EUROPEAN SYMPOSIUM ON LATE COMPLICATIONS AFTER CHILDHOOD CANCER
19–20 APRIL 2007 LUND SWEDEN

PROGRAMME AND ABSTRACT BOOK

www.eslccc2007.com
Table of Contents

Welcome 3
Programme 4
Speakers 7
Useful information & social events 8
Venue overview 9
List of participants 10
Abstracts A - Invited Speakers 14
Abstracts C - Cognition, Psychology and Quality of Life 20
Abstracts E - Endocrinology, Growth and Metabolism 27
Abstracts F - Follow-up 34
Abstracts G - Gonads and Fertility 38
Abstracts M - Miscellaneous 45
Index of Authors 53
Map of Lundagård 55

Sponsors

[Image of sponsors logos]
Welcome to Lund – “the City of Ideas”, located in the centre of the Öresund region. Lund offers a rich selection of cultural experiences, with the Cathedral, Scandinavia’s most distinguished church in the Romanesque style, at centre stage. The events are many and varied, with Lund’s strong tradition of comedy and farce making its mark on many of them. In Lund a creative, dynamic and innovative cultural spirit is alive and well. Lund has charm and wit and will make you feel welcome.

ESLCCC April 19-20 2007
The continuing success of the treatment for childhood cancer is an important medical achievement. It has however become increasingly evident that some survivors may pay a considerable price for their cure.

Late effects after childhood cancer often have a gradual and subtle presentation that may involve any organ system of the body. The follow-up will often require cooperation between several different medical specialities.

The European Symposium on Late Complications after Childhood Cancer in Lund, ESLCCC 2007, is the first major European meeting to focus on several different aspects of this important and developing clinical area.

The meeting is organized from the Department of Paediatrics at the University Hospital, which has a long tradition in the follow-up of late effects after childhood cancer.

Professor Stanislaw Garwicz has pioneered research in this field and this Symposium is held in his honour on his retirement from the Division of Paediatric Oncology at the University Hospital in Lund.

Christian Moëll
On behalf of the Organizing Committee
**European Symposium on Late Complications after Childhood Cancer**  
**Lund April 19–20 2007**

