-grade glioma	B-lineage	t(12;21)	ALL-92/SR	84	<10 years	Early	iCNS	ALL-REZ BFM	No	CNS	Dead
9	PTLD[1]	T-cell	missing	ALL-92/≥HR	4	<10 years	Very early	iEM	ALL-REZ BFM	Yes	TBI	Dead
10	PTLD	B-lineage	other	ALL-92/SR	5	≥10 years	Very early	iBM	ALL-REZ BFM	Yes	TBI	Dead
11	PTLD	B-lineage	normal	ALL-92/IR	9	≥10 years	Late	iBM	ALL-REZ BFM	Yes	TBI	Dead
12	PTLD	B-lineage	other	ALL-92/≥HR	7	≥10 years	Early	iBM	Other	Yes	TBI	Dead

[1]Posttransplantation lymphoproliferative disease (PTLD).[2]Upfront NOPHO trial, none received CNS irradiation during the primary treatment.[3]Time from relapse diagnosis to SMN. [4]Total body irradiation (TBI).

6.1.5 Contemporary treatment of relapsed ALL

In the present landscape of childhood ALL, improvement in the upfront treatment has reduced the frequency of relapses and this is the major reason for the improved survival. However, we observed a significant survival improvement also for relapsed ALL from 1992-2001 to 2002-2011, mainly due to a reduction of second relapses since the TRM rate between these time periods was very similar. Most patients with relapsed ALL reach CR2 with chemotherapy-based treatments. In our study, we did not observe outcome differences between the relapse treatment protocols with regard to the CR2 rate or overall survival. All relapse protocols used during the study period included conventional chemotherapy and recommendations for allogeneic HSCT based on risk group and/or treatment response (in the more recent era). The outcome for patients with relapsed ALL in the Nordic countries was comparable to the outcomes reported by other cooperative groups during the same time period (Paper I, Table 5). Increasing the intensity of the chemotherapy backbone or allocating all patients to allogeneic HSCT could possibly decrease the risk of second relapses but the expected increase in TRM would likely offset the positive effect on overall survival.

Currently, the treatment of childhood ALL is undergoing a paradigm shift. Novel agents and immunotherapies are being introduced both for primary high-risk ALL and relapsed ALL. One of the main purposes of the IntReALL collaboration was to create a platform to harmonize the treatment of relapsed childhood ALL and test different treatment strategies and novel therapies. In recent years, the Nordic countries have been following the treatment protocols proposed by IntReALL, the IntReALL 2010 SR and HR protocols. In these protocols, both SR and HR patients receive a 4-drug (plus bortezomib for HR patients in some countries) induction phase. If a satisfactory MRD remission is achieved, consolidation with block chemotherapy followed by maintenance therapy is recommended for SR patients and block chemotherapy followed by allogeneic HSCT for HR patients. For SR patients with poor MRD response, allogeneic HSCT is recommended. Nonetheless, since the availability of genomic analyses and new therapeutic agents have increased dramatically, the treatment of relapsed childhood ALL has become more tailored to the biology of the disease, response and previous toxicity. Therefore, deviations from the IntReALL protocols are now common. In many Nordic centers, SR patients in whom a good enough MRD remission is not achieved at the end of induction may now receive immunotherapy, most commonly, blinatumomab and/or inotuzumab ozogamicin, before proceeding to allogeneic HSCT. For HR relapse patients, immunotherapy is now the mainstay treatment after the induction phase prior to allogeneic HSCT but chimeric antigen receptor (CAR) T-cell therapy is an alternative to allogeneic HSCT in some countries and centers.

6.2 STUDIES III AND IV

In study III childhood cancer survivors had 35% higher risk of hospitalization for skeletal adverse events than population comparison subjects. Each skeletal adverse event in study III had its unique life time hospitalization pattern. For all adverse events and total joint arthroplasties, the risk estimates were higher among survivors in the period close to the cancer treatment but for most skeletal adverse events the excess risk extended into late adulthood. Due to the rarity of osteonecrosis, osteoporosis, osteoarthrosis and total joint arthroplasties among children and young adults in the general population, the risk estimates for childhood cancer survivors were high, despite the low numbers of events. This needs to be taken into account when interpreting the results of studies III and IV. Among the oldest

survivors, the risk estimates for skeletal adverse events were lower. This could be due to the higher prevalence of osteoporosis and osteoarthrosis among older people in the general population as well as fractures leading to hospitalizations. These finding may also be influenced by higher all-cause mortality among survivors and the healthy survivor effect, a type of selection bias, where lower risk estimates for adverse health outcomes are expected with the increased age of the survivor. [251, 252] In addition, in our survivor cohort, there could be a selection among the oldest survivors for cancer types with a generally good outcome, for example patients with solid tumors that only received local treatment. The majority of the most heavily treated patients do not have as long follow-up time due to very poor survival prior to the 1980´s.

Since we excluded patients who died or emigrated before the start of national population registration, patients from the earliest period of the study are partly underrepresented. Furthermore, we might have missed a proportion of early events during the early era caused by the lag time between the date of patient accrual and the follow-up period. We performed sub-analyses to see whether left-truncation had an impact on our results but the effect was only minimal.

6.2.1 Osteonecrosis

Compared to other skeletal adverse events, the highest risk estimates we found were for osteonecrosis, especially among survivors of leukemia and lymphoma and survivors ≥10 years at cancer diagnosis and <40 years at hospitalization for osteonecrosis. These findings are in accord with previous findings. However, we described the life-time pattern across the spectrum of childhood cancer.

We chose to use one-year survivors instead of five-year survivors to capture early events such as osteonecrosis. Most events of osteonecrosis (65%, 45 of 69 patients) occurred within 5 years from cancer diagnosis. In a sub-analysis where we only included 5-year survivors our overall risk estimates were slightly lower but the main effect was on osteonecrosis since fewer events were captured (38 events instead of 69), resulting in RR of 14.8 (95% CI 7.9-27.6) for 5-year survivors compared to 25.9 (15.0-44.5) for 1-year survivors.

