Childhood Cancer in the Nordic Countries
Report on Epidemiologic and Therapeutic Results
from Registries and Working Groups

Nordic Society of Paediatric Haematology and Oncology

ANNUAL REPORT 2016

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Foreword

Dear NOPHO members,

The NOPHO report 2016 is ready. Thank you for reporting data to the registries and for being active in the working groups! Thanks to the authors for communicating those results to us all and thanks to Jenny Juhlin who once again succeeded to put the report together in due time!

The last NOPHO year has been an exciting one. Above all, the approval of the Lithuanian full memberships comes with a significant and very welcomed strengthening of our society.

International collaboration with partners outside NOPHO is steadily increasing with a challenge to improve our organization in order to facilitate such collaborations even more. We need to have an efficient and fast way of dealing with requests and offers from outside with a smooth pathway to anchor decisions at national levels. The newly formed Solid Tumour Committee is an attempt to organize the solid tumour issues accordingly, parallel to the Leukemia lymphoma committee and Brain Tumour committee. As a part of the structural process, the so called sleeping or inactive working groups have been transferred to the archive part of the website - they could of course be resuscitated if needed.

In January, a working group assigned by the Board, arranged a workshop on legal issues within the Nordic countries. Invited lawyers and representatives from ethics committees, biobanks, medical product agencies and data protection authorities were present and gave valuable advice on how to prepare for future studies and collaborations both within and outside NOPHO, you will find the memos on www.nopho.org under "NOPHO Board".

Once again; thank you all for contributing to NOPHO!

Stockholm April 18th 2016
Cecilia Petersen
Secretary General

NOPHO Board

Members 2015 - May 2016

Secretary-		
-general	Cecilia Petersen (SE)	elected 2014
-elect	Mervi Taskinen (FI)	elected 2014
Treasurer	Peder Skov Wehner (DK)	elected 2015
Auditors of accounts	Gustaf Ljungman (SE)	elected 2005
	Birgitte Klug Albertsen(DK)	elected 2015
Stand in auditor of accounts	Svein Kolmannskog (NO)	elected 2005
Denmark	Peder Skov Wehner	elected 2015
	Lisa Hjalgrim	elected 2014
Finland	Jukka Kanerva	elected 2012
	Satu Lehtinen	elected 2013
Iceland	Ólafur Gisli Jónsson	elected 2000
	Solveig Hafsteinsdottir	elected 2013
Norway	Bendik Lund	elected 2015
	Petter Brandal (radiotherapy)	elected 2012
	Eva Widing	elected 2013
Sweden	Torben Ek	elected 2012
	Per Kogner	elected 2015
Young NOPHO	Jan-Bernd Stukenborg (SE)	elected 2014

NOPHO Secretariat and Webmaster

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Participating clinics/institutions/physicians

Through the years, many colleagues in NOPHO have been involved in treating and reporting of tumor childhood cancer from the Nordic countries. The main contributors are listed below:

Denmark	Copenhagen, Rikshospitalet	Kjeld Schmiegelow, Thomas Frandsen, Karsten Nysom, Catherine Rechnitzer, Birgitte Lausen, Astrid Sehested
	Odense	Peder Skov Wehner, Eckhard Schomerus
	Aarhus	Niels Clausen, Henrik Schrøder, Henrik Hasle, Birgitte Klug Albertsen, Pernille Edslev Wendtland Christine Dahl, Karin Bækgaard Nissen
	Aalborg	Steen Rosthøj, Erik Østergaard, Ruta Tuckuviene
Finland	Helsinki	Kim Vettenranta, Pasi Huttunen, Kirsi Jahnukainen, Jukka Kanerva, Kirsti Sirkiä, Mervi Taskinen, Virve Pentikäinen, Minna Koskenvuo, Samppa Ryhänen, Helena Olkinuora
	Turku	Päivi Lähteenmäki, Marika Grönroos, Anu Huurre Laura Korhonen, Linnea Schuez-Havupalo
	Oulu	Merja Möttönen, Satu Lehtinen, Hanna Juntti, Riitta Niinimäki, Anne Hekkala
	Tampere	Olli Lohi, Mikko Arola, Katriina Parto, Niina Valtanen Päivi Raittinen
	Kuopio	Pekka Riikonen, Kaisa Vepsäläinen, Jouni Pesola, Tuuli Pöyhönen
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	Trondheim	Ann Elisabeth Åsberg, Svein Kolmannsskog, Erling Moe, Harald Thomassen, Bendik Lund
	Bergen	Maria W Gunnes, Dorota Malgorzata Wojcik, Anita Andrejeva, Ingrid Kristin Torsvik
	Tromsø	Tore Stokland, Trond Flaegstad, Niklas Stabell, Tove Nystad

Sweden	Stockholm, KS Solna	Arja Harila-Saari, Mats Heyman, Stefan Söderhäll, Cecilia Petersen, Niklas Pal, Stefan Holm, Tony Frisk, Jonas Karlén, Karin Strålin, Johan Malmros, Pernilla Grillner, Klas Blomgren, Jan-Inge Henter, Per Kogner, Trausti Óskarsson, Susanna Ranta, Nina Mogensen Tatiana Greenwood, Christina Egnell, Mari Wilhelmsson, Petter Svenberg, Jukka Vakkila, Ingrid Øra , Tomas Bexelius, Johan Hamrin
	Stockholm, KS Huddinge	Mikael Sundin, Jacek Winiarski, Lena Catry, Peter Priftakis, Kim Ramme, Lena-Maria Carlson, Petra Byström, Gauti Rafn Vilbergsson
	Lund	Jacek Toporski, Helga Björgvinsdottir, Anders Castor, Lars Hjorth, Helena Mörse, Kees-Jan Pronk, Dominik Turkiewicz, Ingrid Øra, Ulf Tedgård, Annika Mårtensson, Rolf Ljung, Marie Eliasson Hofvander, Patrik Romerius, Johan Svahn, Joakim Wille, Caroline Jepsen, Ladislav Krol, Nicholas Brodszki
	Uppsala	Britt-Marie Frost, Gustaf Ljungman, Johan Arvidson, Josefine Palle, Per Frisk, Åke Jakobson, Anders Öberg, Clary Georgantzi, Annika Englund, Natalja Jackmann
	Göteborg	Karin Mellgren, Jonas Abrahamsson, Birgitta Lannering, Margareta Bergkvist, Gustaf Österlundh, Marianne Jarfelt, Magnus Sabel, Magnus Göransson, Cecilia Langenskiöld, Lene Karlsson, Elizabeth Schepke, Lars Kawan
	Umeå	Ulrika Norén Nyström, Per-Erik Sandström, Erik Forestier, Ulf Hjalmars, Caroline Björklund Mattias Mattsson, Camilla Fahlgård, Frans Nilsson
	Linköping	Mikael Behrendtz, Britt-Marie Holmqvist, Per Nyman Hartmut Vogt, Irene Devenney, Lisa Törnudd

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The Solid Tumor Registry

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Bem Zeller/Finn Wesenberg (Norway)
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NOPHO Educational Course Committee (ECC)

Coordinator	Lisa Lyngsie Hjalgrim
Denmark	Lisa Lyngsie Hjalgrim
	Thomas Frandsen
	Mimi Kjærsgaard
Finland	Marika Grönroos
	Päivi Raittinen
Norway	Bernward Zeller
	Finn Wesenberg
	Trond Flægstad
Sweden	Pernilla Grillner
	Stefan Holm
	Ulf Tedgård
Young NOPHO	Anne Vestli

The Educational course committee has continuously over the last years focused on organizing the NOPHO courses and on developing their curricula. Efforts have in particular centered on the format of the individual courses, and the possibility of making them very case-based and interactive as requested by the participants.

New recommendations for the form of the courses were put online last year, and it is encouraged to use them in the planning of future courses. The course curricula have to comply with SIOPE's "Pediatric Oncology Syllabus" also available online.

A new NOPHO course on pediatric oncology emergencies is planned for 2017. It is hoped that this may be become part of courses offered in the NOPHO setting henceforth.

The financing of the courses comes from: Børnecancerfonden (DK), Barncancerfonden (SE), Barnekreftforeningen (NO) and from different private sponsors in connection with the course in Finland.
The ECC meets every year during the annual meeting and usually has an additional phone meeting during the year. Last year's minutes can be found on the NOPHO website.

There is a wish to strengthen the collaboration with "young NOPHO" concerning course planning and the ECC meeting is open to any young NOPHO member during the annual meeting.

On behalf of the ECC
Lisa Lyngsie Hjalgrim
Rigshospitalet, Copenhagen, April 2016

NOPHO scientific committee

Members 2015-2016

Denmark: Karsten Nysom (chair)

Finland: Markku Heikinheimo.

Iceland: Ragnar Bjarnason

Lithuania: Sonata Trakymiene

Norway: Anne Grete Bechensteen

Sweden: Kees-Jan Pronk

Young NOPHO: Jan-Bernd Stukenborg

The deadline for applications for NOPHO studies is 2 months before each NOPHO board meeting.

For the November 2015 term, 4 applications were submitted and evaluated.

For the May 2016 term, 10 applications were submitted and are currently under evaluation.

For each application term, we have held a 1-2 hour telephone conference some weeks after the application deadline, where the applications have been thoroughly discussed before evaluation notes were subsequently drafted, revised by e-mail, approved and entered into the NOPHO scientific study platform.

Copenhagen, April 12th, 2016
Karsten Nysom

Young NOPHO

Young NOPHO Board

Denmark: Mette Levinsen, Stine Nygaard Nielsen

Finland: Anu Vatanen, Laura Madanat-Harjuoja

Iceland: Thorgerdur Gudmundsdottir (Chair elected)

Lithuania: Audrone Muleviciene

Norway: Simon Kranz, Marta Maria Dirdal

Sweden: Jan-Bernd Stukenborg (Chair), Maria Henningsson

Last year the annual meeting of Young NOPHO (YN) was held together with the annual NOPHO meeting in Oulu, Finland. During this meeting the YN regulations have been updated and revised. Together with the minutes from the meeting, the new regulations can be found at the NOPHO website.

YN continues to be very active. Therefore and, due to the new YN regulations, the membership of all YN members has been revised on an annual basis. The YN regulations, state that, NOPHO members who have completed their sub-specialization as pediatric oncologist/ hematologist, or who hold a permanent position as attending in this field, as well as researchers who have established their own research group are no longer Young NOPHO members. Students working on time-limited research projects within pediatric hematology/ oncology are YN members for the duration of this project. According to these regulations, the status of the memberships will be reviewed on a yearly basis. In April 2016, 75 members (11 members (NO), 21 members (SWE), 22 members (DK), 16 members (FI), 3 members (IS) and 2 members (LIT)) have been registered as YN members. We hope that this positive development will continue during the next year.

Today, YN is represented by 24 YN members in 17 Working Groups (WG). As WGs are open for one YN member from each country, there is still room for more YN members to engage in this important and exciting area of work within NOPHO. Please contact the WG Chair or the YN coordinator if you are interested.

During the last years, the YN Web Portal, a platform for connecting YN, information and discussions, was launched. The Web Portal has been developed by Elisabeth Broby Jensen and Dragi Petkovski together with YN members. However further development and promotion of the Web Portal is still needed to increase the activity in the forum. The responsible YN board members for the Portal are Mette Levinsen and Stine Nygaard Nielsen. We hope that the activity on the Forum will increase during 2016 and that it will be used to stimulate new research collaboration throughout NOPHO.

In 2015 the board of YN met in Stockholm to plan the next steps to further increase the activity within YN. During the YN board meeting, the board decided to:

- send out a questionnaire to evaluate what YN members expect and require from YN.
- assess if the YN members feel that there is a need for the web portal. This question is

inculded in the questionaire send out to all YN members.

- organise the next YN annual meeting in collaboration with NOBOS. NOBOS is now active in the Late Effects WG and would like also to collaborate with YN. Therefore, the YN board decided that this year's meeting will be held together with NOBOS. We hope this will establish a base for more collaboration in the future. The feedback from last annual YN meeting in 2015 was very positive. Participants stated that, YN works as a way of easy access and introduction to NOPHO and is valuable to be introduced to other YN members before the big NOPHO annual meeting, gave a sense of "belonging".

The structure of the annual meeting in 2016, will be similar to the 2015 meeting, but with a more clear division of the scientific programme: 50% research and 50% clinical focus. Again this year we will take topics from the Annual NOPHO meeting and use the YN meeting as an introduction hereto. Preliminary we have chosen the topic "ALL".

The YN board would like to thank the Swedish Childhood Cancer Foundation (Barncancerfonden) for supporting all YN related meetings in 2015 and the upcoming annual meeting in Iceland 2016. Last but not least we would also like to thank all YN members for their activities and energy invested in 2015 to make YN a more active and collaborative WG. Thank you!

11th of April, 2016
On behalf of the YN board,
Jan-Bernd Stukenborg, Sweden, YN Coordinator

Solid Tumour Committee

Participants: Torben Ek (SE), Göran Gustavsson (SE), Solveig Hafsteinsdottir (IC), Mats Heyman (SE), Lisa Hjalgrim (DK) , Lars Hjorth (SE), Jukka Kanerva (FI), Per Kogner (SE), Gustaf Ljungman (SE), Päivi Lähteenmäki (FI), Karsten Nysom (DK), Niklas Pal (SE), Cecilia Petersen (GS), Catherine Rechnitzer (DK), Henrik Schrøder (DK), Jan-Bernd Stukenborg (YN), Goda Vaitkeviciene (LT), Eva Widing (NO), Dorota Wojcik (NO), Bem Zeller (NO), Gustaf Österlundh (SE), Alexandar Jovanovic (DK)

The NOPHO Solid Tumour Committee (STC) was formed November 19th 2015 at a meeting in Copenhagen where interested people from different NOPHO Solid Tumour Working groups and the NOPHO Solid Tumour Registry group were invited. The initiative to form a Solid Tumour Committee was initially taken by the NOPHO GCT group, inspired by the newly formed Brain Tumour Committee.

The GS gave a background for the initiative. The activity of the different NOPHO Solid tumour working groups has been low in recent years with only two WGs being active. It is evident that NOPHO as a society needs a decision making body for solid tumour questions that has the capacity to anchor decisions and disseminate information at a national level. There is an urgent need for more collaboration in certain defined areas, e.g. very rare tumours of relapse projects. There is a need for a platform to appoint NOPHO representatives for different international collaborative projects.

Members from the NOPHO Solid Tumour Registry group presented the current status of the different national registries together with the newly created mirror database of more than 14000 Nordic patients. A scientific publication will be prepared when data from 2014 has been entered. An application for a common Nordic registry study "NOPHO CARE" will be prepared in order to improve future common Nordic registration and make the data usable for research. To avoid some potential legal issues as well as demarcation lines between solid tumours and leukaemias with regard to lymphomas, "NOPHO-CARE" will include all malignant diseases, also leukaemias.

The major part of the meeting was focusing on the formation of the STC. Three members from each country need to be elected by the national societies as formal members of the STC, according to NOPHO statutes. Additionally YN representative should be appointed. Beside the ordinary members there should be an extended mailing list with all other interested NOPHO members that are willing to actively participate in the work. People from the mailing list may participate in STC meetings and be members of WG:s sorting under the STC.

It was agreed that the STC should be a forum for clinical and strategic discussions. More than having stationary WG:s the STC could be the forum to form ad hoc WG:s for upcoming protocols or other burning issues. One such ad hoc WG was formed during the meeting in order to participate in the preparations for a new joint European protocol on rhabdoid tumours.

It was stated that the STC should work side by side with the NOPHO Solid tumour registry group. The STC may also suggest consultation networks within NOPHO for discussion of difficult cases. NOPHO countries do not have to join the same international protocols, but if the there is consensus– it is possible with common NOPHO representatives. The STC should have meetings at least yearly, favorably two-day meetings. The importance of having own studies within the group and studies connected to the registry was emphasized. Next meeting will be held Nov 17-18th 2016 in Stockholm.

/Cecilia Petersen
GS

The Solid Tumor Registry Group

Chair	Vacancy
Denmark	Henrik Schrøder
Finland	Päivi Lähteenmäki
Iceland	Olafur G. Jonsson
Norway	Bem Zeller, Finn Wesenberg
Sweden	Göran Gustafsson
	Mats Heyman (Leukemia registry)
Young NOPHO	Vacancy

The Nordic Childhood Solid Tumor Registry was started up and maintained since 1982 by the Norwegian Cancer Registry. Annual reports have been included in the NOPHO Report since 1995. The NOPHO Board has earlier decided to transfer the responsibility and future maintenance of the Nordic Solid Tumor Registry from the Norwegian Cancer Registry in Oslo to the Childhood Cancer Research Unite in Stockholm.

The first accepted classification of childhood cancer was published by Birch and Marsden in 1987. The diagnoses were divided into 12 diagnostic groups. The second classification was published in 1996 - International Classification of Childhood Cancer (ICCC) and was based on the same 12 main diagnostic groups but further subdivided into sub diagnoses. The third edition of classification (ICCC-3) was published in 2005 and has become internationally accepted.

The NOPHO-report 2013 presented the results from the reclassification of the patients according to the new WHO classification ICCR-3 from 2005.

The Nopho-report from 2014 included detailed analyses on survival for different diagnoses and sub diagnoses based on the new classification. Survival figures according to KM-method for diagnoses and countries were presented and finally figures showing 5-years survival over time for selected diagnoses for the five countries.

The actual Nopho-report 2016 presents data on all reported children diagnosed with solid- and CNS tumors during the 30-years period 1985-2014 in the five Nordic countries. The analyses are focused on 5-years estimations - according to the Kaplan-Meier method - for different diagnoses and for the five Nordic countries separately. Thus, we can compare our Nordic results with other international studies, often based on 5-years survival.

It should be observed that these 5- years' survival data are not the final cure-estimate for corresponding group as the estimations will fall with longer follow up before the results will level out at 10-20 years follow up.

This report has been worked out by the members of the working group through merging data bases from the five Nordic countries.

We have focused on prognostic changed between the three 10-years intervals from 1985 to 2014 and eventual differences between countries for different time periods and diagnoses.

The total database consists of more than 19 000 patients.

The population based cohort contains children < 15 years of age at diagnosis and diagnosed 1985-2014. A preliminary result of a non-population based cohort containing children 15-18 years of age at diagnosis is included for comparison against children < 15 years of age.

In accordance with international recommendations we excluded children with LCH/HLH from further analyses. All patients' status has been updated with date of deaths of deceased patients.

The material covers a time period of 30 years. The material has been divided into three 10-years periods.

This inventory has been possible through collaborative hard work of many oncologists in the five Nordic countries.

1. Survey of the material

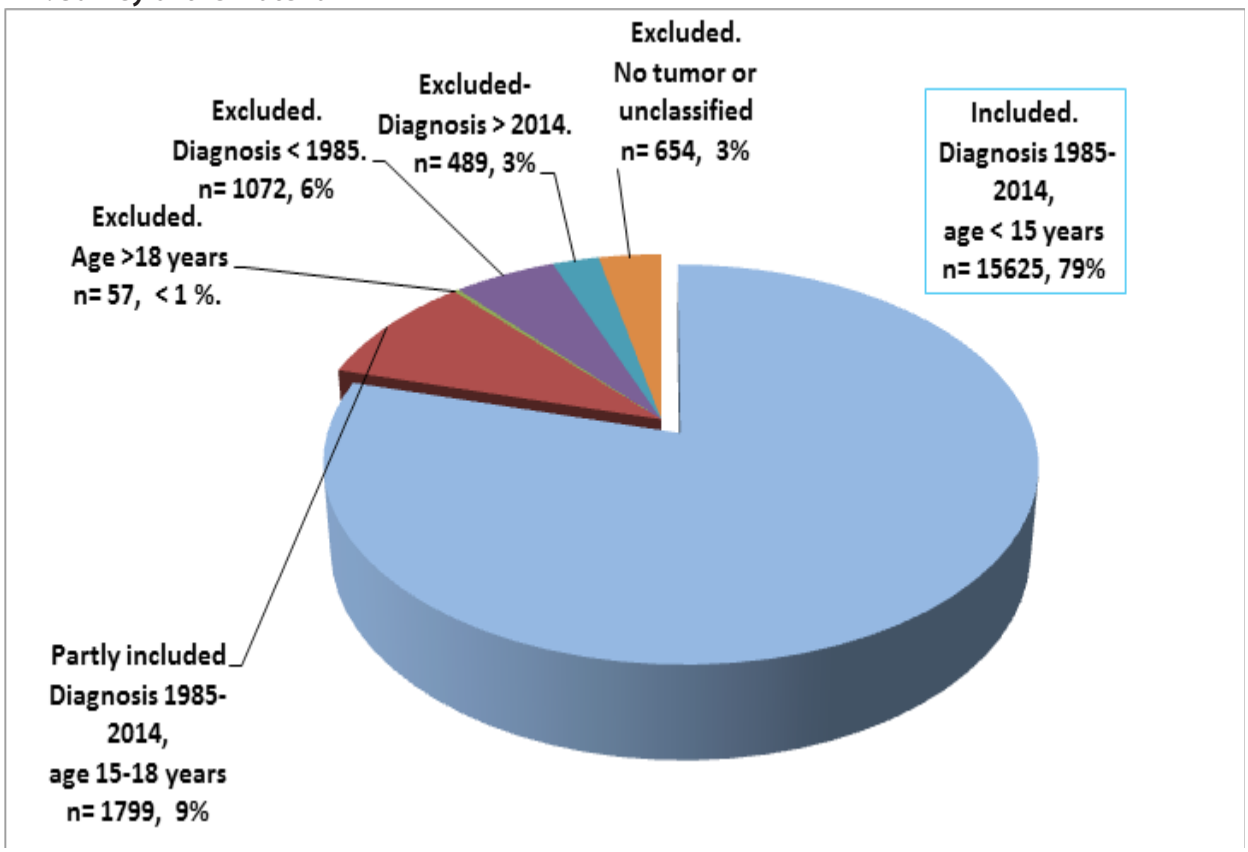

Figure-Survey 1. All patients in the data base. Included/excluded patients. (n=19696)
Diagnosis 1985-2014, age < 15 years: LCH/HLH (n=675) + All others (n=14950)= 15625.
-"- 15-18 years: LCH/HLH (n=26) + All others (n=1773) = 1799.
Children with LCH/HLH are reported to the database but are excluded in the analyses in accordance with international recommendation. The main cohort with children < 15 years of age and diagnosed 1985-2014 is population-based in contrast to the adolescents aged 15-18 years.

Three percent of the children were unclassified or had a tumor that should not be included as cancer.

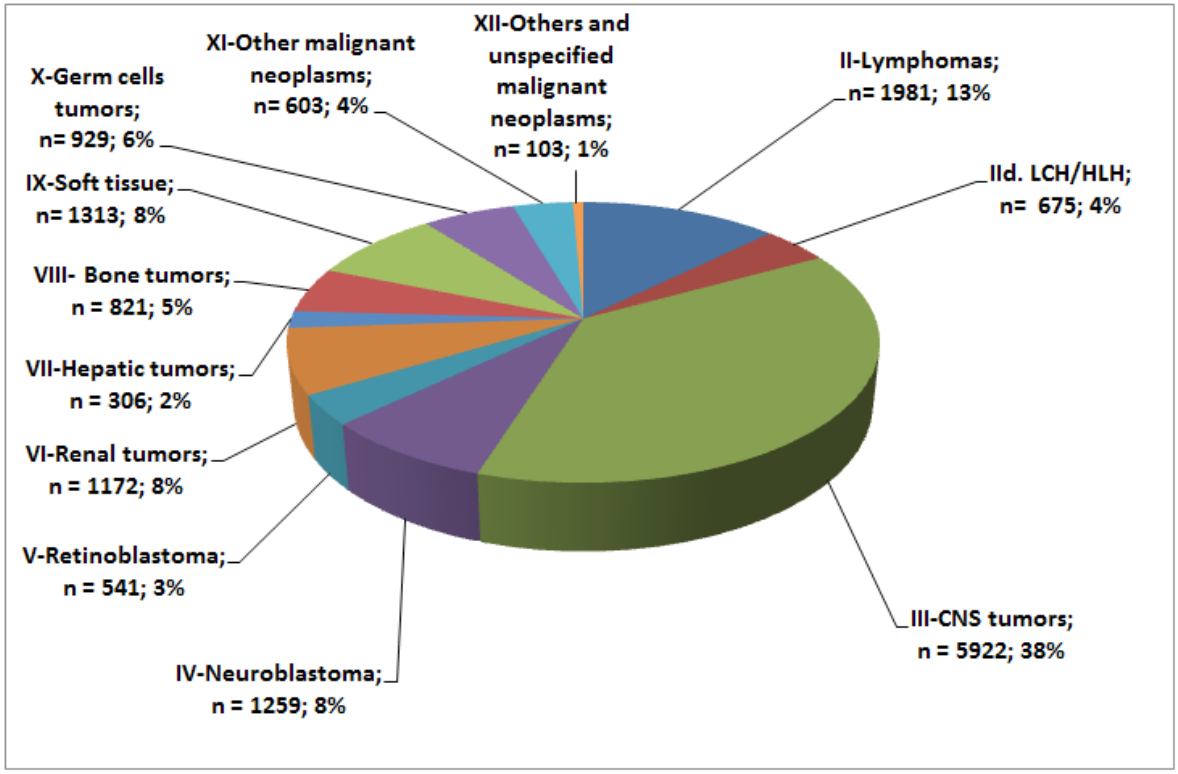

Figure - Survey 2. Distribution of diagnoses in children < 15 years of age at diagnosis (n=15 625)
The distribution of diagnoses is the same as in earlier reports and is broadly in accordance with international figures.

2.1 Survival analyses. Children < 15 years of age. Diagnosis 1985-2014

	N	Survival at 5 years –Kaplan- Meier (± SD)				OS 5 years
		1985-1994	1995-2004	2005-2014	p-value*	1985-2014**
II-XII: All cancer - excl LCH/HLH	14950	0.76±0.01	0.80±0.01	0.84±0.01	<0.01	0.80±0.01
II, IV-XII: Solid tumors-excl LCH/HLH	9028	0.78±0.01	0.83±0.01	0.86±0.01	<0.01	0.82±0.01
III: CNS tumors	5922	0.73±0.01	0.76±0.01	0.80±0.01	<0.01	0.77±0.01
IIa: Hodgkin's	700	0.95±0.02	0.95±0.01	0.97±0.01	0.19	0.96±0.01
IIb:non-Hodgkin's (except Burkitt's)	899	0.76±0.02	0.86±0.02	0.85±0.02	<0.01	0.82±0.01
IIc: Burkitt's	311	0.78±0.06	0.90±0.03	0.91±0.02	0.10	0.89±0.02
IIIa: ependymoma	537	0.66±0.04	0.72±0.03	0.84±0.03	<0.01	0.73±0.02
IIIb: astrocytoma	2322	0.81±0.02	0.82±0.01	0.84±0.01	0.07	0.83±0.01
IIIc: embryonal CNS tumors	1041	0.55±0.03	0.58±0.03	0.62±0.03	0.15	0.58±0.02
IVa: neuroblastoma	1210	0.56±0.02	0.70±0.02	0.74±0.03	< 0.01	0.66±0.01
VIa: Wilms' tumor	1154	0.88±0.02	0.88±0.02	0.92±0.02	0.13	0.89±0.01
VIII: bone tumors-all	821	0.63±0.03	0.72±0.03	0.73±0.03	0.03	0.70±0.02
IXa: rhabdomyosarkoma	682	0.69±0.03	0.74±0.03	0.69±0.04	0.66	0.71±0.02

* p-values between time periods. ** OS at 5 years – whole time period.

Table 1. 5-years estimates of survival over three time periods - all children and selected diagnoses
The prognosis has improved significantly over time for as well all cancer as a whole and solid/CNS tumors separately.
Significant improvement was also seen in non-Hodgkin's' lymphoma, ependymoma and neuroblastoma.
The prognosis for rhabdomyosarcoma seemed to be better during the second time period compared to the last one. This trend – although not significant - could be seen in S, DK and Norway (see later table 5).

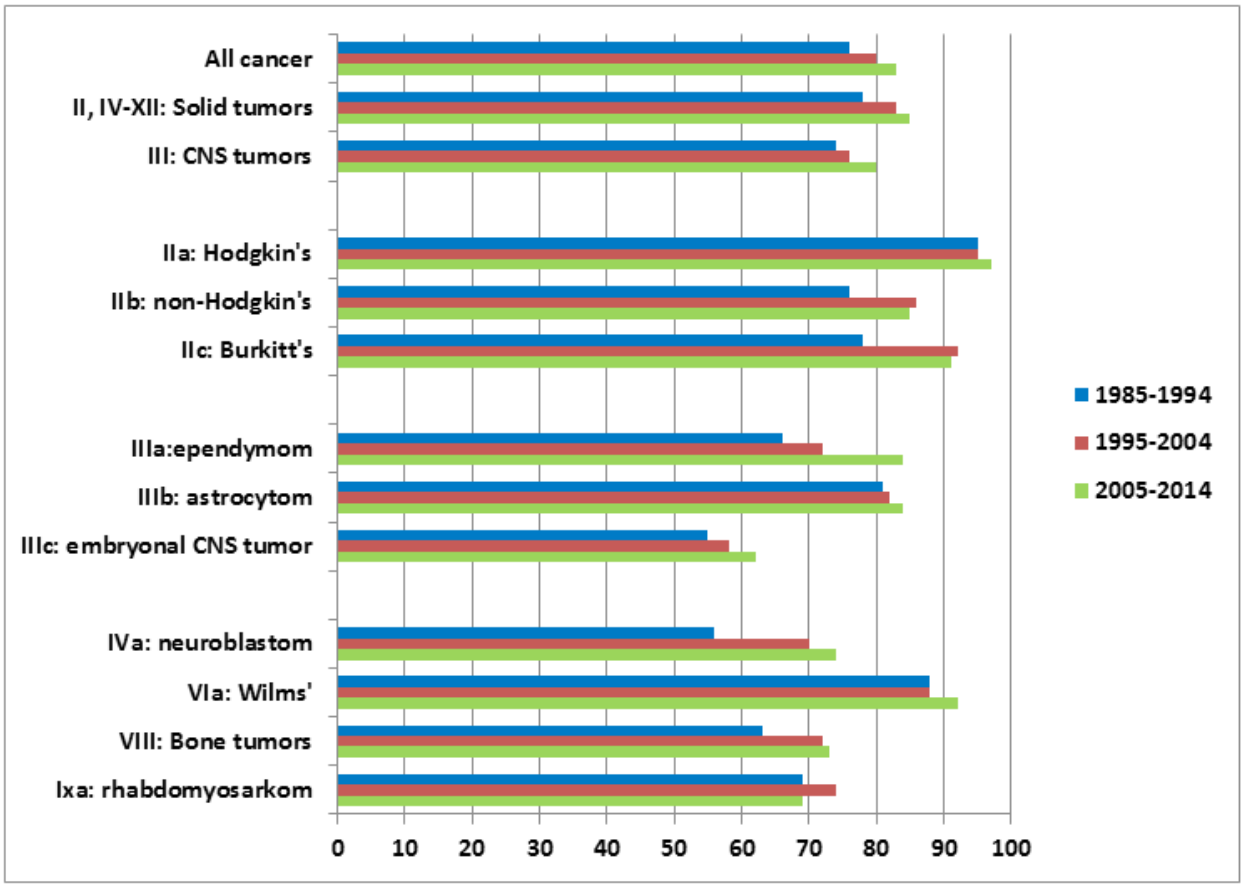

Figure 1. 5-years estimates of survival over three time periods - all children and selected diagnoses
The figure illustrates the results from Table 1.

Embryonal CNS tumor has the worst prognosis with 62% 5 years survival.

Hodgkin's, Burkitt's and Wilms' results exceed 90% in 5 years survival.

Children with Neuroblastomas have increased survival from 56% to 74% which stands for the most prominent improvement in the material.

	N	Survival at 5 years –Kaplan- Meier (± SD)				OS 5 years
		1985-1994	1995-2004	2005-2014	p-value*	1985-2014**
II-XII: All cancer (except LCH/HLH)						
S	5298	0.77±0.01	0.81±0.01	0.83±0.01	<0.01	0.80±0.02
DK	3305	0.72±0.01	0.77±0.01	0.84±0.01	<0.01	0.78±0.01
N	2913	0.74±0.01	0.84±0.01	0.82±0.01	<0.01	0.80±0.01
FIN	3226	0.79±0.01	0.81±0.01	0.83±0.01	0.04	0.81±0.01
I	208	0.83±0.05	0.81±0.04	0.86±0.04	0.61	0.83±0.02
All countries	14950	0.76±0.01	0.80±0.01	0.84±0.01	<0.01	0.80±0.01
II, IV-XII: Solid tumors						
S	3083	0.79±0.01	0.83±0.01	0.86±0.01	<0.01	0.83±0.01
DK	2009	0.72±0.02	0.80±0.02	0.86±0.01	<0.01	0.79±0.01
N	1818	0.76±0.02	0.88±0.01	0.87±0.02	<0.01	0.84±0.01
FIN	1990	0.82±0.02	0.82±0.02	0.82±0.02	0.64	0.82±0.01
I	128	0.83±0.06	0.78±0.06	0.87±0.06	0.51	0.83±0.03
All countries	9028	0.78±0.01	0.83±0.01	0.86±0.01	<0.01	0.82±0.01
III: CNS tumors						
S	2215	0.76±0.02	0.77±0.02	0.80±0.02	0.10	0.77±0.01
DK	1296	0.71±0.02	0.73±0.02	0.82±0.02	<0.01	0.75±0.01
N	1095	0.71±0.02	0.76±0.02	0.74±0.03	0.09	0.74±0.01
FIN	1236	0.73±0.02	0.79±0.02	0.83±0.02	0.03	0.78±0.01
I	80	0.82±0.08	0.82±0.07	0.83±0.07	0.91	0.82±0.04
All countries	5922	0.73±0.01	0.76±0.01	0.80±0.01	<0.01	0.77±0.01

Table 2. 5-years estimates of survival over three time periods - all children and selected diagnoses. Countries separately.

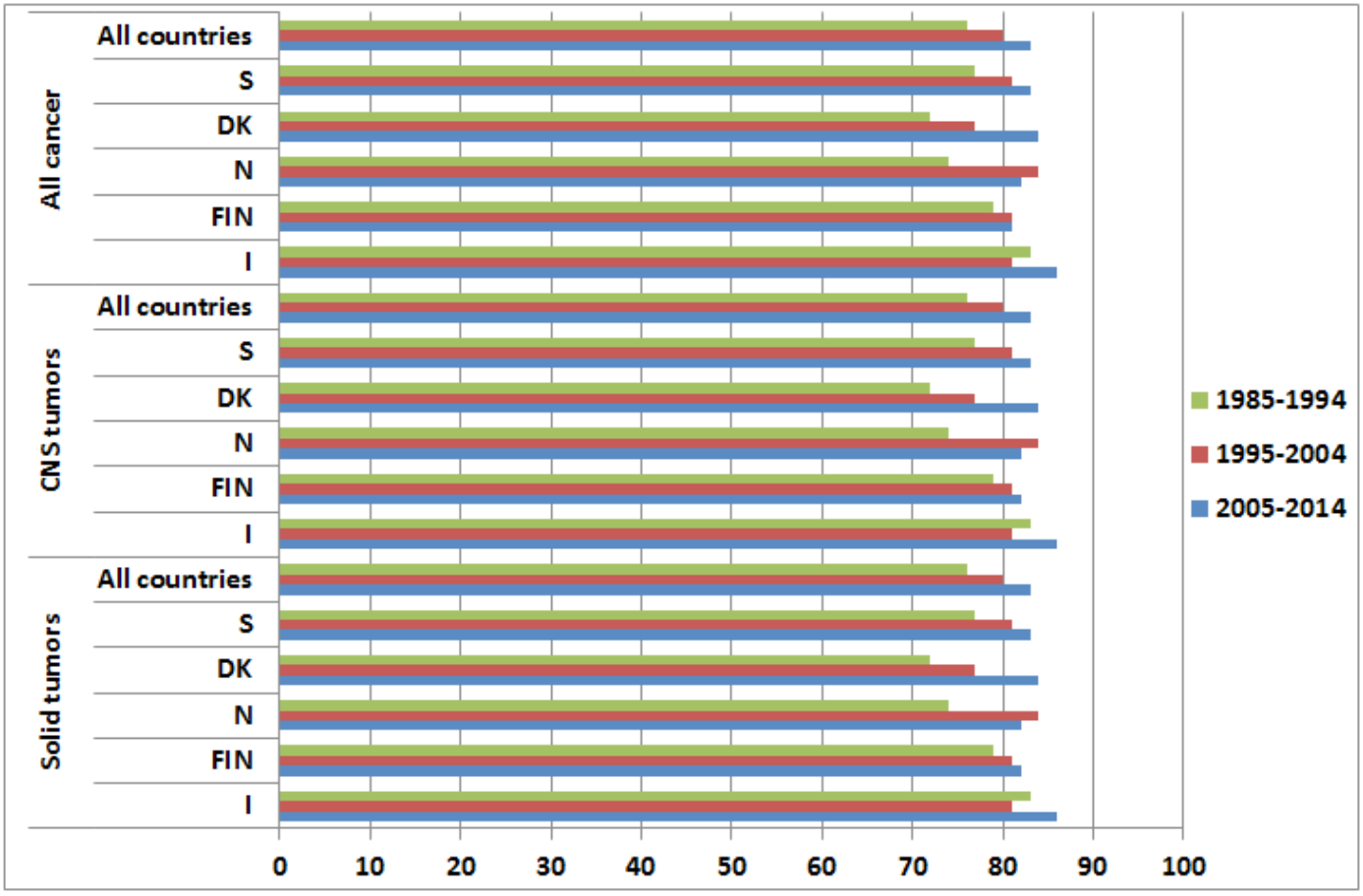

Figure 2. 5-years estimates of survival over three time periods-all children and selected diagnoses. Countries separately.

	N	Survival at 5 years –Kaplan- Meier (± SD)				OS 5 years
		1985-1994	1995-2004	2005-2014	p-value*	1985-2014**
IIa: Hodgkin's						
S	241	0.98±0.01	0.97±0.02	1.00	0.38	0.98±0.01
DK	161	0.88±0.06	0.95±0.03	0.95±0.03	0.19	0.94±0.02
N	127	0.96±0.04	0.96±0.03	0.97±0.03	0.49	0.97±0.02
FIN	160	0.93±0.04	0.95±0.03	0.96±0.03	0.80	0.94±0.02
I	11	1.00	0.75±0.02	1.00	0.42	0.91±0.09
All countries	700	0.95±0.02	0.95±0.01	0.97±0.01	0.19	0.96±0.01
IIb:non-Hodgkin's (except Burkitt's)						
S	340	0.78±0.04	0.82±0.04	0.88±0.03	0.23	0.82±0.02
DK	169	0.68±0.07	0.86±0.04	0.82±0.05	0.03	0.79±0.03
N	157	0.69±0.06	0.90±0.04	0.87±0.06	0.01	0.81±0.03
FIN	227	0.82±0.05	0.87±0.03	0.80±0.06	0.28	0.84±0.03
I	6	-	1.0	1.0	-	1.0
All countries	899	0.76±0.02	0.86±0.02	0.85±0.02	<0.01	0.82±0.01
IIc: Burkitt's						
S	85	0.88±0.08	1.0	0.88±0.06	0.08	0.93-±0.03
DK	102	0.67±0.10	0.90±0.06	0.90±0.04	0.02	0.85±0.04
N	55	0.80±0.18	0.91±0.06	0.93±0.05	0.72	0.91±0.04
FIN	60	1.0	0.81±0.07	0.92±0.05	0.39	0.86±0.05
I	9	-	0.67±0.27	1.0	0.37	0.89±0.10
All countries	311	0.78±0.06	0.90±0.03	0.91±0.02	0.10	0.89±0.02

Table 3. 5-years estimates of survival over three time periods - selected lymphoma diagnoses. Countries separately.