**Thursday April 19, 2007**

<table>
<thead>
<tr>
<th>TIME</th>
<th>SUBJECT</th>
<th>SPEAKER</th>
<th>ABSTRACT</th>
</tr>
</thead>
<tbody>
<tr>
<td>09:00</td>
<td>Welcome</td>
<td>Christian Moëll</td>
<td></td>
</tr>
<tr>
<td>09:10</td>
<td>Introduction of Morning session</td>
<td>Kjeld Schmiegelow</td>
<td></td>
</tr>
<tr>
<td>09:20</td>
<td>Late effects - where do we go from here?</td>
<td>Daniel Green</td>
<td>A:01</td>
</tr>
<tr>
<td>10:00</td>
<td>Modifications of treatment to minimize complications, the Hodgkin experience</td>
<td>Guenther Schellong</td>
<td>A:02</td>
</tr>
<tr>
<td>10:30</td>
<td>Coffee</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11:00</td>
<td>Antracycline cardiotoxicity in children – What is the risk and how can we avoid it?</td>
<td>Leontien Kremer</td>
<td>A:03</td>
</tr>
<tr>
<td>11:30</td>
<td>Discussion</td>
<td>Chairman: K. Schmiegelow</td>
<td></td>
</tr>
<tr>
<td>12.00</td>
<td>Poster viewing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12.30</td>
<td>Lunch</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13:30</td>
<td>Children’s Cancer Foundation 25 years</td>
<td>Olle Björk</td>
<td></td>
</tr>
<tr>
<td>13:40</td>
<td>Introduction of Afternoon session</td>
<td>Olle Björk</td>
<td></td>
</tr>
<tr>
<td>14:30</td>
<td>Presentation of selected posters 1</td>
<td>Christian Moëll</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Poster C:03, page 21</td>
<td>Ilse Schuitema</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Poster E:06, page 29</td>
<td>Dalit Modan-Moses</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Poster M:02, page 45</td>
<td>Marieke De Bruin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Poster M:06, page 47</td>
<td>Marianne Jarfelt</td>
<td></td>
</tr>
<tr>
<td>15:00</td>
<td>Coffee</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15:30</td>
<td>Neurocognitive sequele after brain tumours</td>
<td>Jacques Grill</td>
<td>A:05</td>
</tr>
<tr>
<td>16:00</td>
<td>Neuropsychological consequences of childhood cancer</td>
<td>Christine Eiser</td>
<td>A:06</td>
</tr>
<tr>
<td>16:30</td>
<td>Discussion</td>
<td>Chairman: O.Björk</td>
<td></td>
</tr>
<tr>
<td>18:30</td>
<td>Welcome reception</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIME</td>
<td>SUBJECT</td>
<td>SPEAKER</td>
<td>ABSTRACT</td>
</tr>
<tr>
<td>--------</td>
<td>--------------------------------------------------------------------------</td>
<td>--------------------------------</td>
<td>----------</td>
</tr>
<tr>
<td>09:00</td>
<td>Introduction of Morning Session</td>
<td>Christian Moëll</td>
<td></td>
</tr>
<tr>
<td>09:10</td>
<td>Second neoplasms and late mortality</td>
<td>Stanislaw Garwicz</td>
<td>A:07</td>
</tr>
<tr>
<td>09:50</td>
<td>How is the Follow-up done now?</td>
<td>Lars Hjorth</td>
<td></td>
</tr>
<tr>
<td>10:00</td>
<td>Presentation of selected posters 2</td>
<td>Lars Hjorth</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Poster F:01, page 34</td>
<td>J. Hazelhoff</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Poster F:05, page 36</td>
<td>Kate Absolom</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Poster F:07, page 37</td>
<td>Francesca Fioredda</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Poster F:08, page 37</td>
<td>Thorsten Langer</td>
<td></td>
</tr>
<tr>
<td>10:30</td>
<td>Coffee</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11:00</td>
<td>The role of the nurse in the Follow-up clinic</td>
<td>Faith Gibson</td>
<td>A:08</td>
</tr>
<tr>
<td>11:30</td>
<td>Models of Follow-up after childhood cancer</td>
<td>Andrew Toogood</td>
<td>A:09</td>
</tr>
<tr>
<td>12:00</td>
<td>Discussion</td>
<td>Chairman: L. Hjorth</td>
<td></td>
</tr>
<tr>
<td>12:20</td>
<td>Lunch</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13:20</td>
<td>Introduction of Afternoon session</td>
<td>Hamish Wallace</td>
<td></td>
</tr>
<tr>
<td>13:30</td>
<td>GH deficiency after Childhood cancer – whom to treat?</td>
<td>Stephen Shalet</td>
<td>A:10</td>
</tr>
<tr>
<td>14:10</td>
<td>Presentation of selected posters 3</td>
<td>Hamish Wallace</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Poster G:04, page 39</td>
<td>Yvonne L. Giwercman</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Poster G:09, page 42</td>
<td>Jeanette Falck Winther</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Poster G:06, page 40</td>
<td>M.H. van den Berg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Poster G:12, page 43</td>
<td>Kirsi Jahnukainen</td>
<td></td>
</tr>
<tr>
<td>14:40</td>
<td>Coffee</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15:10</td>
<td>Who is at risk of gonadal dysfunction?</td>
<td>Charles Sklar</td>
<td>A:11</td>
</tr>
<tr>
<td>15:50</td>
<td>Fertility preservation in young people treated for cancer</td>
<td>Victoria Keros</td>
<td>A:12</td>
</tr>
<tr>
<td>16:20</td>
<td>Discussion</td>
<td>Chairman: H. Wallace</td>
<td></td>
</tr>
<tr>
<td>16:40</td>
<td>Presentation of Poster prize</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16:50</td>
<td>Closing remarks</td>
<td>Christian Moëll</td>
<td></td>
</tr>
<tr>
<td>19:00</td>
<td>Symposium dinner</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Welcome to the European Symposium on Late Complications after Childhood Cancer. Please see us at our exhibition stand.

Daniel Richards
F1 Championship
Nürburgring 2022

Treatment is much more than medicine – Novo Nordisk® is dedicated to support at all levels to achieve greater heights

Growing support
Novo Nordisk® is a major supporter of endocrine research as well as meetings and congresses on endocrinology, and we offer a whole range of healthcare professional training initiatives including: training courses (Henning Andersen Courses), fellowship support (ESPE Research Fellowship Awards), conferences, symposia and literature

Growing commitment
Our aspiration is to lead the way in improving the lives of children and adults with growth hormone disturbances through our user-friendly pen systems, training programmes and continued support and education to patients and parents

Speakers

Olle Björk
Children’s Cancer Foundation
Barn cancerfonden
Stockholm, Sweden

Giulio D’Angio
Department of Radiation Oncology
Hospital of the University of Pennsylvania
Philadelphia, USA

Christine Eiser
The University of Sheffield
Sheffield, United Kingdom

Stanislaw Garwicz
Dept of Paediatrics
Lund University Hospital
Lund, Sweden

Faith Gibson
UCL Institute of Child Health
Great Ormond Street Hospital for Children
London, United Kingdom

Daniel Green
Roswell Park Cancer Institute
Buffalo, New York, USA

Jacques Grill
Gustave Roussy Institute
Villejuif, France

Lars Hjorth
Dept of Paediatrics
Lund University Hospital
Lund, Sweden

Victoria Keros
Obstetrics and gynecology
Karolinska University Hospital
Stockholm, Sweden