Most previous studies have used survey data or clinical trial reports to capture symptomatic osteonecrosis. Not all studies use MRI confirmed osteonecrosis as the study endpoint and a severity grade classification system has not existed until recently.[253] Hence, comparing findings between different reports on osteonecrosis is difficult. The ALiCCS study design allowed us to captured only events of osteonecrosis leading to hospitalizations, thus the study sensitivity to asymptomatic and less severe cases of osteonecrosis was limited. The total burden of osteonecrosis in our study may therefore be underestimated. We used RR as the main risk estimate in our study assuming that events were captured equally in both the survivor and comparison cohorts. However, when we only looked at data from the outpatient registries in Denmark and Sweden, the RR for osteonecrosis was lower than in the inpatient registries, RR 12.9 (95% CI 8.6-19.3) compared to 25.9 (15.0-44.5). This could indicate that patients with childhood cancer were more likely to be diagnosed and hospitalized than the comparison subjects (surveillance bias).

Interestingly, nine of the 69 patients with osteonecrosis did not have leukemia or lymphoma. For these nine patients, the pathogenic mechanism could be different than for the hematological malignancies. Case reports have been published on osteonecrosis in patients receiving low dose glucocorticoid therapy due to panhypopituitarism and in children with chronic renal failure.[254-256]

To understand the associations, we observed between cancer types and osteonecrosis, we would have needed access to treatment data. Collecting data on treatment exposure would have required extraction of data from medical records, a very resource-intensive task. The NOPHO ALL registry did not systematically collect data on non-fatal toxicities but there is a comment text variable where it is possible to report serious toxicities. There are 35 patients 1-18 years with BCP or T-cell ALL with reported osteonecrosis in the NOPHO ALL registry, 30 who received treatment according to ALL-92 and five according to ALL-2000, approximately 1% of the patient population. This proportion is significantly lower than reported from other trials. In the NOPHO ALL-2008 trial limited toxicity data was collected prospectively. A total of 29 cases of symptomatic osteonecrosis were reported among 934 patients 1-17.9 years at diagnosis (3.1%) in this protocol.[257] In a study by Mogensen et al, data was collected from medical records and questionnaires on 1489 patients 1-45 years included in the NOPHO ALL-2008 trial with symptomatic osteonecrosis.[160] This study characterized the clinical phenotype and identified treatment-related risk factors for osteonecrosis. The 5-year cumulative incidence of osteonecrosis in

this study was 2.2%, for patients 1-9 years but 20% for patients 10-18.9 years. In another study on the NOPHO ALL-2008 cohort including 1234 patients 1-45 years, the cumulative incidence of osteonecrosis was 2.7% for patients 1-9.9 years,14.9% for patients 10.0-17.9 years and 14.4% for 18-45 years.[176] In the NOPHO ALL-2008 cohort, female patients 10-18.9 years were at higher risk of osteonecrosis compared to the male patients at same age but sex differences were observed for other age groups.[160] In the ALiCCS-design, we did not observe statistically significant sex differences in hospitalizations for osteonecrosis, in general, among patients with hematological malignancies or among patients ≥10 years at cancer diagnosis.

6.2.2 Osteoporosis

The risk for osteoporosis was increased among childhood cancer survivors compared to comparison subjects up to the age of 30 years. The risk was highest in the time period close to the cancer diagnosis but decreased with time. The RR for osteoporosis vas 27.2 (95% CI 15.9-46.7) <5 years from cancer diagnosis, 10.6 (5.3-21.1) years 5-9, 5.7 (2.6-12.4) years 10-19 and if ≥20 years had passed from cancer diagnosis the RR was down to 1.86 (1.2-2.9). These findings indicate that survivors may recover from BMD deficits seen during cancer treatment and shortly after end of treatment. Previous studies have shown the same pattern, particularly among survivors who did not receive radiotherapy.[194, 258-260] The cessation of the chemotherapy and glucocorticoid exposure, increased physical activity, better nutrition and growth are all factors that contribute to improvement in BMD. Radiotherapy, however, is associated with more persistent BMD deficits.[261] Total body irradiation may directly affect the bone growth and bone formation.[262, 263] Growth hormone deficiency can occur after low irradiation doses such as TBI (10-14 Gy) and CNS prophylaxis in patients with childhood ALL (12-24 Gy) but at higher doses (>30 Gy) gonadotropin deficiencies are common.[264, 265] Radiotherapy involving the gonads (abdominal, pelvic, TBI) may cause gonadal insufficiency by permanently damaging the gonadal tissue.[266-269] The negative impact of cranial and gonadal irradiation on BMD is well documented and is likely mediated by the effect of hypogonadism on the bone metabolism.[210] Patients with growth hormone deficiency and hypogonadism are normally treated with growth hormone and sex steroid replacement therapy, however, growth hormone substitution itself has not been shown to improve BMD deficits specifically in childhood cancer survivors.[270]

In contrast to the case with osteonecrosis, we did not find a strong association between age at cancer diagnosis and the risk of osteoporosis. Nevertheless, the risk estimates were

higher for survivors diagnosed 0-9 years compared to 10-19 years. This could reflect both a higher proportion of cancer diagnoses most strongly associated with low BMD in patients younger than 10 years and the extreme rarity of osteoporosis in the younger population. Previous studies have not shown evidence in support of age as a risk factor for impaired BMD after adjusting for other baseline factors.[271, 272] As opposed to the other skeletal adverse events we studied, the RR for osteoporosis were slightly higher among male survivors. Male sex is generally considered an independent predictor for low BMD among childhood cancer survivors.[271, 272]

Osteoporosis does not give symptoms unless it causes bone fractures. In 75% of cases, osteoporosis was the secondary discharge diagnosis for hospitalization (71% in the comparison cohort). We captured only events of osteoporosis reported to the inpatient registries. By including outpatient clinic visits and data from the prescription registries we could have captured more events. Since we only had information on discharge diagnosis, we did not know how osteoporosis was defined in each case, whether it was based on DXA measurements and/or clinical criteria.