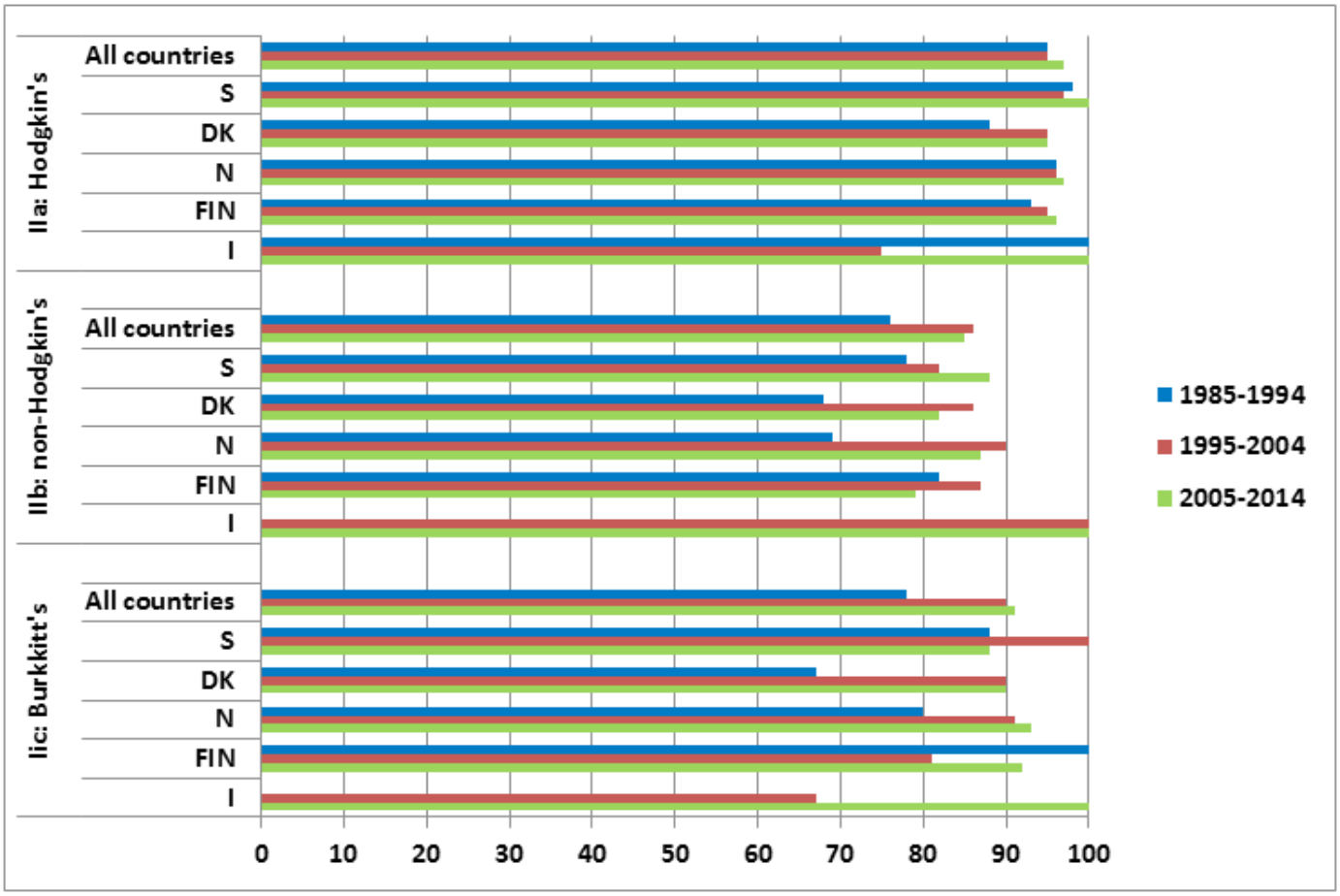

Figure 3. 5-years estimates of survival over three time periods - selected diagnoses. Countries separately.

	N	Survival at 5 years –Kaplan- Meier (± SD)				OS 5 years
		1985-1994	1995-2004	2005-2014	p-value*	1985-2014**
IIIa: ependymoma						
S	207	0.72±0.05	0.76±0.06	0.85±0.05	0.14	0.77±0.03
DK	105	0.54±0.10	0.65±0.07	0.81±0.08	0.29	0.66±0.05
N	94	0.69±0.09	0.71±0.07	0.86±0.08	0.79	0.74±0.05
FIN	126	0.58±0.08	0.78±0.06	0.88±0.06	<0.01	0.73±0.04
I	5	0.75±0.21	-	-		0.75±0.21
All countries	537	0.66±0.04	0.72±0.03	0.84±0.03	<0.01	0.73±0.02
IIIb: astrocytoma						
S	952	0.84±0.02	0.86±0.02	0.87±0.02	0.23	0.86±0.01
DK	449	0.85±0.03	0.75±0.04	0.91±0.02	<0.01	0.83±0.02
N	481	0.73±0.03	0.79±0.03	0.73±0.04	0.41	0.75±0.02
FIN	404	0.76±0.06	0.84±0.03	0.84±0.03	0.60	0.83±0.02
I	36	1.0	0.86±0.09	0.92±0.07	0.73	0.92±0.05
All countries	2322	0.81±0.02	0.82±0.01	0.84±0.01	0.07	0.83±0.01
IIIc: embryonal CNS tumors						
S		0.65±0.04	0.58±0.04	0.60±0.05	0.55	0.61±0.04
DK		0.41±0.06	0.59±0.06	0.63±0.06	0.03	0.54±0.04
N		0.53±0.07	0.51±0.06	0.60±0.06	0.41	0.55±0.04
FIN		0.52±0.06	0.61±0.06	0.68±0.06	0.12	0.60±0.04
I		0.40±0.22	0.80±0.18	0.50±0.25	0.32	0.56±0.13
All countries	1041	0.55±0.03	0.58±0.03	0.62±0.03	0.15	0.58±0.02

Table 4. 5-years estimates of survival over three time periods - selected CNS-diagnoses. Countries separately.

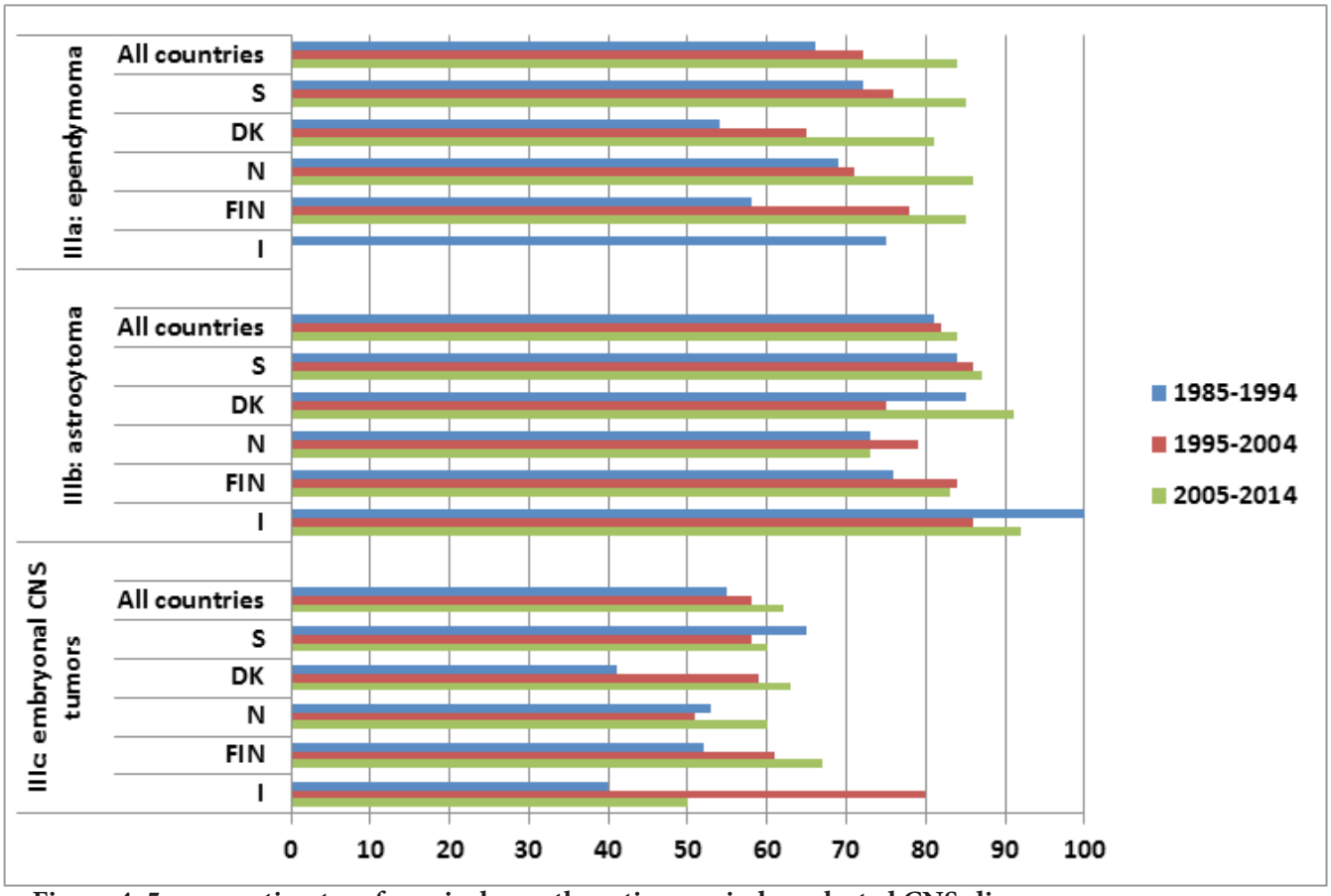

Figure 4. 5-years estimates of survival over three time periods - selected CNS-diagnoses. Countries separately.

	N	Survival at 5 years –Kaplan- Meier (± SD)				OS at 5 years
		1985-1994	1995-2004	2005-2014	p-value*	1985-2014**
IVa: neuroblastoma						
S	420	0.61±0.04	0.66±0.04	0.74±0.04	0.045	0.67±0.02
DK	268	0.39±0.05	0.68±0.05	0.71±0.06	<0.01	0.59±0.03
N	233	0.51±0.05	0.83±0.05	0.88±0.04	<0.01	0.73±0.03
FIN	279	0.68±0.05	0.67±0.05	0.68±0.06	0.93	0.67±0.03
I	11	0.67±0.27	0.75±0.21	0.75±0.21	0.92	0.72±0.14
All countries	1210	0.56±0.02	0.70±0.02	0.74±0.03	< 0.01	0.66±0.01
VIa: Wilms' tumor						
S	446	0.87±0.03	0.84±0.03	0.91±0.02	0.22	0.87±0.02
DK	241	0.82±0.04	0.93±0.03	0.97±0.02	< 0.01	0.90±0.02
N	197	0.97±0.02	0.89±0.04	0.87±0.04	0.18	0.92±0.02
FIN	260	0.91±0.03	0.88±0.04	0.92±0.03	0.78	0.90±0.02
I	10	1.00	0.83±0.15	-		0.87±0.11
All countries	1154	0.88±0.02	0.88±0.02	0.92±0.02	0.13	0.89±0.01
VIII: Bone tumors-all						
S	292	0.65±0.05	0.70±0.05	0.80±0.04	0.14	0.72±0.03
DK	210	0.62±0.06	0.56±0.06	0.69±0.06	0.62	0.63±0.03
N	177	0.51±0.07	0.87±0.04	0.73±0.07	<0.01	0.74±0.03
FIN	128	0.72±0.07	0.77±0.06	0.66±0.09	0.84	0.73±0.04
I	14	0.60±0.22	0.75±0.22	0.60±0.22	0.81	0.64±0.13
All countries	821	0.63±0.03	0.72±0.03	0.73±0.03	0.03	0.70±0.02
IXa: rhabdomyosarcoma						
S	233	0.72±0.05	0.78±0.05	0.69±0.06	0.71	0.73±0.03
DK	203	0.71±0.05	0.72±0.05	0.69±0.08	0.83	0.71±0.03
N	128	0.67±0.07	0.81±0.06	0.77±0.07	0.48	0.74±0.04
FIN	111	0.58±0.09	0.65±0.08	0.66±0.07	0.96	0.62±0.05
I	7	0.50±0.35	0.25±0.21	-	-	0.33±0.20
All countries	682	0.69±0.03	0.74±0.03	0.69±0.04	0.66	0.71±0.02

Table 5. 5-years estimates of survival over three time periods - selected diagnoses groups IV-IX. Countries separately.

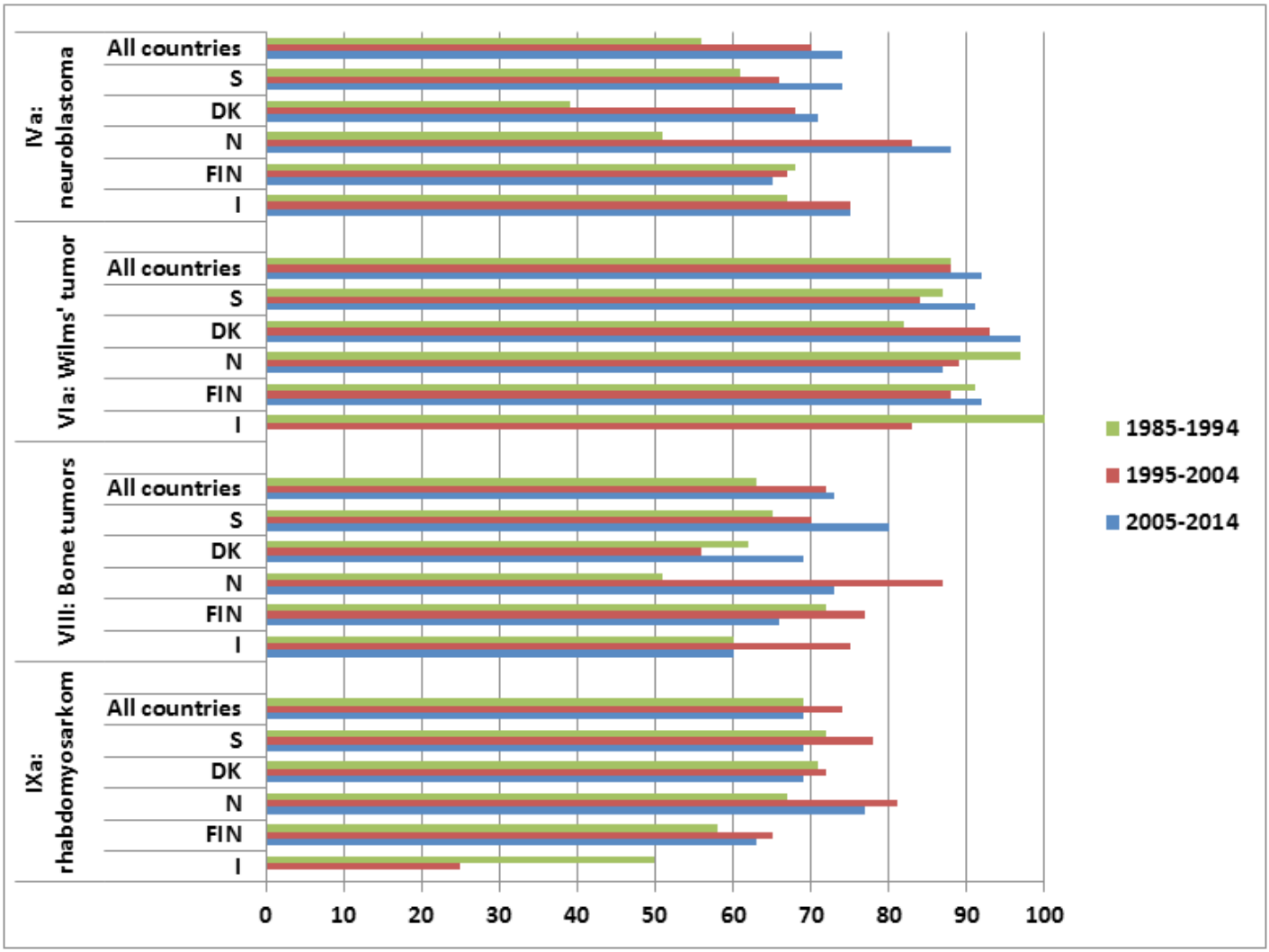

Figure 5. 5-years estimates of survival over three time periods - selected diagnoses groups IV-IX. Countries separately.

2.2 Survival analyses. Children < 15 years of age. Diagnosis 2005-2014.

		Survival at 5 years – Kaplan- Meier (± SD) Diagnosis 2005-2014	
	N	5 yrs surv.	Sign tests (Log Rank)
Groups II-XII: All cancer (except LCH/HLH)			
S	1795	0.83±0.01	p overall: 0.98 p pairwise: No sign difference between countries (n.s.)
DK	1078	0.84±0.01	
N	924	0.82±0.01	
FIN	1049	0.83±0.01	
I	73	0.86±0.04	
All countries	4942	0.83±0.01	
Groups II, IV-XII: Solid tumors (except LCH/HLH)			
S	1040	0.86±0.01	p overall: 0.20 p pairwise: FIN vs N = 0.02, others-no sign.
DK	692	0.86±0.01	
N	593	0.87±0.02	
FIN	631	0.82±0.02	
I	43	0.87±0.06	
All countries	2999	0.85±0.01	
Group III: CNS tumors			
S	757	0.80±0.02	p overall: 0.10 p pairwise: N vs FIN <0.01, N vs DK=0.05. others – no sign.
DK	387	0.82±0.02	
N	351	0.74±0.03	
FIN	418	0.83±0.02	
I	30	0.83±0.07	
All countries	1943	0.80±0.01	

Table 6a. Diagnosis 2005-2014. All tumors and selected diagnoses. Comparison between countries.

		Survival at 5 years –Kaplan- Meier (± SD) Diagnosis 2005-2014	
	N	5 yrs surv.	Sign tests (Log Rank)
Group II: Lymphomas			
IIa: Hodgkin's			
S	74	1.00	p overall: 0.49 p pairwise: n.s.
DK	66	0.95±0.03	
N	53	0.97±0.03	
FIN	50	0.96±0.03	
I	2	1.00	
All countries	245	0.97±0.01	
IIb: non-Hodgkin's			
S	102	0.88±0.03	p overall: 0.76 p pairwise: n.s.
DK	56	0.82±0.05	
N	34	0.87±0.06	
FIN	54	0.80±0.06	
I	3	1.0	
All countries	249	0.85±0.02	
IIc: Burkitt's			
S	33	0.88±0.06	p overall: 0.75 p pairwise: n.s.
DK	51	0.90±0.04	
N	28	0.93±0.05	
FIN	27	0.92±0.05	
I	5	1.0	
All countries	144	0.91±0.02	

Table 6b. Diagnosis 2005-2014. Selected lymphoma diagnoses. Comparison between countries.

		Survival at 5 years – Kaplan- Meier (± SD) Diagnosis 2005-2014	
	N	5 yrs surv.	Sign tests (Log Rank)
Group III: CNS tumors			
IIIa: ependymoma			
S	63	0.85±0.05	p overall: 0.70 p pairwise: n.s.
DK	28	0.81±0.08	
N	26	0.86±0.08	
FIN	47	0.88±0.06	
I	-	-	
All countries	164	0.84±0.03	
IIIb: astrocytoma			
S	291	0.87±0.02	p overall: < 0.01 p pairwise: N vs S: < 0.01, N vs DK: < 0.01, DK vs FIN: 0.02 Others: n.s.
DK	151	0.91±0.02	
N	148	0.73±0.04	
FIN	190	0.84±0.03	
I	13	0.92±0.07	
All countries	793	0.84±0.01	
IIIc: embryonal CNS tumors			
S	135	0.60±0.05	p overall: 0.56 p pairwise: n.s.
DK	67	0.63±0.06	
N	79	0.60±0.06	
FIN	74	0.68±0.06	
I	4	0.50±0.25	
All countries	359	0.62±0.03	

Table 6c. Diagnosis 2005-2014. Selected CNS diagnoses. Comparison between countries.

		Survival at 5 years –Kaplan- Meier (±SD) Diagnosis 2005-2014	
	N	5 yrs surv	Sign tests (Log Rank)
Selected diagnoses.			
IVa: neuroblastoma			
S	130	0.74±0.04	p overall: 0.06 p pairwise: N vs S: 0.02, N vs DK: <0.01, N vs FIN: < 0.01 Norway's data needs to be checked.
DK	79	0.71±0.06	
N	80	0.88±0.04	
FIN	85	0.68±0.06	
I	4	0.75±0.21	
All countries	378	0.74±0.03	
VIa: Wilms' tumor			
S	157	0.91±0.02	p overall: 0.36 p pairwise: N vs DK: 0.04 others n.s.
DK	76	0.97±0.02	
N	66	0.87±0.04	
FIN	75	0.92±0.03	
I	1	-	
All countries	375	0.92±0.02	
VIII: Bone tumors-all			
S	110	0.80±0.04	p overall: 0.45 p pairwise: n.s.
DK	79	0.69±0.06	
N	54	0.73±0.07	
FIN	45	0.66±0.09	
I	5	0.60±0.22	
All countries	293	0.73±0.03	
IXa: rhabdomyosarkoma			
S	78	0.69±0.06	p overall: 0.82 p pairwise: n.s.
DK	43	0.69±0.08	
N	45	0.77±0.07	
FIN	51	0.66±0.08	
I	1	-	
All countries	218	0.69±0.04	

Table 6d. Diagnosis 2005-2014. Selected group IV-IX diagnoses. Comparison between countries.

2.3 Survival analyses. Children 15 -18 years of age. Diagnosis 1985-2014.

	N	Survival at 5 years –Kaplan- Meier (± SD)				OS at 5 years
		1985-1994	1995-2004	2005-2014	p-value	1985-2014
II-XII: All cancer - excl LCH/HLH	1773	0.76±0.02	0.80±0.02	0.85±0.02	<0.01	0.81±0.01
II, IV-XII: Solid tumors-excl LCH/HLH	1267	0.76±0.03	0.82±0.02	0.86±0.02	<0.01	0.82±0.01
III: CNS tumors	506	0.77±0.04	0.77±0.03	0.81±0.03	0.57	0.79±0.02
IIa: Hodgkin's	347	0.97±0.02	0.94±0.02	0.99±0.01	0.22	0.97±0.01
IIb:non-Hodgkin's (except Burkitt's)	146	0.60±0.09	0.73±0.06	0.90±0.04	<0.01	0.76±0.04
IIIb: astrocytoma	172	0.72±0.07	0.79±0.06	0.79±0.05	0.65	0.77±0.03
VIII: bone tumors-all	221	0.56±0.06	0.66±0.05	0.73±0.06	0.03	0.65±0.03

Table 7a. Adolescents 15-18 years at diagnosis. Comparison over time.
Selected groups with > 100 patients.

	N	Survival at 5 years –Kaplan- Meier (± SD)				OS 5 years
		1985-1994	1995-2004	2005-2014	p-value*	1985-2014**
II-XII: All cancer - excl LCH/HLH	14950	0.76±0.01	0.80±0.01	0.84±0.01	<0.01	0.80±0.01
II, IV-XII: Solid tumors-excl LCH/HLH	9028	0.78±0.01	0.83±0.01	0.86±0.01	<0.01	0.82±0.01
III: CNS tumors	5922	0.73±0.01	0.76±0.01	0.80±0.01	<0.01	0.77±0.01
IIa: Hodgkin's	700	0.95±0.02	0.95±0.01	0.97±0.01	0.19	0.96±0.01
IIb:non-Hodgkin's (except Burkitt's)	899	0.76±0.02	0.86±0.02	0.85±0.02	<0.01	0.82±0.01
IIIb: astrocytoma	2322	0.81±0.02	0.82±0.01	0.84±0.01	0.07	0.83±0.01
VIII: bone tumors-all	821	0.63±0.03	0.72±0.03	0.73±0.03	0.03	0.70±0.02

Table 7b. Children < 15 years at diagnosis. Comparison against Table 7a.
(Table is copied partly from Table 1).

3. Summary and conclusions

The Nordic Solid Tumor Registry has been built up by interested pediatric oncologists at each of the 21 University Hospitals in the five Nordic countries. Annual reports have been worked out of the Norwegian Cancer Registry and have been part of the NOPHO Annual Report since 1995.

The Registry has been taken-over by the Childhood Cancer Research Unite at the Karolinska Institute, Stockholm.

The working group has re-classified the diagnoses for all patients according to modern International recommendations and has earlier presented actual follow up data of the patient cohort. In this annual report we have focused mostly on 5-years OS to make it possible to compare our results with other international materials.

Minor but constant improvements in prognosis have been seen over time for most of the diagnoses. A reasonable conclusion could be that we cure 75-80% of children with a solid tumor and 70-75% of children with a CNS-tumor treated according to modern stratified therapy, but with great variations between separate diagnoses.

A system for a future Webb-based reporting of the patients has been worked out but has not – due to legal reasons – been used so far.

As quality registries are not allowed by the law in all NOPHO countries, we cannot directly use the currently collected protocol database. We need a new research project, which we have named the NOPHO-CARE, for storing and also using protocol data after the end of a planned treatment-study period. Therefore we have sent an application the NOPHO Scientific Committee to establish and expand the NOPHO Solid Tumor Registry as a research project called NOPHO-CARE. This seems necessary in order for some countries to be allowed to transfer clinical data to the database. NOPHO-CARE, A Nordic study on epidemiology, biology, treatment, and survival of children with cancer and hematological disorders.

Primary aim

We propose a scientific study called NOPHO-CARE with the overall goal of analyzing factors of importance for the relapse-free and overall survival as well as treatment late-effects of children with leukemia and solid tumours treated since 1985 and up to 2025 in the six NOPHO countries.

Secondary aims

- To study relapse-free and overall survival in all cancer children within NOPHO countries in relation to country- and patient-specific epidemiological factors, disease presentation and therapy.
- To extend the use of tumour/disease characteristics that potentially influence treatments and outcome, namely:
- Molecular biology in hematological diseases and solid tumors, and morphology, sub-site localization and stage at diagnosis in solid tumours.
- To further analyze areas of suboptimal results within selected diagnostic subgroups.
- To analyze the causes of death and their possible changes over the decades when treatments and environmental factors have changed. (Progressive cancer, toxicity of treatment, secondary cancer, other causes of death)
- To create a platform for discussion on the introduction of further common Nordic treatment protocols possibly with a wider European/worldwide collaboration.
- To estimate updated cancer prevalence (complete and by disease duration)
- To estimate updated incidence, survival and prevalence of rare cancers
- To estimate the proportion of cancer patients who are cured of their disease and may be in need for specialized late-effect follow-up services in each country.

- To estimate and analyze the number and proportion of avoidable deaths

The proposal awaits assessment by the Scientific Committee probably before the annual meeting in Iceland.

Our goal with this work has been to establish a solid data base for all sorts of childhood solid- and CNS- cancer. This can hopefully inspire colleagues for future research projects within this interesting and dynamic field. The Nordic Leukemia Registry could stand as model how to develop this project successfully.

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Lymphoma Working Group

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Introduction

The NOPHO Lymphoma group is the combination of the previous Hodgkin Lymphoma (HL) (est. 2014) and non-Hodgkin Lymphoma (NHL) (est. 1992) working groups. It was decided to fuse the two fora at the annual NOPHO meeting in Oulu in May 2015. By thus increasing the number of group members, the idea was to achieve synergy by, e.g., facilitating and improving: 1) The registration of all lymphoma patients in the NOPHO register, 2) The sharing patient experiences and discussing of difficult patients, 3) The involvement of the Nordic countries in international lymphoma protocols and scientific projects, and 4) The creation of an infrastructure for handling, shipment, and analyses of biosamples from patients with various types of malignant lymphomas according to international protocols.

Over the last two decades, the treatment of both HL and NHL in children and adolescents has followed European protocols.

Hodgkin Lymphoma

Since approximately 2006 Norway, Sweden, and Denmark have treated their HL patients according to the international **Euro-Net-PHL-C1 protocol**. This is a PET- CT response-tailored protocol with a central board, which evaluates all PET CT scans and standardizes staging and treatment of all included patients. The protocol is now closed and the survival rates are excellent. Since October 2015, the **Euro-Net-PHL-C2 protocol** has opened and all the Nordic countries plan to join within the

next year, establishing uniform diagnostic risk stratification and treatment of all Nordic HL patients age 0-18 years at diagnosis. Improving HL registration in the NOPHO database creates a unique opportunity for Nordic scientific projects. Countries where the Euro-Net-PHL-C2 protocol have not been initiated follow the **Euro-Net-PHL-C1-interim protocol**.

Non-Hodgkin Lymphoma

NOPHO-NHL group joined the **ALCL 99 protocol** for treatment of children with ***Anaplastic Large Cell Lymphoma*** in 2000 and the protocol is now closed for patient inclusion, but is continuously used as best available treatment in most European Countries. Among more than 400 children included from 15 different countries an EFS of 73% has been be achieved. For ALCL, several new parameters predicting relapse have been identified in the last years. Among them, detection and quantification of minimal disseminated disease (MDD) in bone marrow or blood and low antibody titers against ALK turned out to be powerful prognostic factors for treatment failure. The inverse correlation of high antibody titers and negative MDD suggests a possibly meaningful combination of these parameters to define a very high risk group (HR) of ALCL-patients. MDD positive patients who produce low ALK-antibody titers (≤1:750) constitute a HR group of 20 % of ALCL patients. These HR-patients have a 70-80% risk of relapse with current standard multi-agent chemotherapy, e.g. ALCL 99, and include almost all patients with inherent chemo resistant disease (i.e. those patients who progress during front-line therapy). Another important finding from the international collaboration is that contrary to what is found in many other subtypes of NHL, ALCL relapse can be rescued in more than 70% of the patients. NOPHO contribute with patients to the international ALCL relapse protocol that has now been used in 80 evaluable patients with an EFS and OS of 53±6% and 71±5%, respectively. It appears that Vinblastine monotherapy achieves high remission rates in patients with a late relapse of an ALCL. Furthermore, it appears that autologous SCT was ineffective for patients with relapsed CD3-negative ALCL and that allogeneic SCT achieves a high survival rate for patients with relapse of a CD3 positive ALCL and offers a chance for those with progression during therapy. Work with a new international study, ALCL2 is ongoing.

NOPHO joined the **EURO-LB 02 protocol** for treatment of children with ***lymphoblastic lymphoma*** in 2005. Patient accrual to the study had to be prematurely closed at July 1st 2008 due to an excess of toxic deaths, of 3.8 %. 351 patients were registered in the study of which 319 were eligible (66 pB-LBL, 233 T-LBL, 20 ambiguous), and pEFS at 5 years was at 81+2%. At the moment NOPHO suggest EURO LB 02 as best available treatment for patients with lymphoblastic lymphomas. A new international protocol LBL2014 has been started in some countries aiming to find biological or genetic risk factors for relapse or disease progression. NOPHO will probably join the study during the last part of 2016,

Since 2005 the NOPHO-NHL has used the **B-NHL BFM-04 protocol** for the treatment of children with ***B-cell lymphomas***. The work with the new cooperative study between NOPHO and BFM, B-NHL 2013 is now almost finalized and will be submitted to legal authorities before summer 2016.

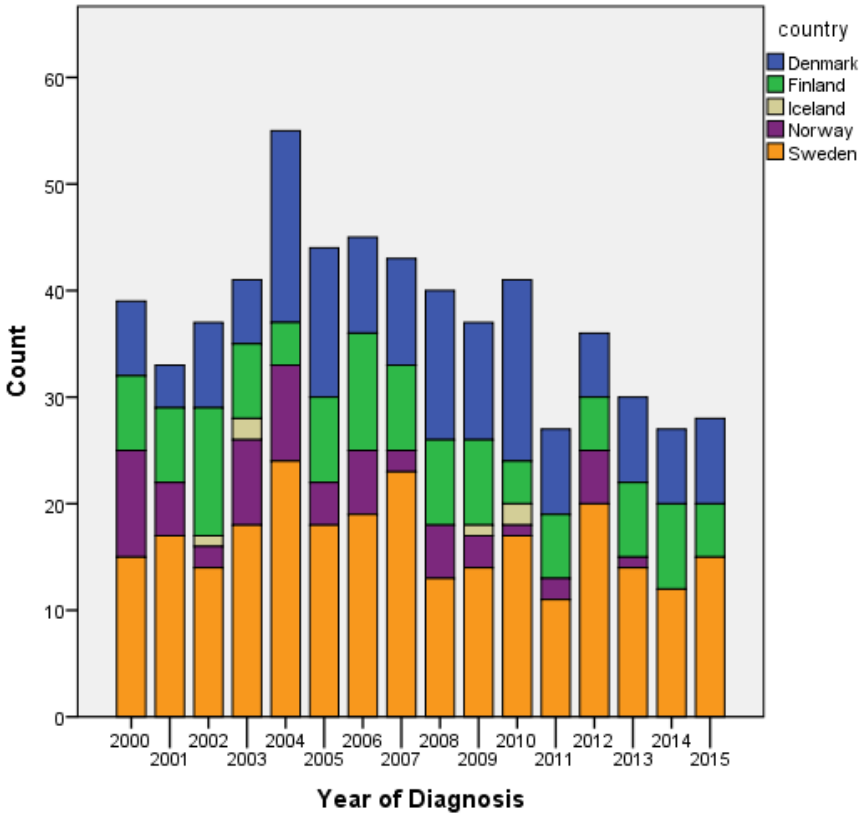
NOPHO is also contributing with patients to the newly opened **European international registry of rare pediatric non Hodgkin lymphomas** and is coordinating an international survey over patients with peripheral T-cell lymphomas.

The NOPHO NHL-group has been working with on-line registration of patients over the last year and the web-based register is open. All former patients have been entered into this register making reporting easier for all clinics. Today, all patients diagnosed with NHL should be reported to the on-line NOPHO database.

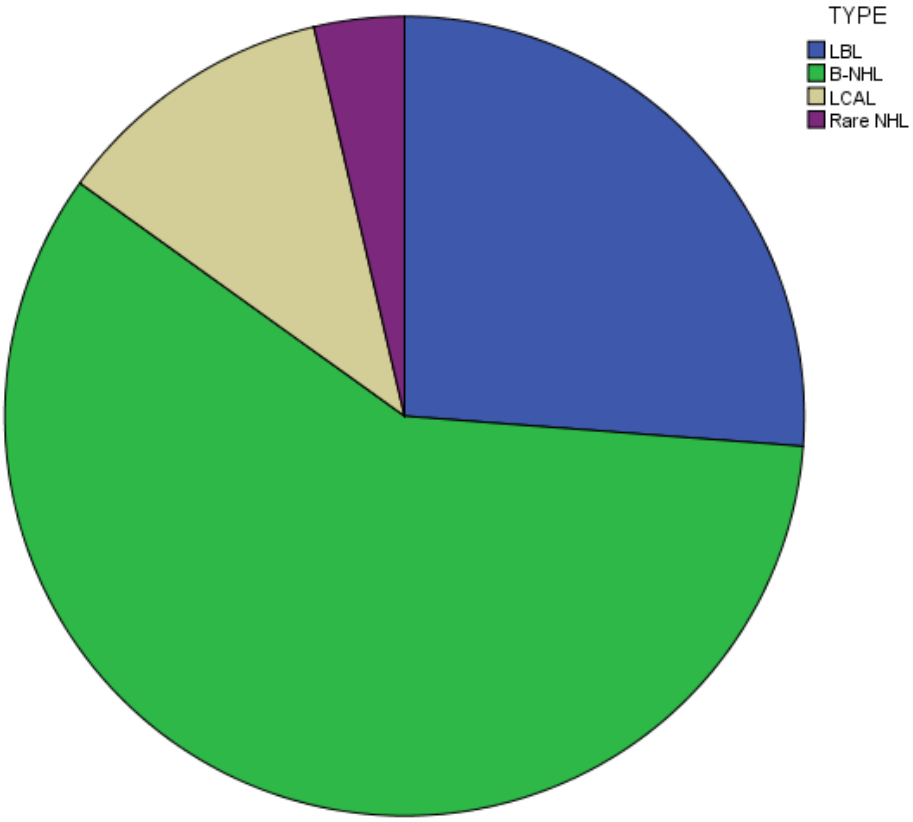
Survey over NHL children diagnosed 1995 - 2015

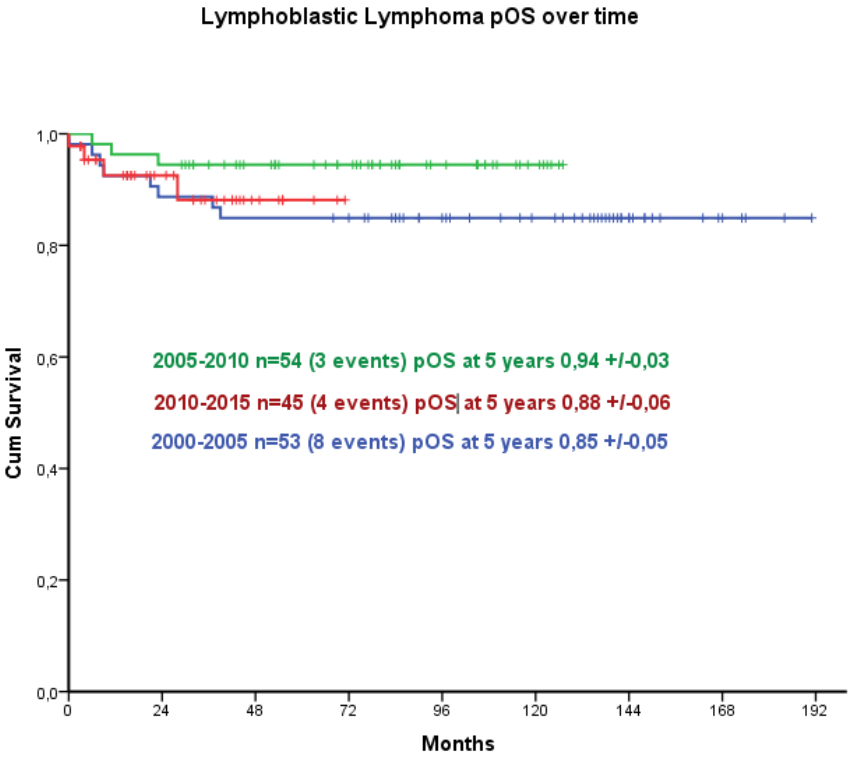
There were 609 reported cases of NHL diagnosed from 1.1.2000 to 31.12.2015 in the five Nordic countries. Patients age 0-18 years have been included in this report. Some data still lack in the database and twenty-six patients were excluded from the analysis because of missing data. The remaining 603 patients are reported here below.