Leontien C.M. Kremer
Pediatric Oncology
Emma Children’s Hospital
Amsterdam, Netherlands

Christian Moëll
Dept of Paediatrics
Lund University Hospital
Lund, Sweden

Guenther Schellong
University of Münster
Münster, Germany

Kjeld Schmiegelow
Pediatric Clinic
University Hospital Rigshospitalet
Copenhagen, Denmark

Stephen M. Shalet
Department of Endocrinology
Christie Hospital
Manchester, United Kingdom

Charles A. Sklar
Department of Pediatrics
Memorial Sloan-Kettering Cancer Center
New York, USA

Andrew Toogood
University Hospital Birmingham
United Kingdom

Hamish Wallace
Royal Hospital for Sick Children
Edinburgh, United Kingdom
Useful information

**BANKS**
Banks are open between 10.00 and 15.00 on weekdays.

**CLIMATE**
The weather in Lund in April is usually nice but showers can occur. For weather forecast please visit www.smhi.com

**CERTIFICATE OF ATTENDANCE**
Will be available at the registration desk on individual request.

**CURRENCY**
The official currency is Swedish Krona (SEK).
USD 1 = SEK 7.00 (April 2007)
EUR 1 = SEK 9.35 (April 2007)

**DISCLAIMER**
The Organizing Committee and Congrex Sweden AB accept no liability for injuries/losses of whatever nature incurred by participants and/or accompanying persons, nor loss of, or damage to, their luggage and/or personal belongings.

**INTERNET**
Wireless LAN will be available to all participants at the Symposium Venue. You will receive your user identity and password upon registration.

**MEALS**
Coffee and lunches are included in the registration fee and will be served daily. Your name badge is your ticket. The lunch will be served at Akademiska Föreningen (Students’ Union).

**LANGUAGE**
The official language of the Congress is English (no translation facilities will be provided).

**TAXI**
We recommend the following taxi companies:
Taxi Skåne, Phone: +46 (0)406 330 330
Taxi Kurir, Phone: +46 (0)406 700 700
Taxi Lund, Phone: +46 (0)46 12 12 12

Social events

**WELCOME RECEPTION**
Thursday 19 April 18.30 at The University Building
Drinks will be served
Included in the registration fee

**SYMPOSIUM DINNER**
Friday 20 April 19.00 at Grand Hotel
Price/person: SEK 400
Venue Overview
List of participants (2007-04-12)