The strongest association we observed between cancer types and osteoporosis was for leukemias and CNS tumors. We found statistically significant RRs for osteoporosis among other cancer types (sympathetic nervous system tumors, renal tumors, hepatic tumors and "other and unspecific malignant neoplasms") but these estimates were based on very few events (1-3) and should be interpreted with caution. Patients with childhood ALL receive high cumulative doses of glucocorticoids during their primary treatment and may be exposed to additional glucocorticoids if relapse occurs and as treatment for GVHD if they undergo allogeneic HSCT. Patients with leukemia who undergo allogeneic HSCT often receive TBI and/or CNS irradiation and patients with CNS tumors commonly undergo CNS irradiation. These patients are at risk for low BMD at older ages.[200, 271-274]

6.2.3 Fractures

In study III, fractures were the most common reason for hospitalization in both cohorts. The risk of fractures was increased among survivors until the age of 60 years. The risk of recurrent hospitalizations for fractures was also higher among the survivors compared to the comparison subjects. We did not observe an association between age at cancer diagnosis and the fracture risk but the overall fracture risk estimate for female survivors was higher than for male survivors, RR 1.52 (95% CI 1.39-1.67) compared to 1.16 (1.09-1.24). For osteoporotic fractures (fractures of distal radius, proximal humerus, vertebrae,

pelvis, hip, distal femur or proximal tibia) the RR was slightly higher, 1.60 (95% CI 1.34-1.90) for female survivors and 1.30 (1.12-1.50) for male survivors. In males <30 years the hospitalization risk for fractures was lower than for the male comparison subjects (data not shown). In the North American CCSS, male survivors had generally a lower risk of fractures than their siblings.[213] This could be explained by less exposure to trauma among male survivors at younger ages than in the general population.

Fractures at older ages are associated with age-related osteoporosis. Even though the risk for osteoporosis was only statistically significantly increased among survivors up to the age of 30 years, the fracture risk extended to the age of 60 years. This could still be due to lower BMD among survivors at older ages and not detected in our study, premature ageing of the skeletal system, increased frailty and the effect of other chronic health conditions on bone health and the risk of falls.[275] We did not observe a significant difference in the risk for fractures between survivors with history of hospitalizations for neurological disorders and survivors that did not have these co-morbidities (Paper III, Table S3, supplementary material). Interestingly, the risk of fractures was not statistically significantly higher among survivors with history of hospitalizations for endocrine disorders compared to comparison subjects. The effect of endocrine disorders on fractures could be mitigated by efficient hormone replacement therapy.

We observed an excess risk for fractures among survivors of leukemia RR 1.2 (95% CI 1.1-1.4), CNS tumors RR 1.6 (1.4-1.7), sympathetic nervous system tumors RR 1.6 (1.3-2.0) and malignant bone tumors RR 2.7 (2.2-3.2). If we only looked at osteoporotic fractures the risk estimates were higher, except for leukemia: leukemia RR 1.2 (95% CI 1.0-1.6), CNS tumors RR 1.9 (1.6-2.3), sympathetic nervous system tumors RR 1.8 (1.1-2.9) and malignant bone tumors RR 3.5 (2.6-4.8). Although low BMD could be the underlying reason for fractures, in malignant bone tumors, local weakness (arthroplasty/surgery-related, local radiotherapy) in the bone may be the predominant cause of fractures.

6.2.4 Osteochondropathies and osteoarthrosis

Hospitalizations for both osteochondropathies and osteoarthrosis were more common among childhood cancer survivors than among comparison subjects, for osteochondropathies up to the age of 20 years and for osteoarthrosis up to the age of 50 years. This is a novel finding since these skeletal adverse events have previously not been described in childhood cancer survivors.

During childhood, the skeletal system is growing rapidly and the more immediate effects of cancer treatment may cause a higher risk of osteochondropathies. In our study, osteochondropathies were a collection of several ICD codes for diseases and disorders involving cartilage and joint surface (Paper III, Table S1, supplementary material). One of these was Legg-Calvé-Perthes disease, a rare disease that affects the hip joint and most often presents during childhood.[276] As in osteonecrosis of the hip, the pathogenic mechanism is ischemic damage to the bone tissues of the femoral head that causes weakness in the bone structures and may ultimately lead to collapse of the hip joint. Legg-Calvé-Perthes disease is coded in ICD as osteochondrosis or osteochondropathy. Since osteonecrosis was not available as a specific ICD code until the implementation of ICD-9 in the 1980s and severe osteochondropathies such as Legg-Calvé-Perthes disease may have similar clinical presentations as osteonecrosis, it is possible that some of these skeletal adverse events were misclassified in our study.

Both osteochondropathies and osteoarthrosis were more common in survivors of leukemia. This finding could have different explanations. Glucocorticoids and systemic chemotherapy might have damaging effects on joints either directly on bone and cartilage forming cells or indirectly by causing avascular necrosis. Furthermore, osteoarthrosis may develop secondary to osteonecrosis, osteochondropathies and fractures. The excess risk of osteoarthrosis among survivors of CNS tumors could for example be secondary to previous fractures. Among patients who undergo TBI prior to allogeneic HSCT, it is possible the TBI causes subclinical joint damage that leads to degenerative changes in bone and cartilage tissues and earlier presentation of osteoarthrosis.[277] The associations we observed between osteochondropathies and osteoarthrosis and some of the solid tumors could be caused by the local treatment, radiotherapy or orthopedic surgery.

6.2.5 Total hip and knee arthroplasties

In study IV, childhood cancer survivors had an 80% increased risk of undergoing total joint arthroplasty compared to the comparison subjects. In general, childhood cancer survivors underwent total joint arthroplasty earlier in life than the comparison subjects. Among the survivors, 66% of the THA and 28% of the TKA were performed before 50 years of age compared to 38% and 24% among the comparison subjects, respectively.

All arthroplasties we captured in our study were primary arthroplasties that occurred at least one year after cancer diagnosis. Ten total hip arthroplasties and 34 total knee arthroplasties were performed among the childhood cancer survivors less than one year after cancer diagnosis. None of the arthroplasties we included as primary arthroplasties were revisions of earlier arthroplasties.