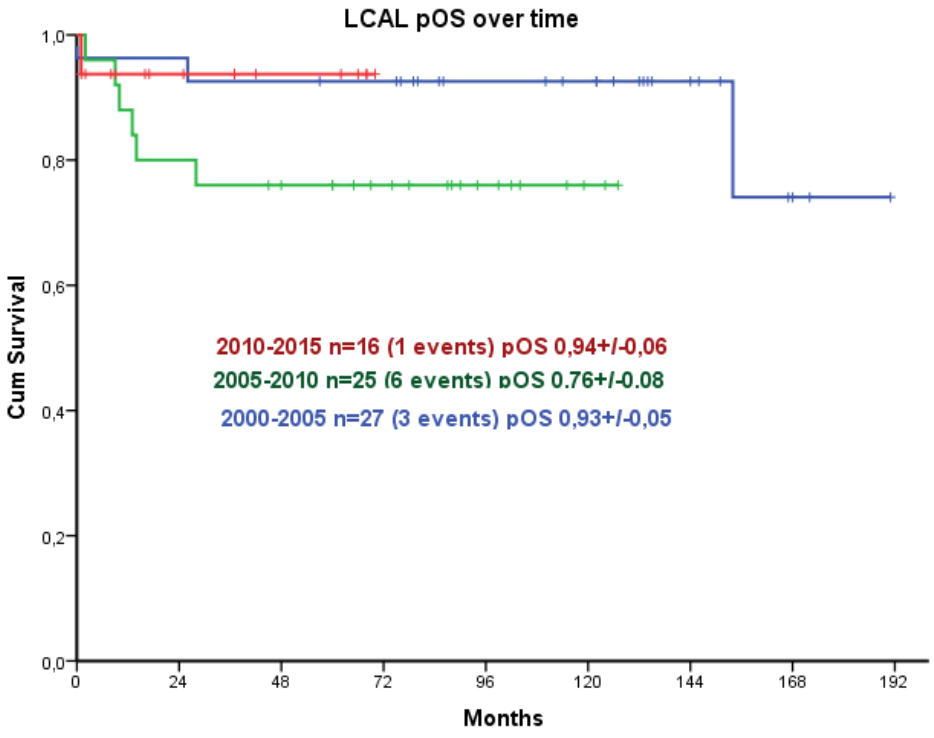
Distribution of patients according to year of diagnosis and country

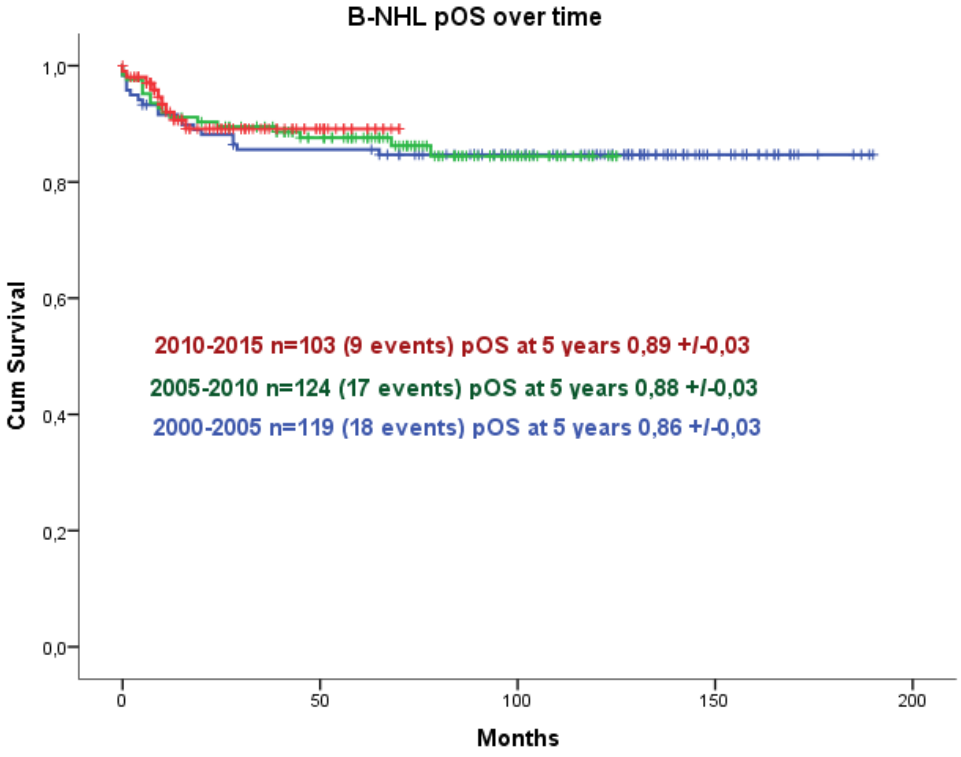


Distribution of phenotype




Lymphoblastic Lymphoma pOS over time
Cum Survival
1,0
0,8
0,6
0,4
0,2
0,0
0
24
48
72
96
120
144
168
192
Months
2005-2010 n=54 (3 events) pOS at 5 years 0,94 +/-0,03
2010-2015 n=45 (4 events) pOS at 5 years 0,88 +/-0,06
2000-2005 n=53 (8 events) pOS at 5 years 0,85 +/-0,05


LCAL pOS over time
Cum Survival
1,0
0,8
0,6
0,4
0,2
0,0
0
24
48
72
96
120
144
168
192
Months
2010-2015 n=16 (1 events) pOS 0,94+/-0,06
2005-2010 n=25 (6 events) pOS 0.76+/-0.08
2000-2005 n=27 (3 events) pOS 0,93+/-0,05



OS for the different types of lymphoma is comparable with what has been described by other groups. The database lack information about some patients.

Summary and conclusions

The results of the present inventory are in accordance with last year's analysis. The results remain relatively stable over time for B-NHL, pre-B NHL and ALCL. Our Nordic results are well comparable with the results from other groups.

Events in patients with NHL are mainly due to progressive disease or relapse, induction deaths and deaths in CCR.

NOPHO takes part of an international collaboration for treatment of NHL. Such cooperation is necessary to identify patients with specific risk-factors within the very heterogeneous group of NHL.

Publications

- **Ceppi F, Weitzman S, Woessmann W, Davies K, Lassaletta A, Bettina R, Mellgren K, Uyttebroeck A, Maia I, Abdullah S, Miakova N, Glaser D, Cohn R, Abla O, Attarbaschi A, Alexander S.** *Safety and efficacy of intrathecal rituximab in children with B cell lymphoid CD20+ malignancies: An international retrospective study.* Am J Hematol. 2016 Feb.
- **Mellgren K, Attarbaschi A, Abla O, Alexander S, Bomken S, Brugieres L, Bubanska E, Chiang A , Csóka, M, Fedorova A, Kabickova E, Kobayashi R, Krenova, Z, Meyer-Wentrup F, Miakova N, Pillon M, Uyttebroeck A, Williams D, Wróbel G, and Kontny U on behalf of the European Intergroup for Childhood Non-Hodgkin Lymphoma (EICNHL) and the international Berlin-Frankfurt-Münster (i-BFM) Group.** *Non-anaplastic peripheral T-cell lymphoma in children and adolescents – an international review of 143 cases.* Submitted.

Germ Cell Tumor (GCT) Working Group

Coordinator	Cecilia Petersen
Denmark	Catherine Rechnitzer, Henrik Schrøder, Jesper Brok
Finland	Markku Heikinheimo, Hanna Juntti
Iceland	Halldora Thorarinsdottir
Norway	Eva Widing, Dorota Wojcik
Sweden	Cecilia Petersen, Britt-Marie Holmqvist
Young NOPHO	Jan-Bernd Stukenborg, Samppa Ryhanen

The NOPHO GCT working group did not meet as a separate group in 2015 due to the start meeting of the Solid Tumour Committee (STC), see separate report.

The group is intending to keep on having contact and as a NOPHO group participating in the upcoming international study on malignant extracranial GCT:s, coordinated from the UK and the US. The protocol is supposed to be finalized in 2016.

Cecilia is stepping down as coordinator after eight years, according to the NOPHO statutes.

The group will meet in connection to the Solid Tumour Committee in Stockholm November 17th-18th 2016.

Retinoblastoma Working Group

Coordinator	Einar Stensvold	einar.stensvold@ous-hf.no
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Finland	Jouni Pesola	jouni.pesola@kuh.fi
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	Mikkel Funding	mikkel.funding@dadlnet.dk
	Niels Clausen	nc@dadlnet.dk
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	Marlies Hummelen	marhum@ous-hf.no
	Einar Stensvold	einar.stensvold@ous-hf.no
	Finn Wesenberg	fwesenbe@ous-hf.no
	Bård Nedregaard	bnedrega@ous-hf.no
	Bjørn Tennøe	btennoe@ous-hf.no
	Ketil R Heimdal	kheimdal@ous-hf.no
	Erlend C.S. Landsend	erllan@ous-hf.no

The NOPHO Retinoblastoma group was established after the first joint Nordic Retinoblastoma meeting held in Oslo in April 2013.

Members of this group are ophthalmologists, geneticist, radiologists and paediatricians with special interest in retinoblastoma. There are members from four Nordic countries; Sweden, Denmark, Norway and Finland are members of the group, but we are interested that people from Iceland become members of the group.

Annual meetings will rotate between the Scandinavian countries. The next meeting will be in Oslo in 14 – 15 of April 2016.

The different national guidelines for the treatment of Retinoblastoma are posted on the homepage. Our plan is to enhance the cooperation further, especially for international cooperation and discussion of complicated patients. At the meeting in Oslo we will focus on finishing common Nordic guidelines.

Publications

2016

Gregersen PA, Urbak SF, Funding M, Overgaard J, Jensen UB, Alsner J. *Danish retinoblastoma patients 1943-2013 - genetic testing and clinical implications.* Acta Oncol. 2016;55(4):412-7.

2014

Bartuma K, Pal N, Kosek S, Holm S, All-Ericsson C. *A 10-year experience of outcome in chemotherapy-treated hereditary retinoblastoma.* Acta Ophthalmol. 2014 Aug;92(5):404-11.

Einar Stensvold
Chair of the NOPHO Retinoblastoma Group
April 13th, 2016

Brain Tumor Committee

Members of the board

Coordinator: Astrid Sehested (DK), stepping down May 2016, to be replaced by Virve Pentikäinen

Denmark: Niels Clausen, Astrid Sehested, Helle Broholm (neuropathologist)

Finland: Mikko Arola, Virve Pentikäinen, Tuula Lönnqvist (neuropaed)

Iceland: Halldora Thorarinsdottir

Norway: Tore Stokland, Harald Thomassen, Einar Stensvold, Petter Brandal (radiotherapist)

Sweden: Birgitta Lannering, Stefan Holm, Irene Devenney, Christoffer Ehrstedt, Bengt Gustavsson (NSurg) Baltic Countries: Rosita Kiudeliene (Lt), Sirje Mikkel (Ee), Zhanna Kovalova (Lv)

Young NOPHO Kristiina Nordfors (F)

NOPHO Solid Tumor Registry: Mats Heyman

SIOP-E BT working group members from NOPHO (also NOPHO representatives in the SIOP brain tumour working groups and where relevant national coordinators for SIOP protocols)

Medulloblastoma/PNET: Birgitta Lannering (S), Finn Wesenberg/Einar Stensvold (N), Astrid Sehested (DK), Virve Pentikäinen (F)

Low Grade Glioma: Tore Stokland (N), Per-Erik Sandström (S), Jon Helgestad, Karsten Nysom, Astrid Sehested (DK), Kamilla Rothe Nissen (opthalmologist), Päivi Lähteenmäki / Tuire Lähdesmäki (F)

High Grade Glioma: Stefan Holm (S), Karsten Nysom (DK), Ingrid Torsvik (N), Virve Pentikäinen (F) Ependymoma: Finn Wesenberg and Bernt Due-Tønnesen (N), Helena Morse (S), Pernille Wendtland Edslev (DK), Kirsti Sirkïa (F)

CNS Germ cell tumors: Randi Nygaard (N), Irene Devenney (S), Astrid Sehested (DK) Craniopharyngioma: Bengt Gustavsson (S)

AT/RT: Karsten Nysom (DK), Pernilla Grillner (S)

DIPG: (Diffusely infiltrating pontine glioma) Sanna Kivivuori (F), Stefan Holm (S), Karsten Nysom (DK), Klas Blomgren (S)

Quality of Survival: Christoffer Ehrstedt

Change of members

Helle Broholm joined as neuropathology representative, and Rosita Kiudeliene (Lt), Sirje Mikkel (Ee), Zhanna Kovalova (Lv) joined as representatives from the Baltic countries.

Meetings

Board meetings

A Board meeting was held in Oulu on 22nd and 23rd May at the NOPHO meeting (minutes and presentations on www.nopho.org). The next board meeting will be in Reykjavik on 27th and 28th May, also at the NOPHO meeting.

Brain tumour meetings

The **SIOP-E Brain Tumour Group** met in Heidelberg from June 4-6th 2015. Minutes of the meeting have been circulated to the SIOP-E BT working group members.

Separate SIOP-E BT working group meetings have also been held in several working

groups (GCT, low- grade glioma, DIPG and HGG).

The PaeNNO 2015 meeting took place from 22nd September (evening) until 25th September (morning) 2015 from Tromsø to Trondheim, on Hurtigruten, Norway. (see www.paenno.org). The meeting was very well- attended and was a great success with an excellent multidisciplinary programme.

The 4. International Multidisciplinary Postgraduate Course on Childhood Craniopharyngioma took place from April 7th – 10th, in Bad Zwischenahn, Germany.

The 2nd Nordic Symposium in Pediatric Proton Therapy took place from 6-7 April 2016, in Nyborg, Denmark.

Future meetings

The next meeting of the **SIOP-E Brain Tumour Group** will take place in Liverpool from June 11th -12th 2016, in conjunction with the **ISPNO** meeting from 12-15th June 2016 (www.ispno2016.com).

The next **PaeNNO meeting** will be in 2017, organisation and date to be determined at the committee meeting in Reykjavik. Tentative responsible country Sweden (or Lithuania, if interested and ready).

Organization of the Brain Tumour Network

It was decided at the meetings in Bergen and Oulu to set up a Brain Tumour Network open to any NOPHO member working with paediatric brain tumours. The practical set-up of this network is not yet finalised.

Nordic CNS research projects

- **The Nordic study of Cerebellar Mutism Syndrome (CMS) in children with brain tumours of the posterior fossa** is open in five countries (Denmark, Sweden, Finland, Norway and Lithuania) and shortly to open in the Netherlands and the UK. Patient accrual is going well. The protocol and forms are on the NOPHO web site under "protocols". The study database has been developed at CCEG at Karolinska and remote data entry is ongoing. There have been several on-line meetings in the study group.
- **Lithium in the treatment of cognitive late effects after cranial radiotherapy** is a study proposed by Klas Blomgren during the PaeNNO meeting in Copenhagen, accepted as a NOPHO study by the NOPHO Board and is planned to run in cooperation with Institut Gustave Roussy in Paris.
- **NOPHO collaboration in a study of brain tumour diagnostics using methylation array analysis** is also anticipated, initiated from Gothenburg, Sweden.

Participation in SIOP brain tumour protocols

Within Europe, the SIOP brain tumour working groups work towards international cooperative protocols and registries to improve treatment for brain tumour patients. The NOPHO Brain Tumour Committee participates in this work through our elected NOPHO representatives, and we intend to have (at least) one Nordic member in the core committees of each of the new SIOP brain tumour protocols. With the present EU legislation, it is necessary to have a national coordinator from each participating country, who is also a member of the SIOPE working group.

Low Grade Glioma (LGG)

The SIOP-LGG 2004 has closed for randomisation in early 2013, but is still open for registration (treatment standard arm). National coordinators: Denmark: Jon Helgestad, Norway: Tore Stokland, Sweden: Per-Erik Sandström. We continue to recommend that all patients with low-grade glioma be registered in the protocol, including patients who do not receive chemotherapy or radiotherapy.

SIOP-LGG 201x, or LOGGIC protocol is still being worked upon, there are at present changes being made to the study design. Patients will be stratified into risk groups (infant, standard risk and diffuse glioma grade II). In addition to PFS as defined by MRI imaging, visual and neurological outcome will be included as primary outcome measures. This will necessitate close cooperation with study ophthalmologists for patients with a visual pathway tumour. A separate protocol for treat-

ment of patients with neurofibromatosis 1 and low-grade glioma is also being developed.

SIOP CNS GCT II

This SIOP protocol for patients with CNS germ cell tumours has opened in Germany, Sweden, Norway, UK and France, not open yet in Denmark. National coordinators: Denmark: Astrid Sehested, Norway: Randi Nygaard, Sweden: Irene Devenney.

PNET/Medulloblastoma

PNET V for low-risk and standard-risk medulloblastoma has opened in Germany, and also in Finland and Sweden, and is planned to open in Norway and Denmark. The study depends on upfront analysis of biological markers in fresh-frozen tumour tissue in order to stratify patients, done on a national basis. The study question is about lowering the dose of therapy (both radiotherapy and chemotherapy) for low-risk patients (a small subset) and randomising to concomitant carboplatin therapy during radiotherapy for standard-risk patients.

Protocols for treatment of infant medulloblastoma and high-risk medulloblastoma are in development; the infant protocol is furthest in its design and will have arms for all infant categories (low-risk, standard risk and metastatic) and will include radiotherapy for patients > 18 months with poor prognosis.

Ependymoma

SIOP Ependymoma 2 has opened in France and the UK, and is in the process of being opened in the Nordic countries. This protocol has 3 different strata (risk categories) with separate randomisations in each strata.

AT/RT

There is no protocol as such, but the European Rhabdoid Registry contains a registry and treatment suggestion (EU-RHAB). The most recent version of the protocol can be found on www.nopho.org . We continue to recommend that patients are discussed with Michael Frühwald in Augsburg, Germany, who coordinates the registry, and that the patients be reported to the registry.

High grade glioma and DIPG

Infant HGG has agreed upon and will be opened when the sponsor gets funding (Göttingen, Germany) The SIOP-e DIPG network is also developing a registry. The registry is not open yet.

BIOMEDE for DIPG has opened in France, and recently also in Copenhagen, Denmark. Sweden is planning on opening the trial.

Relapse protocols

A phase 1 trial with afatinib for relapsed or progressive patients with most brain tumours is open in Copenhagen, Denmark. The trial is currently on hold, but a dose expansion part will soon open, where patients must be selected based on tumour biomarker profile.

The VINILO study for relapsed low-grade glioma is at present closed for patient inclusion in an interim phase between phase 1 and phase 2, but will soon open again in Copenhagen, Denmark.

A dabrafenib trial for relapsed/progressive BRAF V600 mutated tumours will open in Copenhagen shortly.

A trial of PD1 inhibitor (pembrolizumab) in relapsed/progressive PD1 positive solid tumours including brain tumours is open in Lund, Sweden.

A phase 1 trial of tazemetostat for relapsed/progressive INI1-negative tumours including AT/RT is open in Copenhagen, Denmark.

The MEMMAT trial for metronomic anti-angiogenic therapy of relapsed medulloblastoma is now open in Copenhagen, Stockholm, Gothenburg, Uppsala, Umeå, Linköping and Lund.

Radiotherapy

The Skandion clinic in Uppsala has opened in June 2015, and several paediatric brain tumour patients have now received proton therapy there. Craniospinal radiotherapy has not yet been given but will soon become available. The Skandion Clinic represents the first and large step of increase in capacity for proton therapy

in the Nordic countries. A proton facility is also underway in Århus, Denmark, planned to open in October 2018, and Norway is developing its plans for building one or more proton facilities.

Use of the NOPHO web in CNS tumour work

We continue to encourage that active SIOP-e protocols be put on the NOPHO web. The LGG 2004 protocol is on the NOPHO web, as is the EU-RHAB protocol. Minutes of working group meetings should be posted if permission is granted by the working group chair.

Astrid Sehested
Chair of the NOPHO Brain Tumour Committee, April 16th, 2016

ALL Working Group

Coordinator	Mats Heyman
Denmark	Thomas Frandsen
	Birgitte Klug Albertsen
Finland	Päivi Lähteenmäki
	Mervi Taskinen
Iceland	Olafur Gislí Jonsson
Norway	Inga Maria Rinvoll Johannsdottir
	Trond Flaegstad
	Ann Åsberg
Sweden	Jonas Abrahamsson
	Stefan Söderhäll
	Anders Castor
	Johan Malmros
Representative from Baltic countries	
Estonia	Kaie Pruunsild
Lithuania	Goda Vaitkeviciene
Chair of the	
Leukemia and Lymphoma group	Päivi Lähteenmäki
MRD group	Finn Wesenberg
Pharmacology group	Goda Vaitkeviciene
Cytogenetic group	Erik Forestier and Ulrika Noren Nyström
Flow group	Hanne Marquart
MDS group	Henrik Hasle
Infant group	Birgitte Lausen
Event group	Thomas Frandsen
Relapse group	Johan Arvidson
Ph leukemia group	Anders Castor
ALL 2008 protocol committee	Kjeld Schmiegelow
A representative from:	
NOPHO registry	Mats Heyman
General secretary	Cecilia Petersen

The ALL group meets twice yearly, the day after the Leukaemia & Lymphoma Committee meetings. The meetings during the year from the last report have been held at Kastrup, Copenhagen (September 3rd 2015 and in Uppsala March 17th 2016).

The present ALL protocol (NOPHO ALL-2008)

ALL WG has cooperated with the NOPHO ALL 2008 PI-group in the follow-up of the ALL2008 protocol.

- The study protocol has recruited 1718 patients from 1.7.2008 to 31.12.2015. Out of those 1465 were children 1-17.99 years from the Nordic and Baltic countries, 253 adults (age 18-45) from the Nordic and Baltic adults. Since Lithuania has become a NOPHO member country and the Baltic overall outcome is approaching that of the rest of NOPHO, there does not seem to be very useful to divide the cohort into different regions as before. Since the protocol was accepted for use by adult haematologists in Finland, the first two patients have been registered.
- pEFS at five years: children: 0.86 , adults: 0.73.
- pOS at five years: overall: children: 0.92, adults: 0.74.
- The randomised parts (R1: treatment with or without 6MP increments during consolidation for SR and IR-patients; R2: 2-weekly vs 6-weekly PEG-Asp during post-consolidation therapy for SR and IR-patients) have been recruiting slower than expected, which has led to a necessity to prolong the studies. Analyses of the leukaemia-specific outcomes, in the case of R2 also balanced against toxicity have been submitted yearly to the data-safety monitoring committee (DSMC). The analyses 2015 included newly, through detailed focus-group studies acquired, data on the cumulative incidence of PEG-Asp related toxicities. These analyses showed a pronounced increased toxicity for the 2-week interval arm of R2 compared to the experimental 6-week interval arm, at the same time as the leukaemia-specific outcomes were very similar. This led the DSMC to recommend the termination of this randomization and the future use of the experimental arm as standard of care. A decision to this effect was taken by the PI-group, the LLC and the NOPHO Board in March 2016.
- A discussion in the ALL-group about what should be done with the remaining time until a new protocol has been prepared and approved has started. Several suggestions of pilot-studies have been suggested and some of these are under consideration by the scientific committee.
- It has been decided that the first publication based on the NOPHO ALL-2008 protocol should be the comparison between adult (18-45 years) and paediatric (1-17 years) patients. A large number of additional publications have been planned based on the protocol.

The next ALL-protocol

During the year, the international collaboration started in 2013 to form an international consortium for a common ALL protocol ("ALLTogether") has continued and matured. The initial motivation was primarily the difficulties asking meaningful study-questions in smaller study-groups, due to the very good overall results, particularly for the lower-risk patients. There is also a wish to collaborate on research issues making use of the expertise in the different groups. The participating study groups are currently: NOPHO, UK-ALL, DCOG and COALL. The DFCI has declined participation on formal grounds. Mats Heyman, Kjeld Schmiegelow and Mervi Taskinen are the NOPHO representatives and in a meeting in April 2016 Mats Heyman was appointed coordinator of the common effort.

The NOPHO ALL-2016 group has thus been re-vamped into the NOPHO "ALLTogether"-group to support the NOPHO representatives and make sure that the protocol work is firmly based in the NOPHO membership.

Implictions for ALL from the Nordic Study Day

The legal basis for the NOPHO registry was discussed at a meeting in January 2016 together with legal, medical, ethical and regulatory

expertise from several Nordic countries. It was concluded that the legislation in the different countries were diverse and that the legal basis for the accumulation of population-based data in the NOPHO registry was uncertain. All involved parties accepted that the use of this type of data had a value in itself and that it would probably be most adequate to reshape this collaboration as a long-term research project: "NOPHO-care" for the explicit purpose of following up diagnoses and therapy of childhood cancer in the NOPHO countries. Further discussions are ongoing to get this new framework set up.

The ALL-WG as an ALL forum

Several working- and ad hoc groups, for instance the ALL-biology group, the pharmacology group and the event-group have presented their projects to the ALL-group for feedback and discussion.

The ALL WG has also served as discussion-forum for NOPHO-studies pertaining to ALL-issues giving recommendations for amendments and further handling by the LLC.

International collaborations

Internationally, the NOPHO ALL working group has been represented in the I-BFM collaborative ALL working group, the Interfant 2006-, EsPhALL- and IntReALL relapse- study groups as well as an ad-hoc working group for the registration and treatment of patients with Mb Down and ALL originally started within the PdL collaboration.

An important contribution is the initiative from KS to the PdL-group to coordinate toxicity-registration internationally. Several meetings have been conducted and working-groups with representatives from the different study-groups have prepared consensus-documents for a long list of pre-defined toxicities. The efforts are planned to result in a consensus-paper. The first collaborative paper on Pancreatitis is under preparation and CNS-toxicity and Osteonecrosis have been chosen as second in line for consensus papers compiling clinical data and biologic material for GWAS-analysis.

Stockholm, Springtime, 2016
Mats Heyman

Leukemia – ALL Registration Working Group

Coordinator	Mats Heyman
Denmark	Niels Clausen
Finland	Kim Vettenranta
Iceland	Olafur Gisli Jonsson
Norway	Inga Maria Johannisdottir
Sweden	Jonas Abrahamsson, Mats Heyman
Data management group Stockholm	
	Mats Heyman
	Matteo Bottai
	Göran Gustafsson
	Trausti Óskarsson
	Kristian Lindström
	Lili Zheng
	Mats Nordström
Data checks Copenhagen (NOPHO ALL-08)	
	Kjeld Schmiegelow (PI, NOPHO ALL-08)
	Thomas Frandsen
	Louise Rold Helt
	Kirsten Kørup Rasmussen
	Nina Toft

Introduction

The NOPHO ALL-2008 trial has now been open for nearly 8 years. From 1.7.2008 to 31.12.2015, 1962 patients were diagnosed with ALL and entered in the NOPHO ALL registry. Infants <1 years (n=65) and patients >45 years (n=1) were excluded from the NOPHO ALL-2008 trial enrollment. In addition, 178 patients, 141 children (1-17 years) and 37 adults (18-45 years), were excluded since they did not meet the trial criteria for eligibility (Figure 1). The total number of patients analyzed in the annual report is 1718 patients. The follow-up time is getting longer, allowing a better capture of late events such as SMN and late relapses.

In previous reports, Baltic patients, NOPHO ALL-2008 Pilot patients, young adult patients treated in pediatric clinics and patients younger than 18 years treated in adult clinics were excluded from the all analyses. In this year report we include these patients but other exclusion criteria remain.

The special focus of this year annual report was on the subgroups of patients excluded from the trial that have not been described in earlier NOPHO reports (Down syndrome, pre-treatment and diagnosis abroad), a better description of primary events with a special focus on relapses.

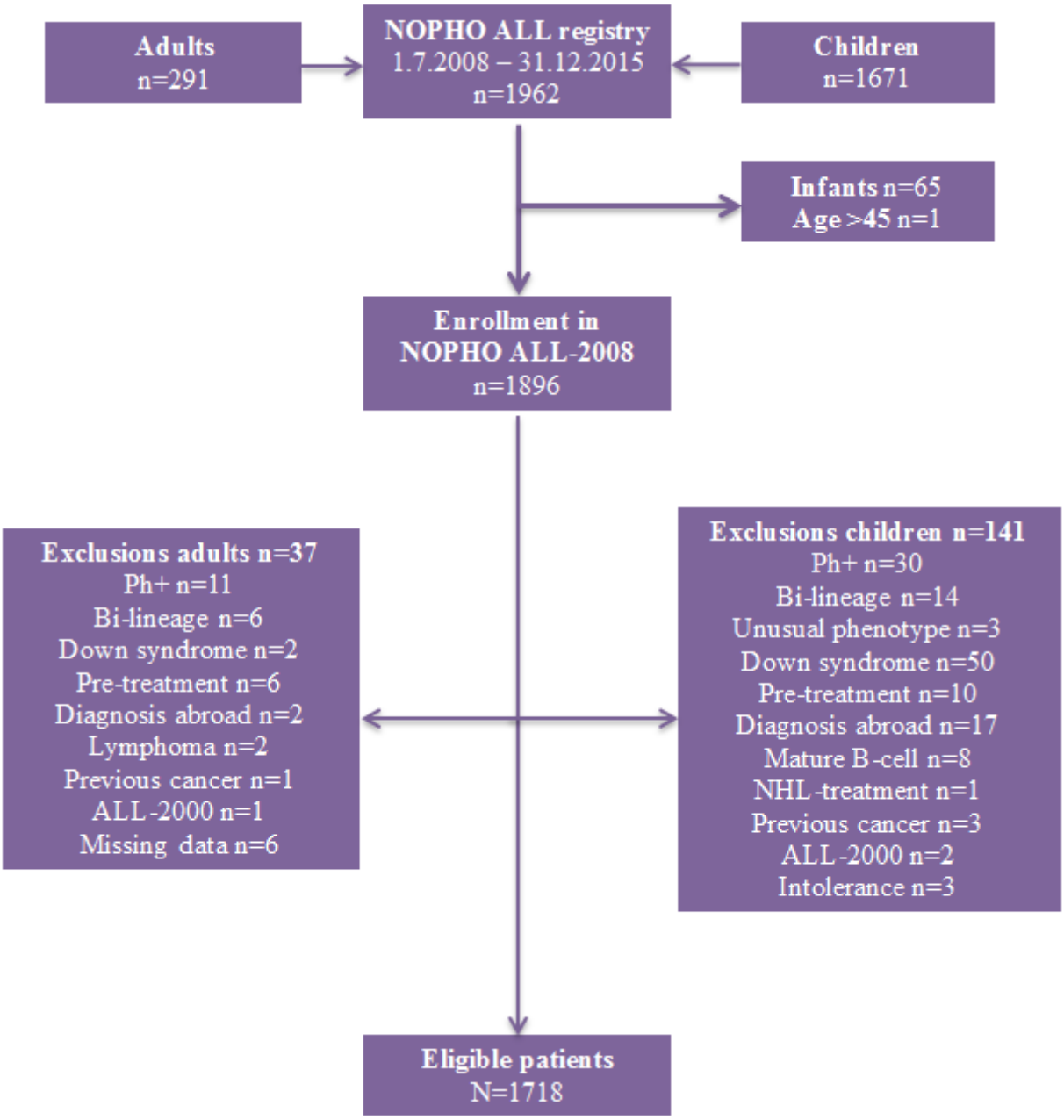


Figure 1. NOPHO ALL-2008 trial enrollment and exclusions.

Patient characteristics and risk stratification

The characteristics of patients eligible for the NOPHO ALL-2008 trial are described in Table 1. In general, adults had a higher proportion of adverse baseline factors compared to children, worse MRD response and were more often stratified to higher treatment intensity.

Table 1. Patient characteristics, by age groups.

	All patients	1-17 years	18-45 years
Overall	1718	1465	253
Gender			
Boys	948 (55.2)	792 (54.1)	156 (61.7)
Girls	770 (44.8)	673 (45.9)	97 (38.3)
WBC at primary diagnosis			
<100 x 10^9/l	1623 (95.1)	1393 (95.6)	230 (92.4)
≥100 x 10^9/l	83 (4.9)	64 (4.4)	19 (7.6)
Immunophenotype			
Pre-B ALL	1450 (84.4)	1275 (87.0)	175 (69.2)
T-cell ALL	268 (15.6)	190 (13.0)	78 (30.8)
CNS involvement			
CNS1	1498 (87.3)	1269 (86.6)	229 (91.2)
CNS2	139 (8.1)	127 (8.7)	12 (4.8)
CNS3	71 (4.1)	65 (4.4)	6 (2.4)
Missing data	8 (0.5)	4 (0.3)	4 (1.6)
Cytogenetics			
Unfavorable cytogenetics	82 (4.8)	59 (4.0)	23 (9.1)
MLL rearrangements	64 (3.7)	45 (3.1)	19 (7.5)
Hypodiploidy	19 (1.1)	15 (1.0)	4 (1.6)
Intermediate cytogenetics	108 (6.3)	95 (6.5)	13 (5.1)
t(1;19)	49 (2.9)	42 (2.9)	7 (2.8)
iAMP21	31 (1.8)	27 (1.8)	4 (1.6)
dic(9;20)	27 (1.6)	25 (1.7)	2 (0.8)
Favorable cytogenetics	808 (47.0)	781 (53.3)	27 (10.7)
t(12;21)	330 (19.2)	328 (22.4)	2 (0.8)
High-hyperdiploidy	478 (28.6)	453 (30.9)	25 (9.9)
Other	377 (21.9)	293 (20.0)	84 (33.2)
Normal	288 (16.8)	206 (14.1)	82 (32.4)
Missing data	55 (3.2)	31 (2.1)	24 (5.1)
MRD day 29			
≥25%	18 (1.0)	14 (1.0)	4 (1.6)
≥5% - <25%	55 (3.2)	33 (2.3)	22 (8.7)
≥0.1% - <5%	437 (25.4)	354 (24.2)	83 (32.8)
<0.1%	543 (31.6)	485 (33.1)	58 (22.9)
<0.1% negative	601 (35.0)	539 (36.8)	62 (24.5)
Blocks direct	37 (2.2)	21 (1.4)	16 (6.3)
Missing data	22 (1.3)	18 (1.3)	4 (1.6)
No marker	5 (0.3)	1 (0.1)	4 (1.6)
Risk group			
Standard risk	770 (44.8)	720 (49.1)	50 (19.8)
Intermediate risk	611 (35.6)	506 (34.6)	104 (41.1)
High risk chemo	200 (11.6)	147 (10.0)	53 (20.9)
High risk HSCT	118 (6.9)	75 (5.1)	43 (17.0)
No risk group assigned	2 (0.1)	0	2 (0.1)
Induction Failure	17 (1.0)	14 (1.0)	3 (1.2)

Risk stratification

The decision on the final risk group of patients is made on the ”intention-to-treat” basis. All cases undergo central review for the final risk group, cytogenetics and MRD response. Two patients could not be assigned a risk group since there was insufficient data for risk stratification (Figure 2). Seventeen patients died during induction and could therefore not be assigned a risk group.

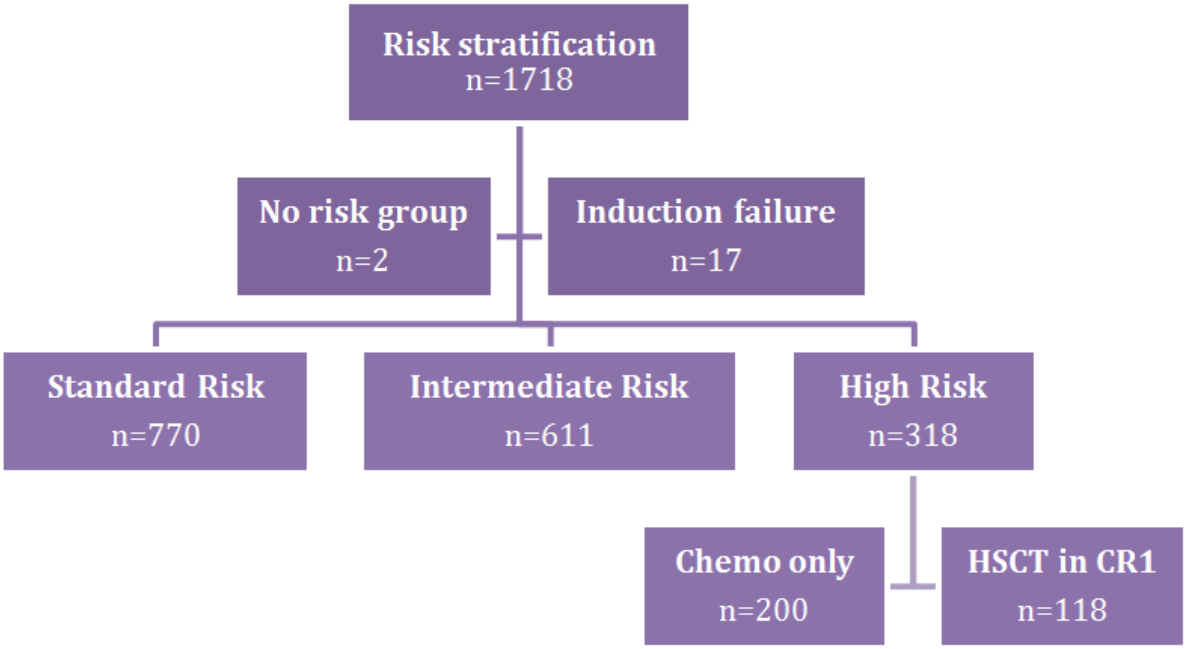


Figure 2. Final risk stratification of patients included in analyzes, as intention to treat.

Pre-treatment

Sixteen patients were excluded from the trial because of pre-treatment with glucocorticoids or other immunosuppressive drugs. Four patients were treated for suspected rheumatic disease and one for immune thrombocytopenic purpura. Table 2 describes the characteristics of these patients. Induction failure occurred in one patient and relapse in one patient. Pre-treatment did not have a negative effect on the event-free survival or the overall survival.

Table 2. Characteristics of patients that received pre-treatment.

Pre-treatment	Number of patients
Overall	16
Age	
Children	10
Adults	6
Gender	
Boys	12
Girls	4
WBC at primary diagnosis	
$<100 \times 10^9/l$	15
$\geq 100 \times 10^9/l$	1
Immunophenotype	
Pre-B ALL	13
T-cell ALL	3
Cytogenetics	
Unfavorable cytogenetics	2
Intermediate cytogenetics	0
Favorable cytogenetics	4
Normal	6
Other	4
Country	
Denmark	4
Finland	4
Iceland	0
Norway	2
Sweden	2
Estonia	3
Lithuania	1
Survival	
5-year overall survival ± s.e.	93.8 ± 6.1%
5-year event-free survival ± s.e.	85.2 ± 9.8%

Diagnosis abroad

Nineteen patients were diagnosed abroad and started treatment with glucocorticoids or received chemotherapy according to a different ALL protocol. One patient received full treatment for ALL abroad but was treated for ALL relapse in Sweden.

Table 3. Characteristics of patients diagnosed abroad.

Diagnosis abroad	Number of patients
Overall	19
Age	
Children	17
Adults	2
Gender	
Boys	9
Girls	10
WBC at primary diagnosis	
$<100 \times 10^9/l$	7
$\geq 100 \times 10^9/l$	0
Missing data	12
Immunophenotype	
Pre-B ALL	17
T-cell ALL	2
Cytogenetics	
Unfavorable cytogenetics	1
Intermediate cytogenetics	0
Favorable cytogenetics	5
Normal	2
Other	2
Missing data	9
Country	
Denmark	1
Finland	1
Iceland	0
Norway	0
Sweden	15
Estonia	1
Lithuania	1
Location of diagnosis	
Asia	9
Africa	1
Australia	1
Europe	7
Missing info	1

Down syndrome

Patients with Down syndrome were excluded from the trial but received modified treatment according to the protocol amendment to limit the risk of toxicities. Table 4 describes the characteristics of patients with Down syndrome. One patient had a Ring chromosome 21 and was labeled as Down syndrome and excluded from the trial.