<table>
<thead>
<tr>
<th>A</th>
<th>Absolom, Kate</th>
<th>University of Sheffield</th>
<th>Department of Psychology</th>
<th>Western Bank</th>
<th>Sheffield, S10 2TP, United Kingdom</th>
</tr>
</thead>
<tbody>
<tr>
<td>Å</td>
<td>af Sandeberg, Margareta</td>
<td>Atrid Lindgrens Hospital</td>
<td>Pediatric Oncology</td>
<td>Karolinska University Hospital</td>
<td>171 76 Stockholm, Sweden</td>
</tr>
<tr>
<td>Å</td>
<td>Aknes, Liv Heger</td>
<td>Rikshospitalet-Radiumhospital Medical Centre</td>
<td>Cancer Clinic</td>
<td>Montebello</td>
<td>0310 Oslo, Norway</td>
</tr>
<tr>
<td>Å</td>
<td>Albanese, Assunta</td>
<td>The Royal Marsden NHS Foundation Trust</td>
<td>Paediatric Oncology</td>
<td>Downs Road</td>
<td>Sutton SM2 5PT, United Kingdom</td>
</tr>
<tr>
<td>Å</td>
<td>Alston, Aileen</td>
<td>Royal Marsden Hospital</td>
<td>Paediatric Endocrinology</td>
<td>Downs Road</td>
<td>Sutton SM2 5PT, United Kingdom</td>
</tr>
<tr>
<td>Å</td>
<td>Amoroso, Loredana</td>
<td>Istitut Gustave Roussy</td>
<td>39 Rue Camille Desmoulins</td>
<td>94805, France</td>
<td></td>
</tr>
<tr>
<td>Å</td>
<td>Andersson, Christina</td>
<td>Gavle-Dala Barncancerförening</td>
<td>Sweden</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Å</td>
<td>Andersson, Yvva</td>
<td>Barncancerfonden</td>
<td>Box 5408</td>
<td>114 84 Stockholm, Sweden</td>
<td></td>
</tr>
<tr>
<td>Å</td>
<td>Arvidsson, Johan</td>
<td>Department of Womens and Childerns Health</td>
<td>Akademiska Sjukhuset</td>
<td>752 85 Uppsala, Sweden</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>Bahshore, Lisa</td>
<td>Cook Children's Medical Center</td>
<td>Hematology/Oncology, Survivorship</td>
<td>901 7th Avenue, Suite 220</td>
<td>Fort Worth, Texas, United States</td>
</tr>
<tr>
<td>B</td>
<td>Behrends, Mikael</td>
<td>University Hospital</td>
<td>Department of Pediatrics</td>
<td>581 85 Linköping, Sweden</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>Berg, Rickard</td>
<td>Norge Nordisk Scandinavia</td>
<td>GHT Team, Box 50587</td>
<td>202 15 Malmö, Sweden</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>Bergsträsser, Eva</td>
<td>University Children's Hospital</td>
<td>Oncology</td>
<td>Sennwiesenstr. 75</td>
<td>8032 Zürich, Switzerland</td>
</tr>
<tr>
<td>B</td>
<td>Bjørk-Eriksson, Thomas</td>
<td>Sahlgrenska Universitetssjukhuset</td>
<td>Dep of Oncology</td>
<td>Blå Straketr 2</td>
<td>413 45 Göteborg, Sweden</td>
</tr>
<tr>
<td>B</td>
<td>Björk, Olle</td>
<td>University Children's Hospital</td>
<td>Western Bank</td>
<td>Sheffield S10 2TH, United Kingdom</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>Björk, Thomas</td>
<td>Centre for Children's Cancer and Blood Disorders</td>
<td>High Street, Randwick</td>
<td>2029 Sydney, Australia</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>Bokkenkamp, Arend</td>
<td>University Hospital</td>
<td>Pediatric Hematology and Oncology</td>
<td>De Boelaan 1117</td>
<td>1081 HV Amsterdam, Netherlands</td>
</tr>
<tr>
<td>B</td>
<td>Boller, Jeff</td>
<td>University Medical Center Groningen</td>
<td>Pediatric Oncology</td>
<td>Hanzeplein 1</td>
<td>9700 GB Groningen, Netherlands</td>
</tr>
<tr>
<td>B</td>
<td>Børresen, Dorte</td>
<td>University Hospital</td>
<td>Pediatric Hematology and Oncology</td>
<td>PO Box 901</td>
<td>6000 HB Nijmegen, Netherlands</td>
</tr>
<tr>
<td>C</td>
<td>Caffi, Shari</td>
<td>Pediatric Oncology</td>
<td>Kinderhospital</td>
<td>CH-6000 Luzern 16, Switzerland</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>Carlson, Annette</td>
<td>University Hospital</td>
<td>Dept of Paediatrics</td>
<td>Lund University Hospital</td>
<td>221 85 Lund, Sweden</td>
</tr>
<tr>
<td>C</td>
<td>Carlsson, Gisela</td>
<td>Atrid Lindgrens Barnsjukhus</td>
<td>Bar宋onkologen</td>
<td>Karolinska Universitetssjukhuset Solna</td>
<td>171 76 Stockholm, Sweden</td>
</tr>
<tr>
<td>C</td>
<td>Clausen, Niels</td>
<td>University Hospital</td>
<td>Pediatric Hematology and Oncology</td>
<td>PO Box 9101</td>
<td>6050 HB Nijmegen, Netherlands</td>
</tr>
<tr>
<td>D</td>
<td>D'Angio, Giulio</td>
<td>Hospital of the University of Pennsylvania</td>
<td>Department of Radiation Oncology</td>
<td>HUP, Donner 2</td>
<td>Philadelphia, PA 19124, United States</td>
</tr>
<tr>
<td>D</td>
<td>Dahlberg, Karin</td>
<td>Barn och Ungdomssjukhuset</td>
<td>Oncologi</td>
<td>221 85 Lund, Sweden</td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>Davies, Helena</td>
<td>Sheffield Childrens Hospital</td>
<td>Western Bank</td>
<td>Sheffield S10 2TH, United Kingdom</td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>De Bruin, Marieke</td>
<td>Netherlands Cancer Institute</td>
<td>Epidemiology</td>
<td>Plesmanlaan 121</td>
<td>1066CX Amsterdam, Netherlands</td>
</tr>
<tr>
<td>E</td>
<td>Edberg-Pusse, Ebba</td>
<td>Karakterklinikken</td>
<td>Karolinska Universitetssjukhuset, B44, Huddinge</td>
<td>141 86 Stockholm, Sweden</td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>Elstered, Chris</td>
<td>Uppsala University Hospital</td>
<td>Child Neurology</td>
<td>Munklevägen 15</td>
<td>756 46 Uppsala, Sweden</td>
</tr>
<tr>
<td>E</td>
<td>Eiser, Christine</td>
<td>The University of Sheffield</td>
<td>Sheffield S10 2TP, United Kingdom</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>Edling, Bård</td>
<td>Børkgården</td>
<td>Långsjukhuset</td>
<td>30185 Halmstad, Sweden</td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>Elsdon, Ruth</td>
<td>Bristol Royal Hospital for Children</td>
<td>Oncology Day Beds</td>
<td>Upper Maudlin Street</td>
<td>Bristol BS2 8BJ, United Kingdom</td>
</tr>
<tr>
<td>E</td>
<td>Enriquez, Raquel</td>
<td>Children Hospital Aarau</td>
<td>Pediatric Oncology</td>
<td>Tullivasse</td>
<td>5000 Aarau, Switzerland</td>
</tr>
<tr>
<td>E</td>
<td>Edhalmn, Debra</td>
<td>Children's Medical Center Dallas</td>
<td>1935 Motor Street</td>
<td>Dallas , TX 75235, United States</td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>Ewers, Sven-Börje</td>
<td>University Hospital</td>
<td>Dept of Oncology</td>
<td>University Hospital</td>
<td>221 85 Lund, Sweden</td>
</tr>
<tr>
<td>F</td>
<td>Fahlin, Eva</td>
<td>Barnscancerföreningen i Vastra Sverige, Sweden</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>Fioredda, Francesca</td>
<td>Giannina Gaslini Children Hospital</td>
<td>Haematology-Oncology</td>
<td>Largo Gerolamo Gaullini 5</td>
<td>16134 Genova, Italy</td>
</tr>
<tr>
<td>F</td>
<td>Folini, Cecilia</td>
<td>Endocrin, Kraftragan 7b</td>
<td>231 34 Lomma, Sweden</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(Note: The list continues with participants from various institutions across different countries.)
Survival after the diagnosis of cancer in children and adolescents has become the rule. Adult survivors of childhood cancer have concerns regarding treatment effects on their longevity, fertility and offspring. The standardized mortality ratio (SMR) for male five-year survivors who participated in the Childhood Cancer Survivor Study (CCSS) was 8.5, and was 18.2 for female CCSS participants. The most frequent causes of premature mortality are the original cancer, cardiac disease and second malignant neoplasms (SMNs). Data which are population based from the Nordic countries are similar. The SMR for males was 9.2 for males and 14.6 for females.