Previous studies have shown that survivors of leukemia and lymphoma are at higher risk of total joint arthroplasties. In our study, the risk estimates for THA were statistically significantly increased among survivors of leukemia and lymphoma (nearly six-fold increased risk) and survivors of extra-cranial solid tumors other than malignant bone tumors (56% increased risk) but not among survivors of CNS tumors and malignant bone tumors, compared to comparison subjects. The most likely explanation for the association between THA and leukemia and lymphoma, is the higher incidence of osteonecrosis among survivors of leukemia and lymphoma. Our findings in study III support this. Osteonecrosis of the hip has been associated with pelvic radiotherapy and could therefore be one the explanations for the excess risk among survivors with solid tumors.[278] Approximately 80% of survivors the underwent either THA or TKA were ≥10 years at cancer diagnosis. This could reflect the increased risk for osteonecrosis in this age group in study III and the higher incidence of malignant bone tumors in children ≥ 10 years of age.

To find vulnerable subgroups we compared risk factors within the cohort of childhood cancer survivors. We did not confirm previous findings that patients ≥10 years at cancer diagnosis were at higher risk of undergoing arthroplasty than younger patients after adjusting for sex and cancer diagnosis, although the crude and adjusted risk estimates indicate some associations between older age at cancer diagnosis and THA. In the adjusted regression models, leukemia and lymphoma were an independent risk factor for THA and malignant bone tumors for TKA.

As for the general population, osteoarthrosis was the most common operation indication for both THA and TKA among the childhood cancer survivors. Osteonecrosis was registered as the operation indication for THA in 14% of the survivors but only in 1% of the comparison subjects. We suspect that a number of patients with osteonecrosis were classified as “other reason” which covered nearly 30% of the survivors but only 6% among comparison subjects. Malignancy was the operation indication for TKA in 12% of survivors. This could be due to relapse or metastatic lesions.

Our study was underpowered to conduct analyses on implant survival. The median time from primary THA to surgical revision was similar for the survivor and the comparison cohorts (8.0 vs 7.4 years) but the median time from primary TKA to surgical revision was shorter for the survivors (1.0 vs 3.7 years).

With the growing number of childhood cancer survivors reaching older ages and improved access to joint replacements, more childhood cancer survivors are expected to receive total joint arthroplasties. Until the we find ways to decrease the risk of serious skeletal adverse events total joint arthroplasties will continue to be the definitive treatment of severe skeletal morbidity in the up-coming decades.

7 STRENGTHS AND LIMITATIONS

7.1 STRENGTHS

7.1.1 Studies I and II

The nationwide coverage in all of the Nordic countries, the long follow-up time, few patients lost to follow-up and the high data quality in the NOPHO ALL registry are all major strengths of studies I and II. Furthermore, patients included in the studies received a highly standardized primary treatment and were derived from a population with very similar health care services in all of the Nordic countries. These preconditions are very helpful when studying rare diseases and late occurring events. The size of our cohort enabled us to identify subgroups of patients with worse outcome with sufficient statistical power for stratifications and inclusion of multiple variables in regression models.

How end-points are defined are not always consistent between studies and trials. This can make it very difficult to compare results between different studies. In study II, we used a definition of TRM that was developed by the International Pediatric Oncology Mortality Classification Group and published in 2015.[130] This will allow for more accurate comparisons with future studies that use the same definition. In study II, we used the definition of remission and relapse that has been used in the NOPHO countries over the last decades. The Ponte-di-Legno Consortium has very recently published a paper defining consensus definitions of remission, treatment failure and relapse.[279] However, this consensus paper does not specify whether other definitions apply for second remission or second relapse. These definitions are similar to the ones used in studies I and II in the absence of MRD. Although bone marrow remission and relapse status are now mainly based on MRD measurements, CNS remission and relapse status is still based on cytomorphology.

7.1.2 Studies III and IV

The nationwide coverage, the large cohort size, long follow-up time, few patients/comparison subjects lost to follow-up, a population with similar access to health care, robust outcome variables and the very reliable Nordic registry data are all major strengths of studies III and IV. The North American Childhood Cancer Survivor Study (CCSS) does not have a nationwide coverage and does not include all cancer types. As in the British CCSS, self-reported outcomes are used and compared to sibling comparison

subjects (Table 2 - Introduction). Studies that rely on self-reported outcomes can be subject to both information bias and selection bias. Information bias (misclassification and recall bias) may be introduced when answers from study participants are incorrect, incomplete or missing. Selection bias may occur for example if survey non-responders are systematically different than the responders (non-response bias) resulting in lack of generalizability to the whole childhood cancer survivor population.[280, 281]

The ALiCCS study design has been validated by a number of studies on other types of adverse events than in the skeletal system. The results of these studies are in accord with findings from studies using different study designs, thus giving us confidence regarding the generalizability of our findings. To our knowledge, no study has previously described the lifetime pattern of skeletal adverse events and arthroplasties among survivors across the spectrum of childhood cancer and no large-scale study has described osteoarthrosis and osteochondropathies among childhood cancer survivors. In study III, we also conducted sensitivity analyses to check the robustness of our study design, which did not expose any significant flaws. In these analyses, we searched for potential effect modification by other somatic adverse events, specifically endocrine and neurological diseases, but did not find a major effect on the study risk estimates. The Nordic arthroplasty registries are excellent and validated sources of data with nearly complete nationwide coverage of all total hip and knee arthroplasties. Using data on arthroplasties from the hospital registries would have been difficult due to the heterogenous coding through the course of time. Furthermore, data on the operation indication would not have been accessible.