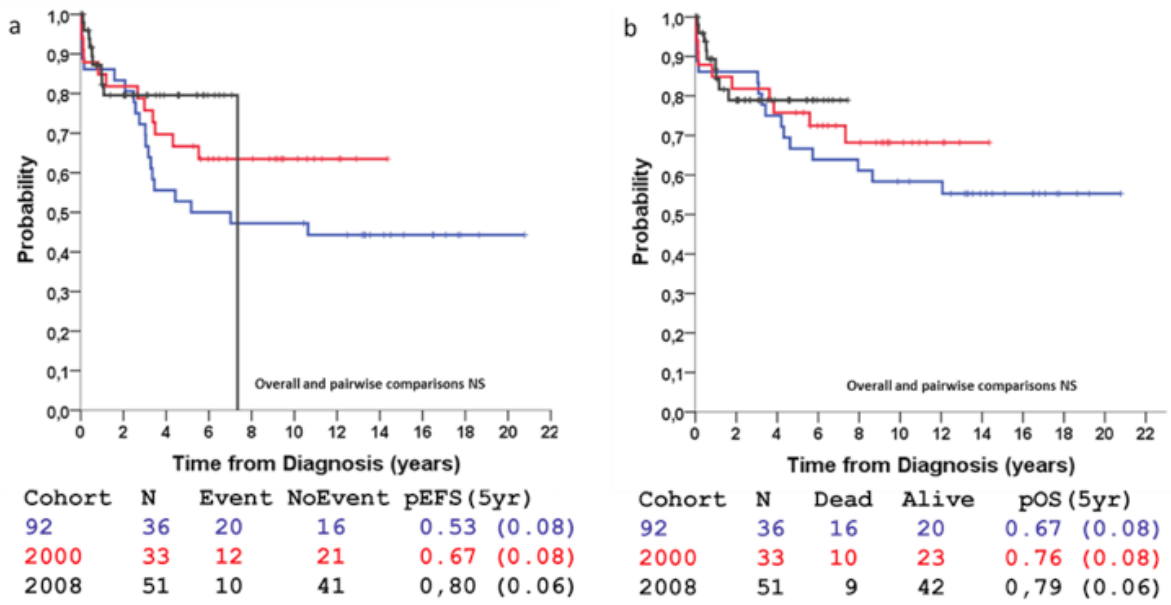
Although 3 patients were stratified to HR+HSCT based on the treatment response none underwent HSCT in CR1. Both relapses occurred on-protocol (very early iBM and very early iCNS relapses), hence stratified as High Risk relapses, both patients died after relapse. Two patients died of infection during induction and three of infection in CR1. One patient that died in CR1 had a missing data on the cause of death. Two patients experienced SMN; both had received modified block treatment according to the High Risk arm. One developed AML one year after start of treatment, but the other had signs of MDS in bone marrow at the end of Maintenance II but was not considered a candidate for HSCT because of underlying morbidity. That patient developed AML approximately 5 years after the cession of primary treatment.

Table 4. Characteristics of patients with Down syndrome.

Down syndrome	Number of patients
Overall	51
Age	
Children	49
Adults	2
Gender	
Boys	25
Girls	26
WBC at primary diagnosis	
<100 x 10^9/l	48
≥100 x 10^9/l	2
Missing data	1
Immunophenotype	
Pre-B ALL	51
T-cell ALL	0
Cytogenetics	
Unfavorable cytogenetics	0
Intermediate cytogenetics	1
Favorable cytogenetics	5
Normal	24
Other	18
Missing data	3
CNS status at diagnosis	
CNS1	44
CNS2	6
CNS3	1
Risk group	
Standard Risk	0
Intermediate Risk	43
High risk chemo	2
High risk HSCT in CR1	3
Insufficient data	3
Primary events	
CR1	41
Induction failure	2
DCR1	4
Relapse	2
SMN	2
Survival	
5-year overall survival ± s.e.	78.9 ± 6.3%
5-year event-free survival ± s.e.	79.6 ± 6.1%

Both overall survival (p=0.005) and event-free survival (p=0.03) was significantly lower in patients with Down syndrome compared to patients that did not have Down syndrome. One of the main reasons for worse outcome in patients with Down syndrome was the high frequency of treatment-related mortality (7 deaths, 13.5%).

The outcome for patients with Down syndrome is still inferior to other patients with pre-B ALL. The 5-year overall survival (OS) was 78.9% (±6.3%) and 5-year event-free survival (EFS) 79.6% (±6.1%). The survival has not improved significantly compared to ALL-92 and ALL-2000 (Figure 3), but there is a trend in the EFS-analysis, which with longer follow-up may translate into an improvement. It should also be kept in mind that as far as we know, all patients with Mb Down in the latter period have received therapy. A few cases from the older cohorts have not been treated due to co-morbidities.



Cohort	N	Event	NoEvent	pEFS(5yr)
92	36	20	16	0.53 (0.08)
2000	33	12	21	0.67 (0.08)
2008	51	10	41	0,80 (0.06)

Cohort	N	Dead	Alive	pOS(5yr)
92	36	16	20	0.67 (0.08)
2000	33	10	23	0.76 (0.08)
2008	51	9	42	0,79 (0.06)

Figure 3. Outcome of patients with Down syndrome in NOPHO ALL-92, ALL-2000 and ALL-2008 protocols. a. Event-free survival b. Overall survival.

Induction failure

Induction failure occurred in 17 patients. The median time to death was 19 days from diagnosis (range 1-50 days). Interestingly, females were in majority and 5 of 17 had unfavorable cytogenetics (all MLL positive) (Table 5). Twelve were registered with infection as the cause of death; four with bleeding. One patient did not have data on the cause of death.

Table 5. Characteristics of patients with induction failure.

Induction failure	Number of patients
Overall	17
Age	
Children	14
Adults	3
Gender	
Boys	6
Girls	11
WBC at primary diagnosis	
$<100 \times 10^9/l$	9
$\geq 100 \times 10^9/l$	4
Missing data	4
Immunophenotype	
Pre-B ALL	13
T-cell ALL	4
Induction treatment	
Non-high risk induction	9
High risk induction	8
Cytogenetics	
Unfavorable cytogenetics	5
Intermediate cytogenetics	0
Favorable cytogenetics	5
Normal	3
Other	4

Second malignant neoplasm

Second malignant neoplasms (SMN) have occurred in 13 patients, mostly children with hematological SMN (Table 6). In contrast to other primary adverse events, SMN mainly occurred in patients with a low risk baseline characteristics; pre-B immunophenotype, no hyperleukocytosis at diagnosis, good response etc. One patient had undergone HSCT in CR1. The patient with sarcoma had a synovial sarcoma. Second malignant neoplasm originating in lymphoid tissues, were Hodgkin's lymphoma, B-cell lymphoma, lymphomatoid granulomatosis and post-transplantation lymphoproliferative disease (PTLD). The median time to SMN was 741 days (range 273-1932 days). Ten of the 13 patients with SMN are alive at the time of follow-up.

Table 6. Characteristics of patients diagnosed with second malignant neoplasm as a primary event.

SMN	Number of patients
Overall	13
Age	
Children	12
Adults	1
Gender	
Boys	7
Girls	6
WBC at primary diagnosis	
$<100 \times 10^9/l$	13
$\geq 100 \times 10^9/l$	0
Immunophenotype	
Pre-B ALL	13
T-cell ALL	0
Cytogenetics	
Unfavorable cytogenetics	2
Intermediate cytogenetics	0
Favorable cytogenetics	10
Normal	0
Other	1
MRD day 29	
≥5%	0
≥0.1% - <5%	2
<0.1%	4
<0.1% negative	7
Risk group	
Standard risk	10
Intermediate risk	1
High risk chemo	2
High risk HSCT	0
SMN type	
MDS	4
AML	4
Lymphoma	4
Sarcoma	1

Death in first complete remission

Death in CR1 occurred in 53 patients (3.1%) and as in cases where induction deaths occurred patients had more adverse clinical and cytogenetic factors, worse MRD response and were stratified to higher treatment intensity (Table 7). Eight of the DCR1 events occurred after HSCT in CR1. Information on the exact cause of death needs to be supplemented since the current data in the ALL registry is insufficient.

Table 7. Characteristics of patients that died in first complete remission.

DCR1	Number of patients
Overall	53
Age	
Children	39
Adults	14
Gender	
Boys	29
Girls	24
WBC at primary diagnosis	
<100 x 10^9/l	48
≥100 x 10^9/l	5
Immunophenotype	
Pre-B ALL	33
T-cell ALL	20
Induction treatment	
Non-high risk induction	26
High risk induction	27
Cytogenetics	
Unfavorable cytogenetics	7
Intermediate cytogenetics	4
Favorable cytogenetics	10
Other	19
Normal	12
Missing data	1
MRD day 29	
≥25%	1
≥5% - <25%	4
≥0.1% - <5%	19
<0.1%	7
<0.1% negative	15
Blocks direct	6
Missing data	1
Risk group	
Standard risk	9
Intermediate risk	16
High risk chemo	20
High risk HSCT	8

Relapse

In total, 126 relapses occurred as a first event, 88 in children and 38 in adults (Table 8). Compared to data on ALL relapse in children 1-14.9 years that were treated in the NOPHO ALL-92 and ALL-2000 trials the pattern of relapse was similar except for a higher proportion of T-cell relapses in the ALL-2008 trial, 27% (25% if 1-14 years, n=81) compared to 12% (1-14 years) in the ALL-92 and ALL-2000 trials. The CNS was involved in 29% of ALL relapses, similar to the ALL-92 and ALL-2000 trials (28%). Six of the patients with CNS involvement at relapse were CNS3 at diagnosis. Interestingly 12 patients with CNS2 status at diagnosis relapsed, eight with iBM relapse, two with iCNS relapse and two with combined relapse. Both, the immunophenotype and CNS involvement at relapse could be affected by the short time of follow up since most T-cell and CNS involving relapses occur on-treatment. In the ALL-2008 trial, 21.8% received HR-induction but among the patients that relapsed, 42.6% had undergone HR-induction.

Patients were assigned a risk group at relapse according to the IntReALL protocol, which uses the immunophenotype, time from diagnosis to relapse and the site of relapse, to group patients to High Risk or Standard Risk relapses. High Risk if a very early relapse, early and late T-cell bone marrow involving relapse and early pre-B isolated bone marrow relapse. All other relapses were stratified as Standard Risk.

There has been a shift in the treatment of ALL relapses in the NOPHO countries from the ALL-REZ BFM protocols to the newer ALLR3 and IntReALL protocols. The IntReALL study is now formally open in Denmark, Norway and Finland.

Table 8a) Characteristics of patients with relapse as a primary event. b) Characteristics at relapse

a)

Relapse	Number of patients
Overall	126
Age	
Children	88
Adults	38
Gender	
Boys	73
Girls	53
WBC at primary diagnosis	
<100 x 10^9/l	106
≥100 x 10^9/l	18
Missing data	2
Immunophenotype	
Pre-B ALL	92
T-cell ALL	34
Induction treatment	
Non-high risk induction	73
High risk induction	53
Cytogenetics	
Unfavorable cytogenetics	11
Intermediate cytogenetics	7
Favorable cytogenetics	30
Normal	25
Other	46
Missing data	7
CNS status at diagnosis	
CNS3	104
CNS2	12
CNS1	9
Missing data on CNS status	1
MRD day 29	
≥25%	1
≥5% - <25%	8
≥0.1% - <5%	56
<0.1%	30
<0.1% negative	18
Blocks direct	12
Missing data	1
Risk group	
Standard risk	24
Intermediate risk	43
High risk chemo	37
High risk HSCT	20
No risk group assigned	2
HSCT in CR1	
Yes	18
No	108

Table 8b) Characteristics at relapse

b)

Relapse	Number of patients
Site of relapse	
Isolated bone marrow relapse	79
Combined relapse	19
Isolated extramedullary relapse	28
CNS involvement at relapse	
Yes	36
No	90
Time to relapse	
<18 months - Very early	62
≥18 months to 36 months - Early	41
≥ 36 months - Late	23
Relapse risk group (IntReALL)	
Standard Risk	41
High Risk	85
Relapse treatment	
IntReALL	24
BFM REZ-ALL	14
NOPHO-High Risk arm	10
ALL-R3	20
RALLE	3
Other	34
Missing data	21
5-year overall survival ± s.e.	
All relapses	26.3 ± 4.8%
Standard Risk	54.6 ± 11.4%
High Risk	14.8 ± 4.4%

In general, outcome after relapse was poor, 5-year overall survival was 26.3 ± 4.8%, 54.6 ± 11.4% for Standard Risk relapses and only 14.8 ± 4.4% for High Risk relapses. Register data was not sufficient to analyze treatment response during relapse treatment, second events, event-free survival and HSCT in CR2.

Compared to the outcome of ALL relapse in children 1-14.9 years that were treated in the NOPHO ALL-92 and ALL-2000 trials the outcome has not improved. For patients 1-14 years (patients that underwent HSCT in CR1 excluded) and relapsed during or after the NOPHO ALL-2008 trial the 5-year OS was 35.4% ± 7.1% (n=75) compared to 51.5 ± 2.3% (n=485) in the ALL-92 and ALL-2000 era. The 5-year OS for children with Standard Risk relapses (n=30) was 70.7 ± 12.9% but for High Risk relapses (n=45) the 5-year OS was very poor, 15.9 ± 6.5%. Figure 4 illustrates overall survival after relapse in Standard Risk and High Risk relapses in the ALL-92, ALL-2000 and ALL-2008 trials. The overall survival for High Risk relapses in ALL-2000 was superior to High Risk relapses in ALL-2008 (p=0.001).

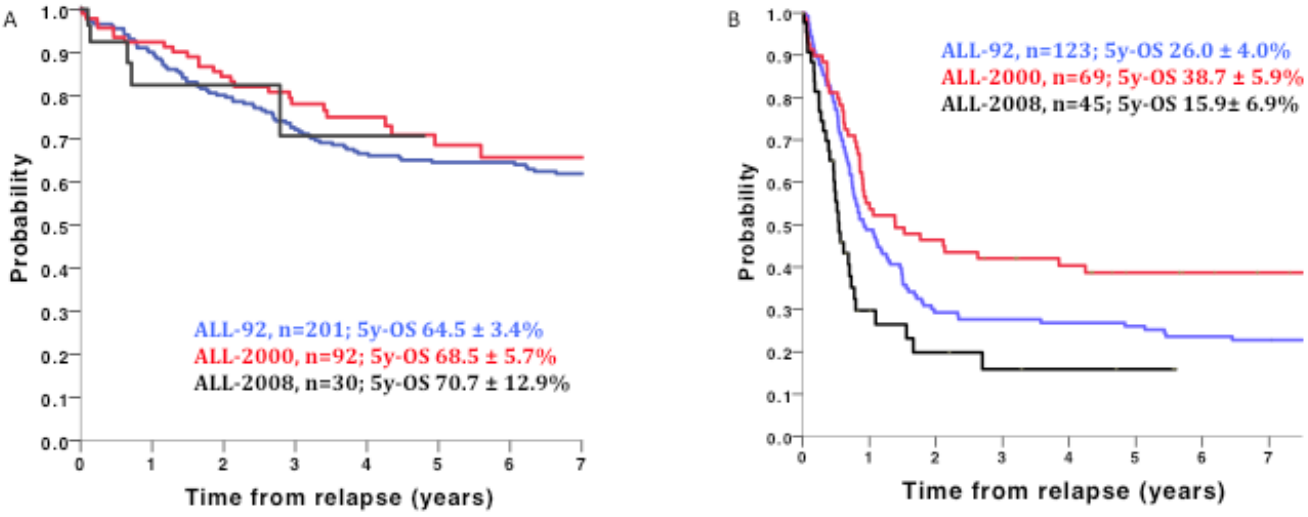


Figure 4. Overall survival after relapse, age 1-14 years. HSCT in CR1 excluded.
A. Standard Risk relapse. B. High Risk relapse.

When comparing relapses in the ALL-2008 trial to previous trials, both shorter follow-up time and lower relapse rate have to be taken into account. Sixty percent of the ALL-92/ALL-2000 relapses were Standard Risk but only 33% of the relapses that have occurred in the ALL-2008 trial are Standard Risk. As mentioned above, High Risk relapses have a very poor outcome. Table 9 illustrates the pattern of relapse by the time of relapse. The lower relapse rate in ALL-2008 and a higher proportion of patients initially stratified as HR (57% vs. 41%) could also cause a selection of treatment resistant relapses.

Table 9. Pattern of relapse by the time from diagnosis to relapse.

	< 18 months Very early	≥18 months to 36 months Early	≥36 months Late
Total number	62	41	23
WBC at primary diagnosis			
<100 x 10^9/l	48 (77.4)	36 (90.0)	22 (100)
≥100 x 10^9/l	14 (22.6)	4 (10.0)	0
Immunophenotype			
Pre-B ALL	38 (61.3)	33 (80.5)	21 (91.3)
T-cell ALL	24 (38.7)	8 (19.5)	2 (8.7)
Risk group			
Standard risk	7 (11.3)	10 (24.4)	7 (30.4)
Intermediate risk	13 (21.0)	16 (39.0)	14 (60.9)
High risk	40 (64.5)	15 (36.6)	2 (8.6)
No RG assigned	2 (3.2)	-	-
Cytogenetics			
Unfavorable	7 (11.3)	4 (9.8)	0
Intermediate	1(1.6)	4 (9.8)	2 (8.7)
Favorable	7 (11.3)	14 (34.1)	9 (39.1)
Normal	18 (29.0)	3 (7.3)	4 (17.4)
Other	27 (43.5)	12 (29.3)	7 (30.4)
Missing data	2 (3.2)	4 (9.8)	1 (4.3)
MRD day 29			
≥25%	1 (1.6)	0	0
≥5% - <25%	7 (11.3)	1 (2.4)	0
≥0.1% - <5%	24 (38.7)	19 (46.3)	13 (56.5)
<0.1%	14 (22.6)	13 (31.7)	3 (13.0)
<0.1% negative	6 (9.7)	6 (14.6)	6 (26.1)
Blocks direct	9 (14.5)	2 (4.9)	1 (4.3)
Missing data	1 (1.6)	0	0
Site of relapse			
iBM	43 (69.4)	20 (48.8)	16 (69.6)
Combined	6 (9.7)	9 (22.0)	4 (17.4)
iEM	13 (21.0)	12 (29.3)	3 (13.0)

Cytogenetics

Cytogenetic aberrations are reviewed regularly by the NOPHO Cytogenetic Working Group. When comparing the data on cytogenetic finding in the ALL registry and from the central review, some discrepancies were observed, mainly in cases of t(12;21) and high-hyperdiploidy (HeH) (Table 10).

Table 10. Cytogenetic results reported from clinics (columns) and results from central review (rows).

Central review/clinics	MLL	<45 chr	45 chr	t(1;19)	iAMP21	dic(9;20)	t(12;21)	HeH
MLL	**64**						**2**	**3**
Hypodiploidy		**16**						**1**
t(1;19)				**49**				**3**
iAMP21					**31**			**1**
dic(9;20)					**1**	**25**	**1**	
t(12;21)					**1**	**1**	**322**	**14**
HeH			**1**	**1**	**3**	**1**	**8**	**413**
Other	**1**	**1**	**4**	**1**	**1**		**4**	**17**
Normal		**1**	**1**	**1**	**2**		**6**	**6**
Missing								**2**
Total	**65**	**18**	**6**	**52**	**39**	**27**	**343**	**460**

As expected, patients with unfavorable cytogenetics experienced more adverse primary events (Table 11). Five (16.1%) patients positive for iAMP21 relapsed.

Table 11. Primary events by cytogenetics central review

Cytogen./ Prim.event	Total number	CR1	Induction failure	DCR1	Relapse	SMN
MLL	64	44 (68.8)	5 (7.8)	5 (7.8)	9 (14.1)	1 (1.6)
Hypodiploidy	19	13 (68.4)	0	3 (15.8)	2 (10.5)	1 (5.3)
t(1;19)	49	47 (95.9)	0	1 (2.0)	1 (2.0)	0
iAMP21	31	25 (80.6)	0	1 (3.2)	5 (16.1)	0
dic(9;20)	27	25 (92.6)	0	1 (3.7)	1 (3.7)	0
t(12;21)	330	312 (94.5)	1 (0.3)	5 (1.5)	10 (3.0)	2 (0.6)
HeH	478	441 (92.3)	4 (0.8)	5 (1.0)	20 (4.2)	8 (1.7)
Other	377	307 (81.4)	4 (1.1)	19 (5.0)	46 (12.2)	1 (0.3)
Normal	288	248 (86.1)	3 (1.0)	12 (4.2)	25 (8.7)	0
Missing	55	47 (85.5)	0	1 (1.8)	7 (12.7)	0

Treatment

Induction treatment

A majority (1343, 78.2%) of patients received induction treatment according to the non-HR arm and 375 patients (21.8%) received HR-induction. In the ALL registry there were 12 patients with pre-B Immunophenotype and hyperleukocytosis that started HR-induction but were switched to prednisolone when t(12;21) was confirmed, as recommended in the protocol amendment. In addition, there were registered modifications in the induction treatment in 19 patients, mostly regarding the steroid treatment, for example delays in the start of steroid treatment and switch between dexamethasone and prednisolone.

Protocol adherence

Most, but not all patients were treated according to their assigned risk group. Protocol adherence was higher among the pediatric patients 97.7%, compared to 91.6% in adults (Table 12 and 13).

Table 12. Protocol adherence - Final risk-group (patients 1-17 years)

Admin\RG	RG=SR	RG=IR	RG=HR-chemo	RG=HR-SCT	Total
Admin=SR	704	6	0	1	711
Admin=IR	11	498	2	5	512
Admin=HR	2	6	145	69	222
Other	3	1	0	0	4
Total	720	507	147	75	1449

Protocol adherence: Risk group = Administered (RG = Adm): 704+498+145+69/1449 (97.7%)

Table 13. Protocol adherence - Final risk-group (patients 18-45 years)

Admin\RG	RG=SR	RG=IR	RG=HR-chemo	RG=HR-SCT	Total
Admin=SR	45	6	0	0	51
Admin=IR	5	91	0	1	97
Admin=HR	0	2	53	40	95
Other	0	4	0	2	7
Total	50	104*	53	43	250

Protocol adherence: RG = Adm: 45+91+53+40/250 (91.6%). *One patient had missing information on administered treatment.

Among the HR patients, 92 of the 118 patients stratified to HR+HSCT underwent HSCT in CR1 but 21 of the 200 patients in the HR chemo group underwent HSCT in CR1. Table 14 describes the reasons for not adhering to the HSCT indication in patients stratified as HR+HSCT and Table 15 describes the indications for performing HSCT in CR1 in patients stratified to HR+chemo. One patient stratified as SR underwent HSCT in CR1 as initial karyotyping showed hypodiploidy but central review confirmed t(12;21). One patient with T-ALL was stratified as IR but underwent HSCT because of rising MRD between d79, d87 and d121. There were several reasons for patients stratified as HR+chemo to undergo HSCT (10 adult, 11 children). The most common reasons were unfavorable cytogenetics (MLL or hypodiploidy) and the interpretation of the MRD response, for example poor MRD response during block therapy or discrepancies between MRD measured with flow cytometry and PCR.

Table 14. Treatment adherence to the HSCT indication in High-Risk patients.

HR+HSCT admin/not admin	Number of patients
Risk group HR+HSCT	118
HSCT in CR1	92
No HSCT in CR1	26
DCR1	2
Relapse	5
Toxicity	2
On-going block therapy	5
No donor available	2
IR-arm treatment given	6
Other	1
Missing info	3

Table 15. HSCT in CR1 in patients not stratified as High Risk with HSCT.

HR+chemo Admin HSCT in CR1	Number of patients
Risk group HR+chemo	200
HSCT in CR1	21
Unfavorable cytogenetics	8
Poor MRD response during block therapy	5
PCR MRD high	3
Rising MRD	2
Toxicity	2
Other	1

Primary events - children

Table 16. NOPHO ALL-2008 - treatment-results – all events
Patients 1-17 years treated in Nordic and Baltic centres.

Event	BCP WBC<100 n=1179		BCP WBC>100 n=96	T-cell n=190	Total n=1465
Induction failure	**9**		**2**	**3**	**14**
Resistant disease	0		0	0	0
Induction death	9		2	3	14
CR-reached	**1170**		**94**	**187**	**1451**
Remission %	**99.2**		**97.9**	**98.4**	**99.0**
CR1, no RG d29*	2		0	0	2
	SR n=720	IR n=507	HR-chemo n=147	HR-SCT n=75	n=1449
Death in CR1	8	11	14	6	39
Relapses	22	30	27	7	86 (88)**
BM	11	15	20	6	52 (54)**
CNS	5	9	4	0	18
BM+CNS	3	4	3	0	10
BM+CNS+testis	1	1	0	0	2
BM+Other site	1	1	0	1	3
SMN	10	1	1	0	12
All events	40	42	42	13	137 (153)**
CCR number	680	465	105	62	1312 (1312)**
CCR %	94.4	91.7	71.4	82.7	90.5 (89.6)**
CR>/=2 (n)	22	20	6	4	52 (52)**
pDFS (60 mo)	0.92 (0.01)	0.88 (0.02)	0.67 (0.04)	0.77 (0.06)	0.87 (0.01)***
pEFS (60 mo)	-	-	-	-	0.86 (0.01)
All dead	18	22	36	9	85 (101)**
All alive	702	485	111	66	1364 (1364)**
alive %	97.5	95.7	75.5	88.0	94.1 (93.1)
pOS (60 mo)	0.97 (0.01)	0.95 (0.01)	0.71 (0.04)	0.85 (0.05)	0.93 (0.01)
Overall pOS (60 Mo)	-	-	-	-	0.92 (0.01)

*Two patients with very severe infectious complications during induction. Long time in ICU and completely modified post-induction therapy. No RG-assignment possible. Both patients relapsed and died of disease.
** Figures in parenthesis include the outliers without risk-group. For "All Events"","CCR number", "All dead", "All Alive" and "alive %", they also include the induction deaths.
***For the risk-groups the estimates correspond to pDFS. In the Total column the pDFS/pOS for the whole group of patients that could be risk-grouped is given. The total overall pEFS and pOS also include the patients who could not be risk-grouped and the induction deaths.

Follow-up time for surviving patients: median 1309 days (range 19-2747).

Events since the last survey

Induction failures

There was one induction death:
A one-year old girl with MLL-rearranged ALL and an initial WBC of 95 died 20 days from diagnosis of RSV-infection causing progressive pulmonary failure. It is presently unknown at the moment if the leukaemia had responded to initial therapy or not.

Table 17. Post-induction Events by risk-group (final stratification)

Event	SR	IR	HR-chemo	HR-SCT	Total
Relapse	3	8	2	1	14
DCR1	0	0	1	1	2
SMN	3	1	1	0	5
Total	6	9	4	2	21

Table 18. Relapses by site and risk-group (final stratification)

Rel site	SR	IR	HR-chemo	HR-SCT	Total
BM	0	6	2	1	9
CNS	1	1	0	0	2
BM+CNS	1	0	0	0	1
BM+Other	1	1	0	0	2
Total	3	8	2	1	14

Deaths in CR1 (n=2)

HR-chemo-group: 1 case
A 14-year old boy at diagnosis with T-cell disease and WBC <10, CNS1 and no stratifying genetic changes responded very poorly to induction and was shifted to HR-blocks day15. Despite seemingly good response to block therapy, he underwent SCT in CR1 and died of unspecified complications to SCT more than three years after SCT. The death was reported late and occurred 2014.

HR-SCT group: 1 case
A 17-year old girl at diagnosis with BCP, WBC <10, CNS1 and no stratifying genetic changes responded very poorly to induction therapy, but responded well to HR-blocks. She underwent SCT in first remission, but developed pulmonary GvHD and died of an intercurrent RSV-infection 16 months after SCT.

SMNs (n=5)

Three cases from the SR-group, one case in the IR-group and one in the HR-chemo group.
SR-group: 3 cases
All of these were boys less than 10 years old, one with high hyperdiploidy, two with t(12;21) – one of which also had >67 chromosomes developed synovial sarcoma (the boy with HeH), MDS (the boy with t(12;21)) and AML (the boy with t(12;21) and >67 chromosomes) 30, 54 and 33 months after diagnosis respectively.
IR-group: 1 case
A girl 7 years old at diagnosis with BCP ALL and t(12;21) developed a lymphoproliferative disease judged as an SMN by the event-group towards the end of maintenance. Since the disease was related to the immunosuppression of the anti-leukemic therapy, the protocol-therapy was stopped and Rituximab was started. The diagnosis was actually made 2012, but the judgment of the event was made in the course of the work with the "defined publication cohort".
HR-chemo-group: 1 case
A 13 year-old girl with BCP ALL, a hypodiploid karyotype and a good response to induction therapy was treated according to the HR-chemo arm of the protocol and was diagnosed with AML during the maintenance phase 20 months after diagnosis.

Table 19. NOPHO ALL-2008 - treatment-results – all events
Patients 18-45 years mostly treated in Nordic and Baltic adult haematology clinics

Event	BCP WBC<100 n=158		BCP WBC>100 n=17	T-cell n=78	Total n=253
Induction failure	0		2	1	3
Resistant disease	0		0	0	0
Induction death	0		2	1	3
CR-reached	158		15	77	250
Remission %	100		88.2	98.7	98.8
	SR n=50	IR n=104	HR-chemo n=53	HR-SCT n=43	n=250
Death in CR1	1	5	6	2	14
Relapses	2	13	10	13	38
BM	1	8	6	10	25
CNS	0	3	1	0	4
Testis	1	1	0	0	2
BM+CNS	0	0	1	1	2
BM+other site	0	0	0	1	1
Other site	0	1	2	1	4
SMN	0	0	1	0	1
All events	3	18	16	15	53 (56)*
CCR number	47	86	37	28	197 (197)*
CCR %	94.0	82.7	69.8	65.1	78.8 (77.9)*
CR>/=2 (n)	0	2	0	2	4 (4)*
pDFS (60 mo)	0.90 (0.06)	0.80 (0.05)	0.63 (0.08)	0.59 (0.08)	0.74 (0.03)**
pEFS (60 mo)	-	-	-	-	0.73 (0.03)
All dead	3	16	16	13	48 (51)
All alive	47	88	38	29	202 (202)
alive %	94.0	84.6	70.4	69.0	80.8 (79.8)
pOS (60 mo)	0.88 (0.07)	0.82 (0.04)	0.62 (0.08)	0.59 (0.09)	0.75 (0.03)
Overall pOS (60 Mo)	-	-	-	-	0.74 (0.03)

* Figures in parenthesis including induction deaths for "All Events""CCR number", "All dead", "All Alive" and "alive %".
** For the risk-groups the estimates correspond to pDFS. In the Total column the pDFS/pOS for the whole group of patients that could be risk-grouped is given. The total overall pOS also includes induction deaths.

Follow-up time for surviving patients: median 1080 days (range 28-2716).

Events since the last survey

Induction failures

There were no induction deaths.

Table 20. Post-induction Events by risk-group (final stratification)

Event	SR	IR	HR-chemo	HR-SCT	Total
Relapse	1	2	2	3	8
DCR1	0	0	1	1	2
SMN	0	0	0	0	0
Total	1	2	3	4	10

There were about half as many new events in the adults as in the paediatric population, which is clearly disproportionate. Longer follow-up will be needed to see if this is a trend, or just an effect of the increased recruitment of new adult patients, who contribute early events.

Table 21. Relapses by site and risk-group (final stratification)

Rel site	SR	IR	HR-chemo	HR-SCT	Total
BM	0	2	2	2	6
Testis	1	0	0	0	1
Other	0	0	0	1	1
Total	1	2	2	3	8

Deaths in CR1 (n=2)

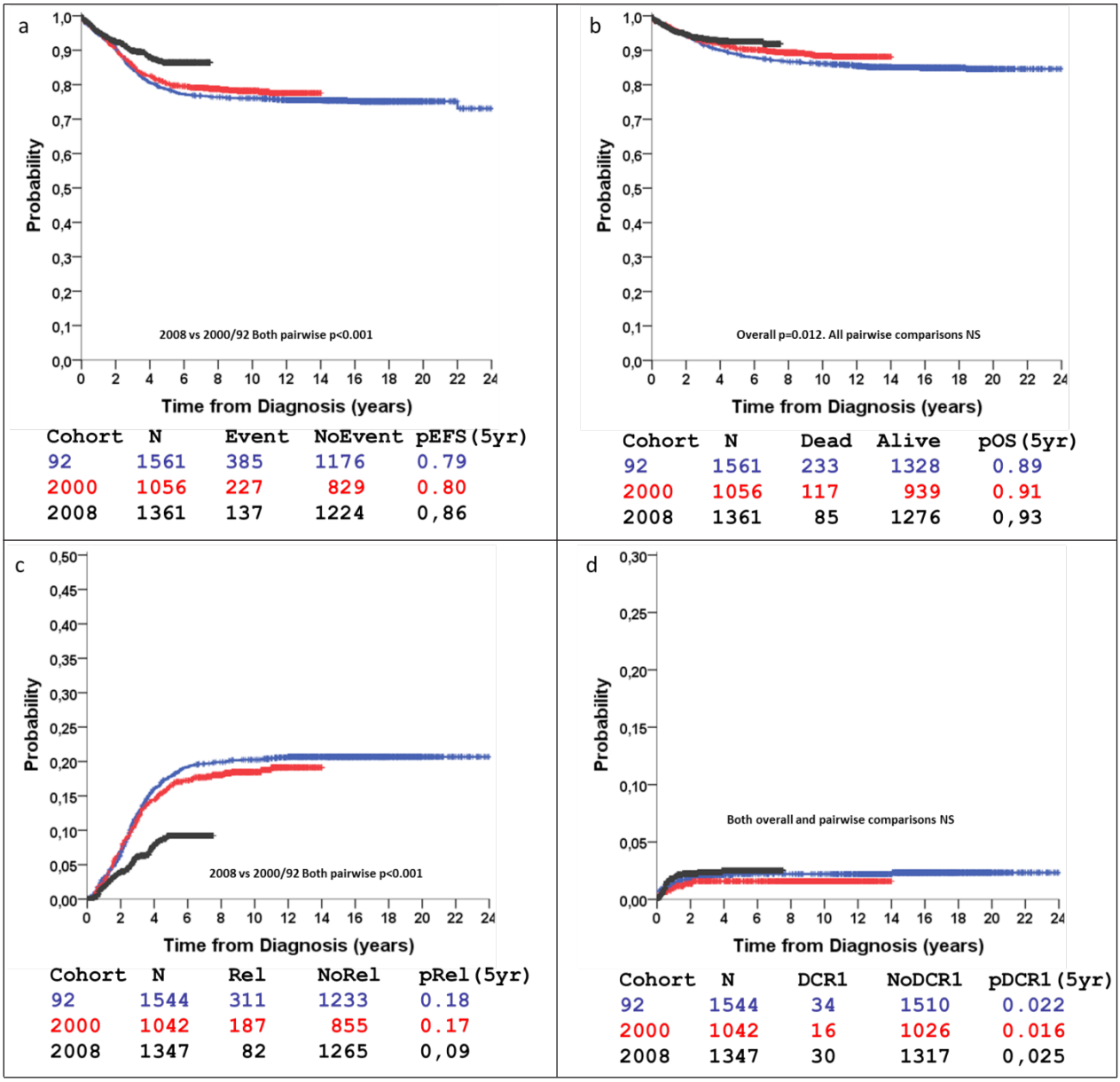
HR-chemo-group: 1 case

A 20-year old man who had T-cell disease, WBC >100, CNS1 and no stratifying genetic changes as well as high MRD at day 15 and 29, but not enough to qualify for SCT. He died after the C3-block from complications to septic shock with multi-resistant gram-negative bacteria.

HR-SCT group: 1 case

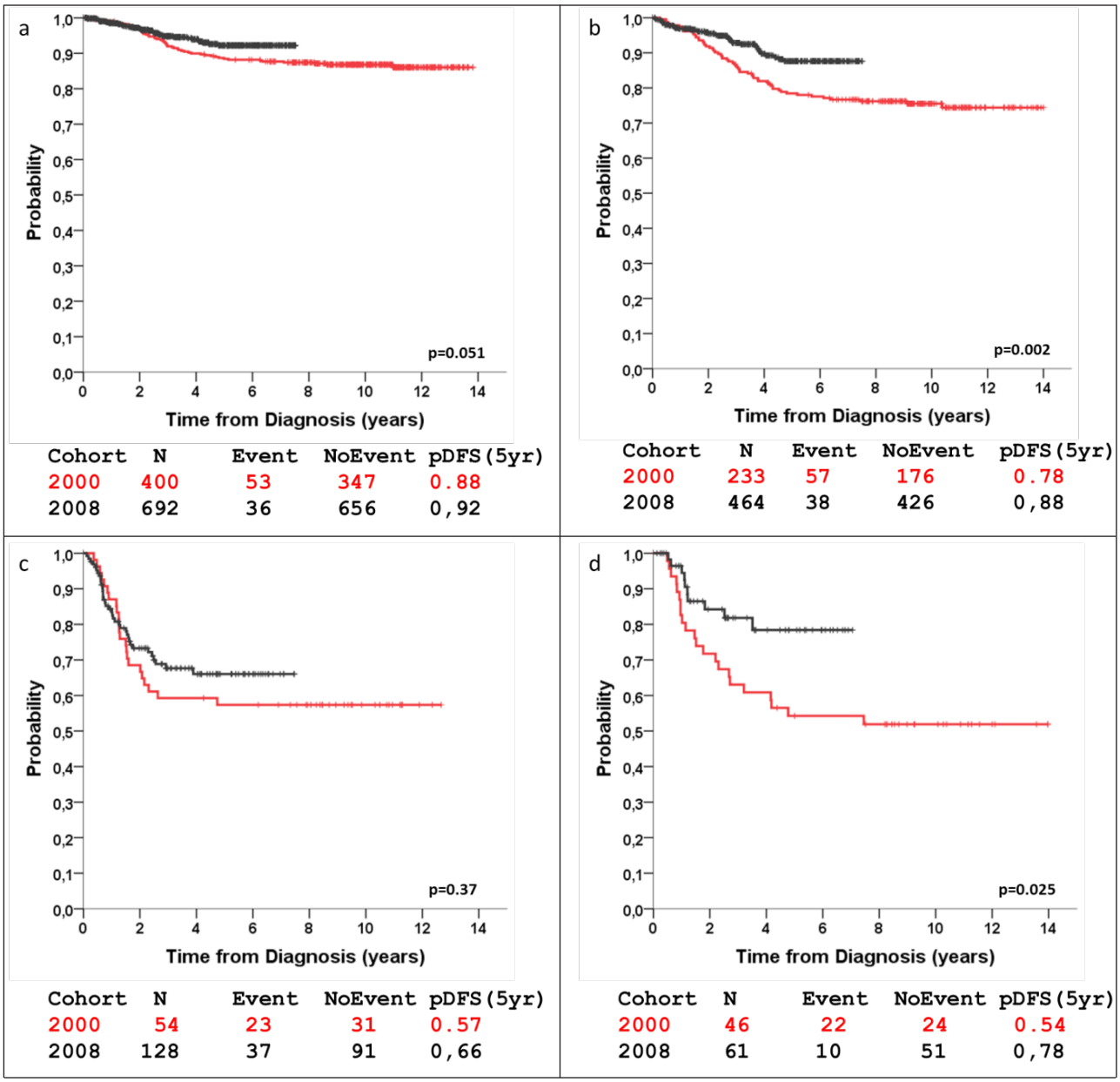
A 37-year old man with BCP, WBC <100, CNS1 and without stratifying genetic changes responded poorly to induction therapy and died from unspecified complications to allo-SCT in CR1.

Figure 5. NOPHO ALL-92, NOPHO ALL-2000, NOPHO ALL-2008, Non-B cell ALL 1-<15 years at diagnosis. EFS (a), OS (b), cum inc of relapse (c) and DCR1 (d).