Anthracyclines antibiotics and direct cardiac irradiation cause cardiac morbidity. The risk factors for anthracycline cardiomyopathy include the cumulative dose of anthracycline received, exposure of the left ventricle to radiation. Radiation therapy can damage the cardiac valves, coronary arteries, myocardium and pericardium. Female childhood cancer survivors who were treated with > 20 Gy have a relative risk (RR) of obesity (body mass index > 30) of 2.59. The RR of obesity for males was 1.86. Obesity predisposes individuals for diabetes mellitus, hypertension and dyslipidemia, factors that will interact with known treatment effects on cardiac health. Growth hormone deficiency may underlie several of these abnormalities.

The fertility of childhood cancer survivors is impaired. The adjusted relative fertility of survivors, compared to that of their siblings was 0.85 (95% CI - 0.78 - 0.92). Fertility may be impaired by the absence of sperm and ova or abnormal uterine structure. The offspring of female CCSS participants who received pelvic irradiation were at increased risk (RR - 1.84) of weight < 2500 grams at birth. Most chemotherapeutic agents are mutagenic. Recent studies have not identified an increased frequency of major congenital malformations, genetic disease or childhood cancer in the offspring of childhood cancer survivors.

The standardized incidence ratio (SIR) for a SMN among CCSS participants who had a median follow-up of 15.4 years after diagnosis was 6.38. The SIR reported for Nordic pediatric cancer patients who had a mean follow-up of 6.1 years after diagnosis was 3.6. Risk factors for SMNs include genetic predisposition, gender and treatment factors. Thyroid carcinoma, breast cancer, brain tumors and skin cancer are among the more frequently diagnosed radiation related SMNs. Tobacco use increases the risk of subsequent lung cancer in patients who received lung irradiation. CCSS participants reported smoking rates that were significantly lower than those of the general population. However 19% of males and 17% of females were current smokers, increasing their risks for lung disease, heart disease and SMNs. SMNs may develop after exposure to alkylating agents and topoisomerase II inhibitors.

Medical care for childhood cancer survivors must be based on accurate knowledge of the treatment exposures of the survivor and informed assessment of the survivor by medical professionals. Only 72% of CCSS participants accurately reported their diagnosis. Recall by CCSS participants of treatment with specific chemotherapeutic agents or exact radiation therapy treatment volumes is poor. Exposure specific care will be difficult unless the patient is given a written record of his/her diagnosis and treatment.