7.2 LIMITATIONS

7.2.1 Studies I and II

In all registries, data may not be complete and there is always a risk of misclassifications and coding errors. To counter this issue, we reviewed the registrations for each patient regarding consistency and missing data and asked the recruiting centers for clarifications or additional data, when necessary. A major limitation of studies I and II was the lack of reliable information on possible changes in the genetics of the leukemic clone at relapse but, likely even more important, the lack of MRD data both during the primary and relapse treatments. In the Nordic countries MRD analyses started to be implemented between 2001 and 2003. Measurements of MRD are now a central tool in the risk stratification and it would have been interesting and possibly added valuable information to include MRD

values to our regression models in which we examined the effect of baseline factors on overall survival. Furthermore, it would have been interesting to compare the MRD response at primary diagnosis and at relapse. We could only rely on the data available in the NOPHO ALL registry, but access to medical records would have allowed us to examine for example non-lethal toxicity and the effect of treatment modifications due to toxicity and treatment delays on survival.

For patients <18 years information on the current follow-up status is very reliable in the NOPHO ALL registry but for those that have been transferred to the adult clinics, information on actual follow-up status is more sporadic. This is a major shortcoming of the NOPHO ALL registry and creates uncertainties regarding its ability to capture events that occur when then patients have left the pediatric clinics. Although the median follow-up time of patients surviving in CR2 was relatively long (12 years for ALL-92 and 5 years for ALL-2000), we did not have complete follow-up time for all patients. Generally, this is mainly of concern for patients who have completed their follow-up at the pediatric clinics and to evaluate the risk of late occurring events (second relapse, SMN and late all-cause or health-related mortality). Therefore, it is possible that our studies did not capture all second events resulting in some overestimation of survival outcomes after relapse.

Because of the rarity of some entities, we felt obliged to group the cytogenetic aberrations to gain power for statistical analyses. Analyzing each type of cytogenetic aberration separately would have been preferable but due to the low number of patients with the less common aberrations we chose to analyze cytogenetic aberrations associated with similar outcomes together. Since all the genetic aberrations we used are almost exclusive to the BCP group (except *KMT2A*-rearrangements), including T-cell ALL as a separate subgroup would have been more correct than including T-cell ALL in the group “other cytogenetics”. Access to biomaterial (germline and malignant) for additional analyses when data were missing would have been very helpful and could have given new insights into possibly new underlying genetic factors for the outcome of patients with relapsed ALL.

Since the focus of the NOPHO-registration has been the primary chemotherapy protocol therapy, the NOPHO ALL registry, contains limited data on hematopoietic stem cell transplant (HSCT) donor type, donor mismatch, conditioning regimens, immunosuppression and graft-versus-host disease (GVHD) severity and treatment.

Therefore, we were not able to take into account and adjust for these important HSCT-related factors in our analyses in studies I and II.
Access to more detailed HSCT data is available in the European Group for Bone Marrow Transplantation (EBMT) registry. The Nordic countries have registered patients that undergo HSCT in the EBMT registry since the 1980´s. However, the coverage is not complete in all countries, especially during the 1980´s and 1990´s and access to registered data is somewhat cumbersome. We did not have access to the EMBT registry data but it would have been interesting to add more detailed HSCT data, especially in study II.

7.2.2 Studies III and IV

A major limitation in studies III and IV was the lack of treatment data. To some extent, the use of uniformly applied treatment protocols, the cancer type and the time-period the cancer was treated may serve as a proxy for the administered treatment. However, to be able to make reliable inferences on causalities, access to treatment data is necessary. We were able to retrieve data on allogeneic HSCT and radiation therapies from the Danish NPRs but the data was not complete and this is the reason we chose not to analyze it further. Relapse of leukemia was available as separate codes in ICD-9 and ICD-10 but not for other types of cancer. Since patients with leukemia relapse constitute a heavily treated population, who are likely to be at risk for many types of serious adverse events, it would have been interesting to look further at this subgroup of survivors – but as we learned from study I, the number of long-time survivors would have been low.

The coding differences between the four subsequent versions of the ICD classification system may have influenced our results. Osteonecrosis was for example not available as a diagnostic code in ICD-7 or ICD-8 (1955-1986), therefore adverse events due to osteonecrosis were most likely underreported in study III. How osteonecrosis was coded during the ICD-7 and ICD-8 era is unknown but it is possible that some cases of osteonecrosis were coded as osteochondropathies.

In study III, we counted only skeletal adverse events reported to the national NPRs as inpatient discharge diagnoses. The nationwide coverage of the Nordic NPRs has been excellent over the last decades but some events that occurred during early phases of the NPR recruitment periods might have been missed. In addition, coding errors, translation errors and diagnostic errors have been described in the NPRs.[282] However, since these factors are general limitations of registry studies, they most likely affected both the survivor

cohort and comparison subjects equally and therefore the impact on the risk estimates in study III is probably only minimal.

Adverse events that do not need hospitalizations are underreported in the ALiCCS studies. We conducted a sensitivity analysis on the available data from outpatient visits in Denmark (from 1995) and in Sweden (from 2001) and found that the risk estimates were generally lower in the outpatient setting. This could indicate that survivors were more likely to be hospitalized than comparison subjects introducing a hospitalization/surveillance bias. However, it could also mean that survivors are at risk for more serious skeletal adverse events than the comparison subjects.

Although the coverage of the Nordic arthroplasty registries is now nearly complete, not all hip and knee arthroplasties performed during the early phases of the study period were likely to be captured. The Nordic arthroplasty registries mostly, include the same type of information but the coding and the list of variables are not uniform. This creates difficulties during data linkage across registries. In study IV, merging the operation indication data was challenging due to the heterogeneity of the data registration. For example, in the Finnish arthroplasty registries only three groups of operation indications are available in contrast to the Swedish knee arthroplasty registry where 14 groups exist. Data on osteonecrosis was only available in the Danish and Swedish arthroplasty registries. The nine groups of operation indications we assigned the study participants to in study IV, is therefore limited by how the operation indication was coded in each registry. With more detailed data, the group “other indication” would have been smaller and we would probably had identified a number of additional cases with osteonecrosis.