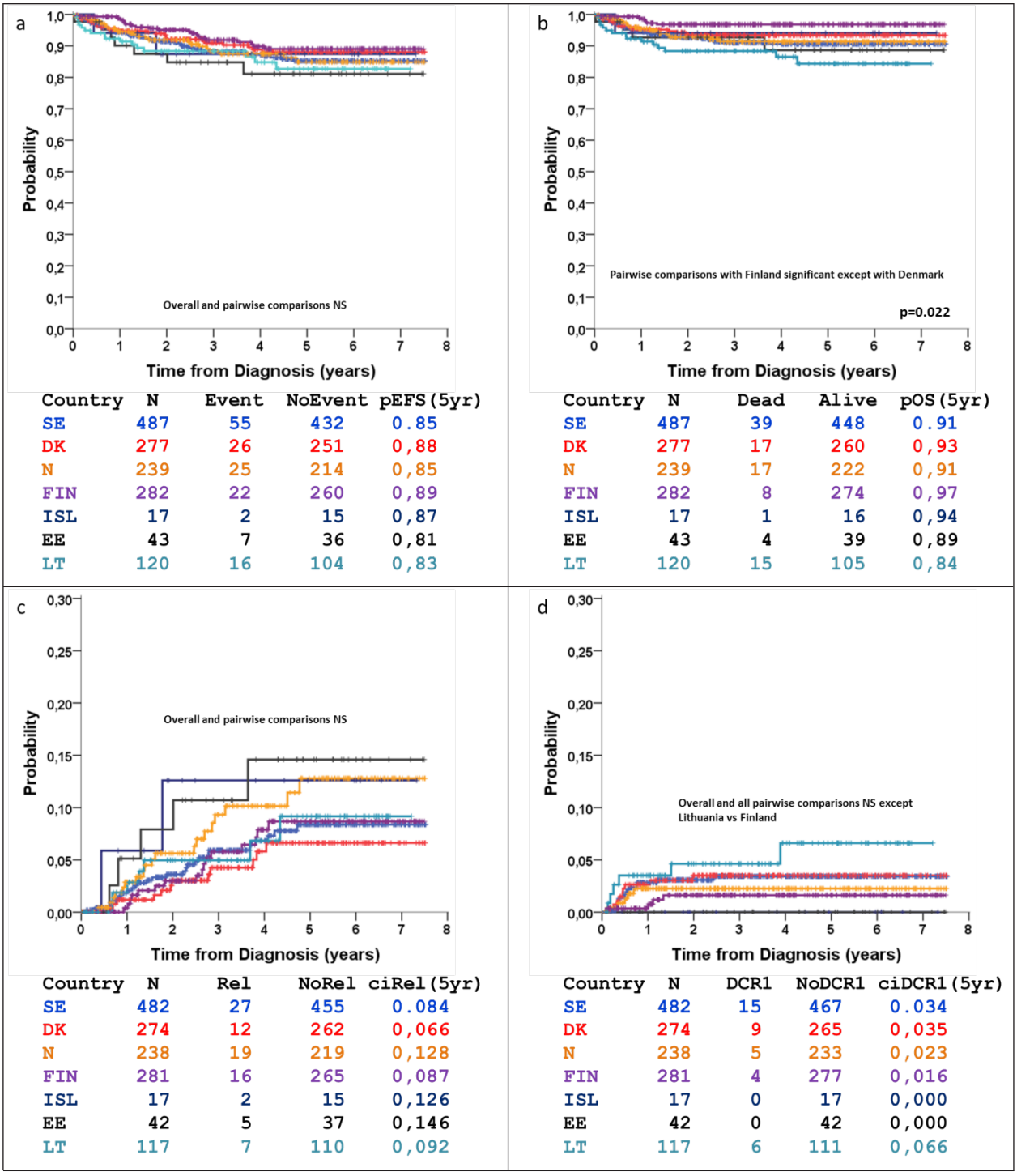
With completely comparable cohorts with regard to age, the improvement, particularly the reduction of the relapse-rate is obvious. This effect is no longer offset by increased toxic deaths. In previous comparisons, the 2000-patients 15-18 years at diagnosis have been included. This age group has been identified as vulnerable with regard to toxic events and this partly explains the relative improvement.

Figure 6. NOPHO ALL-92, NOPHO ALL-2000, NOPHO ALL-2008, Non-B cell ALL 1-<15 years at diagnosis. DFS-Analysis by risk-group (a), SR (b), IR (c) HR-chemo (d) HR-SCT.



This comparison revisits the part of the NOPHO ALL-2000 cohort that has MRD-values recorded to allow a simulated stratification according to the NOPHO ALL-2008 principles. The improvement in the overall results has occurred across the risk-groups. The group, which shows the least relative improvement, is the HR-chemo group, which has also been identified as the most problematic in the 2008 protocol.

Figure 7. NOPHO ALL-2008, NOPHO and Estonian children <18 by Country
a) EFS, b) OS, c) cum incidence of Relapse, d) cum incidence of DCR1.



Country	N	Event	NoEvent	pEFS(5yr)
SE	487	55	432	0.85
DK	277	26	251	0,88
N	239	25	214	0,85
FIN	282	22	260	0,89
ISL	17	2	15	0,87
EE	43	7	36	0,81
LT	120	16	104	0,83

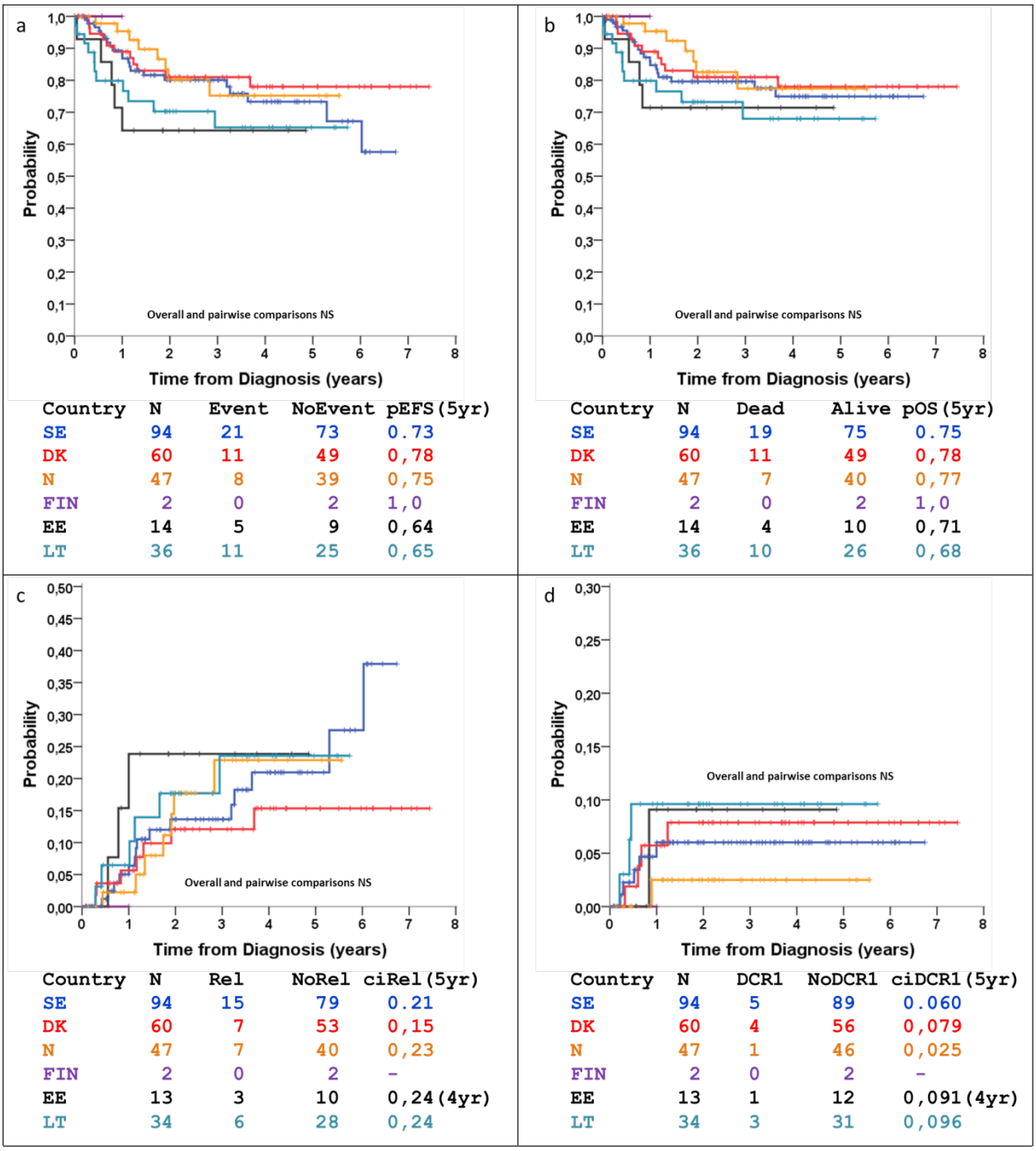
Country	N	Dead	Alive	pOS(5yr)
SE	487	39	448	0.91
DK	277	17	260	0,93
N	239	17	222	0,91
FIN	282	8	274	0,97
ISL	17	1	16	0,94
EE	43	4	39	0,89
LT	120	15	105	0,84

Country	N	Rel	NoRel	ciRel(5yr)
SE	482	27	455	0.084
DK	274	12	262	0,066
N	238	19	219	0,128
FIN	281	16	265	0,087
ISL	17	2	15	0,126
EE	42	5	37	0,146
LT	117	7	110	0,092

Country	N	DCR1	NoDCR1	ciDCR1(5yr)
SE	482	15	467	0.034
DK	274	9	265	0,035
N	238	5	233	0,023
FIN	281	4	277	0,016
ISL	17	0	17	0,000
EE	42	0	42	0,000
LT	117	6	111	0,066

The differences in OS are mostly due to differences in treatment-related mortality even if these differences do not reach statistical significance. Finland has a very low TRM-rate whilst maintaining a "normal" relapse combining into an excellent OS. Estonia partly compensates a relatively high relapse-rate with an absence in DCR1.

Figure 8. NOPHO ALL-2008, NOPHO and Baltic adults 18-45 years by Country
a) EFS, b) OS, c) cum incidence of Relapse, d) cum incidence of DCR1.



Country	N	Event	NoEvent	pEFS(5yr)
SE	94	21	73	0.73
DK	60	11	49	0,78
N	47	8	39	0,75
FIN	2	0	2	1,0
EE	14	5	9	0,64
LT	36	11	25	0,65

Country	N	Dead	Alive	pOS(5yr)
SE	94	19	75	0.75
DK	60	11	49	0,78
N	47	7	40	0,77
FIN	2	0	2	1,0
EE	14	4	10	0,71
LT	36	10	26	0,68

Country	N	Rel	NoRel	ciRel(5yr)
SE	94	15	79	0.21
DK	60	7	53	0,15
N	47	7	40	0,23
FIN	2	0	2	-
EE	13	3	10	0,24(4yr)
LT	34	6	28	0,24

Country	N	DCR1	NoDCR1	ciDCR1(5yr)
SE	94	5	89	0.060
DK	60	4	56	0,079
N	47	1	46	0,025
FIN	2	0	2	-
EE	13	1	12	0,091(4yr)
LT	34	3	31	0,096

The much fewer patients in the adult cohort makes up for much wider confidence intervals for the estimates and none of the apparent differences thus reach statistical significance. The overall higher relapse-rate as well as death in CR1-rate in the adult cohort is mostly explained by the very different risk-group profile.

Randomization

Stop of Randomization 1 and 2

Some of the most important aspects of the NOPHO ALL-2008 protocol are the R1 and R2 randomizations. They were terminated by decision of the LLC and NOPHO-board in March 2016 and this section is meant to communicate to the NOPHO membership the background information on which this decision was taken (Figure 9).

The results were included in the report to the DSMC-report and the decision to stop the randomizations was based on their recommendation.

NB! The analyses shown are not updated with recently randomized patients and current follow-up. Many additional analyses remain before publication and the results may change.

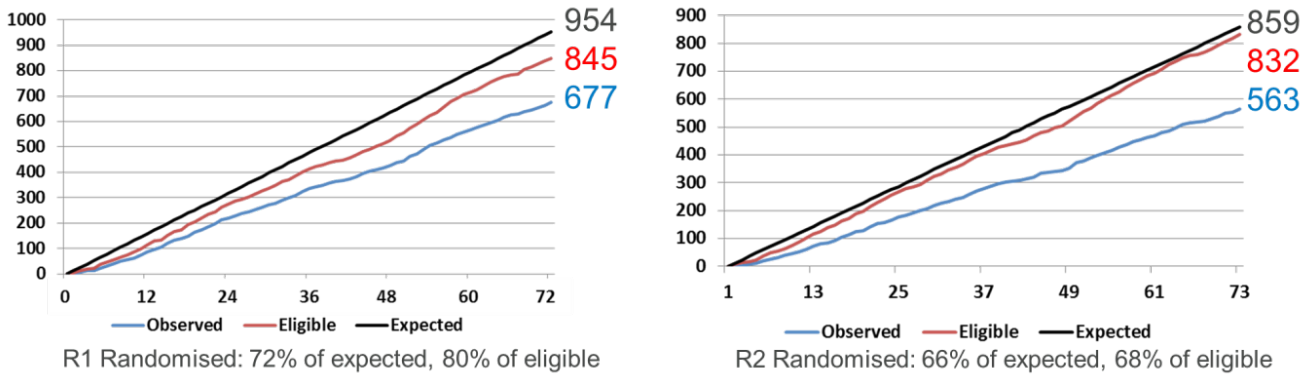


Figure 9. The recruitment to both randomizations were lower than expected. The expected (black), eligible (red) and randomized (blue) patients.

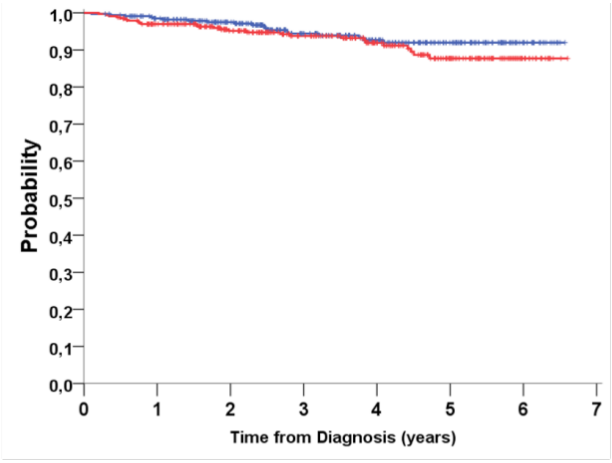
The R1 randomization

The R1 randomization was designed to test whether an attempt at increasing the dose of 6-Mercaptopurine during the consolidation-phase would yield a higher percentage of MRD-negative patients at the end of consolidation (d79) in SR- and IR-patients (primary end-point) and if this would translate into better leukaemia-specfic outcomes (secondary end-point). Not all patients were informative = (MRD-positive at day 29), which hampered the power of the study.

Figure 10 shows the secondary end-point: DFS for the different randomized groups.

The interim-analysis showed that out of 195 SR-patients, who were positive at the end of induction, 103 were randomized to fixed dose and 92 to increased dose. Out of the 103 fixed-dose patients 76 (74%) became negative and the corresponding fraction was 81/92 (88%) in the increased dose group (p=0.018). In the IR-group 87/109 (80%) of the fixed-dose patients and 77/100 (77%) became negative (p=0.74). Thus the primary end-point was met in the SR-group, but not the IR-group (and not in the combined population). The secondary end-point analysis showed superimposable DFS-curves for the randomized groups.

The recommendation by the DSMC with regard to R1 was that continued randomization was optional and in the light of the lack of difference in leukaemia-specific outcomes was not likely to yield important information if the recruitment was to continue.



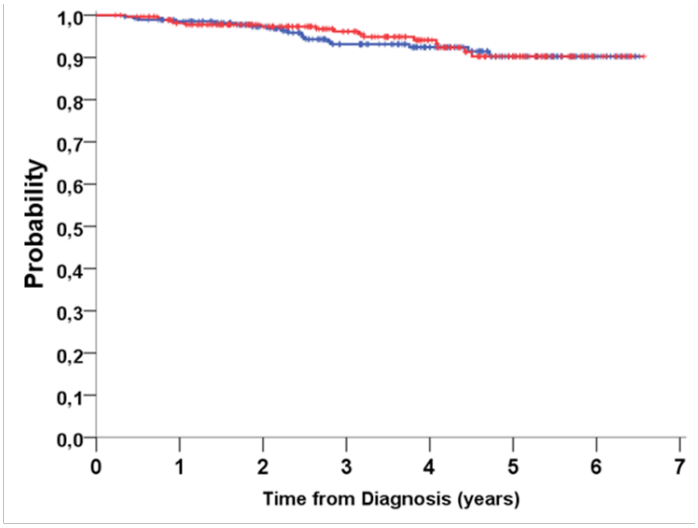
Cohort	N	Event	NoEvent	pDFS(5yr)
6MP const	342	19	323	0.92 (0.02)
6MP Incr	335	26	309	0.88 (0.03)

Figure 10. DFS for the randomized groups in the R1-randomisation

The R2-randomization

The R2 randomization was designed to test whether the number of doses and the dose-interval of PEG-Asp therapy in the post-consolidation phase of SR- and IR-therapy could be safely reduced from 10 doses at 2-week intervals to 3-doses at 6-week intervals. The primary end-point was DFS for the randomized patients, but the results should be "balanced against Asp-induced toxicity". For some time, the toxicity was only measured as fractions of patients with specific toxicities, without taking the cumulative incidence of the ongoing study into account. Studies focusing on different toxicities retrieved the detailed information on several toxicities (allergy, pancreatitis, thrombosis, osteonecrosis and fungal infection) possibly related to PEG-Asp, thus making it possible to perform survival analyses with cumulative incidence of these toxicities by randomized group as end-point.

Figure 11 shows the primary end-point (DFS by randomized group) as well as the event-profile of these groups.



Event	2-weeks	6-weeks
Relapse	10	13
DCR1	3	1
SMN	5	2
Total	18	16

Cohort	N	Event	NoEvent	pDFS(5yr)
2-weeks	282	18	264	0.90 (0.02)
6-weeks	281	16	265	0.90 (0.03)

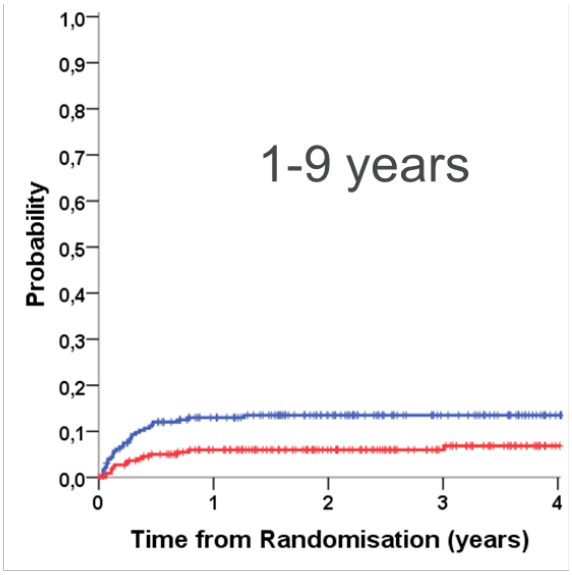
Figure 11. Primary end-points (DFS by randomized group).

There is no detectable difference in outcome between the randomized groups, but a small tendency to more toxic events in the 2-week group and somewhat more relapses in the 6-week group.
These outcomes were to be balanced against toxicity (Table 22). Allergy, pancreatitis, thrombosis, osteonecrosis and fungal infections were investigated. In addition, they were combined to show "at least one" toxicity ("any toxicity").

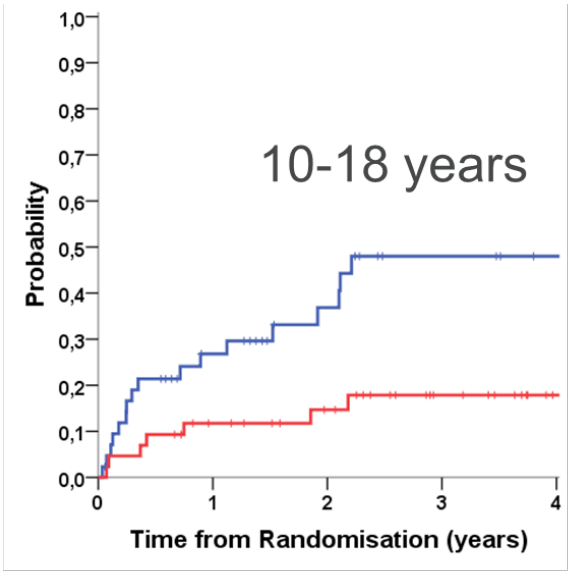
Table 22. Toxic outcomes by randomized group.

Cumulative risk	2w cum inc	6w cum inc	p
Allergy	2.2%	1.5%	ns
Thrombosis	4.4%	1.8%	0.09
AAP	6.1%	1.5%	0.004
ON	8.4%	4.5%	0.15
ON >10y	36.7%	14.7%	0.046
Fungal infections	3.8%	1.1%	0.08
Any toxicity*	18.6%	8.7%	0.001
Any toxicity, 1-9y	13.5%	6.8%	0.008
Any toxicity, 10-17y	48.0%	17.9%	0.013

There was a clear tendency for the toxicities to be more pronounced in the older age-group – as expected, this age-dependency was particularly pronounced for osteonecrosis, which had a much higher incidence in the older age-group, particularly the girls. A teenage girl had an accumulated incidence of osteonecrosis of about 40% in the 2-week group. However, also the younger children had a higher incidence in the 2-week group as shown in Figure 12.



Cohort	N	Tox	NoTox	pTox
2-weeks	227	18	264	0.135
6-weeks	224	16	265	0.068



Cohort	N	Tox	NoTox	pTox
2-weeks	43	17	26	0.480
6-weeks	43	7	36	0.179

Figure 12. Cumulative incidence of "any toxicity" in the randomized groups, stratified by age.

In stratified analyses, the "any toxicity" end-point was significant for both sexes, SR- and IR-patients analyzed separately and in a multivariate model including age-group, sex, risk-group and randomized group age-group (10-17) and randomized group (2-week intervals) came out as independently associated with toxicity (p=0.001).

Based on these results, the DSMC recommended to stop the R2 randomization and to change the therapy from the standard-arm to the experimental arm as best available therapy. A decision to that effect has since then been taken by the PI-group, the LLC and the NOPHO Board.

Concluding remarks

It has been quite a dramatic year. We have stopped the two remaining randomizations in the NOPHO ALL-2008 protocol and even if we still have a few more years to go before we change, we can look back on eight years of very interesting development.

Firstly, we have shown that improvement in leukaemia-specific outcomes is still possible. We have reduced the relapse-rate to below 10% for our core cohort of children, who were the base of our previous protocols. But that improvement has come at a high price: the improvement has been partly offset by an increase in toxic death, which for a long time looked like it would stand in the way of improvement of the overall results. The organization has risen to the challenge of amending the protocol and overcome these difficulties, but in this process we have realized that we have reached a limit for how much intensification the patient population can take before it becomes counterproductive.

Secondly, we have brought new patient populations into our community. We have welcomed the active participation of colleagues from the Baltic states and Lithuania has even joined the organization formally. We have also reached out to the adult haematologists and found important partners in development and research. We have learned a lot from this expansion. The impressive and rapid improvement in the results of the Baltic states is truly impressive. We have also been able to study the differences in some aspects of the biology that makes ALL of the small child different from the disease of the adolescent or young adult. Not all lessons have been easy, but the importance of recording and trying to understand the experience of the entire age-spectrum cannot be underestimated.

Finally, the protocol has created a scientific platform, which has been used to increase the scientific production of NOPHO considerably. This in turn has led to intensified international interest in our efforts and in all likelihood contributed to the new community of collaboration to which NOPHO has been invited as a partner.

None of this would have been possible without the diligent work of the clinicians and recording-staff which has been called upon, not only to perform the basic registration, but also numerous extra-tasks in conjunction with a myriad of research projects. We owe these hard workers our gratitude and thank them for their efforts along with the development-team in Stockholm and the data-checks staff in Copenhagen.

We are now looking forward to the development of the next protocol, while we make the best of the void created by the stopped randomizations. We shall make every effort possible to make sure that the NOPHO spirit of professional collaboration but also real and heartfelt friendship is transferred to the new consortium, taking the best of NOPHO with us into our future endeavors.

Stockholm, springtime 2016

Mats Heyman & Trausti Oskarsson

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For details on recruitment and outcome see NOPHO Annual Report ALL2008-section and presentations from previous ALL2008 WG meetings at www.nopho.org.

Meetings

The ALL2008 study committee has merged with the ALL committee, and updates and research on ALL2008 patients are presented at ALL committee meetings and subsequently posted at www.nopho.org. In addition, results and challenges relating to NOPHO ALL2008 has been presented at various meetings in pharmacology WG, MRD WG, ALL event WG, ALL biology WG, and adult ALL meetings. At the NOPHO annual meeting 2015 it was decided to publish ALL2008 results based on 2008-2014 cohort. The ALL2008 study committee (listed above) has subsequently had two telephone conferences and a physical meeting (29, March 2016) to discuss distribution of manuscript authorships.

Baltic countries

Outcome has improved significantly during the last 5 years and pEFS is now very similar for the Nordic and Baltic Pediatric centers. Lithuania became full NOPHO member in 2015 and will be fully eligible for the next ALL protocol, including randomisations. No decisions has been taken re Estonia.

Adults

The first Finnish adult patients have been treated according to ALL2008 and the first patients have been entered in the database. Nina Toft (DK, adult hematologist in training) continues as coordinator for the adult ALL activities. More than 300 adult patients (>17.9 years) have been registered by April 2016. This is beyond the target of 200+ patients >18 years in the ALL2008 protocol.

Randomisations

The protocol was opened July 1st 2008. The three randomised studies opened for children January 1st 2009, but with some delays in entering of patients depending on the approval process in the involved countries. Recruitment has been somewhat below what was projected. Not least R2 (asparaginase at 2 vs. 6 wks intervals) would need several more years of accrual for the study to be sufficiently powered. This reflects poorer recruitment rates (partly explained by toxicities during consolidation) and overall lower relapse rate than originally projected. A detailed report was filed to the DSMC December 2015 presenting outcome and toxicity data. Based on these data the DSMC recommended closure of the Rx1 and Rx2, and both studies were closed March 1st 2016 (decided by NOPHO ALL2008 PIs, Board and LLC members at a telephone conference). The regulatory authorities and all NOPHO members were subsequently notified. Rx1 and Rx2 publication are expected to be submitted for publication during 2016. Rx3 (+/- Depocyte in HR maintenance) has already been closed due to insufficient recruitment and problems with drug supply. A publication on Rx3 has been submitted for publication with Mette Levinsen and Arja Harila-Saari as primary authors.

Risk grouping

For patients <15 years, the risk group stratification has been very close to what was projected. Even with identical therapy and risk grouping criteria, older patients are heavily skewed towards the higher risk groups. This has been analysed in detail and published (18).

Events

By March 28th 2016, 1903 patients had been registered. Relapse rates for various subsets are given elsewhere in the annual report.

Toxicity

The compliance to toxicity registration (20 specified toxicities to be registered at 3 months intervals) has been close to 100%, i.e. all centers register toxicities. However, scrutinization of patient files have revealed that for some toxicities (e.g. peripheral neuropathy) the toxicity data that are routinely captured do not reflect the true incidence. For others including allergy, pancreatitis, thrombosis, and osteonecrosis, the reported toxicity frequencies seem reliable. Approximately 50% of all patients experience one or more of the 20 toxicities. Several of these have been registered in more than 50 patients (allergy, thrombosis, pancreatitis etc) are being or have been scrutinised in detail (and published). Although the simplified MRD-based risk stratification and the major changes in the ALL2008 protocol compared to our previous treatment strategies seem to have reduced the overall relapse rate (especially for T-ALL), the protocol have been burdened by toxic death. The toxic death rate for SR and IR patients is acceptable, but was as high as 20% following block therapy. Several amendments to the blocks have aimed to counteract this, and since the latest amendments November 2011 (see www.nopho.org) the toxic death rate for HR-ALL has been acceptable (<5%).

Add-on research

Three large add-on studies are integrated into ALL2008:

a. Host genomics: Host DNA has been collected from approximately 90% of the patients. The first ~1300 patients have been exome-enriched SNP-profiled (Illumina Human OmniExome 2.5M). The phenotypes currently addressed are pancrea-

titis, hyperleukocytosis, CNS leukemia, thrombosis, osteonecrosis, MTX/6MP metabolism, MRD and relapse rates. The first paper on AAP has been submitted for publication. Collaboration with the Australian/NZ group has been initiated to address thrombosis in a metanalysis setting.

b. Maintenance therapy monitoring: Blood sampling has been below the set target. Still, approximately 100 samples are being received per week. Some centers collect 20 samples per patient during therapy. Others only 3 on average. Guidelines for micro-sampling (capillary blood) has been posted on NOPHO.org and sent to the centres. A manuscript on associations between 6MP/MTX metabolite profiles and risk of relapse will be submitted for publication late summer 2016.

c. Asparaginase antibody monitoring: Sampling is satisfactory with approximately 8-9 samples having been received per patient.

Publications

Much of the work done as part of the preparation for the protocol has been published, submitted for publication, or is in the writing phase:

Published studies important for the ALL2008 protocol:

1. **Schmiegelow K, Forestier E, Kristinsson J, Söderhäll S, Vettenranta K, Weinshilboum R, Wesenberg F**. *Thiopurine methyltransferase activity is related to the risk of relapse of childhood acute lymphoblastic leukemia - results from the NOPHO ALL-92 study.* Leukemia 2009; 23: 557-64.
2. **Schmiegelow K, Al-Modhawi I, Andersen MK, Berendtz M, Forestier E, Hasle H, Heyman M, Kristinsson J, Nersting J, Nygaard R, Svendsen AL, Vettenranta K, Weinshilboum R.** *Methotrexate/6-mercaptopurine maintenance therapy influences the risk of a second malignant neoplasm after childhood acute lymphoblastic leukemia - results from the NOPHO ALL-92 study.* Blood 2009; 113: 1077-84.
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4. **Schmiegelow K, Heyman M, Kristinsson J, Mogensen UB, Rosthøj S, Vettenranta K, Wesenberg F, Saarinen-Pihkala U.** *Oral methotrexate/6-mercaptopurine may be superior to a multi-drug LSA2L2 maintenance therapy for higher risk childhood acute lymphoblastic leukemia.* J Ped Hematol Oncol 2009; 31:385-92.
5. **Schmiegelow K, Forestier E, Hellebostad M, Heyman M, Kristinsson J, Söderhäll S, Taskinen M; Nordic Society of Paediatric Haematology and Oncology.** *Long-term results of NOPHO ALL-92 and ALL-2000 studies of childhood acute lymphoblastic leukemia.* Leukemia. 2010; 24:345-54.
6. **Schmiegelow K, Heyman M, Gustafsson G, Lausen B, Wesenberg F, Kristinsson J, Vettenranta K, Schroeder H, Forestier E, Rosthoej S.** *The degree of myelosuppression during maintenance therapy of adolescents with B-lineage intermediate risk acute lymphoblastic leukemia predicts risk of relapse.* Leukemia 2010; 24: 715-20.
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8. **Vaitkevciene G, Forestier E, Hellebostad M, Heyman M, Jonsson OG, Lähteenmä-**

ki PM, Rosthoej S, Söderhäll S, Schmiegelow K. On behalf of the Nordic Society of Paediatric Haematology and Oncology (NOPHO). *Should white blood cell count at diagnosis of childhood acute lymphoblastic leukaemia be included in risk stratification in contemporary treatment protocols? Results from the NOPHO ALL-92 and ALL-2000 studies.* Eur J Haematol 2011; 86:38-46.

9. **Lund B, Åsberg A, Heyman M, Kanerva J, Harila-Saari A, Hasle H, Söderhäll S, Jonsson OG, Lydersen S, Schmiegelow K. On behalf of the Nordic Society of Paediatric Haematology and Oncology (NOPHO).** *Risk factors for treatment related mortality in childhood acute lymphoblastic leukaemia.* Ped Blood Cancer 2011; 56: 551-9.
10. **Relling MV , Gardner EE , Sandborn WJ , Schmiegelow K , Pui CH , Yee SW , Stein CM , Carrillo M , Evans WE , Klein TE.** *Clinical pharmacogenetics implementation consortium guidelines for thiopurine methyltransferase genotype and thiopurine dosing.* Clin Pharmacol Ther. 2011, 89:387-91
11. **Toft N, Schmiegelow K, Klausen TW, Birgens H.** *A national population-based retrospective study on acute lymphoblastic leukaemia in Denmark 1998-2008.* Br J Med 2012; 175: 87-104.
12. **Levinsen M, Shabaneh D, Bohnstedt C, Harila-Saari A, Jonsson OG, Kanerva J, Lindblom A, Lund B, Andersen EW, Schmiegelow K - for the Nordic Society of Paediatric Haematology and Oncology (NOPHO).** *Pneumocystis jiroveci pneumonia prophylaxis during maintenance therapy influences methotrexate/6-mercaptopurine dosing but not event-free survival for childhood acute lymphoblastic leukaemia.* Eur J Haematol 2012; 88: 78-86.
13. **Bohnstedt C, Levinsen M, Rosthøj S, Zeller B, Taskinen M, Hafsteinsdottir S, Björgvinsdóttir H, Heyman M, Schmiegelow K.** *Physicians Compliance during Maintenance Therapy in Children with Down Syndrome and Acute Lymphoblastic Leukemia.* Leukemia 1013: 27:866-70.

Publications critical for the randomized or add-on targeted ALL2008 projects:

14. **<u>R1:</u> Frandsen TL, Abrahamsson J, Lausen B, Vettenranta K, Heyman M, Behrentz M, Castor A, Wehner PS, Frost B-M, Andersen EW, Schmiegelow K.** *Individualized toxicity-titrated 6-mercaptopurine increments during high-dose methotrexate consolidation treatment of lower risk childhood acute lymphoblastic lymphoma. A NOPHO pilot study.* Br J Haematol 2011;155:244-7.
15. **<u>Host genomics:</u> Wesolowska A, Dalgaard MD, Borst L, Gautier L, Bak M, Weinhold N, Nielsen BF, Helt LR, Audouze K, Nersting J, Tommerup N, Brunak S, Ponten TS, Leffers H, Schmiegelow K, Gupta R.** *Cost-effective multiplexing before capture allows screening of 25,000 clinical relevant SNPs in childhood acute lymphoblastic leukemia.* Leukemia 2011; 25: 1001-6.
16. **<u>Host genomics:</u> Wesołowska-Andersen A, Borst L, Dalgaard MD, Yadav R, Rasmussen KK, Wehner PS, Rasmussen M, Ørntoft TF, Nordentoft I, Koehler R, Bartram CR, Schrappe M, Sicheritz-Ponten T, Gautier L, Marquart H, Madsen HO, Brunak S, Stanulla M, Gupta R, Schmiegelow K.** *Genomic profiling of thousands of candidate polymorphisms predicts risk of relapse in 778 Danish and German childhood acute lymphoblastic leukemia patients.* Leukemia 2015; 29:297-303.
17. **<u>Maintenance therapy:</u> Jacobsen JH, Schmiegelow K, Nersting J.** *Liquid chromatography-tandem mass spectrometry quantification of 6-thioguanine in DNA using endogenous guanine as internal standard.* J Chromatogr B 2012; 15: 881-2.
18. **<u>Maintenance therapy:</u> Schmiegelow K, Levinsen M, Attarbaschi A, Baruchel A, Devidas M, Escherich G, Gibson B, Heydrich C, Horibe K, Ishida Y, Liang D-C, Locatelli F, Michel G, Pieters T, Piette C, Pui C-H, Raimondi S, Silverman L, Stanulla M, Stark B, Winick N, Valsecchi MG.** *Second Neoplasms after Treatment of Childhood Acute Lymphoblastic Leukemia.* J Clin Oncol 2013; 31: 2468-76.
19. **<u>Maintenance therapy:</u> Schmiegelow K,**

Nielsen SN, Frandsen TL, Nersting J. *Mercaptopurine/ Methotrexate maintenance therapy of childhood acute lymphoblastic leukemia: clinical facts and fiction.* J Pediatr Hematol Oncol 2014; 36:503-17.

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20. **Raja R, Schmiegelow K, Frandsen T.** *Asparaginase-associated pancreatitis in children.* Br J Haematol 2012;159:18-27.
21. **Toft N, Birgens H, Abrahamsson J, Bernell P, Griškevičius L, Hallböök H, Heyman M, Holm MS, Hulegårdh E, Klausen TW, Marquart HV, Jónsson OG, Nielsen OJ, Paulsen PQ, Taskinen M, Vaitkeviciene G, Vettenranta K, Åsberg A, Schmiegelow K.** *Risk group assignment differs for children and adults 1–45 years with acute lymphoblastic leukemia treated by the NOPHO ALL-2008 protocol.* Eur J Haematol 2013; 90: 404-12.
22. **Ebbesen MS, Nersting J, Jacobsen JH, Frandsen TL, Vettenranta K, Abramsson J, Wesenberg F, Schmiegelow K.** *Incorporation of 6-thioguanine nucleotides into DNA during maintenance therapy of childhood acute lymphoblastic leukemia – the influence of thiopurine methyltransferase genotypes.* J Clin Pharmacol 2013; 53: 670-4.
23. **Rasmussen MM, Christensen RH, Gregers J, Heldrup J, Nersting J, Schmiegelow K.** *Can SLC19A1 80G>A polymorphisms predict risk of extremely delayed MTX-excretion after high dose Methotrexate?* J Ped Hematol Oncol 2013; 35: 417-8.
24. **Vaitkeviciene G, Heyman M, Jonsson OG, Lausen B, Harila-Saari A, Stenmarker M, Taskinen M, Zvirblis T, Asberg A, Groth-Pedersen L, Rageliene L, Schmiegelow K.** *Early morbidity and mortality in childhood acute lymphoblastic leukemia with very high white blood cell count.* Leukemia 2013; 27: 2259-62.
25. **Frandsen TL, Heyman M, Abrahamsson J, Vettenranta K, Åsberg A, Vaitkeviciene G, Pruunsild K, Toft N, Helt L, Bach KF, Schmiegelow K.** *Complying with the European Clinical Trials Directive while surviving the administrative pressure - an alternative approach to toxicity registration in a cancer trial.* Eur J Cancer 2014; 50: 251-9.
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27. **Levinsen M, Taskinen M, Abrahamsson J, Forestier E, Frandsen TL, Harila-Saari A, Heyman M, Jonsson OG, Lähteenmäki PM, Lausen B, Vaitkevičienė G, Asberg A, Schmiegelow K; Nordic Society of Paediatric Haematology and Oncology (NOPHO).** Pediatr Blood Cancer. 2014; 61:1416-21.
28. **Vaitkevičienė G, Matuzevičienė R, Stoškus M, Žvirblis T, Ragelienė L, Schmiegelow K.** *Cure rates of childhood acute lymphoblastic leukemia in Lithuania and the benefit of joining international treatment protocol.* Medicina (Kaunas). 2014;50(1):28-36.
29. **Henriksen LT, Nersting J, Raja RA, Frandsen TL, Rosthøj S, Schrøder H, Albertsen BK; Nordic Society of Paediatric Haematology and Oncology (NOPHO) group.** *Cerebrospinal fluid asparagine depletion during pegylated asparaginase therapy in children with acute lymphoblastic leukaemia.* Br J Haematol. 2014;166: 213-20.
30. **Henriksen LT, Harila-Saari A, Ruud E, Abrahamsson J, Pruunsild K, Vaitkeviciene G, Jónsson ÓG, Schmiegelow K, Heyman M, Schrøder H, Albertsen BK; Nordic Society of Paediatric Haematology and Oncology (NOPHO) group.** *PEG-asparaginase allergy in children with acute lymphoblastic leukemia in the NOPHO ALL2008 protocol.* Pediatr Blood Cancer 2015; 62: 427-33.
31. **Nina Toft, Henrik Birgens, Jonas Abrahamsson, Laimonas Griskevicius, Helene Hallböök, Mats Marshall Heyman, Tobias Klausen, Ólafur Gísli Jónsson, Katrin Palk, Kaie Pruunsild, Petter Quist-Poulsen, Goda Vaitkeviciene, Kim Vettenranta,**

Ann Asberg, Louise Rold Helt, Thomas Frandsen, Kjeld Schmiegelow. *Toxicity profile and treatment delays in NOPHO ALL2008 – comparing adults and children with Philadelphia chromosome-negative acute lymphoblastic leukemia.* Eur J Haematol 2016; 96:160-9.