Future research will be necessary to determine the most effective follow-up program for survivors. Several models, including prolonged follow-up at a cancer center, transition of care to appropriately trained physicians in a specialty setting, or transition to community physicians supported by computer based practice guidelines, have been suggested. Many current follow-up evaluations are based primarily on expert opinion. Research is necessary to document that expert opinion results in care that is cost effective and reduces morbidity and/or mortality. Such studies require large sample sizes and prolonged follow-up.
Anthracycline-induced cardiotoxicity is a widely prevalent problem. The consequences of anthracycline-induced cardiotoxicity are extensive. First, it can cause a reduction in the amount of anthracyclines that a patient was supposed to receive and as a result, the chance of survival of that patient can be reduced. Also, it can lead to cardiac death. The risk of developing heart failure remains a lifelong threat, especially to children who have a long life-expectancy after successful antineoplastic treatment.

Several risk factors for anthracycline-induced cardiotoxicity, like a higher cumulative anthracycline dose, different anthracycline derivatives, a higher anthracycline peak dose, radiation therapy involving the heart region, female sex, younger age at diagnosis, black race, additional treatment with for example cyclophosphamide or mitoxantrone and presence of trisomy 21 have been identified.

Serial monitoring of the cardiac function of children receiving anthracyline therapy allows early identification of cardiac damage. During therapy, the anthracycline dosage can then be adjusted or anthracycline therapy can be even stopped, which, hopefully, can prevent more cardiac damage to occur. Unfortunately, at the moment, there is no evidence on the most optimal way to monitor cardiac function in children treated with anthracyclines.

If cardiotoxicity could be prevented or at least be reduced, higher doses of anthracyclines could potentially be used, thereby possibly further increasing cancer survival. Extensive research has been devoted to the identification of methods or agents capable of ameliorating anthracycline-induced cardiotoxicity. The following methods for primary prevention have been identified: 1) Avoiding the use of anthracyclines in the treatment of childhood cancer, 2) The use of possible less cardiotoxic anthracyline analogues and anthracenediones, 3) Reducing the cumulative dose of anthracyclines, 4) Reducing the anthracycline peak dose, 5) Use of cardio-protective agents.

Important insight in the current state of the evidence on anthracycline cardiotoxicity is provided.
As prognosis of brain tumors is improving, concerns are growing for the quality of survival. As for other neoplasms, strategies to mitigate sequelae have been developed to minimize the use of irradiation. These strategies rely on the assumption that irradiation is the principal cause of treatment related side effects. However, surgery and chemotherapy may bring additional and substantial morbidity. In the modern age, it is of paramount importance that all the caregivers are aware of the specific sequelae associated with each treatment modality alone and in combination, before definite therapeutic decisions are made. It is now possible for some tumors like medulloblastoma to draw algorithms to predict long-term cognitive outcome based on the principal parameters that can influence IQ: age at diagnosis, interval since diagnosis and irradiation volume and dose, anatomical and neurologic damage. This later risk factor being the most important one in our later studies.

Studying the long-term results of patients treated with old-fashioned strategies can learn us a lot when choosing a given new strategy. Indeed, one can guess the late sequelae of a given modality based on the type of refinement of the treatment. In addition, any new modality has to be fully evaluated on the long-term (or with appropriate surrogates such as early MRI changes), before it can be adopted as a standard. Certainly in the future, all new protocols will need to incorporate careful evaluation of late sequelae.

In addition to treatment related risk factors, age at diagnosis is a major predictor for impaired cognitive outcome. Damage to specific structures may have a strong impact on further development of brain functions and this impact may depend on the age at which the structure is damaged. There will be critical period for each brain region, eg around two years for the cerebellum. We may need to take into account these issues for treatment planning in the future.

Finally, rehabilitation by dedicated teams is still the best guarantee to lower the burden of disease and treatment-related late complications.

Concern about the neuropsychological consequences of cancer and its treatment initially focused on treatment of acute lymphoblastic leukaemia (ALL) in children. Although the earliest reports suggested there were no identifiable effects, burgeoning work in the 1970s and 1980s pointed to intellectual deficits for many children. Younger age on diagnosis was identified as a risk factor, as was female gender. There was also much discussion about whether the deficit was a general one, or specific to certain skills. Attention and concentration were viewed as especially vulnerable.

Cranial irradiation was initially seen to be the most likely cause of any deficits, though subsequent work focused on comparisons between standard and reduced dose radiation, and later chemotherapy alone. In practice, it is clear that many factors determine neuropsychological outcomes, including treatment protocols, as well as socioeconomic and family variables.

Many issues remain. Critical is the question of the underlying cause of the condition. Two main hypotheses have been proposed. The first is that treatment disrupts elementary psychological processes such as attention or learning, and this compromises further development and acquisition of subsequent skills. The second involves a physiological process that is ongoing and results in continued neuronal damage.