8 GENERAL CONCLUSIONS

Studies I and II highlight the need for new therapeutic approaches for relapsed childhood ALL. Although we observed improvements in survival over time, overall survival, especially for high-risk relapse patients is still poor. The trade-off between long-lasting remission and treatment toxicities is a balance that is hard to maintain with chemotherapy-based strategies and allogeneic HSCT. Subsequent relapse is the main threat to cure but TRM and SMN both contribute significantly to the poor outcome. Baseline risk factors and treatment response reflect the biology of the underlying disease and the host genomics. Therefore, it is of utmost importance to identify genetic risk factors and subsets of patients to refine the risk stratification further and optimize the difficult balance between prolonged second remission and treatment toxicity. If the relapse rate continues to decrease, the remaining relapses will be harder to cure due to inherent treatment-resistance. This was seen in the NOPHO ALL-2008 trial, where the relapse rate for patients 1-14.9 years decreased significantly but for those who relapsed, no improvement in the overall survival or the incidence of TRM was observed (unpublished data). Hopefully, now with the introduction of novel agents and modes of immunotherapy, continuing individualization of the relapse treatment will result in improved survival and less long-term side effects. To accomplish this goal, large international collaborations are needed in addition to successful cooperation with regulatory authorities and the pharmaceutical industry.

The lessons from studies I and II may be generalized to other types of relapsed cancer. Short time in first remission, high risk clinical features and unfavorable genetic profiles are in general the strongest predictors for poor outcome in patients with relapsed cancer.[283-286] However, these factors are normally not used to guide the relapse treatment. Thorough risk stratification, identification of targetable lesions and development of novel therapies are more likely to succeed in improving the outcome after relapse than further modification of conventional chemotherapies and more aggressive local treatments.

Studies III and IV gave estimations on the risks and patterns of skeletal adverse events and total joint arthroplasties in a treatment era extending over many decades. Childhood cancer survivors had an increased risk of skeletal adverse events and total joint arthroplasties compared to the comparison subjects, especially survivors of hematological malignancies. During the last decades, response- and risk-based therapies have evolved to adjust treatment intensities. Nevertheless, only minimal changes have been made in the backbone treatment for the majority of childhood cancer subtypes and multiple efforts to improve survival by

treatment intensification have often failed and resulted in increased toxicity.[287, 288] Although the expectations regarding individualized therapies are high, little is known about the long-term toxicities and a new spectrum of toxicities might emerge that could affect the future health of childhood cancer survivors. There is for example mounting evidence that targeted therapies may affect growth and bone metabolism adversely.[289, 290] The excess risk of long-term toxicity is therefore expected to continue in the near future.

In this thesis we studied relapsed childhood ALL and skeletal adverse events in childhood cancer survivors by using data from the Nordic health registries. We were able to establish large cohorts of study participants which enabled us to identify vulnerable subgroups and factors associated with adverse outcomes. The long follow-up time allowed us to capture late-occurring events and by tracking study participants through different registries we could map the life time patterns of skeletal adverse events and total joint arthroplasties. Our studies confirm that the Nordic health registries a are valuable source of information on childhood cancer and can be used to gain new knowledge that may be used to identify possible targets for improvement in outcome for patients and survivors. Continuing efforts to improve data integrity and data linkage approaches are important to maintain the high quality of the Nordic health registry-based research. The regulatory framework should work on finding ways to promote registry-based research and research collaborations without compromising data safety and at the same time protecting the autonomy and integrity of the study participants.

9 FUTURE PERSPECTIVES

9.1 PREVENTING ALL RELAPSE

The most obvious way to improve survival in patients with childhood ALL is by preventing the occurrence of relapse. In the ongoing ALLTogether trial a more individualized risk stratification was implemented by including more advanced genetic profiling and MRD measurements and by adding age back as a stratifying factor. In addition, an upfront use of tyrosine kinase inhibitors in patients with ABL-class fusions and the possibility to use immunotherapies for DS-ALL and high-risk patients with BCP-ALL were made available. Hopefully, these strategies will further reduce the frequency of relapse.

9.2 THE PROBLEM OF CNS INVOLVING RELAPSE

The high proportion of CNS involving relapses in the NOPHO ALL trials indicates that better strategies are needed for CNS-directed ALL therapy. Historically and up to now, CNS involvement has been detected with and defined by cytology findings. Flow cytometry is a more sensitive and specific method and could provide better prediction of BCP relapse than cytology only.[291] More sensitive methods such as PCR and high-throughput sequencing for measuring CNS involvement both at primary diagnosis and for measuring treatment response during treatment could be helpful in identifying patients who need intensified CNS-directed therapy. The same applies to ALL relapse. CNS-directed therapies include both systemic and intrathecal chemotherapy as well as irradiation of the CNS. Therapies that target CNS infiltration, CNS survival pathways or CNS quiescence mechanisms specifically are currently not available for patients with childhood ALL.[100] CNS irradiation has been abandoned by most cooperative groups during the primary treatment but it is still commonly used during the relapse treatment. No randomized studies have been designed to test the importance of CNS irradiation among patients with ALL relapse but in the InReALL 2010 trial patients with CNS-involving SR and HR relapses are recommended to receive CNS irradiation. Continuing development of better diagnostic methods for CNS leukemia and more specific and less toxic CNS-directed therapies are warranted.