32. **Tulstrup M, Larsen HB, Castor A, Rossel P, Grell K, Heyman M, Abrahamsson J, Söderhäll S, Åsberg A, Jonsson OG, Vettenranta K, Frandsen TL, Albertsen BK, Schmiegelow K; Nordic Society of Paediatric Haematology, and Oncology (NOPHO).** *Parents' and Adolescents' Preferences for Intensified or Reduced Treatment in Randomized Lymphoblastic Leukemia Trials.* Pediatr Blood Cancer 2016; 63:865-71.

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ALL2016 group had two on-site meetings (18th August 2015, and 12th November 2015). The analyses of the NOPHO ALL2008 data concentrated in

a. finding a very low risk group which would be eligible for treatment without anthracyclins. This group was not identifiable by early MRD (D15) and thus biological and clinical factors present at diagnosis would be needed for stratification and downgrading of the therapy.
b. identifying outcome and timing of the relapses of the pts ending up to the HR/HR+SCT arms through different pathways. Majority of the HR-chemo (50%) and HR-SCT (67%) patients came from Dexamethason induction and had high level of MRD at the end of Induction. The highest cumulative incidence of relapse was among those HR pts with poor very early response to therapy (D15 MRD). In the HR-chemo a substantial amount of relapses occurred in the Interim Maintenance.
c. B-other group having other than stratifying cytogenetic markers. Analyses are on-going to clarify the role of IKaros as a risk factor to relapse among these pts. Particularly adult pts with B-other cytogenetics and stratified to IR therapy have been challenging in respect of relapse.
d. finding ways to decrease the proportion of

CNS relapses in the lower risk groups. Still 40% of the LR relapses involve also CNS.

e. identifying the pathways and outcome of the SCT pts. The outcome of the SCT pts has been good (pOS 0.81). Pre-SCT MRD does not impact the outcome, pts transplanted in the CR1 do the best.

ALL2016 group continued its work until November 2015 in parallel with the preparations for a more international ALL protocol. At that point the decision was taken that NOPHO will fully be committed to the work for an ALLTogether 2018 protocol which would be in common with the UK-ALL, DCOG, DFCI and CoALL groups (DCFI signed out in January 2016). This meant that the activity of ALL2016 group was closed in the November meeting and it continues as ALLTogether NOPHO working group chaired by Mats Heyman.

NOPHO is allowed to have one representative in each ALLTogether working group. NOPHO representation in the ALLTogether work aimed to have a balanced representation from each member country acknowledging expertise and activity within the field. NOPHO working groups identified the candidates and ALL WG and LLC have discussed and confirmed the nominations. The working groups that have been active so far have been MRD- , HR-, Asparaginase- and Maintenance therapy. The NOPHO PI in the international ALLTogether protocol will be Mats Heyman.

March 31st 2016

Mervi Taskinen

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Organisation

The group has held two meetings during 2015. The main focus of the meetings have been on supervision of the treatment protocol NOPHO-DBH AML2012. We have actively worked, on strengthening the scientific cooperation between NOPHO and the Dutch and Belgian groups and several collaborative projects have been initiated during 2015. Also we have initiated and reviewed several NOPHO AML research projects and pursued NOPHO participation in international collaborative scientific studies. As in previous years, the members have an intensive mail communication between the meetings mainly addressing problems in treatment of individual patients and treatment protocol issues.

Introduction

NOPHO has from 1984 until 2013 treated children with AML on four common protocols: NOPHO-AML84, -88-. -93 and -2004. All protocols have been based on induction therapy with anthracycline, cytarabine and 6-thioguanin with etoposide added from 1988

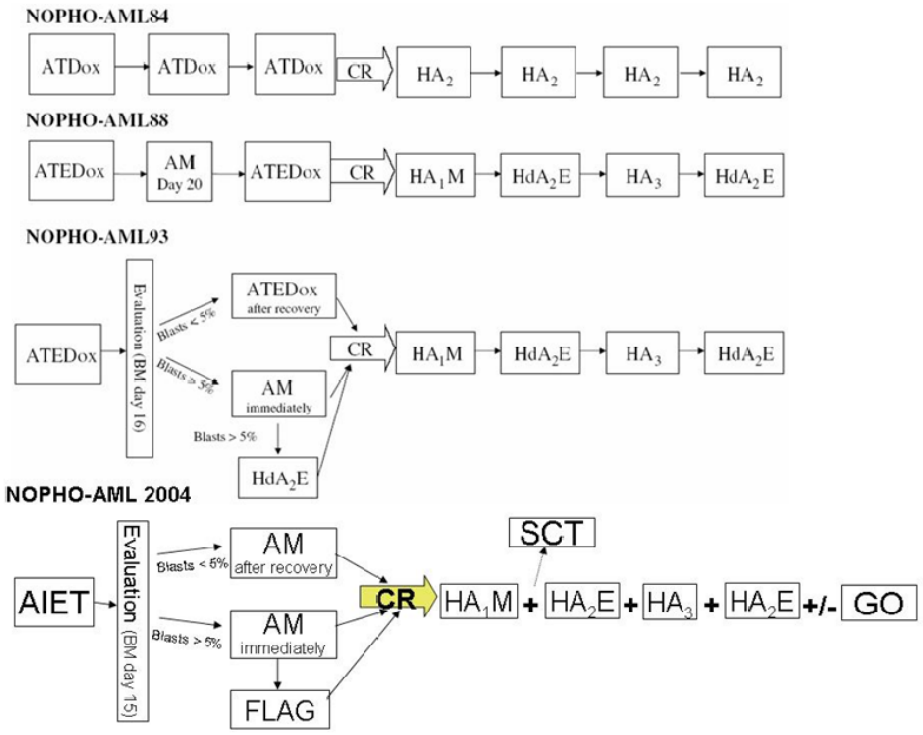


Figure 1. Overview of previous NOPHO treatment protocols from 1984-2012.

followed by consolidation based on high-dose cytarabine. Since 1993 a response guided induction strategy has been used, allowing hematological recovery for children in remission after the first course prior to giving the second course. Compared to the previous intensively timed induction this markedly reduced mortality in induction. From NOPHO-AML84 to NOPHO-AML93, outcome improved significantly and the NOPHO-AML93 had a 5 year EFS of 50%. Overall survival was 65% which at that time was the highest reported in childhood AML.

However, the steady trend towards improvement was broken with the NOPHO AML 2004 protocol. Although survival increased to 70% the five year EFS was disappointingly low at 47%. When analysing the relatively poor outcome the main conclusions were that the second induction course in the AML 2004 protocol was not intensive enough and that idarubicin seemed to be less effective in patients with RUNX1/RUNX1T1 (t8;21) AML. Therefore, the group worked intensely to produce the new protocol which was finalised in december 2012. Denmark and Sweden were the first countries to obtain approval for the protocol and the first patients were treated in March 2013.

During 2014 the main work in the group has focused on

1. Supervising the efficiency, toxicity and logistic framework for the NOPHO-DBH AML 2012 protocol.
2. Implementing the NOPHO-DBH AML 2012 protocol in Hong Kong and Israel.
3. Increasing the scientific collaboration, both within the framework of the AML 2012 protocol and generally in AML biology, between NOPHO and the Belgian and Dutch groups.
4. Compiling and publishing data from the NOPHO AML protocols.
5. Planning and participating in international collaborative research projects.

NOPHO-AML2004

The protocol opened in January 2004 and was officially closed in december 2013. Hong Kong has continued to use the protocol as standard of care until AML 2012 can be opened. The 2004 protocol with flow charts and amendments can be accessed at www.nopho.org.

Patient accrual

NOPHO AML-2004 included a randomized comparison of the potential benefit of Gemtuzumab as post-consolidation therapy for standard risk AML. As from the end of 2010 the randomised study had accrued the target number of 120 and therefore was closed for randomisation but continued to be used as standard therapy without Gemtuzumab. Between 2004 and December 2013, at which time the protocol was officially closed, 323 protocol patients were registered from the Nordic countries and Hong Kong. The protocol was also used as standard therapy for childhood AML in Estonia and Latvia. During 2010-2013 both the Netherlands and Belgium conducted a study based on a modified version of NOPHO-AML2004 (identical treatment except for omission of the third course HAM and no stem cell transplant in first remission). This study recruited 113 patients and had a EFS of 60% and OS of 76% at two years.

Toxicity

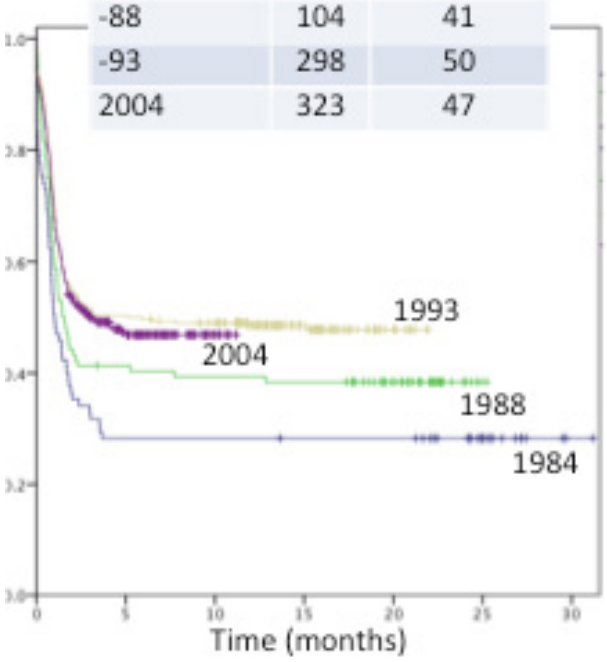
The toxic death rate in AML2004 was relatively low with a frequency of induction deaths of 3.1% and deaths in CR1 2.8%. The frequency of resistant disease was 5%, second malignancy 1.9% and 40% experienced relapse.

As the treatment blocks were very intensive, bone marrow aplasia was long and the rate of neutropenic fever very high after each block ranging from almost 100% after the first induction course to 74% after HA3. The acute and long-term cardiac toxicity has been very low and of 169 patients reported at one year and 55 at five years none have cardiac failure.

Outcome

The overall results are now stable with a five year EFS of 47% compared to 50% in NOPHO-AML93. The overall survival has improved to 69% from 65% in AML93.

Protocol	N	EFS 5y %
-84	85	28
-88	104	41
-93	298	50
2004	323	47



Protocol	N	OS 5y %
-84	85	38
-88	104	46
-93	298	65
2004	323	69

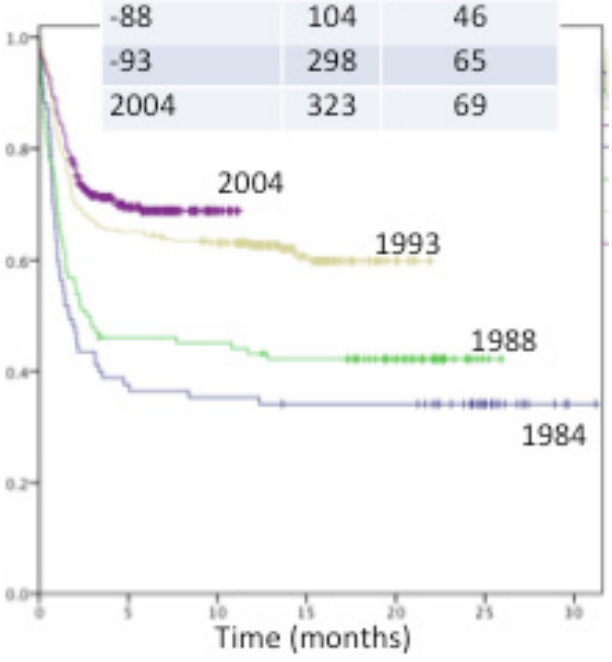


Figure 2. Overall survival (right figure) and event-free survival (right figure) in NOPHO-AML2004 (purple), NOPHO-AML93 (beige), NOPHO-AML88 (green) and NOPHO-AML84 (blue).

When analysing the relatively poor EFS it was found that patients with an intermediate response to AIET had a very high relapse rate as did patients with RUNX1/RUNX1T1 regardless of response. The AML group concluded that the second induction course – AM – was too weak in these patient subsets and in 2010 an amendment was made recommending FLADx as second course for patients with RUNX1/RUNX1T1 or an intermediate response to AIET. The amendment can be found on http://www.nopho.org. Of ten patients with t(8;21), treated with a FLA-based second course, only one has relapsed and all are alive. The same excellent results when using AIET as first course followed by FLA or FLADx in RUNX1/RUNX1T1 AML was seen in the Dutch/Belgian AML01 and the combined results from the groups were presented at ASH 2014.

Although analysis of the results with respect to subgroups is not finalized it is evident that the changes in induction made in the 2004 protocol affected survival differently for several cytogenetic subgroups. Thus, even when using conventional chemotherapy for AML, patient with different subgroups may benefit from tailored therapy.

Stem cell transplant in CR1

In NOPHO-AML2004 high-risk patients were recommended SCT with any matched donor. Initially MLL aberration other than t(9;11) was a high risk criterion but interim analysis showed that compliance to the SCT recommendation in these patients was poor and consolidation with chemotherapy resulted in a satisfactory outcome. Thus, an amendment in 2009 removed MLL aberrations as a high-risk criteria.

On the other hand, increasing evidence that patients with FLT3-ITD mutations without concomitant NPM1 mutation had a very poor prognosis which might be improved by stem cell transplant, led to the addition of FLT3-ITD mutations as a high risk criterion in an amendment in 2010. 17% (56/323) of patients received SCT as consolidation in CR1 or following resistant disease. This is a low rate compared to most other childhood AML protocols.

Gemtuzumab randomization

The results from the randomized study including 120 patients were published 2012 (Hasle et. al. Blood). Gemtuzumab was well tolerated with no toxic deaths. Although GO treated patients had a tendency for later relapses, no effect was observed on either EFS or OS. Thus, the conclusion is that Gemtuzumab neither reduces the relapse rate nor increases survival when administered as post-consolidation therapy.

NOPHO-DBH AML2012

The protocol was finalized in december 2012 and the AML2012 database was opened in March 2013. After approval by the competent authorities and setting up of national GCP monitoring the protocol opened in Denmark and Sweden in March 2013, followed by Finland in April and Norway in June. The Netherlands started recruiting patients January 2014 and Belgium in May 2014. Hong Kong has had some difficulties in obtaining the study drug DaunoXome but will hopefully open the protocol spring 2016. During 2015 several other national pediatric AML study groups have expressed interest to participate. During 2015 the MRD group and the NOPHO registry has worked intensely with colleagues from Israel and they are planning to start recruiting patients during 2016. Furthermore, Spanish pediatric oncologists has expressed a strong interest in joining the protocol and a collaboration has been established with regard to MRD determinations. The study has EUDract number 2012-002934-35 and clinical trials identifier NCT01828489

The study is expected to recruit 300 patients within a time frame of six years and will provide a strong basis for biological and clinical add-on research studies.

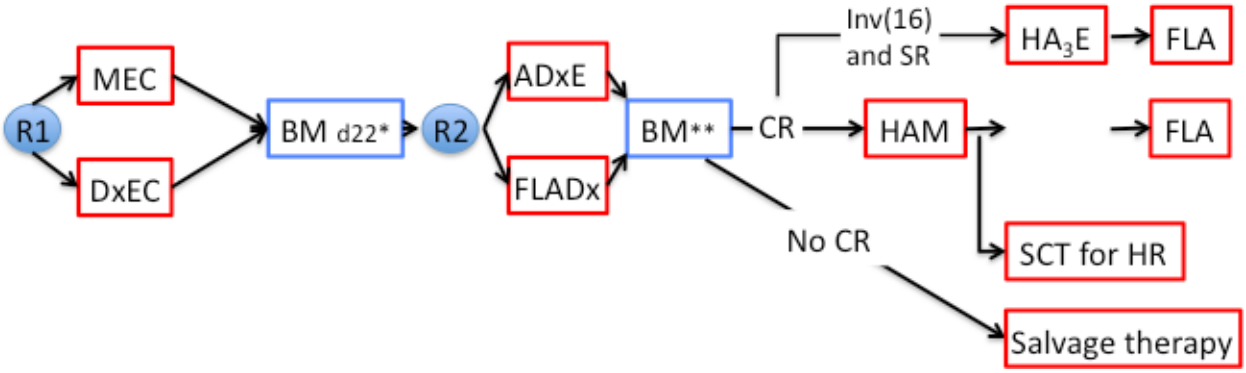


Figure 3. Overview of NOPHO-DBH AML 2012. Evaluation of therapy response is performed on day 22 after the first course and immediately before consolidation.

The main assumptions, which to a large extent were deducted from experiences from AML2004, behind the major changes in standard treatment in AML2012 as compared to AML2004 are that:

- prognosis can be improved by using more intensive induction therapy
- detection of minimal residual disease following the two induction courses identifies a subset of patients with a very poor prognosis when treated with chemotherapy alone
- stem cell transplant can reduce the negative prognostic impact of poor response to induction therapy

The risk stratification in AML2012 is mainly based on treatment response which we assumed would be possible to evaluate by flow cytometry in the majority of patients. Since MRD flow is very difficult in AML the MRD group have set up strict logistics and a standardized protocol but strive to improve by several quality control procedures. Thus, besides meeting regularly, all laboratories partake in twinning so that each patients MRD data are reviewed by two centers. Furthermore quality control rounds are performed twice yearly where all laboratories review the same data files. All MRD data files are accessible through a common server.

Children with ≥15% leukemic cells after the first course or ≥ 0.1% after the second course are classified as high risk (HR). In addition, patients with FLT3-ITD and no NPM1 mutation are HR patients. Children and adolescents in the HR group are recommended stem cell transplant. All other patients are classified as standard risk and receive consolidation therapy with three blocks containing high dose cytarabine. An exception is standard risk patients with inv(16) who only receive two consolidation blocks.

AML2012 includes two randomised studies both aiming at increasing treatment outcome. The efficacy and toxicity (in particular cardiac) of mitoxantrone and DaunoXome in the first induction course are compared. The second study compares the efficacy and toxicity of FLADx to the BFM course ADxE. Both studies are evaluated by using MRD flow after the respective courses as primary endpoint. AML2012 has three other important research aims

1. to evaluate the prognostic significance of measurement of fusion gene transcript levels after the first and second course
2. to perform a comprehensive genetic characterisation of the leukemic cells
3. to use fusion gene transcript determinations to detect molecular relapse of AML during follow-up.

As of October 2015, 120 patients have been treated on the protocol. Of these 76% have been randomised for course 1 and 87% for course 2. The randomisation frequency in the Nordic countries have been around 90%. The adherence to protocol guidelines, particularly regarding diagnostic evaluations and MRD measurements, has been very good. A very high proportion of patients, 68%, have had AML-specific cytogenetic aberrations, of which 13% have CFBB-MYH11 (Inv(16)), that in good responding patients stratifies treat-

ment to only two consolidation blocks, and 8% FLT3-ITD mutation without NPM1 mutation that stratifies to HR treatment. Response evaluation with MRD flow has been feasible in 90% of patients which is slightly higher than expected and verifies that our multicenter approach to MRD determination functions very well.

The response to induction therapy has been excellent with only three patients having resistant disease following two courses and an additional four with between 0.1% and 5% leukemic cells after course 2 (HR criterion).

As expected the toxicity of the protocol has been high and figure 4 shows the time-points for the six toxic deaths that have occurred.

Figure 4 shows that there were three induction deaths in spring 2014. This prompted the AML group to write guidelines for management of febrile infection which have been distributed to all investigators and published on the NOPHO web. Toxicity registration shows that 65% of patients have documented sepsis after the first course and 15% have typhlitis. Almost 20% require care at ICU. Nevertheless, the toxicity has been manageble and, although no strict statistical analysis has been made, it seems that it is similar to that seen in AML2004. However, it must be emphasized that extreme vigilance is necessary and supportive care must be of the highest standard in these patients. There is a trend for toxicity registration to be delayed for the consolidation courses which is not acceptable in a randomised clinical trial. Investigators are therefore kindly requested to do this at the start of the subsequent course.

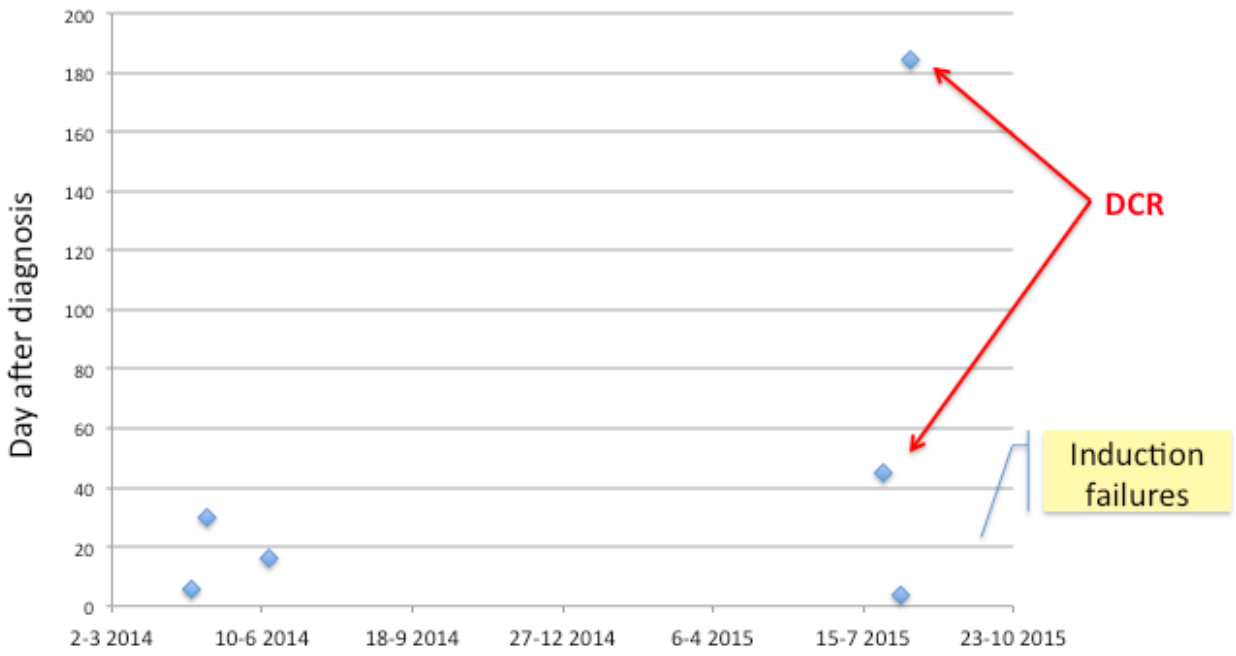


Figure 4. The time-point in treatment of toxic deaths in NOPHO-DBH AML2012 in relation to protocol start. Induction deaths are in the shaded area. DCR – Death in complete remission.

It is still too early to draw definite conclusion regarding the relapse rate in the protocol. However, only thirteen of the 120 patients had experienced a relapse until October 2015. Figure 5 shows the EFS and OS at this time.

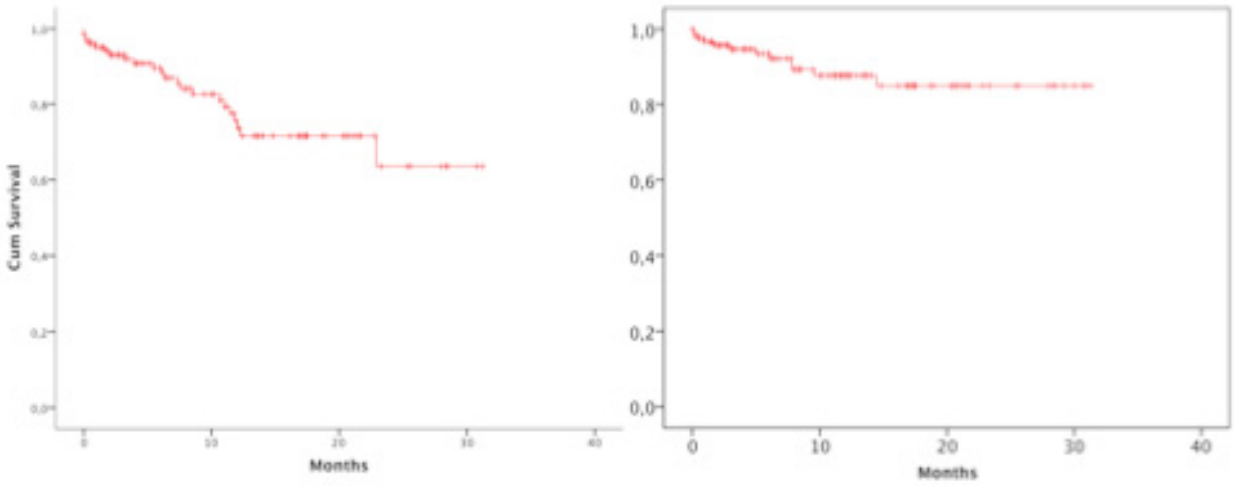


Figure 5. EFS (left) and OS (right) for 120 patients treated on NOPHO-DBH AML2012. The number of patients at risk after 18 months is low so the confidence intervals are very large after this time.

In conclusion, the NOPHO-DBH AML2012 protocol is now well established and the logistics around the protocol works good. Initial results on treatment efficacy are encouraging. Several other national groups will join or have expressed interest in joining the protocol.

Intergroup studies

Myeloid leukemia of Down syndrome

The International DS study ML-DS 2006 reduced the dose in each course and the total number of courses from 6 to 4. The protocol is found at www.nopho.org

An add-on study on MRD using WT1 analyses is centralized in Aarhus. The protocol and practical information about how to send samples are found at www.nopho.org

AML-M3 APL

In 2009, The NOPHO-AML group recommended joining the international ICC APL study 01 as a registration only study. The outcome in this protocol has been excellent with an OS of 94% at three years. A new protocol, ICC APL study 02, is now being prepared and almost finalized. A major change will be that patients with standard risk APL will be treated only with retinoic acid and arsenictrioxide. The APL study group have issued interim guidelines for treatment of patients with SR APL which the AML group during 2015 decided to recommend as best available therapy. The guidelines are published on the NOPHO web. High risk patients should continue to be treated according to the old protocol until the final new protocol is approved.

PCR MRD monitoring is mandatory and should be centralized to Aarhus for all Nordic patients.

Data entry will be done centrally.

For the guidelines for APL SR, the ICC APL study 01 protocol for APL HR and PCR MRD invoice please see www.nopho.org

International relapsed AML study

A new relapse protocol has been finalized and approval has been obtained from the competent authorities in several countries including Denmark and Sweden. This new relapse protocol will investigate, in a randomised setting, if addition of Gemtuzumab to FLADx will improve early response. Unfortunately there has been some problems in initializing the study mainly related to distribution of gemtuzumab

and change of sponsor. While awaiting the new relapse protocol a recommendation for relapse strategy can be found at www.nopho.org.

Common European protocol

During 2012, BFM and DCOG took the initiative to investigate the possibilities to establish a common European de novo AML protocol. The main incentives are to obtain higher patient numbers in order to complete randomisations in a shorter time frame and to achieve power for subgroup analyses. A committee was established and representatives from the NOPHO AML group have taken part of meetings twice yearly and also taken on tasks that have been distributed within the committee. The current aim is to find common grounds for a protocol with the hope of having a proposal for a study that can be launched in 2019-2020.

Publications involving the NOPHO AML WG from 2014

- **Julie Damgaard Sandahl, Eigil Kjeldsen, Jonas Abrahamsson, Shau-Yin Ha, Jesper Heldrup, Kirsi Jahnukainen, Ólafur G. Jónsson, Birgitte Lausen, Josefine Palle, Bernward Zeller, Erik Forestier, and Henrik Hasle.** *Ploidy and Clinical Characteristics of Childhood Acute Myeloid Leukemia. A NOPHO-AML study.* Genes Chromosome and Cancer 2014 53(8):667-75.
- **Sandahl JD, Coenen EA, Forestier E, Harbott J, Johansson B, Kerndrup G, Adachi S, Auvrignon A, Beverloo HB, Cayuela JM, Chilton L, Fornerod M, de Haas V, Harrison CJ, Inaba H, Kaspers GJ, Liang DC, Locatelli F, Masetti R, Perot C, Raimondi SC, Reinhardt K, Tomizawa D, von Neuhoff N, Zecca M, Zwaan CM, van den Heuvel-Eibrink MM, Hasle H.** *t(6;9)(p22;q34)/DEK-NUP214-rearranged pediatric myeloid leukemia: an international study of 62 patients.* Haematologica 2014 99(5):865-72.
- **Skou AS, Glosli H, Jahnukainen K, Jarfelt M, Jónmundsson GK, Malmros-Svennilson J, Nysom K, Hasle H.** *Renal, gastrointestinal, and hepatic late effects in survivors of childhood acute myeloid leukemia treated with chemotherapy only-a NOPHO-AML study.* Pediatr Blood Cancer 2014 61(9):1638-43.
- **Damgaard Sandahl J, Kjeldsen E, Abrahamsson J, Ha SY, Heldrup J, Jahnukainen K, Jónsson ÓG, Lausen B, Palle J, Zeller B, Forestier E, Hasle H.** *The applicability of the WHO classification in paediatric AML. A NOPHO-AML study.* Br J Haematol 2015 169(6):859-867.
- **Inaba H, Zhou Y, Abla O, Adachi S, Auvrignon A, Beverloo HB, de Bont E, Chang TT, Creutzig U, Dworzak M, Elitzur S, Fynn A, Forestier E, Hasle H, Liang DC, Lee V, Locatelli F, Masetti R, De Moerloose B, Reinhardt D, Rodriguez L, Van Roy N, Shen S, Taga T, Tomizawa D, Yeoh AE, Zimmermann M, Raimondi SC.** *Heterogeneous cytogenetic subgroups and outcomes in childhood acute megakaryoblastic leukemia: a retrospective international study.* Blood 2015 126(13):1575-84.
- **Zwaan CM, Kolb EA, Reinhardt D, Abrahamsson J, Adachi S, Aplenc R, De Bont ES, De Moerloose B, Dworzak M, Gibson BE, Hasle H, Leverger G, Locatelli F, Ragu C, Ribeiro RC, Rizzari C, Rubnitz JE, Smith OP, Sung L, Tomizawa D, vandenHeuvel-Eibrink MM, Creutzig U, Kaspers GJ.** *Collaborative Efforts Driving Progress In Pediatric Acute Myeloid Leukemia.* J Clin Oncol 2015 33(27):2949-62.
- **Jarfelt M, Andersen NH, Glosli H, Jahnukainen K, Jónmundsson GK, Malmros J, Nysom K, Hasle H.** *Cardiac function in survivors of childhood acute myeloid leukemia treated with chemotherapy only: A NOPHO-AML study.* Eur J Haematol 2015:Sep 18.
- **Wennstrom L, Wendtlant Edsløv P, Abrahamsson J, Maxweell Nørgaard J, Fløisand Y, Forestier E, Gustafsson G, Heldrup J, Hovi L, Jahnukainen K, Jonsson OG, Lausen B, Palle J, Zeller B, Holmberg E, Juliuson G, Stockelberg D, Hasle H.** *Acute myeloid leukemia in adolescents and young adults in the nordic countries – outcome according to pediatric and adult treatment protocols.* Pediatr Blood & Cancer 2016 63(1):83-92.
- **Anne M. Tierens, Björklund E, Siitonen**

S, Marquart Hv, Wulff-Juergensen G, Pelliniemi TT, Erik Forestier, Henrik Hasle, Kirsi Jahnukainen, Birgitte Lausen, Olafur G Jonsson, Josefine Palle, Bem Zeller, Linda Fogelstrand & Jonas Abrahamsson. *Residual disease detected by flow cytometry is an independent predictor of survival in childhood acute myeloid leukemia: results of the NOPHO-AML 2004 study.* Accepted Br J of Haematol

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The Leukemia Cytogenetic group meet once a year divided in two two-day-meetings. All participants with two exceptions are clinical geneticists working at the laboratories responsible for the cytogentic diagnostics in the Nordic countries. The coordinators are both pediatric oncologists and they together with Bertil Johansson participate in both meetings. In May 2015 we met in Umeå and the Swedish leukemia patients diagnosed in 2014 were reviewed during the first meeting. In the second meeting the rest of the Nordic leukemia patients were reviewed. All pediatric AML patients as well as both pediatric and some of the adult ALL patients (the Swedish, Norwegian and Danish) were evaluated.

During the review meetings all diagnostic cytogenetic results are reviewed, such as karyograms, targeted analyses for the mandatory aberrations (FISH- and/or PCR), but also, if they exist, results from SNP-arrays or other types of analyses done at diagnosis are discussed. A conclusive karyotype is settled, taking into account all diagnostic results we know of for each patient. The cytogentic group defining the patient in the treatment protocol is finally decided by the "worst counts" -principle.

Cytogenetic results for NOPHO children diagnosed with ALL in 2014

Aberration	n	%
T-cell	23	12,4
MLL/11q23	6	3,2
t(9;22)	6	3,2
Hypodiploid (<45 chr)	3	1,6
dic(9;20)	8	4,3
t(1;19)	4	2,2
"other"	26	14,1
Normal	11	5,9
No result	2	1,1
51-67 chr	56	30,3
t(12;21)	35	18,9
iAMP21	4	2,2
>67 chr	1	0,5
Total	185	100

Five children were diagnosed abroad and therefore not reviewed and excluded.

Quality control of DNA-index results for the ALL patients

The DNA-index result is not reviewed at our meetings, but the DNA-index reported in the NOPHO registry is always noted, since it is part of the evaluation of the ploidy of the leukemia. Over the years it has been noticed that the DNA-index reported sometimes do not fit with the other cytogenetic results for the patient. In the 2014 cytogenetic review 10%(n=21) of the NOPHO ALL children were found with a suspected incorrect DNA-index reported, and for the 29 adult ALL patients in the registry 27% (n=8). To investigate the reasons behind this the 11 Swedish pediatric cases were discussed with the local laboratories. 3 patients were incorrectly reported from lab or incorrectly registered. For the majority of the remaining DNA-index values it was discovered that an incorrect method had been used for the analyses or too few cells investigated. These errors will be dealt with at the laboratory in question. We are planning to produce a list with all NOPHO patients treated according to the ALL 2008 protocol with a suspected incorrect registration of DNA-index, for each national PI to investigate in a similar way. The main aim of this quality control is to minimize the risk of not detecting hypodiploid patients in the future.

Cytogenetic results for NOPHO children diagnosed with AML in 2014

All Nordic pediatric AML patients diagnosed in 2014 were reviewed. The molecular analyses for FLT-ITD- and NPM1-mutations were not reviewed, but checked for in the NOPHO registry. Three patients with FLT-ITD mutation and a concurrent NPM1-wild type, were cytogenetically normal in two cases and positive for t(15;17) in one case. See table below.

Cytogenetic results for NOPHO children diagnosed with AML in 2014

Cytogenetic groups	n	%
Down	2	6,1
t(8;21)	3	9,1
inv(16)	4	12,1
t(15;17)	2	6,1
"other"	5	15,2
MLL-rearr	7	21,2
t(7;12)	1	3,0
FLT-ITD + NPM1wt	3	9,1
no result	1	3,0
normal	5	15,2
Total	33	100

Future plans

In 2016-2017 the diagnostic genetic laboratories will start to register their results up front in a new part of the NOPHO registry in parallel with the cytogenetic registration from the clinic (just as the MRD results are reported from both sides). This work is ongoing at the NOPHO registry and a proposal for the registration in detail will be discussed in the upcoming cytogenetic review meetings this year in May, and then hopefully implemented.

Umeå 13-04-2016
Ulrika Norén Nyström

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In collaboration with the NOPHO AML group

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The 7th International Symposium on Myelodysplastic syndromes, JMML, and Bone Marrow Failure Syndromes was successfully held in Aarhus, from 1st to 3rd October 2015. More than 150 participated from around the world including several Nordic colleagues.

The NOPHO web includes a checklist for diagnosing, registration and treatment of MDS and JMML. The checklist is linked to all relevant protocols, invoices and registration forms.

Therapy

AML-like intensive therapy in JMML and MDS is associated with a lower remission rate, a higher risk of cytopenia related death, and a higher relapse rate than in AML. Hematopoietic stem cell transplantation (HSCT) is the only therapy with a realistic potential of cure. Conditioning with Busulfan, Cyclophosphamide, and Melphalan has shown favorable event-free survival in both advanced MDS and JMML. Patients with advanced MDS 12 years or older are recommended to be conditioned with thiotepa, treosulfan, and fludarabine to reduce toxicity.

The main problem following HSCT in MDS is toxicity, whereas the major problem following HSCT in JMML is relapse. Intensive chemotherapy before HSCT is not recommended. Early HSCT is the treatment of choice for patients with JMML and MDS, excluding the JMML-like picture in infants with Noonan syndrome, JMML with CBL mutation, or the stable refractory cytopenia of childhood (RCC) without adverse cytogenetics.

Patients with hypoplastic RCC without adverse cytogenetics are candidates for immunosuppressive therapy with cyclosporine, prednisolone and ATG. Several recent studies have suggested that horse ATG is superior to rabbit ATG, it is therefore recommended to treat patients with hypocellular RCC with indications for IST with horse ATG (Atgam® Pfizer, 40 mg/kg/day for 4 days). The recommendations for the use of CSA, methylprednisolone, and G-CSF are unchanged.

Azacitidine therapy

Treatment with demethylating agents (azacitidine and dacarbazine) has shown effects in adults with MDS.

An investigator phase I-II study on azacitidine (Vidaza) in relapsed MDS or JMML opened in 2013. Aarhus is the only site open within NOPHO. Two patients with JMML relapsed after HSCT have been treated in Aarhus. Please contact Henrik Hasle in case of potential candidates for the study.

A company (Celgene) initiated study on azacitidine in newly diagnosed JMML and advanced MDS was opened in 2015 in Copenhagen. Gothenburg, and Stockholm. So far one MDS patients has been treated in Stockholm. To be eligible morphology review should be done by Gitte Kerndrup.

EWOG-MDS 2006

The protocol, EWOG-MDS 2006 includes guidelines on diagnostics and treatment.
A separate HSCT protocols for RCC using non-myeloablative conditioning in hypoplastic RCC is available as well as guidelines for HSCT in RAEB and JMML.
The protocols and forms are available at www.nopho.org and www.ewog-mds.org.