While the focus of research has been on identifying whether or not deficits occur, the more pressing question of remediation has received less attention. Drawing to a large extent on the brain injury rehabilitation literature, several techniques have now been described, including pharmacotherapy, cognitive remediation and ecological interventions. The latter emphasises the important role of schools and families in acknowledging the child’s problems and engaging them in the child’s education.

School achievement and acquisition of skills is vital for successful adult functioning, and especially so given the excellent survival rates now being achieved. Waiting until the child is a long-term survivor before considering these issues is not acceptable, and regular assessment, and associated remediation if needed, is vital.
Second malignant neoplasms and late mortality as complications after cancer in childhood and adolescence

Garwicz, Stanislaw
Division of Pediatric Oncology, Department of Pediatrics, Lund, Sweden

Second malignant neoplasms
The observations that children treated for cancer are at increased risk of developing second malignant neoplasms (SMN) are not new. Starting with single case reports more than four decades ago, the literature now encompasses more than hundred publications of various size and quality. Combining elements of pediatric oncology, adult oncology, cancer epidemiology, radiobiology, legislation and statistics, every investigation of SMN must address several methodological issues, which are sometimes not readily recognizable. At the same time, when interpreting the results, readers should be aware of different approaches in different studies.

In the hospital-based studies, the standardized incidence ratio (SIR) of SMN is between 5 and 20 and the cumulative risk at 20 years of follow-up is between 3% and 12%. In the population-based studies the corresponding figures are: SIR 3.6 - 6.4 and cumulative risk 2.6% - 3.6%, compared with 0.6% expected. Absolute excess risk (AER) is between 1 and 3.5 cases of SMN per 1,000 person-years. The risk is higher in the patients treated more recently.

As SMN, bone and connective tissue tumors, breast cancer, CNS tumors and thyroid cancer have highest SIR. The interval between first and second cancer is in average more than 10 years, being shortest for leukemia and longest for breast cancer and tumors of the digestive tract as SMN. Among specific combinations of the first and second cancers, especially worrying is the high cumulative risk of breast cancer among women surviving Hodgkin lymphoma. Results of the investigations on the etiological factors in the development of SMN are partly conflicting. Genetic factors, radiation therapy, chemotherapy and possibly also relapse of the primary tumor per se, are all incriminated in increasing the risk of SMN, but their quantitative contribution is difficult to establish and it varies greatly depending on the nature of first and second cancer.

Late mortality
Cumulative mortality among 5-year survivors diagnosed in sixties through eighties is 8 - 10% at 15 years after diagnosis and 12 - 14% at 25 years. Standardized mortality ratio (SMR) is about tenfold higher than in the general population, SMR is highest at 5 - 10 years after diagnosis and decreases with longer follow-up. Absolute excess risk (AER) is about 7 deaths per 1,000 person-years at risk. Cumulative mortality is higher in males than females, while SMR is higher in females, depending on lower background mortality in women. The highest percentage of deaths is observed among patients with Hodgkin lymphoma, CNS tumors and leukemia. Relapse status in the first 5 years after diagnosis, age at diagnosis, treatment era and treatment modality appear to be important prognostic indicators. The pattern of causes of death depends on primary diagnosis and varies with the length of follow-up. While recurrence of the primary tumor dominates greatly at shorter follow-up, second malignant neoplasms, cardiac toxicity and pulmonary complications emerge as important causes of death with longer follow-up. Since mortality continues to be excessive many years after diagnosis, further long-term follow-up of survivors of cancer in childhood and adolescence is mandatory.

What is the role of the nurse in the late effects practice/clinic?

Gibson, Faith
UCL Institute of Child Health and Great Ormond Street Hospital for Children, Centre for Nursing and Allied Health Research, London, United Kingdom

Though cure from cancer is not guaranteed, children’s chances of survival have increased significantly. As a result the paediatric oncology community is focused on providing appropriate follow-up care to an increasing number of cancer survivors. However, while there is theoretical agreement about how future follow-up care should be designed and delivered the current service remains somewhat inconsistent and fragmented. There remains some uncertainty around ‘whom’, ‘how’, ‘when’ and ‘why’ in relation to follow-up care: with some tensions existing between health care professionals and young person’s views. This presentation mainly addresses the ‘who’ factor in this debate, focusing exclusively on the role of the nurse, but within this context the ‘why’ will also receive some attention: drawing on both professional and service users perspectives.