9.3 TAILORING THE RELAPSE TREATMENT

Most current ALL relapse trials are starting to implement genetic findings and MRD response to guide the choice and intensity of the relapse treatment. The advances in molecular technologies have led to identification of genetic subgroups of relapsed ALL with distinct outcome patterns and potential targets for novel therapies. High resolution genomic profiling will therefore be a central tool in future risk stratification of ALL relapses. Currently, flow cytometry and PCR-based MRD techniques are the standard methods used for MRD analysis. Further refinements in the risk stratification by the use of ultra-sensitive techniques such as high-throughput sequencing for measuring treatment response (both in the bone marrow and CSF) could allow for more precise risk adjustments.[292, 293]

9.4 NEW DIRECTIONS IN THE TREATMENT OF RELAPSED ALL

The addition of tyrosine kinase inhibitors to the backbone chemotherapy was a giant leap towards personalized treatment of *BCR-ABL1*-positive ALL in children and adolescents.[294, 295] ABL-class fusions (*BCR-ABL1*-like fusions) are associated with poor outcome but recent upfront ALL trials have shown improved survival in patients with ABL-class fusion positive BCP ALL when tyrosine kinase inhibitors are added to the standard treatment.[296, 297] In adults with *BCR-ABL1*-positive BCP ALL chemotherapy-free strategies (glucocorticoids, dasatinib and blinatumomab) have shown very promising results and will hopefully be tested among children in the near future.[298] Similarly, studies have shown patients with mutations in the JAK-STAT signaling pathway might benefit from the addition of JAK inhibitors such as ruxolitinib.[299]

The emergence of immunotherapies for patients with refractory and relapsed B-precursor ALL have revolutionized the treatment landscape of high-risk and relapsed ALL.[300-303] Bispecific antibodies (blinatumomab), immune-directed chemotherapy (inotuzumab ozogamicin) and CAR-T cells are either used as a definitive treatment or as a bridge to allogenic HSCT. Reports from clinical trials on children and young adults have shown very encouraging results and long-time follow-up studies have shown that durable remission can be obtained, especially among those where the treatment is followed by allogeneic HSCT.[304-306] When immunotherapies are used as a definitive treatment, relapses are still a major obstacle.[307, 308] However, later generations of CAR-T cells have shown promising results with more durable remissions.[304] Patients with relapse of T-cell ALL generally have poor prognosis and few new effective therapeutic alternatives have emerged. The addition

of nelarabine to the upfront chemotherapy for T-cell ALL and relapsed T-cell ALL has shown promising results.[309, 310] Currently, CAR-T cells are commercially not available for T-cell ALL, but in a phase I study on donor-derived CD7 CAR-T cells a high complete remission rate was achieved with tolerable toxicity.[311]

In the Nordic countries, the new IntReALL 2020 trial for SR and HR ALL relapse is expected to open in 2022. In this trial, genetic features and MRD response will be used in addition to immunophenotype, the time to relapse and the site of relapse to stratify patients between SR or HR relapses and determine the indication of allogeneic HSCT. Furthermore, immunotherapy will be integrated in both the SR and HR arms of the trial.

9.5 IMPROVING THE SKELETAL HEALTH OF FUTURE CHILDHOOD CANCER SURVIVORS

The most important step in reducing the burden of skeletal morbidity among childhood cancer survivors is minimizing the exposure of glucocorticoids and irradiation during the cancer treatment. Attempts to reduce treatment-related bone toxicity have mainly been focused on reducing the occurrence and severity of osteonecrosis in patients with ALL.[165] Glucocorticoids are an integral part of the treatment for lymphoid malignancies but despite recent advances in the leukemia treatment, patients still receive high cumulative doses of glucocorticoid. The incidence of osteonecrosis, glucocorticoid-induced BMD deficits and total joint arthroplasties in long-term survivors is therefore not expected to decrease in the near future. Patients with Duchenne muscular dystrophies receive high cumulative doses of glucocorticoids but the incidence of osteonecrosis is low. However, low BMD and fractures are common.[312] Studies are ongoing to investigate the effectiveness of glucocorticoid analogues, such as vamorolone, that cause minimal bone toxicity but retain the anti-inflammatory activities.[313] No studies have been published yet on the effect in childhood cancer.

To minimize the effect of cancer treatment on the accrual of peak bone mass in children and adolescents, modifiable factors such as physical exercise, body weight and diet should be optimized and calcium and D-vitamin deficiencies prevented. An interventional study, iBoneFIT, is ongoing and will test bone health promoting interventions in childhood cancer survivors (6-18 years) after cessation of treatment.[179] Early diagnosis and treatment of treatment-induced endocrinopathies is very important since it can mitigate the negative effect of hormone deficiencies on the bone health. Tools to identify survivors at high risk for low

BMD have been developed but in 2021, the International Late Effects of Childhood Cancer Guideline Harmonization Group (IGHG) published clinical BMD surveillance guidelines for childhood, adolescent and young adult cancer survivors patients.[210, 271] In these guidelines, BMD surveillance is recommended for survivors that received CNS irradiation and is considered reasonable for survivors that underwent TBI prior to allogeneic HSCT. Due to the lack of evidence and the heterogeneity of previous studies, no specific recommendations could be formulated for different exposures of glucocorticoids.

In survivors where low BMD is detected, pharmacological interventions with bisphosphonates or other bone resorption inhibitors are likely to improve or are least stop further decline of the BMD. Randomized studies are needed to test whether pharmacological interventions decrease the fracture risk in childhood cancer survivors with low BMD.

No specific treatment interventions are currently available for osteonecrosis. The main focus has been on the pain management but pharmacological interventions aimed at reducing the severity or progress of osteonecrosis have failed to show beneficial effect.[167] In patients where the joint surface has not collapsed, local treatments could be a therapeutic option in the future. Studies on core decompression with insertion of mesenchymal stem cells have shown promising results and deserve further research.[314, 315] To reduce the direct toxic effects of chemotherapy and radiotherapy on the bone tissue, methods that ameliorate or prevent bone toxicities/bone loss are under development.[278, 316]

9.6 STUDIES ON BONE MORBIDITY IN CHILDHOOD CANCER SURVIVORS

The gold standard when studying the health of childhood cancer survivors is a prospective collection of health-related information as well as inclusion of detailed disease and treatment data and host genomics. This approach was adapted in the St Jude LIFE and DCOG LATER studies.[59, 317] In both of these studies, childhood cancer survivors undergo medical examinations and various investigations such as DXA scans. These two studies are expected to be major contributors to future research on bone morbidity in childhood cancer survivors. The German OPAL and the British BONES studies are both ongoing prospective studies on adolescents and young adults with lymphoid malignancies that study osteonecrosis by performing MRI examinations at certain timepoints during the treatment.[166, 318]

In the Nordic countries, the ALL-STAR study will examine adverse health events in survivors treated according to the NOPHO ALL 2008 protocol. Survivors will be invited to undergo medical examinations at their local clinics and different types of investigations will be performed including DXA scans and for patients with a history of osteonecrosis even MRI of the affected localizations. The NOPHO CARE project will collect detailed baseline, treatment and outcome data on all childhood cancer survivors in the Nordic countries. The NOPHO CARE registry will be a valuable resource of data for studying health-outcomes in childhood cancer survivors in the future.