Morphology review

Gitte Kerndrup has reviewed smears and biopsy material from more than 700 patients with a suspicion of MDS or JMML since 1995. Samples from 40-50 patients are each year sent for review to Gitte Kerndrup and Trine Plesner. For some patients several samples are sent. MDS or JMML is confirmed in a 10-15 patients each year, corresponding to 40% of the samples received.

When you suspect MDS or JMML

When MDS or JMML is suspected in a child from the Nordic countries blood and bone marrow smears and preferentially biopsy material should be sent to Gitte Kerndrup and Trine Plesner, Laboratory Center, Department of Pathology, Aarhus University Hospital, Aarhus, Denmark
Please find the invoice at www.nopho.org under Working group MDS – Diagnostics.

For patients with suspected JMML heparinized blood and preferentially bone marrow for molecular testing should be sent to Charlotte Niemeyer, University Children's Hospital, Freiburg, Germany. Invoice on www.nopho.org under Working group MDS – Diagnostics
The cells will be examined for mutations in N-RAS, K-RAS, CBL, and PTPN11.

When a diagnosis of MDS or JMML has been confirmed, the completed registration forms should be sent to Henrik Hasle, Department of Pediatrics, Skejby Hospital, DK-8200 Aarhus N, Denmark, Phone: +45 7845 1426, E-mail: hasle@dadlnet.dk

Invoice forms and registration forms are available from Henrik Hasle and at www.nopho.org
For questions or problems please contact your National MDS coordinator or Henrik Hasle. Phone: +45 7845 1426, E-mail: hasle@dadlnet.dk

Recent EWOG-MDS based publications with NOPHO contributions

2016

Wlodarski MW, Hirabayashi S, Pastor V, Starý J, Hasle H, Masetti R, Dworzak M, Schmugge M, van den Heuvel-Eibrink M, Ussowicz M, De Moerloose B, Catala A, Smith OP, Sedlacek P, Lankester AC, Zecca M, Bordon V, Matthes-Martin S, Abrahamsson J, Kühl JS, Sykora KW, Albert MH, Przychodzien B, Maciejewski J, Schwarz S, Göhring G, Schlegelberger B, Cseh A, Noellke P, Yoshimi A, Locatelli F, Baumann I, Strahm B, Niemeyer CM. *Prevalence, clinical characteristics and prognosis of GATA2-related MDS in children and adolescents.* Blood 2016; 127: 1387-97.

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	Jesper Heldrup (immunophenotyping)
Young NOPHO	

The main activity of the NOPHO Infant Leukemia group is to take care of the international Interfant studies. The group had a meeting in January 2015. The annual meeting in the international Interfant group was held in May 2015 during the I-BFM-meeting in Budapest.

Status of Interfant-06

The current protocol opened in 2006 with Rob Pieters from Rotterdam as chair of the study. The recruitment is in line with the expected one, and target sample size will be reached in 2016. Overall outcome seems equal to Interfant-99. However, the outcome from the "original study groups" is better than the outcome for Interfant-99, but the outcome for patients belonging to "other groups" is significantly lower and these groups constitute a large part of the whole study, possibly due to different rate of recruitment.

Status of Interfant-06 and Infant ALL in NOPHO

The protocol was approved in Finland in 2006 and in Denmark in 2011, thus solely Danish and Finnish patients can be randomised to experimental AML-like therapy.

A total of 73 patients are (or have been) treated according to the Interfant-06 protocol, the main part not randomised and thus following the standard arm (December 31st 2015). Four infant ALL patients have been treated according to the NOPHO ALL2008 protocol in Sweden. Almost all patients treated according to Interfant-06 in Denmark, Finland and Sweden are registered in the Monza-database, irrespective of protocol status.

The MLL-PCR-MRD-measurements are mandatory in MLL-rearranged patients, and the analyses are free of cost for the diagnostic sample and sample from time point 5. All centres are requested to send samples from MLL-rearranged infant ALL patients from time of diagnosis and Time point 5 to the MRD-lab. in Copenhagen.

Survival: 5-years OS is 59 % for MLL+ patients (N=34) treated according to Interfant-06 in the Nordic countries – and 87 % for MLL-neg patients (N=27) (December 31st 2015).

Ongoing studies

- **A retrospective study in the Nordic infant ALL patients** was approved by the

NOPHO Board and Scientific Committee in Nov. 2012. The plan is to describe and analyse survival data of the cohort of infant ALL patients from the beginning of NOPHO registry up to 2012.

- **A study of maintenance treatment in infant ALL patients** was approved by the NOPHO Board and Scientific Committee in Nov. 2012. The national members of the working group acts as national PI's.
- **The SNP study in Infant ALL** was approved by the NOPHO Board and Scientific Committee in Nov. 2011. The study is both a retrospective and prospective study. The national members of the working group acts as national PI's.

Publications on Infant ALL-studies, where NOPHO is involved

- **Mann G, Attarbaschi A, Peters C, Schrappe M, Lorenzo P De, Hann I, Rossi G De, Felice M, Lausen B, LeBlanc T, Szczepanski T, Ferster A, Janka-Schaub G, Rubnitz J, Silverman L B, Stary J, Campbell M, Li C K, Suppiah R, Biondi A, Vora A, Valsecchi MG and Pieters R on behalf of the Interfant-99 Study Group.** *Improved outcome with hematopoietic stem cell transplantation in a poor prognostic subgroup of infants with mixed-lineage-leukemia (MLL)-rearranged acute lymphoblastic leukemia - Results from the Interfant-99 Study.* Blood 2010; 116 (15): 2644-2650
- **Van der Linden M, Valsecchi MG, De Lorenzo P, Möricke A, Janka G, Leblanc TM, Felice M, Biondi A, Campbell M, Hann I, Rubnitz JE, Stary J, Szczepanski T, Vora A, Ferster A, Hovi L, Silverman LB and Pieters R.** *Outcome of congenital acute lymphoblastic leukaemia treated on the Interfant-99 protocol.* Blood 2009; 114: 3764-3768.
- **Lönnerholm G, Valsecchi MG, De Lorenzo P, Schrappe M, Hovi L, Campbell M, Mann G, Janka-Schaub G, Li CK, Stary J, Hann I, Pieters R; Interfant-99 study group.** *Pharmacokinetics of high-dose methotrexate in infants treated for acute lymphoblastic leukemia.* Pediatr Blood Cancer. 2009 May; 52(5): 596-601.
- **Pieters R, Schrappe M, De Lorenzo P, Hann I, De Rossi G, Felice M, Hovi L, LeBlanc T, Szczepanski T, Ferster A, Janka G, Rubnitz J, Silverman L, Stary J, Campbell M, Li CK, Mann G, Suppiah R, Biondi A, Vora A, Valsecchi MG.** *A treatment protocol for infants younger than 1 year with acute lymphoblastic leukaemia (Interfant-99): an observational study and a multicentre randomised trial.* Lancet 2007; 370: 240-250.

Copenhagen 12th April 2016
Birgitte Lausen
Chair of the NOPHO Infant Leukemia working group

Pharmacology Working Group

Chair	Goda Vaitkeviciene
Denmark	Birgitte Klug Albertsen
	Kjeld Schmiegelow
	Henrik Schrøder
Finland	Jukka Kanerva
	Riitta Niinimäki
Iceland	Ólafur G. Jónsson
Norway	Ann Åsberg
	Tove Anita Nystad
Sweden	Arja Harila-Saari
	Cecilia Langenskiöld
	Johan Malmros
	Malin Lindqvist Appel (Pharmacogenetic)
	Ranaa El-Edelbi (Chair of Pharmacists wg)
	Staffan Eksborg
	Jesper Heldrup (MTX)
Lithuania	Goda Vaitkeviciene
Young NOPHO	Louise Tram (DK)
	Mette Frandsen Levinsen (DK)
	Nina Mogensen (SE)
	Samppa Ryhänen (FI)
	Stine Nygaard Nielsen (DK)
	Thommy Svahn (SE)

The NOPHO Pharmacology group has met twice within the last year (minutes at www.nopho.org) on September 8th, 2015 and February 9th, 2016 in Copenhagen.

Young NOPHO representatives from Norway, Iceland and Lithuania are lacking and are welcome.

Pharmacology WG continues working on the following issues

The Pharmacology wg continued with studies on maintenance therapy, asparaginase related issues, HD MTX, vincristine, SMNs, concentrating its attention to the issues important for the development of the next ALLTogether protocol.

Maintenance therapy (Kjeld Schmiegelow)

A prospective randomised clinical trial as a pilot before ALLTogether protocol testing MTX/6MP/6TG maintenance in IR-patients has been conducted. Interindividual variability in response to 6MP is strongly associated with genetically determined activity of the 6MP metabolizing enzyme TPMT. Addition of 6-thioguanine (6TG) to MT of patients with high TPMT activity (and even some with TPMT heterozygocity) will mimic the more

favorable thiopurine metabolite profile seen in patients with low TPMT activity, as 6TG is a poor substrate for TPMT and 6TG is more directly metabolized to TGNs.

The trial is planned to be run in Copenhagen, but more large centers willing to participate are welcome.

Maintenance therapy/SMN study (Stine Nygaard)

In the NOPHO ALL2008 protocol, 7 out of 10 SMNs had occurred during the MT phase. All cases had occurred in the SR patients. Compared to the previous protocols, more patients in ALL2008 are downgraded to the SR and are therefore determined to a longer MT exposure. Also, WBC target interval is lower.

The aim of the study is to describe pharmacokinetics and -dynamics of MT with an attempt to find the best metabolite model to describe delta-WBC (difference in off- and on-therapy WBC) as a surrogate parameter of treatment intensity. Time-dependent cox regression analysis on data with DNA-TG will investigate it as a predictor of relapse.

Asparaginase (Birgitte Klug Albertsen)

Asparaginase therapeutic dose monitoring (TDM)

Around 13% of patients in the ALL2008 protocol develop allergic reactions. No asparaginase activity was detected for these patients throughout treatment. The reasons might be anti-Asp or anti-PEG antibodies, or fast metabolism.

About 20% of patients in the ALL2008 protocol have insufficient Asp activity due to different reasons. Presence of IgG antibodies against PEG-asp was not a predictor of asparaginase activities. These patients would benefit from TDM. TDM is planned to be implemented in the next ALL treatment protocol. Pilot study is planned to be run in Aarhus.

GRASPA study

GRASPA, which is an E. coli-derived L-asparaginase encapsulated in ABO/Rh compatible red blood cells, could be as an alternative pharmacological agent for patients with allergic reaction to PEG-Asp. Clinical NORGRASP study to explore pharmacodynamics/-kinetics and side-effects of GRASPA in children and adults (1-45 years of age) with ALL receiving first-line chemotherapy according to the Nordic/Baltic NOPHO ALL2008 protocol was constructed. The study proposal was supported by Pharmacology WG on February 3, 2015 and by the NOPHO ALL WG on March 11, 2015. The study is awaiting for the final NOPHO SC, LLC and Board approval.

Carboxypeptidase G2 study (Jesper Heldrup, Torben Mikkelsen, Arja Harila-Saari)

Clinical study that was run in collaboration with the pharmaceutical company representing carboxypeptidase G2 (Voraxaze®) (Swedish Orphan), which reimbursed the used drug, was stopped. Manuscript is under preparation. Registration of delayed high dose MTX excretion in ALL2008 protocol is continued.

HD methotrexate studies (Torben Mikkelsen, Jesper Heldrup)

HD MTX clearance does not always correlate with the caused toxicity. Also, HD MTX toxicity may have an influence on subsequent 6MP dosing.

Detailed lab data are collected from a number of the NOPHO ALL2008 participating centers. The data are going to be used to evaluate MTX toxicity on different organs and systems – bone marrow, CNS, gastrointestinal tract, kidneys, incidence of infections; to compare toxicity in different phases of the protocol.

Treatment related pain in children with cancer (Luana Jensen)

According to published data, in children with advanced cancer pain is more intense and frequent in children's reports compared to nurses' reports. Vincristine related pain was prominent in all the units that reported their data.

A prospective study aiming to investigate experience and management of pain for children with ALL is under preparation. An app for iPhones and androids for children and their parents to register the symptoms is under construction. Better symptoms capturing in real-time and also accuracy of symptoms registration will be improved.

Future work of the group

The group will continue working on aforementioned projects and studies. The most important issues that will be supported by the group are those related to the development of the new ALL protocol. Pharmacology group will continue close collaboration with the NOPHO Pharmacy group.

Next meeting will be held on Tuesday, the 6th of September, 2016 at 10.00 – 17.00 in Copenhagen.

Goda Vaitkevičienė
Chair of the NOPHO Pharmacology WG
April 20, 2016

SCT Working Group

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	Mikael Sundin (SE)	mikael.sundin@ki.se

Ongoing studies

Most Nordic allogenic stem cell transplant centers participate in the FORUM study comparing conditioning with a TBI containing regiment with a chemotherapy only regiment.

Also the collaboration regarding microchimerism following allogenic bone marrow transplantation is continuing with more and more centers in the Nordic countries participating. Denmark has started the project. Norway and Finland will soon be joining and Sweden is still waiting for ethical approval.

The Nordic SCT group is now working on an agreement regarding a coming study looking at stem cell transplantation in first remission of ALL.

The main topic is the examination of survival and adverse effect as compared to the high risk ALL group, not transplanted.

A discussion is taking place regarding the participation in a European study comparing conditioning for AML with BuCyMel (or BuCy), compared with FluBu (or other lower intensity regimen).

SCT meeting

Only one meeting has been held in 2015, October 29; here Jaap Boelens was invited. The main topic was the use of umbilical cord blood as donor graft in children allo stem cell transplantation.

Coming SCT meetings

A meeting is planed for May 19, 2016.

Carsten Heilmann
Co-ordinator

ALL Relapse Working Group

Members 2015	
Coordinator	Johan Arvidson
Sweden	Stefan Söderhäll (PI SR Sweden)
	Mats Heyman (Registration)
	Petter Svenberg (PI HR Sweden)
Denmark	Thomas Frandsen (PI SR/HR Denmark)
	Peder Skov Wehner
Finland	Päivi Lähteenmäki (PI SR/HR Finland)
	Kim Vettenranta (SCT)
Iceland	Olafur G. Jónsson
Norway	Marit Hellebostad (PI SR Norway)
	Jochen Büchner (SCT, PI HR Norway)
	Dorota Malgorzata-Wojcik
	Finn Wesenberg
Lithuania	Goda Vaitkeviciene (PI Lithuania)
Young NOPHO	Trausti Óskarsson
On the mailing list	Jonas Abrahamsson
	Henrik Hasle
	Mervi Taskinen

NOPHO relapse group had had four telephone meetings during the last year:

150504	Telephone meeting
150914	Telephone meeting
151221	Telephone meeting
160314	Telephone meeting

Minutes are posted on the working group site at NOPHO.org.

Events during the year

IntReALL SR

The protocol for SR patients is recruiting patients in Norway, Denmark and Finland but not in Sweden. No protocol specific difficulties so far. Randomisation procedures are working. The study drug is available.

IntReALL HR

The protocol for HR patients has been finalized, and the Nordic HR PIs have started to contact national medical agencies and ethical committees. New sponsor delegations and new site contracts have to be written.

PIs for Denmark and Finland will be the same as for SR study. For Norway, Jochen Buchner, Oslo will be the PI and for Sweden Petter Svenberg, Stockholm.

MARVIN

MARVIN, the online reporting system, is running, although not to everyones satisfaction.

FORUM study

All Nordic countries have joined the study and included patients in the randomisation between chemo only and chemo TBI conditioning regimen. Jochen will report details in Reykjavik.

Experimental therapies

Copenhagen has ongoing studies at their ITCC phase 1 and phase 2 trial unit, see NOPHO site, "Protocols page – Novel therapy".

Stockholm is planning to open a ITCC trial unit in the future.

Oslo just stopped including patients in a CAR-T treatment study.

Meetings

Most PIs attended BFM resistant disease/IntReALL meeting in Bruxelles 5-7 February.

The 27th annual I-BFM meeting will be held in Athens 23-24 April, and NOPHO relapse group will be represented with several delegates.

Next NOPHO meeting

The NOPHO relapse group will join in Reykjavik, Friday May 27, at 9 o´clock.

For the working group
Johan Arvidson
Uppsala, Sweden

Events Working Group (EVG)

Members

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Since last annual report the NOPHO Events group has met 2 times. The main focus of our work has been the adverse effect monitoring of NOPHO-ALL 2008 protocol; especially toxic phenotypes (both as single projects, as part of the NOPHO SNP study and as part of The iBFM/PdL toxicity consensus work), relapses, toxicity related deaths and fungal infections. The group participates in the work towards the next ALL protocol - ALLTogether.

The main issues discussed during the last year

SAEs in NOPHO-ALL 2008

Focus groups have scrutinized data on the issues mentioned below and have already reported data in publications and presentations

and more publications are on their way:

Pancreatitis, vincristine related toxicity, thrombosis, osteonecrosis, VOD and fungal infections

PdL/IBFM Toxicity Consensus Definition working group

Consensus definitions has been reached for 14 toxicities. The consensus definitions are now published in Lancet Oncology (in press at the moment (april 2016) and should be out by the time the Annual meeting is ongoing) (Table 1).

At the IBFM meeting in Athens the PdL toxicity working group will be discussing strategies for capturing these SAE definitions as well as the group will be discussing the first "business case" of an SAE toxicity defined by these new criterias. Pancreatitis phenotypes on more than 600 pancreatitis cases collected by MD, PhD student Benjamin Ole Wolthers will be presented and discussed at the meeting. DNA is available for SNP/GWAS profiling on more than 300 of these patients. The group will also be planning the work for the next 2 SAE's to be scrutinized by the PdL toxicity working group. These SAE's will be Osteonecrosis and PRES (+ central neurotoxicity). Questionnaires on these toxicities will be prepared and distributed to the participating leukemia groups within the next 6-12 months.

- Kjeld Schmiegelow is coordinating this international Ponte di Legno toxicity working group
- NOPHO members working with selected toxicities are participating in this work

Table 1. PdL Definitions and gradings of acute toxicities associated with treatment of childhood acute lymphoblastic leukaemia*

Toxicity	Consensus definition
Hypersensitivity to asparaginase	An adverse local or general response from exposure to Asparaginase characterised by flushing, rash, urticaria, drug fever, dyspnoea, symptomatic bronchospasm, oedema/angiooedema, hypotension and/or anaphylaxis. Grading: 1.Mild: transient flushing or rash or drug fever <38° C, 2.Severe: drug fever >38° C; allergy-related edema/angiooedema; dyspnoea and/or symptomatic bronchospasm with or without urticarial; and/or hypotension and anaphylaxis) with indication for Asp infusion interruption and parenteral medication (e.g. antihistamines, glucocorticosteroids).
Silent inactivation of asparaginase	No clinical allergy, but trough Asparaginase activity levels below lower level of quantification (preferably measured in two independent samples). In case of biweekly PEG-Asparaginase, a day 7 Asparaginase activity level <100 IU/L and/or a day 14 level <LLQ. In case of Erwinia Asparaginase (2-3 times a week) a 48 hours post-dose level <LLQ
Allergic-like reaction to asparaginase	Intolerance (e.g. vomiting, stomach ache, or rash) usually occurring later in the infusion than real Asparaginase allergy that in general occurs at the first drops. Note: Distinction between hypersensitivity and allergic-like reactions is critical, since clinical hypersensitivity (even mild) is closely associated with Asparaginase inactivation. Asparaginase activity measurements may distinguish and guide decision on switch to other Asparaginase preparations.
Hyperlipidemia	Grading: 1.Mild: triglycerides/cholesterol <10 times UNL, 2.Moderate: triglycerides/cholesterol 10-20 times UNL, 3.Severe: triglycerides/cholesterol >20 times UNL. Note: Routine measurements only as part of research protocols. Dose modification based only on laboratory findings is not recommended.
Osteonecrosis	Osteonecrosis results from the temporary or permanent loss of the blood supply to the bones, which can cause pain, limitation in ADL, and may result in collapse of a articulating surface with enhanced pain and development of arthritis. It should be confirmed by magnetic resonance imaging. Grading: 1.asymptomatic with findings only by MRI, 2.symptomatic, not limiting or only slightly limiting self-care ADL. Lesions only outside joint lines in non-weight-bearing bones, 3.symptomatic, not limiting or only slightly limiting self-care ADL. Lesions in weight-bearing bones or affecting joint lines in non-weight-bearing bones, 4.symptomatic with deformation by imaging of one or more joints and/or significantly limiting self-care ADL.
Asparaginase-associated pancreatitis	At least two of three features must be fulfilled: i) abdominal pain strongly suggestive of pancreatitis, ii) serum lipase or amylase ≥3 times UNL, iii) characteristic imaging findings of AAP (US/CT/MRI). Re-exposure should only be considered in mild cases. Grading: 1.mild: symptoms and enzyme elevations above UNL that last <72 hours, 2.severe: symptoms and enzyme elevations above UNL that last ≥72 hours or haemorrhagic pancreatitis or pancreatic abcess or cyst, 3.death from pancreatitis.
Arterial hypertension	SBP and/or DBP ≥95th percentile for sex, age, and height on ≥3 occasions (3 consecutive days, or separate clinic visits if outpatient). Grading: 1. SBP/DBP in the 90th-95th percentile for age and/or BP exceeding 120/80 mmHg, 2.recurrent or persistent SBP/DBP above 95th UNL for age at three separate measurements or lasting more than 72 hours with monotherapy indicated, 3.recurrent or persistent SBP/DBP above 95th UNL for age at three separate measurements or lasting more than 72 hours and needing more than one drug or more intensive therapy than grade 2 for BP control, 4.life-threatening consequences, e.g. hypertensive crisis with transient or permanent neurologic deficit with urgent intervention needed, 5.death from hypertension.
Posteror reversible encephalopathy syndrome	PRES is a clinical diagnosis based on any combination of transient headache, confusion, seizures and visual disturbances in combination with characteristic, but transient, contrast-enhanced and DWI MRI findings (see supplementum S3). Diagnosis can be supported by EEG findings, occurrence during early months of therapy, and presence of arterial hypertension. No grading.
Seizure	A disorder characterised by sudden, involuntary skeletal muscle contractions of cerebral/brainstem origin. Grading: 1.brief partial seizure, 2.brief generalised seizure, 3.multiple seizures despite medical intervention, 4.life-threatening, prolonged or repetitive seizures, 5.death from seizures.
Depressed level of consciousness	Abnormal changes in 1) level of arousal or 2) altered content of a patient's thought processes. 1) Quantified by Glasgow Coma Scale or the patient being alert (appear wakeful and aware of self and environment), lethargic (mild reduction in alertness), obtundated (moderate reduction in alertness with increased response time to stimuli), stuporous (deep sleep; arousal only by vigorous/repetitive stimulation and return to deep sleep when discontinued), or comatose (unconscious, sleep-like appearance and behaviorally unresponsive to all external stimuli). 2) Can involve simple capabilities (speech, calculations, spelling) and more complex modalities (emotions, behavior or personality) with confusion, disorientation, hallucinations, poor comprehension, or verbal expressive difficulty.
Methotrexate-related, stroke-like syndrome	Neurotoxicity occurring within 21 days of intravenous or intrathecal MTX with three characteristics: 1.new onset of one or more of paresis/paralysis; movement disorder or bilateral weakness; aphasia/dysarthria; altered mental status including consciousness (e.g. somnolence, confusion, disorientation, emotional lability); and/or seizures with at least one of the other symptoms, 2.either characteristic, but often transient, white matter changes indicating leukoencephalopathy on MRI or a characteristic clinical course with waxing and waning symptoms usually leading to complete (sometimes partial) resolution within a week, 3.no other identifiable cause. Note: Characteristic oval-shaped lesions of the subcortical white matter (mostly frontal or parietal) on MRI are best seen on diffusion-weighted (hyperintense) or apparent diffusion coefficient (hypointense) images. Can be graded 1-5 according to CTCAEv4.03 for "Encephalopathy".
Peripheral neuropathy	Peripheral motor/sensory neuropathy, including pain and constipation, due to inflammation or degeneration of the peripheral motor/sensory nerves. Grading: 1.loss of deep tendon reflexes, slight paresthesia, numbness or pain that do not limit instrumental ADL or require treatment, 2.moderate symptoms somewhat limiting instrumental ADL, e.g. alters fine motor skills (ex. buttoning shirt) and/or paresthesia, numbness or pain that are controllable by non-narcotic medications, 3.severe symptoms limiting self-care ADL, including gait impairment, inability to perform fine motor tasks; and/or paresthesia, numbness or pain that require narcotics, 4.complete paralysis or life-threatening consequences (e.g. vocal cord paralysis) with urgent need for intervention or severe pain that is not controlled by narcotics, 5.death from peripheral neuropathy (e.g. vocal cord paralysis).
Severely delayed MTX clearance	Increase in plasma creatinine by >0·3 mg/dl and/or a relative increase of 1·5 above a baseline value (measured within four days prior to hydration preceding high-dose MTX) together with plasma MTX concentrations at one or more time-points after initiation of the MTX infusion: 36 hours MTX >20 µM and/or 42 hours MTX >10 µM and/or 48 hours MTX >5 µM.
Sinusoidal obstruction syndrome	Fulfilment of at least three out of five criteria: i) hepatomegaly, ii) hyperbilirubinaemia >UNL), iii) ascites, iv) weight gain of at least 5%, and v) thrombocytopenia (transfusion-resistant and/or otherwise unexplained by treatment, e.g. myelosuppression). Doppler ultrasound may document changes in hepatic portal venous flow and rule out alternative causes, but normal findings do not exclude sinusoidal obstruction syndrome. Grading: 1.mild: bilirubin <103 µM and weight gain <5%; 2.moderate: bilirubin 103-342 µM and/or weight gain ≥5% or ascites; 3.severe: bilirubin ≥342 µM and/or respiratory or renal failure or hepatic encephalopathy; 4.death due to SOS.
Thrombo-embolism	Venous and/or arterial TE. Confirmation by imaging or by autopsy is required for grade 2 and higher. Grading: 1. superficial thrombophlebitis or CVL-associated deep venous thrombosis with neither symptoms (e.g. pain, shortness of breath) nor objective signs (e.g. swelling, discoloration, collaterals); or causing only CVL dysfunction. Systemic anticoagulation not given, 2A. asymptomatic TE (including asymptomatic cerebral thrombosis). Systemic anticoagulation is usually given (not evidence-based), 2B. symptomatic DVT, systemic anticoagulation indicated, 3. symptomatic pulmonary embolism or cardiac mural thrombus without cardiovascular compromise or symptomatic cerebral sinovenous thrombosis or arterial ischaemic stroke; all grade 3 require systemic anticoagulation/antiaggregation, 4.life-threatening TE, including arterial insufficiency, haemodynamic or neurologic instability. Urgent intervention needed, 5.death due to TE.
Pneumocystis jirovecii pneumonia	1.Confirmed PJP: presence of PJ organisms^{a} from a patient with fever, abnormal chest X-ray compatible with PJP infection, and/or hypoxaemia, 2.Probable PJP: pneumonia of undetermined origin (fever, PJP compatible chest X-ray, and/or hypoxaemia) and responding to empiric treatment with co-trimoxazole. ^{a}through cytological examination (Gomori-Grocott or Gram-Weigert staining), PJ specific PCR, or PJ immunofluorescence in a lung sample (broncho-alveolar lavage, bronchial aspiration, transbronchial biopsy, transthoracic needle aspiration, lung biopsy, or sputum)

TRM

Jukka Kanerva, Henrik Hasle and Kjeld Schmiegelow has participated in a working group within the IBFM network, developing a classification system for the systematic assessment of treatment related mortality. The manuscript has been published in Lancet Oncology (see reference list below). In addition Jukka Kanerva and Bendik Lund are collecting questionnaires for a NOPHO manuscript on TRM in the NOPHO ALL 2008 protocol. The classification system was deloped across malignancies of childhood – including hematologic malignancies as well as malignant solid tumors.

Upcoming ALLTogether protocol

Mats Heyman coordinates the NOPHO participation in the upcoming joint ALLTogether protocol. During the last year this work has matured and is now a joint changed focus from the idea of a NOPHO protocol, to exploring the possibilities of a common ALL protocol across 4 different groups: DCOG, UKALL, COALL and NOPHO. This process is ongoing.

SNP/GWAS studies

A large number of SNP/GWAS studies are ongoing at the moment

- Infection Related deaths (Bendik Lund)
- Pancreatitis (Benjamin Ole Wolters – manuscript has been submitted)
- ON (Signe Mogensen – manuscript in preparation)
- VOD (Thomas Frandsen – manuscript in preparation)
- CNS-leukemia (Mette Levinsen)
- Hyperleukocytosis (Goda Vaitkeviciene)
- Thrombosis (Morten Tulstrup and Ruta Tuckuviene)

Future work of the group

The function as a reference group for problem ALL patients will continue.

Monitoring and analyzing life threatening adverse events and AE's not directly associated with chemotherapy (e.g. infections) are tasks for the Events Working Group.

Annual evaluation of SAE:s will be performed to find out which SAE:s should be studied in detail.

Toxicities and relapses continue to be the major focus issues.

Next meeting Sept 5th , 2016 Copenhagen.

Copenhagen 13.4.2016 Thomas Frandsen

Events group related Publications 2015-2016

Alexander S, Pole JD, Gibson P, Lee M, Hesser T, Chi SN, Dvorak CC, Fisher B, Hasle H, Kanerva J, Möricke A, Phillips B, Raetz E,Rodriguez-Galindo C, Samarasinghe S, Schmiegelow K, Tissing W, Lehrnbecher T, Sung L; International Pediatric Oncology Mortality Classification Group. *Classification of treatment-related mortality in children with cancer: a systematic assessment.* Lancet Oncol. 2015 Dec;16(16):e604-10. doi: 10.1016/S1470-2045(15)00197-7.

Schmiegelow K, Attarbaschi A, Barzilai S, Escherich G, Frandsen TL, Halsey C, Hough R, Jeha S, Kato M, Liang D-C, Mikkelsen TS, Möricke A, Niinimäki R, Piette C, Putti MC, Raetz E, Silverman LB, Skinner R, Tuckuviene R, van der Sluis I, Zapotocka E - on behalf of the Ponte di Legno toxicity working group. *Consensus definitions of fourteen severe acute toxicities during childhood lymphoblastic leukaemia therapy.* Lancet Oncol 2016 (In press).

NOPHO Leukemia Biobank Committee

Coordinator	Trond Flægstad
Denmark	Henrik Hasle, Karsten Nysom (SC chair), Mette Levinsen (Young NOPHO)
Finland	Kim Vettenranta
Iceland	Halldora K Thorarinsdottir
Norway	Trond Flaegstad
Sweden	Britt-Marie Frost (locally responsible) Josefine Palle (locally responsible), Mats Heyman

The main task of the board has been concerned with the framework of rules and regulations surrounding the NOPHO leukemia biobank. A form for withdrawal of biobank material has been developed and can be found on the NOPHO-web. The board has had two meetings.

We have now a very good financing for the next four years. We got a great amount of money from Barncancerfonden. These money makes it possible to improve the biobank. At the moment we are modernizing the data systems. We are also preparing for DNA preparation of all samples.

Additional items discussed have to do with the legal framework of sending samples to the bank and IT-links with the NOPHO leukaemia registries. It has been decided that the NOPHO leukaemia registries should contain basic information about the fact that the patient is represented in the biobank and which date the sample was taken. The work to identify and match patients in the registries and biobank has started. The development of the infrastructure within the registries is also prioritized.

LL Biology Working Group

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The LLC meeting in November 2012 took the decision to form the Biology group, because of the increasing complexity/diversity of methods in leukemia(ALL and AML) and lymphoma research in combination with "demands" from the ALL-WG of new prognostic genetic factors for stratification in the next protocol. The first ALL Biology group meeting was held in Stockholm in March 2013 and the group has had 6-monthly meetings since then, seven in total.

The task for the group was intially to be a platform where ALL biology researchers and clinicians could meet and discuss research projects for translational effect, which in the end will benefit the patients. The primary goal for the group is to promote research collaborations between groups in the Nordic countries and especially to promote high quality research projects for the NOPHO biobank. The meetings have been successful in bringing researchers together in several cooperative research projects. This is one of the reasons why the group has expanded gradually and since 2015 both AML- and NHL-researchers and clinicians have been incorporated into the meetings and the group has been re-named Leukaemia & Lymphoma Biology Group.

The constitution of the ALL Biology group

MH and UNN have coordinated the group until the beginning of 2016. At the end of 2015, MH was appointed NOPHO-representative to the new ALL-protocol group and for that reason there was a nomination-procedure in which Linda Fogelstrand and Olli Lohi were selected to succeed as new coordinators.

Further meetings will continue to be held back-to-back with the ALL-WG. All Nordic research groups represented and ALL/AML and NHL- clinicians attending the meetings are members of the group because of their interest in the field and not because of their nationality. The LL Biology group will report to the LLC, but many of the items will also be discussed in the ALL-group. The financing of the group has so far been sponsoring, either by funds from the Swedish Barncancerfonden, or corporate sponsoring (for the meetings). Travel expenses are covered by the institutions of the participants.

The tasks assigned to the ALL Biology group

- To assist the NOPHO Scientific committee (if/when they want assistance) in evaluating and maybe ranking research proposals for the NOPHO Biobank
- To follow the development in methodology and learn from each other
- To promote research projects for the NOPHO biobank material and promote collaboration between research groups.

Resources and further suggestions for communication/collaboration

The NOPHO registry and NOPHO biobank will be the major sources for the collaborative research projects (if supported by the SC).
A web-forum for discussions, postings and suggestions for collaborative projects has been in place since March 2014 and is managed by Vasilios Zachariadis, Stockholm.

Progress since the last report

Two meetings have been held 2nd of September 2015 at Kastrup, Copenhagen and the other was held in Uppsala on the 16th of March 2016. There is an increasing turnout at the meetings, which are turning into small symposia in their own right. At the last meeting in Uppsala in excess of 60 persons participated.

New and ongoing projects (details to be found in the minutes of the meetings):

- Some time has been spent going through the mission of the group again (because of all the newcomers) as well as NOPHO structure and the way to get a NOPHO-application through the system.
- The new collaboration within the ALLTogether consortium was discussed and how this will affect the diagnostics, research-activities and collaborations within and outside of NOPHO.
- Presentations of NHL- and AML-based projects and the expansion of the group into these areas have been presented.
- There is always a point disussing the optimisation of a standardized procedures for the preservation of material in the NOPHO biobank – with the aim to create a consensus protocol.

Springtime, 2016,
Mats Heyman and Ulrika Norén Nyström

Platelet Working Group

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Associated members		
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The Working Group met in Oslo, April 6th 2016. We discussed the following clinical issues and future projects:

- We will write a draft for NOPHO recommendations for diagnosis, care, and medical treatment in acute and chronic ITP in the NOPHO countries.
- We discussed the use of TPO mimetics in ITP children. If a child with ITP has significant and severe bleeding symptoms, treatment with TPO mimetics may be relevant. At this stage, we find it relevant at least to discuss the use of TPO mimetics with a pediatrician, with significant experience in treating ITP children.
- We will try to count the number of chronic ITP patients we follow-up in the NOPHO countries.
-

Next meeting January 25th 2017 in Copenhagen.

Aplastic Anemia Working Group

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Sweden	Dominik Turkiewicz	dominik.turkiewicz@skane.se
Young NOPHO observer	Tania Masmas	tania.nicole.masmas@rh.regionh.dk

The group made unanimous recommendations in 2012.

We agreed to collect and complete Nordic data, and we preferred to transfer data to the NOPHO database. We recommended to join the European SAA study, see below.

Background

The EWOG-group has formed an EWOG-SAA group to perform studies based on cooperation between the SAA-groups in Germany, Austria, Switzerland, Netherlands, Belgium, Czech republic, Italy and the Nordic countries. The idea is to take advantage of the existing EWOG-MDS network of researchers in the clinic and research labs. A thorough diagnostic work-up in SAA comprising T-cell receptor rearrangements, surface markers and micro-array analyses is offered. Surveillance for clonal development is included. The treatment follows the lines set up in NOPHO 2000, but the intention is to develop treatment trials later on. A protocol was finalized in 2011.

Nordic action

The NOPHO SAA working group agreed in 2012 to join the EWOG-SAA study.

The Ethics Committees in Denmark have approved the protocol. The Danish patients are registered in the study.

The application forms necessary for joining the study and the application letters used in Denmark for the Ethics committees and The Data protection Agency have been distributed to the other Nordic countries. None of the other Nordic countries has applied for approval.

Future

The intention was to develop a common Nordic registry for patients with SAA and transfusion dependent anemias. This work has been lacking progress.

Furthermore, only one Nordic country has joined the EWOG-SAA.

Under these conditions we recommend to the NOPHO board to close the SAA working group.

Histiocytosis Working Group

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Langerhans Cell Histiocytosis (LCH)
LCH-IV has now been opened in Denmark. Sweden and Norway are preparing their applications. For update on the situation in your country, contact your national coordinator above.

LCH-III is closed for new randomizations. Until LCH-IV is opened, the recommended treatment is LCH-III:

1)Group 1: RISK patients are treated according to the risk protocol, Arm A in LCH-III (the standard arm without methotrexate).
2)Group 2: LOW RISK patients receive treatment arm LR12 in LCH-III, with 12 months treatment duration.
3)Group 3: Multifocal bone / special site patients are treated as scheduled in LCH-III.

LCH-IV
Note that for LCH, each country will have a separate coordinator. LCH-IV includes altogether seven interconnected studies ("strata"):
STRATUM I: First-Line Treatment
STRATUM II: Second Line Treatment for non-risk LCH
STRATUM III: Salvage Treatment For Risk LCH
STRATUM IV: Stem Cell Transplantation For Risk LCH (HSCT)
STRATUM V: Monitoring and Treatment of Isolated Tumorous and Neurodegenerative CNS-LCH
STRATUM VI: Natural History and Management of "Other" SS-LCH
STRATUM VII: Long-Term Follow-up

Summary of LCH-III, LCH-Salvage-2005, and LCH-HSCT-2006
LCH-III:
The study is closed. For a summary of conclusions, see below. The study was published in 2013: Gadner H, et al. Blood 2013;121:5006-14.

Risk patients: Involvement of the hematopoietic system, the liver, the lungs or the spleen:
- The treatment is prolonged to 12 months.
- A second initial treatment (wk 7 – 12) is administered if intermediate response at 6 weeks.
- A randomized study upfront, with one arm in the risk protocol including methotrexate, whereas the other arm is without methotrexate. After study closure, the arm without mtx is recommended.

Low risk patients:

- PDN and VBL, the treatment duration is randomized between 6 and 12 months. After study closure, the recommended treatment is 12 months.

Multifocal Bone Disease:

- PRD and VBL for 6 months.

Special sites: Single bone lesions with involvement of the facial bones or anterior or middle cranial fossa (temporal, sphenoidal, ethmoidal, zygomatic bone, orbital bones) with intracranial tumor extension, OR soft tissue masses that may lead to spinal cord compression

- PRD and VBL for 6 months.

LCH-Salvage-2005: This is a highly toxic regimen based on 2CdA and ARA-C. Because of the severe toxicity, all patients for whom salvage therapy is considered are suggested to be discussed with the Nordic LCH-study coordinator (Jan-Inge Henter). The treatment is part of LCH-IV.

LCH-HSCT-2006: This regimen is based on a reduced intensity regimen (RIC), with Campath, Fludarabine and Melphalan. The study is part of LCH-IV.

Hemophagocytic Lymphohistiocytosis (HLH)

HLH-94: The Histiocyte Society protocol HLH-94 was based on the combination of chemotherapy and immunotherapy (VP-16, steroids and cyclosporin A), followed by HSCT. This protocol was succeeded by the HLH-2004 protocol. The final HLH-94 study summary was published in 2011 (Trottestam H, et al, Blood 2011;118:4577-84).