The large EU funded PanCareLife and PanCareSurFup project did not examine bone morbidity. The new PanCareFollowUp project will not investigate bone morbidity specifically but facilitate the implementation of harmonized recommendations and survivorship care across Europe. A person-centered guideline-based model of care and lifestyle interventions will be developed.[319] The North American CCSS is now conducting a study on total joint arthroplasties where treatment data will be included.[320] This study may provide some of the treatment-related data we could not provide in our registry-based study.

9.7 THE CURRENT LANDSCAPE AND PARADOXES

There are high hopes that novel therapies will contribute to improved treatment and outcomes of patients with childhood cancer. It may seem paradoxical that, when the ambition is to move towards more individualized approaches for our patients to come, great efforts are being placed in establishing large international collaborations to integrate more harmonized treatments for childhood cancer. However, this is necessary, since uniform treatment gives opportunities to explore treatment de-escalations, improve risk stratification and creates a platform to compare new therapeutic strategies to the standard treatment. Although immunotherapies and targeted agents have shown promising response rates in subgroups of patients, we do not presently know how they will affect long-term survival and how the spectrum of their side effects, especially when given in combination with other novel therapies or standard chemotherapy, will affect the future health of childhood cancer patients. We are a long way from omitting conventional chemotherapy, allogeneic HSCT and radiotherapy in the treatment of childhood cancer. Childhood cancer patients will therefore continue to be exposed to treatments with potential serious toxicities and long-term side effects. This emphasizes the need for further optimization of supportive care, continuing development of evidence-based follow-up recommendations and improved access to survivorship care.

10 ACKNOWLEDGEMENTS

First of all, I want to thank my main supervisor **Mats Heyman**. It has been a "blast" working with you on this PhD project and on all of our leukemia-related side projects. Thank you for paving the way for me into the field of childhood cancer epidemiology, giving me opportunities to develop as a researcher and for your great support, patience and encouragement all these years. You are a true role model.

My co-supervisors, **Arja Harila-Saari**, **Cecilia Petersen** and **Scott Montgomery**. I am very thankful for all your help, advice and input during the different stages of the project.

Jeanette Falck-Winther, Head of Childhood Cancer Research Group at the Danish Cancer Society Research Center and supervisor of the ALiCCS project. Thank you for an enjoyable collaboration, your help with all study coordination and your hospitality during our meetings in Copenhagen.

Ásgeir Haraldsson and **Ólafur Gísli Jónsson**. Thank you for giving me the opportunity to start my cancer research career during my work at the Children´s Hospital, Reykjavík. I am very grateful that your mentorship has now evolved into a long-lasting friendship.

Anna Nilsson and **Niklas Pal**. Thank you for your clinical mentorship and all valuable life (and culinary) lessons. You have shaped me as a clinician and I look forward to learning more from you in the future.

Pernilla Grillner. Thank you for giving me the opportunity to work on my research in parallel with my clinical work as well as helping me grow as a clinician.

I have had the opportunity to work with a group of very talented statisticians. **Matteo Bottai**, **Ida Hed Myrberg**, **Cristina Boschini**, **Anne Katrine Duun-Henrikssen** and **Christian Dehlendorff,** thank you all for your excellent work and being understanding when I have been totally lost in the statistical jungle. You "R" awesome.

I also want to thank the data managers at the Danish Cancer Society Research Center, **Andrea Bautz**, **Anja Krøyer** and **Thomas Tjørnelund Nielsen**, for their part in preparing the large datasets and for their work on the ALiCCS studies.

I want to thank the Nordic arthroplasty registries for the collaboration. Specially, I want to thank **Göran Garellick** the former supervisor of the Swedish Hip Arthroplasty Registry for the advice on the study design and help with data collection.

I want to thank all of my friends and colleagues at Barncancerforskningsenheten (BCFE), especially **Désirée Gavhed** and **Jenny Juhlin** for all their administrative support, enjoyable cooperation and friendship.

I am very thankful for the help I got from the **national PI´s**. Applying for ethical permissions and data access to registry data is very time consuming and for studies you are not directly involved in, it may be hard to find the motivation. In the ALL relapse studies we also asked **local PI´**s for data supplementation if the registry data was incomplete. Thank you all for your help and contribution to my studies.

My **co-authors** have all contributed to the final outcome of my papers and I am very thankful for their input.

While writing my thesis and planning for the dissertation, **Åsa Dickson** was very helpful and encouraging. Thank you for your enthusiasm and for sharing your experiences with me.

To all of my wonderful **colleagues and staff** at the pediatric oncology department, Karolinska University Hospital. It is a true joy and a privilege to work with you. You make this difficult work much easier. Onc´n´roll.

I want to thank **Barncancerfonden** for funding my clinical research position (ST-forskartjänst). This position was extremely valuable and gave me the opportunity to combine my research with the clinical work.

My **patients and families**. You inspire me to be better every day and find ways to improve the care and outcomes of patients with cancer.

Dear family and friends, thank you for supporting me and believing in me. **Gallerí Brisi** for creative inspirations, my best friend **Flóki** for always being there for me and special thanks to my mother, **Guðný**, you are a savior. It makes all the difference to have your people encouraging you at the side lines during this long run.

My dear **Katarina**. I know it has not always been easy for you when I am racing the deadlines or when I am deeply absorbed in work. You have taught me that even though I take a time off sometimes it does not translate into poor work ethics. Your support has been invaluable and I am immensely grateful to have you in my life. I look forward to our future journey.

Lastly, **Elí and Una**, my gems. I have always tried my best to be there for you. Thank you for helping me see life from the right perspective. I love you so much.

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