HLH-2004: This study was opened in January 2004, with only minor differences in comparison to the HLH-94 protocol (Henter JI, et al, Pediatr Blood Cancer 2007;48(2):124-31). The formal study was closed in Dec 31, 2011.

NOTE: The Histiocyte Society recommends the HLH-94 protocol as standard of care, since it cannot be shown that HLH-2004 is superior to HLH-94. The HLH-2004 diagnostic criteria (5/8 criteria) are still recommended. HLH-2004 will be open to f-up on enrolled patients until 5 years after start of therapy or 5 years after SCT, but no later than Dec 31, 2017.

You are welcome to contact the Study Center (e-mail: jan-inge.henter@ki.se or Tatiana.Greenwood@ki.se) in case of questions. For pre-treatment sampling of diagnostic value, contact Yenan.Bryceson@ki.se.

Novel Therapy Working Group

Members 2015-2016

Denmark: Karsten Nysom (chair), Kjeld Schmiegelow

Finland: Sanna-Maria Kivivuori, Olli Lohi, Matti Korhonen, Susanna Ranta (Young NOPHO)

Iceland: pending

Norway: Trond Flægstad

Sweden: Stefan Holm, Per Kogner, Jacek Toporski, Mats Heyman

The working group had a physical meeting during the annual meeting in Oulu. Minutes are on the NOPHO web site. This year, a meeting is planned Saturday May 28th, 07:30-08:55.

An up-to-date overview of all early phase trials and all phase 3 trials with targeted agents, open for children with cancer in any Nordic or Baltic country, is maintained by the working group and available at www.nopho.org under "Protocols".

More and more early phase trials as well as phase 3 trials with targeted agents are becoming available in the Nordic and Baltic countries and an increasing number of patients are referred between the Nordic and Baltic centres for therapy on such trials, in line with the ambition of the working group members.

Copenhagen, April 13th, 2016
Karsten Nysom

NOPHO novel therapy working group – Overview of ongoing trials – Updated 23 March 2016 **Page 1 of 3**

Phase 1-2 trials

Trial (link)	Targeted agent	Other agents	Diagnoses	Age	Open in	Phase	Contact
BEACON	Bevacizumab	Temozolomide, irinotecan, topotecan	Relapsed HR neuroblastoma	1-21.9y	Copenhagen	2	Karsten Nysom
DACOGENAML2004	Decitabine	Cytarabine	Relapsed AML	0.1-17.9y	Copenhagen	2	Karsten Nysom
DC1	Dendritic cell therapy	-	Relapsed high grade glioma	3-39.9y	Stockholm	2	Stefan Holm
ITCC-015	Azacitidine	-	Relapsed MDS or JMML	1-17.9y	Aarhus	1	Henrik Hasle
CREATE EORTC-90101	Crizotinib	-	Locally advanced and/or metastatic ALCL, inflammatory myofibroblastic tumour, papillary renal cell carcinoma type 1, alveolar soft part sarcoma, clear cell sarcoma, or alveolar rhabdomyosarcoma	>15.0y	Oslo	2	Kirsten Sundby-Hall
BI 1200.120	Afatinib	-	High grade glioma, diffuse intrinsic pontine glioma, low grade astrocytoma, medulloblastoma/PNET, ependymoma, neuroblastoma, rhabdomyosarcoma, or other tumour with known ErbB pathway deregulation	2-17.9y	Copenhagen	(Pause before phase 2)	Karsten Nysom
AZA-AML-004	Azacitidine	-	First molecular relapse of AML with known t(8;21), inv(16), t(9;11), NPM1-mutation, or FLT3-ITD-mutation	0.25-17.9y	Copenhagen	2	Karsten Nysom
AZA-JMML-001	Azacitidine	-	Newly diagnosed JMML or advanced MDS (RAEB, RAEB-t)	0.1-17.9y	Copenhagen, Gothenburg, Stockholm	2	Karsten Nysom, Jonas Abrahamsson, Karin Belander-Strålin

Late Effects Working Group

Members 2015

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Meetings

The group had a meeting during the NOPHO Annual meeting, Oulu 23 May 2015.

Specific activities

1) The new ALLtogether. Role of late effects group in planning work. ALLtogether group is chaired by Mats Heyman. NOPHOs vision for ALLtogether has been discussed and work with other participating groups is ongoing. The late effects group will have a role in ALLtogether protocol. Late effects group aims to revise the recommendations for minimum late effect follow up for the new protocol. Late effect group can further work with ALLtogether group to identify the late effect measures that could be registered to database. Inga Maria Johannsdottir has been chosen to be the late effects group presentative in the protocol work.

Osteonecrosis might be a severe complication of ALL treatment. ON has been captured in the toxicity registration in NOPHO ALL 2008 protocol. However, guidelines for follow-up and treatment adaptations due to toxicity have been missing. Riitta Niinimäki has been chosen to presentative in the protocol work.

2) Registration of parameters from end of therapy document into the Nordic databases. NOPHO register includes a possibility for an online follow-up registration. Increasing number of Swedish and other Nordic survivor data has been registered into the database. Individualized survivor passport can be printed from database.

3) NORDFERTIL. The website of NORDFERTIL (www.nordfertil.org) is online since last autumn. This project has always been closely connected to the late effect group, so the link has been put onto the website under the working group.

4) Pancare activities. Pancare activitiesPancare had 15th meeting in Dublin, May 27–29 and 16th meeting in Vienna September 23-25, 2015.

5)Collaboration with NOBOS. NOBOS has been interested in participating in the late effect working group. Nurses from all five Nordic countries will join the meeting for the first time in Reykjavik.

Oulu, April 12, 2016
Riitta Niinimäki
Chair of the NOPHO Late effect working group

Thrombosis and Haemostasis Working Group

Chair:	Ruta Tuckuviene (DK)
Denmark:	Birgitte Klug Albertsen
Estonia:	Kadri Saks
Finland:	Pasi Huttunen, Kaisa Vepsäläinen
Iceland:	Olafur Gislí Jonsson
Norway:	Ellen Ruud, Jon Helgestad
Lithuania:	Sonata Trakymiene
Sweden:	Susanna Ranta, Ulf Tedgård, Tony Frisk
Young NOPHO:	Nadine Gretenkort Andersson (SE), Kirsten Jarvis (NO)

Meetings

The Working Group met in Oslo January 8th 2016. A telephone meeting is planned in September 2016 and the next on-site meeting in January 2017.

Change of members

Jon Helgestad became a representative for Norway, Pasi Huttunen and Kaisa Vepsäläinen replaced Anne Mäkipernaa (FI), Kadri Saks replaced Kaie Pruunsild (ES), Maria Winther Gunnes (NO) has left the group. Kirsten Jarvis (NO) became a Young NOPHO member.

Status on ongoing registration of thromboses

During July 2008 – November 2015 there are 89 reported cases of TE (thromboembolism) among children (1-18 ye) and 39 adults (18-45 ye) in NOPHO Toxicity Register. Detailed clinical data on TE is collected from 85 children and from 34 adults. The collection of data (including adults) continues as we aim to obtain information from all TE in NOPHO-ALL 2008 protocol. Nina Toft (DK) is the coordinator for data collection from adults (18-45 ye).

Main results from registration of TE in children (1-18 ye)

a. The cumulative incidence of TE was 6.1% (95% CI, 4.8–7.7), with the highest incidence (i.e. 20.5%; 95% CI, 12.6–29.7) among adolescents (15–17 years old) (Fig. 1).
b. TE occurred most frequently during the last 2 weeks of the induction and in the early consolidation phase (Fig. 2).
c. Age ≥ 15 years and residual disease ≥ 5% after induction therapy was significantly associated with TE.
d. The most common consequence of TE was truncation of ASP therapy (21/58; 36.2%).
e. No children in our cohort died due to complications of LMWH treatment. The TE-associated 30-day case fatality of 6.4%.

GWAS analyses among TE patients are ongoing. The collaboration with Australian ALL group is initiated regarding meta-analysis.

Work in Ponte di Legno (PdL)/I-BFM Toxicity Group regarding TE

PdL thrombosis group has worked on a consensus definition and a grading of TE. The

issue for the upcoming meeting is to agree on requirements for data registration for future comparison of incidences across different ALL protocols.

Updated recommendations on treatment of TE in ALL patients are placed on NOPHO website, Protocols, ALL section. Thrombosis news from ASH meeting 2015: The consensus to pause therapeutic doses of LMWH if platelets<20, and to reduce 50% LMWH if platelets <50.

Upcoming studies

Kirsten Jarvis (NO) starts PhD study in autumn 2016 (main supervisor Ellen Ruud). The aims of the study are to examine i) predefined single nucleotide polymorphisms (SNPSs) associated with increased risk of TE in ALL patients with and without thromboses, ii) long-term outcomes in patients with ALL and TE.

Future plans

Research on preventive strategies of TE in setting of the upcoming ALL protocol. Thromboprophylaxis study in patients treated according NOPHO protocol is not possible due to missing statistic power. The further research in TE among adult ALL patients is planned as a part of the possible PhD study, supervised by Nina Toft (DK).

New publications

Tuckuviene R, Ranta S, Albertsen BK, Andersson NG, Bendtsen MD, Frisk T, Gunnes MW, Helgestad J, Heyman MM, Jonsson OG, Mäkipernaa A, Pruunsild K, Tedgård U, Trakymiene SS, Ruud E. *Prospective study of thromboembolism in 1038 children with acute lymphoblastic leukemia: a Nordic Society of Pediatric Hematology and Oncology (NOPHO) study.* J Thromb Haemost. 2016 Mar;14(3):485-94.

Aalborg, March 2016
Ruta Tuckuviene
Chair of the NOPHO Thrombosis and Haemostasis Working Group

Figure 1. Cumulative incidence of TE in patients with ALL aged 1 to 17 years

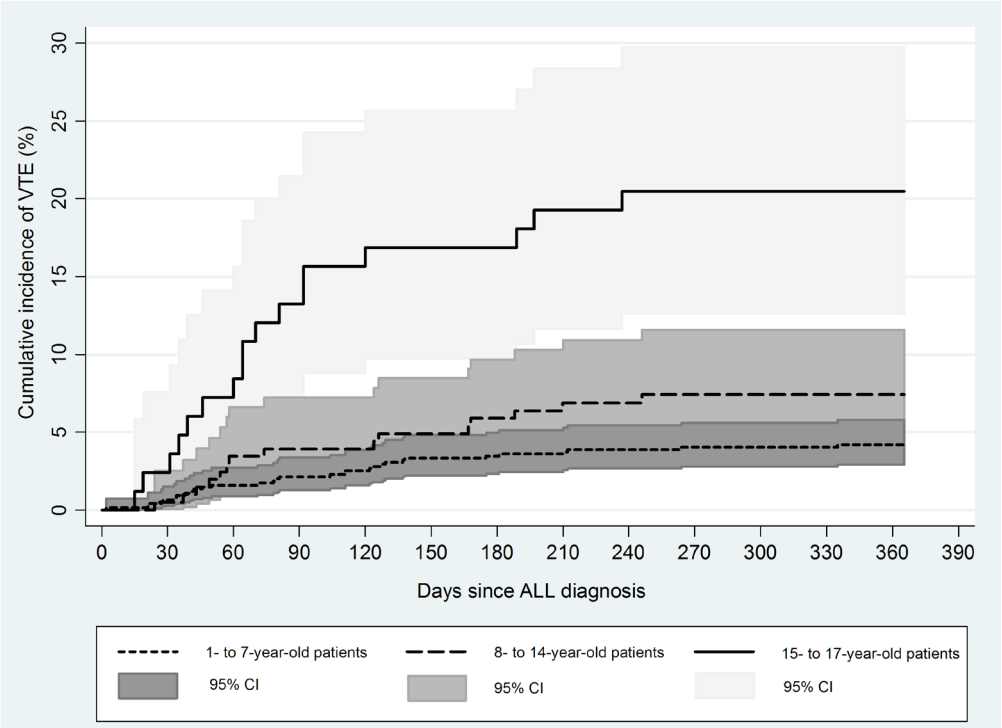
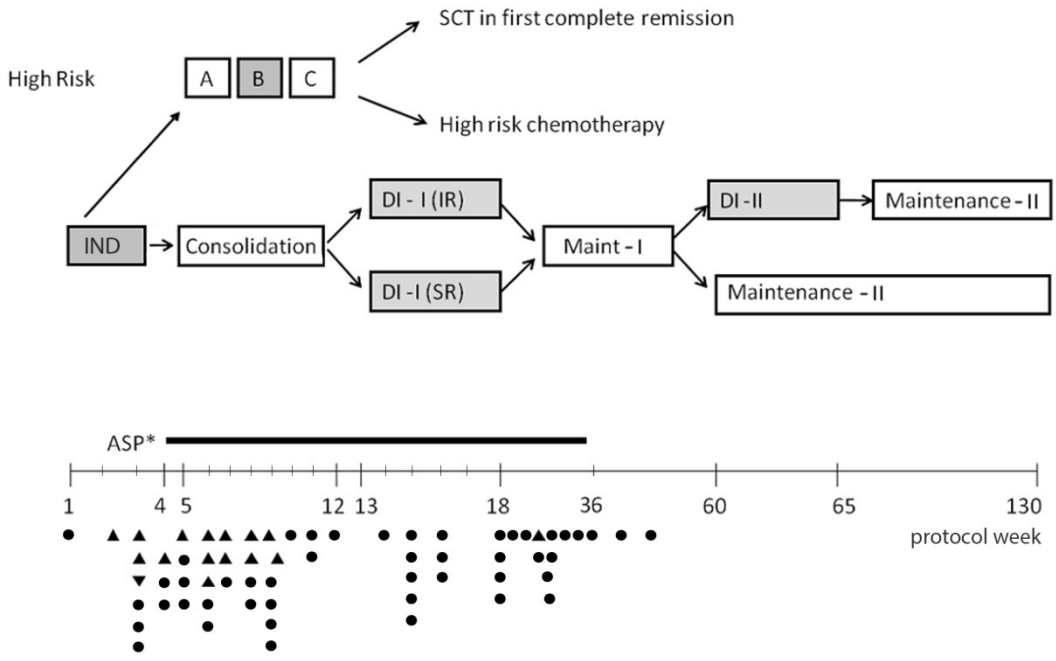


Figure 2. Treatment overview in the NOPHO ALL 2008 protocol and time point for diagnosis of TE



A indicates block A in high-risk treatment; ASP, pegylated asparaginase; B, block B in high-risk treatment; C, block C in high-risk treatment; IND, induction with dexamethasone or prednisolone; DI-I, first delayed intensification; DI-II, second delayed intensification; IR, intermediate risk protocol; Maint-I, first maintenance; SR, standard risk protocol; SCT, stem cell transplantation. Thromboembolism (TE) cases marked with triangles (▲) indicate TE patients treated according to the high-risk protocol. TE cases marked with dots (●) indicate TE patients treated according to the non-high-risk protocol. One patient (▼) died before stratification. Treatment weeks on the bottom of the figure apply to non-high-risk treatment.Treatment phases with steroids are indicated in grey. * The treatment phase containing continuous ASP ranges from the end of induction to maintenance I as indicated with solid line. All the high-risk blocks contain ASP.

Childhood Cancer Etiology Working Group

Members (1st meeting)	
Denmark	Jesper Brok
	Henrik Hasle
	Henrik Hjalgrim
	Torben Stamm Mikkelsen
	Marianne Olsen
	Kjeld Schmiegelow
	Morten Rytter Tulstrup
	Karin Wadt
Finland	Olli Lohi
Iceland	Ólafur Gísli Jónsson
Lithuania	Egle Ramanauskiene
	Jelena Rascon
Sweden	Arja Harila-Saari
	Ann Nordgren
	Vasilios Zachariadis (chair)

Mailing list

DK: Astrid Marie Sehested, Ramneek Gupta, Rachita Yadav, Ulrik Stoltze; FI: Päivi Lähteenmäki, Laura-Maria Madanat-Harjuoja, Tekla Järviaho; IS: Laufey Tryggvadóttir; NO: Monica Cheng Munthe-Kaas; SE: David Gisselsson Nord, Per Kogner

The Childhood Cancer Etiology working group was initiated during spring 2015, with the first meeting held in Copenhagen on April 7th 2015. Attending were 15 members with wide national and professional representation. The group was formally accepted as a working group under NOPHO at the annual meeting in Oulu.

Initial discussions in the group have focused on defining common objectives and identifying clinical needs, common research goals and key knowledge gaps concerning childhood cancer etiology in the Nordic setting.

The overall aims of the Childhood Cancer Etiology working group is to:

a. Increase our understanding of predisposing germline genetic variation (both rare and common) and environmental factors in childhood cancer
b. To expand and facilitate national and international research collaborations concerning the etiology of childhood cancers
c. To help guide the implementation of childhood cancer etiology knowledge into clinical practice; including registration, routines and ethical aspects for informed consent, genetic testing, and reporting of results

In the immediate term, work is focused on increasing awareness and improving registration

of significant co-morbidities, family history of cancer, and any congenital malformations in children diagnosed with cancer. Further, work is ongoing to coordinate ethical approvals, disseminate know-how on large-scale genetic analyses, and link national registries to further improve Nordic collaborations in these research areas. To achieve this, the working group brings together people with expertise in pediatric oncology, clinical genetics, epidemiology, bioinformatics, molecular biology, medical ethics, including several young researchers.

The 2nd meeting of the working group is planned for May 2016 in Copenhagen.

On behalf of the working group,

Vasilios Zachariadis
Stockholm, April 2016

Radiotherapy Working Group

Chair	Yasmin Lassen
Denmark	Yasmin Lassen
	Akmal Safwat
Finland	Kristiina Koskela
	Merja Korpela
	Satu Lehtinen
Iceland	Vacant
Norway	Petter Brandal
Sweden	Jonas Karlen
	Kristina Nilsson
	Ulla Martinsson
Lithuania	Vacant

The Nopho pediatric radiotherapy working group had its first meeting at the annual Nopho meeting in Oulu in 2015. The aims of the working group are to:

- build an active network and forum for Nordic pediatric radiation oncologists
- promote Nordic pediatric radiotherapy oncologist collaboration
- enhance focus on and knowledge about radiotherapy for our Nordic non-radiation pediatric oncologist colleagues
- enhance focus on pediatric radiotherapy among radiation oncologists
- aim at active radiotherapy oncologist participation in other NOPHO WGs
- discuss radiotherapy part of international protocols in which Nordic countries are involved
- arrange radiotherapy workshops with dedicated radiation therapy themes (such as delineation of target volumes and organs at risk)

In the actual working group, we have members from Denmark, Sweden, Finland and Norway, during the year contacts have been made to be able also to include members from Iceland and Lithuania.

At the first working group meeting, we have established an overview over how pediatric radiotherapy is organized in the different Nordic countries. In general children are in all represented countries discussed in MDT conferences and treated by dedicated clinical oncologists in different centers.

The treatment protocols in the different countries for the different diseases were discussed in details. Often the same treatment protocols are used.

Proton radiotherapy and the access to it for children from the Nordic countries was also a discussion point. In Sweden the Skandion clinic, a modern protonradiotherapy clinic, opened last year. Norway and Denmark have been sending children for proton radiotherapy abroad if indicated and if it does not imply treatment delays.

For 2016 the plan is to organize at the next working group meeting also a workshop for target delineation and treatment techniques about craniospinal irradiation.

We will also focus on education about pediatric radiation oncology and how pediatric radiation oncology can be represented in other Nopho multidisciplinary working groups.

The next working group meeting and the workshop will be organized at the annual meeting in Reykjavik.

Yasmin Lassen, for the Nopho Pediatric Radiation Oncology Working Group.

NOPHO/NOBOS Working Group on Ethics (WGE)

Denmark	Trine Brøner, nurse
	Gitte Petersen, nurse
	Astrid Sehested, physician
	Pernille Wendtland Edslev, physician
Finland	Kristian Juusola, nurse
	Satu Lehtinen, physician
Iceland	Sigrún Þóroddsdóttir, nurse
Norway	Hilde Frøland Hauge, nurse
	Heidi Glosli, physician
Sweden	Cecilia Bartholdson, nurse
	Anders Castor, physician
	Britt-Marie Frost, physician
	Sara Karlsson, nurse
	Pernilla Pergert, nurse (chair)
	Jennie Stigmar, nurse
	Lisa Törnudd, physician (secretary)

Most working groups in NOPHO are trying to gain knowledge through various treatment protocols in order to optimize what we can do in regards to cure. The NOPHO/NOBOS WGE was established in 2008 and is occupied by issues related to what we should do rather than what we can do. The aims of clinical ethics support include helping healthcare professionals to handle ethical issues and to reflect on what should be done in treatment and care. Clinical ethics support can be performed in various ways, for example, participating in ethics committees, facilitating ethics case reflections in the team, and offering ethics education.

The intention of the WGE is to be a Nordic competence group in clinical ethics that offers ethics support and puts the ethical questions within paediatric oncology on the agenda, by developing and disseminating knowledge and methods.

Organisation

The group meets, at a minimum, for two meetings per year. The 2-day meetings rotate between the countries whereas the 1-day meetings have been held in Copenhagen because proximity and easy accessibility for all members have been prioritized. This year the WGE have had two 2-day meetings. Most work is performed locally by the members.

Meetings of the WGE during the last year

20-21 April 2015, Dragør, Denmark
8-10 November 2015, Hurdal, Norway
3-5 April 2016, Rimbo, Sweden

Upcoming meetings of the WGE

20-22 November 2016, Helsinki, Finland
26-28 March 2017, Dragør, Denmark

Funding

The WGE has received grants for 2015-2017 (PL2014-0003) from the Swedish Childhood

Cancer Foundation, the main funders of the group. Support for the rotating 2-day meetings is applied for from local foundations. The Danish Børnecancerfonden funded the 2-day meeting in Dragør and the Norwegian Childhood Cancer organisation Barnekreftforeningen funded the meeting in Hurdal.

Activities of the WGE during the last year

The group has worked with the Open Space method (http://openspaceworld.org/wp2/) during meetings to "identify and develop concrete ideas that members are prepared to invest time and energy on, together with one or more members of the group." Open space groups have been working on several ideas including:

- An article about the legal context for paediatric patients
- A Nordic study on communication over language barriers, moral stress and the ethical climate in childhood cancer care
- A nationwide (Sweden) course in facilitating Ethics Case Reflection (ECR) sessions
- Guideline on ethical collaboration/teamwork

Clinical ethics support activities

Local clinical ethics support performed by members includes:

- offering and facilitating ECR sessions in healthcare teams and/or in committees
- teaching ethics to nursing and medical professionals/students
- performing research projects in clinical ethics
- serving as members of national, regional or local clinical ethics committees/societies

Furthermore, members of the WGE have initiated and/or participated as members of clinical ethics committees in paediatrics, including:

- Clinical ethical committee, Pediatric Department, Oulu University Hospital, Finland
- Pediatric ethical committee, Skane University Hospital, Sweden
- Pediatric regional ethics committee, Östergötland, Sweden
- Clinical ethics committee of paediatrics, Rigshospitalet, Copenhagen, Denmark

Research activities

The WGE has been an expert group in a research project on communication over language barriers, moral stress and the ethical climate in Swedish paediatric oncology. A national cross-sectional survey has been performed with support from the members of the WGE and a dialogue and/or lectures about clinical ethics have been offered by the research group (WGE members) after the healthcare professionals have had the opportunity to complete the questionnaire. The plan is now to perform this study in the other Nordic countries and an application has been sent to the board of NOBOS and to the scientific committee of the NOPHO and it will be decided jointly by these boards if the study can be performed within the frameworks of these organisations.

International meetings/courses on ethics, attended by members in 2015

- Continued education: Facilitating moral case deliberation, VU medisch centrum (At the meeting in Dragør, Denmark) 20-21 April, 2015 (14 members)
- International Conference on Clinical Ethics and Consultation (ICCEC), NY, USA 20-22 May, 2015 (Castor, Pergert, Törnudd, Stigmar, Wendtland Edslev).
- 1st International Care Ethics (ICE) Observatory and 16th Nursing Ethics Conference, University of Surrey, Guildford, UK, 17-18 July, 2015, (Bartholdson, Pergert).
- Annual Intensive Course in Medical Ethics, Faculty of Medicine, Imperial College London, School of Professional Development, London, UK. 14-18 September, 2015 (Stigmar, Törnudd).
- Master Class: Ethics in Pediatric, University Medical Center Groningen, the Netherlands, 17-18 November, 2015 (Bartholdson, Pergert).

Abstracts on ethics presented at international conferences from the group or with group members as co-authors during 2015

- 47th Congress of the International Society of Paediatric Oncology (SIOP), Cape Town, South Africa, 8-11 October, 201
  – af Sandeberg, M, Lützén, K., Wen-

emark, M., & **Pergert, P.** (2015) Cultural adaptation and validation of the moral distress scale to the pediatric oncology context. (SIOP Meeting Abstract) *Pediatric Blood & Cancer,* 62, (Suppl. 4), p.S196-197. (Oral presentation by Pergert)
– **Bartholdson, C**., af Sandeberg, M., Lützén, K., Blomgren, K., & **Pergert, P.** (2015) Health care professionals perceptions of the pediatric hospital ethical climate in childhood cancer care. (SIOP Meeting Abstract) *Pediatric Blood & Cancer*, 62, (Suppl. 4), p.S194-195. (Oral presentation by Bartholdson)
– **Bartholdson, C**., Lützén, K., Blomgren, K., & **Pergert, P.** (2015) Consolidating care by clarifying perspectives: Health care professionals' experiences of ethics case reflection sessions. (SIOP Meeting Abstract) *Pediatric Blood & Cancer*, 62, (Suppl. 4), p.S195. (Oral presentation by Bartholdson)
– **Frøland Hauge, H**. Chair of a round table on ethical dilemmas at the nursing session.

- International Conference on Clinical Ethics and Consultation (ICCEC), NY, USA 20-22 May, 2015
  – **Pergert, P.**, et al on behalf of the NOPHO/NOBOS Working Group on Ethics. A Nordic Platform for Clinical Ethics in Pediatric Oncology. (Oral presentation by Pergert)
- 1st International Care Ethics (ICE) Observatory and 16th Nursing Ethics Conference, University of Surrey, Guildford, UK, 17-18 July, 2015
  – **Pergert, P**., et al. on behalf of the NOPHO/NOBOS Working Group on Ethics. A Nordic Platform for Clinical Ethics in Pediatric Oncology. (Oral presentation by Pergert)
  – **Bartholdson, C**., af Sandeberg, M., Lützén, K., Blomgren, K., & **Pergert, P**. Health care professionals perceptions of the pediatric hospital ethical climate in childhood cancer care. (Oral presentation by Bartholdson)
  – **Bartholdson, C**., Lützén, K., Blomgren, K., & **Pergert, P**. Consolidating care by clarifying perspectives: Health care professionals' experiences of ethics case reflection sessions. (Oral presentation by Bartholdson)

Publications on ethics from the group or with group members as co-authors during 2015

- Bartholdson, C., Lützén, K., Blomgren, K., & **Pergert, P**. (2015). Experiences of ethical issues when caring for children with cancer. Cancer Nursing, Mar-Apr;38(2):125-32.
- Bartholdson, C., Lützén, K., Blomgren, K., & **Pergert, P**. (2015) Clarifying perspectives: ethics case reflection sessions in childhood cancer care. Nursing Ethics, Mar 3. [Epub ahead of print]
- Bartholdson, C., af Sandeberg, M., Lützén, K., Blomgren, K., & **Pergert, P**. (2015) Healthcare professionals' perceptions of the ethical climate in paediatric cancer care. Nursing Ethics, Jun 26. [Epub ahead of print]
- Uldall, P., Andersen, M., Greisen, G., Hagelund Hansen, B., Holte Kofoed, E., Bresson Ladegaard Knox, J., Nabe-Nielsen, H., **Petersen, G**., Ploug T., & **Sehested, A**. (2015) Landets første klinisk etisk komite for pædiatri. Ugeskrift for læger.

On behalf of NOPHO/NOBOS Working Group on Ethics
Pernilla Pergert, Stockholm

NOPHO Pharmacists

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Denmark	Anni Christensen	annichst@rm.dk

Changes in Group Composition

Mattias Paulsson, Uppsala, and Anni Christensen, Aarhus, joined our WG in December 2015. Anni Christensen withdrew from the WG in January 2016. Ranaa will be on maternity leave from May 2016 to May 2017 and Magnus Dahlander is appointed chair from March 2016 until the end of May 2017.

Meetings

The Pharmacists Working Group has had two physical meetings during 2015.

23rd May in Oulu (Finland) and 20th November in Oslo (Norway). In between these meeting we also had 9 short meetings via Lync/Skype.

Projects

The main focus of the working group is the development of an extravasation guideline. A first draft was available at the NOPHO Annual Meeting in Oulu and a revised draft was sent to reviewers early in February 2016.

Ranaa and Magnus also prepared a presentation on "Conventional and liposomal Vincristine toxicity, effect and pharmacokinetics" which was presented at the NOPHO Pharmacology Group meeting February 9th 2016 in Copenhagen.

Magnus Dahlander
Chair of the NOPHO Pharmacists WG
Gothenburg, April 18, 2016

NOPHO Publications

Publications based on cooperative projects within NOPHO.

1983

Moe PJ. *Combined Nordic Meeting of Pediatric Hematology and Oncology.* Am J Hematol Oncol 1983; 4:438.

1986

Moe PJ, Hertz H, Ludvigsson J, Siimes M, Jonmundsson G. *Feilmedisinering hos barn – profylakse og terapi.* Nordisk Medicin 1986; 101:8-9.

1987

Gustafsson G, Garwicz S, Hertz H, Jonmundsson G, Johanesson G, Moe PJ, Salmi T, Seip M, Siimes MA, Yssing M and Åhström L for NOPHO. *A Population-based study of childhood acute lymphoblastic leukemia diagnosed from July 1981 through June 1985 in the five Nordic countries.* Acta Paediatr Scand 1987; 76: 781-788.

1989

Gustafsson G, Berglund G, Garwicz S, Hertz H, Jonmundsson G, Moe PJ, Salmi TT, Seip M, Siimes MA, Yssing M for NOPHO. *A population-based study of children with stanard risk acute lymphoblastic leukemia in the five Nordic countries.* Acta Paediatr Scand 1989; 78: 104-109.

Nygaard R, Moe PJ. *Outcome after cessation of therapy in childhood leukemia. A population-based Nordic study of 986 patients. I and II.* Acta Paediatr Scand 1989, Suppl. 354:1-24.

Nygaard R, Moe PJ, Brincker H, Clausen N, Nyman R, Perkkiö M, Eilertsen ME, Johansen OJ, Väre M, Brinch L, Siimes MA. *Late relapses after treatment for acute lymphoblastic leukemia in childhood. A population-based study from the Nordic countries.* Med Ped Oncol 1989;17:45-47.

Schmiegelow K, Siimes MA, Agertoft L, Berglund L, Storm-Mathiesen I, Andreassen M, Salmi TT, Nygaard R, Wiebe T, Kreuger A, Hayder S. *Radio-lodobenzylguanidine scientigraphy of neuroblastoma: Conflicting results, when compared with standard investigations.* Med Ped Oncol 1989;17:126-130.

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Clausen N, Garwicz S, Glomsten A, Jonmundsson G, Kruus S, Yssing M. *Medulloblastoma in Nordic children, I. Incidence and mortality.* Acta Pædiatr Scand 1990, suppl.371:5-11.

Jacobsen BB, Garwicz S, Glomstein A, Jonmundsson G, Kruus S, Yssing M. *Medulloblastoma in Nordic children. III. Long term growth and endocrine sequelae.* Acta Pædiatr Scand 1990;271:20-27.

Lie S, Berglund G, Gustafsson G, Jonmundsson G, Siimes M, Yssing M for NOPHO. *High dose ARA-C as a single agent consolidation therapy in childhood AML. In: Haematology and Blood Transfusion.* Acute Leukemia II. pp 215-221. Springer Verlag, 1990.

Yssing M, Garwicz S, Glomstein A, Jonmundsson G, Kruus S. *Medulloblastoma in Nordic children. II. Neurologic and social prognosis in long term survivors.* Acta Pædiatr Scand 1990, suppl.371:12-19.

1991

Kreuger A, Garwitz S, Hertz H, Jonmundsson G, Lanning M, Lie SO, Moe PJ, Salmi TT, Schroeder H, Siimes MA, Wesenberg F, Yssing M, Åhström L and Gustafsson G for NOPHO. CNS disease in childhood acute lymphoblastic leukemia. Prognostic factors and treatment results. Pediatr Hem Oncol 1991; 8:291-299.

Lie SO on behalf of the Nordic Society for Pediatric Hematology and Oncology (NOPHO). *Progress in treatment of childhood*

leukemias. Eur J Cancer 1991; suppl.2:11.

Nygaard R. *Long-term survival in childhood leukemia. Relapses and late effects after completed therapy.* Thesis, University of Trondheim, Tapir, 1991.

Nygaard R, Clausen N, Siimes MA, Marky I, Skjeldestad FE, Kristinsson JR, Vuoristo A, Wegelius R, Moe PJ. *Reproduction following treatment for childhood leukemia: A population-based prospective cohort study of fertility and offspring.* Med Ped Oncol 1991;19:459-466.

Nygaard R, Garwicz S, Haldorsen T, Hertz H, Jonmundsson GK, Lanning M, Moe PJ. *Second malignant neoplasms in patients treated for childhood leukemia. A population-based cohort study from the Nordic countries.* Acta Pædiatr Scand 1991;80:1220-1228.

1992

Lanning M, Garwitz S, Hertz H, Jonmundsson G, Kreuger A, Lie SO, Moe PJ, Salmi TT, Schröder H, Siimes M, Wesenberg F, Yssing M, Åhström L and Gustafsson G for NOPHO. *Superior treatment results in girls with high risk acute lymphoblastic leukemia compared to boys.* Acta Paediatr Scand 1992; 81:66-68.

Lie Sverre and Gustafsson Göran on behalf of the Nordic Society for Pediatric Hematology and Oncology (NOPHO). *Progress in the treatment of childhood leukemias.* Review article Annals of Medicin 1992; 24:319-323.

1993

Siimes MA, Lie SO, Andersen O, Marky I, Rautonen J, Hertz H. *Prophylactic cranial irradiation increases the risk of testicular damage in adult males surviving ALL in childhood.* Med Ped Oncol 1993;21:117-121.

Olsen JH, Garwicz S, Hertz H, Jonmundsson G, Langmark F, Lanning M, Lie SO, Moe PJ, Möller T, Sankila R and Tullinius H. *Second malignant neoplasma after cancer in childhood or adolescence.* Br Med J 1993; 307: 1030-1036.

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Moell C, Marky I, Hovi L, Kristinsson J, Rix M, Moe PJ and Garwicz S. *Cerebral irradiation causes blunted pubertal growth in girls treated for acute leukemia.* Med Pediatr Oncol 1994;22:375-379.

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Schröder H, Garwicz S, Gustafsson G, Kristinsson J, Siiemes MA and Wesenberg F on behalf of NOPHO. *Outcome after relapse in children with acute lymphoblastic leukemia.* Med Ped Onc 1995; 25:372-378.

Schmiegelow K, Schröder H, Gustafsson G, Kristinsson J, Glomstein A, Salmi T, and Wranne L for NOPHO. *Risk of relapse in childhood acute lymphoblastic leukemia is related to RBC methotrexate and mercaptopurine metabolites during maintenance chemotherapy. Nordic Society for Pediatric Hematology and Oncology.* Journal Clin Oncol 1995; 13:345-351.

Marky I, Jonsson O, Kreuger A, Gustafsson G, Perkkio M, Schmiegelow K, Storm-Mathiesen I and Langmark F. *Childhood Non Hodgkin´s Lymphoma (NHL) in the five Nordic countries. A five year population based study.* Am Journal Pediatr Hem/Onc.; 17(2): 163-166, 1995.

1996

Saarinen U, Mellander L, Nyström K, Ringden O, Schroeder H, Glomstein A and Gustafsson G for NOPHO. *Allogeneic bone marrow transplantation in first remission for children with very high risk acute lymphoblastic leukemia: A retrospective case-control study in the Nordic countries.* Bone Marrow Transplantation; 17 (3):357-363 1996.

Lie S, Jonmundsson G, Mellander L, Siimes MA, Yssing M and Gustafsson G on behalf of NOPHO. *A population based study of 272 children with acute myeloid leukemia treated on two consecutive protocols with different intensity: Best outcome in girls, infants and in children with Down´s syndrom.* Br Journal of Hematology 1996; 94:82-88

Clausen N, Kreuger A, Salmi T, Storm-Mathisen I, Johannesson G. *Severe aplastic anaemia in the Nordic countries: a population based study of incidence, presentation, course, and outcome.* Arch Dis Child 1996;74; 319-22

Sankila R, Garwicz S, Olsen JH, Dollner H, Hertz H, Kreuger A, Langmark F, Lanning M, Moller T and Tulinius H. *Risk of subsequent malignant neoplasms among 1641 Hodgkin´s disease patients diagnosed in childhood and adolsescence. A population based cohort study in the five Nordic countries.* JCO, 1996;14(5):1442-46.

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Lie SO, Jonmundsson GK, Mellander L, Siimes MA, Yssing M, Gustafsson G. *Chemotherapy of acute myelocytic leukemia in children.* Ann N Y Acad Sci. 1997;824:84-90. Review.

1998

Gustafsson G, Lie SO. *Acute leukemias.* In: Cancer in children, clinical management, 4th edn. (ed PA Voute, C Kalifa, A Barrett). Oxford University Press, London, 1998, 99-118.

Sankila R, Olsen JH, Anderson H, Garwicz S, Glattre E, Hertz H, Langmark F, Lanning M, Möller T and Tulinius H. *Risk of cancer among offsprings of childhood-cancer survivors.* New Engl J Med, 1998;338:1339.

Gustafsson G, Kreuger A, Clausen N, Garwicz S, Kristinsson J, Lie SO, Moe PJ, Perkkiö M, Yssing M and Saarinen-Pihkala U. *Intensified treatment of acute childhood lymphoblastic leukemia has improved prognosis, especially in non-high-risk patients: the Nordic experience of 2648 patients diagnosed between 1981 and 1996.* Acta Paediatr, 1998;87:1151-61.

Jahnukainen K, Salmi TT, Kristinsson J, Müller J, Madsen B, Gustafsson G. *The clinical indications for identical pathogenesis of isolated and non-isolated testicular relapse in acute lymphoblastic leukemia.* Acta Paediatr,1998,87:638-643

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Schroeder H, Gustafsson G, Saarinen-Pihkala U, Glomstein A, Jonmundsson G, Nysom K, Ringden O and Mellander L. *Allogeneic bone marrow transplantation in second remission of childhood acute lymphoblastic leukemia: a population-based case control study from the Nordic countries.* Bone Marrow Transplant, 1999,Mar;23(6):555-560

2000

Garwicz S, Anderson H, Olsen JH, Döllner H, Hertz H, Jonmundsson G, Langmark F, Lanning M, Möller T, Sankila R, Tulinius H. *Second malignant neoplasms after cancer in childhood and adolescence: A population-based case-control study in the 5 nordic countries.* Int J Cancer 88: 672-678, 2000.

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Gustafsson G, Schmiegelow K, Forestier E, Clausen N, Glomstein A, Jonmundsson G, Mellander L, Mäkipernaa A, Nygaard R, Saarinen-Pihkala U-M. *Improving outcome through two decades in childhood ALL in the Nordic countries: the impacr of high-dose methotrexate in the reduction of CNS irradiation.* Leukemia, 2000, 14: 2267-2275.

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