Nurses can play a key role in follow-up care: by decreasing the full impact of long-lasting effects of treatment; assisting the child/young person and family to cope effectively while monitoring and treating late effects; helping them and their family gain perspective on the cancer experience so that they can be vigilant toward potential late effects. There is evidence already in existence that supports maximising the role of the nurse in follow-up care. For example, nurse-led follow-up clinics have been in place in the USA since 1983, and in the UK there is evidence that nurses have begun to take a role in long-term follow-up. However, some roles are not consistent in either approach or intentions and outcomes are rarely described, leaving posts fragile when service re-organisations take place. This presentation draws on data collected from nurses working in late effects in the UK and elsewhere with the specific aim of capturing a moment in time to describe the characteristics of this evolving role. There is a need to move beyond traditional frameworks of treatment and care that are situated in historical professional boundaries in order that we embrace enhanced cancer care for survivors.
The evolution of multidisciplinary management of malignant disease that occurs during childhood has led to improved survival into adult life. However, this success has come at a cost. In excess of 60% of survivors of childhood cancer have one or more on-going medical problem and are at risk of additional problems such as endocrine dysfunction or second malignancy. Consequently this cohort of patients require life-long follow-up in a service that provides appropriate management of the conditions the patient already suffers and surveillance for those they may develop in the future. To a certain extent long-term follow-up services have evolved out of necessity and their nature has been dependent upon local geographical arrangement of services and personnel who are willing to be involved.

The ideal service should facilitate seamless care of patients from treatment in childhood to independent living young adults. Transition between paediatric and adult services is important. Many patients are lost to follow up during this period so a robust process needs to be in place to ensure that the necessary information and the patient are moved between the two services. Each part of the service must provide education, psychological support and access to specialist facilities appropriate to the patient’s age.

Further evaluation of current models is required to determine the optimal follow up strategies of this complex cohort of patients.

In 1981, the first results of the experience with GH treatment were reported in 6 children who had survived a brain tumour (CBT). All responded to GH therapy, and growth rates increased to 6.0-10.1 cm during the first year. Final height outcomes in CBT survivors treated with GH were subsequently reported by various centres, with a significant proportion of children reaching final heights above the third centile. A study of the effects of spinal irradiation on final height in 79 CBT patients (not treated with GH) estimated the radiation-related spinal height loss to be at least 9 versus 7 versus 5.5 cm when irradiation was given at the age of 1 versus 5 versus 10 years, highlighting the vulnerability of very young children to suffer the most severe spinal growth retardation.

Another factor, often encountered in CBT survivors, contributes to the relatively poor spinal growth response: early (although less frequent true precocious) puberty, which tends to be of normal duration. The predicted age of onset of puberty is positively correlated with the age at cranial irradiation. Both the radiation osteitis of the spine and abnormal pubertal tempo in the context of early onset contribute to the poor response of sitting height to GH treatment. Analysis of auxological data of the last 25 years of GH treatment in CBT survivors in our unit revealed a gradual improvement in final height outcome for both cranial irradiation (r=0.5, p=0.03) and craniospinal irradiation patients (r=0.6, p<0.001. The main factors contributing to that success were the improved and higher GH dosing regimes, the earlier introduction of GH treatment after completion of radiotherapy and the additional use of GnRH analogue therapy for early puberty in selected patients. Lag times between completion of RT and initiation of GH therapy were reduced from a mean 5.8 years to 3.3 years for patients treated before versus after 1988. GnRH analogue therapy conferred additional height benefits in selected patients, although final height gains were often achieved at the expense of increased skeletal disproportion.
Female survivors of childhood cancer are at risk of developing ovarian dysfunction. Risk factors include age at treatment, exposure to ovarian radiation and exposure to alkylating agents. A subset of survivors will suffer loss of ovarian function during or shortly after completing their treatment (referred to as acute ovarian failure [AOF]). Data from the multicenter Childhood Cancer Survivor Study (CCSS) indicated that ~6% of some 3000 female survivors developed AOF. Predominant risk factors included exposure to >1000 cGy ovarian radiation and exposure to the alkylating agents procarbazine, at any age, and cyclophosphamide, at ages >12 yrs. For females who retained ovarian function following their cancer treatment, data from the CCSS indicated that ~8% went on to develop menopause prior to age 40 yrs (referred to as premature menopause). The major risk factors for premature menopause included older attained age, exposure to ovarian radiation and any alkylating agents, and a diagnosis of Hodgkin lymphoma. For survivors treated with abdomino-pelvic radiation plus alkylating agents, the estimated cumulative incidence was 30%. Male survivors are at high risk of experiencing damage and loss of sperm producing cells. Data suggest that ~50% of male survivors develop oligo-azoospermia. While age at treatment does not appear to be a significant risk factor, exposure to >200 cGy testicular radiation and high-dose alkylating agent therapy (eg, cyclophosphamide doses > 7.5-9 gm/m2) are key risk factors for germ cell failure. Current biomarkers such as serum FSH and inhibin-B are not sensitive enough to establish fertility status in a given individual; sperm analysis is required. Leydig cell failure is much less common compared to germ cell dysfunction and is seen primarily following testicular radiation >2000 cGy.

Timely diagnostics and advanced treatment of childhood cancer results in increased survival of treated patients. On the other hand, high doses of chemotherapy and radiotherapy frequently cause long term or permanent infertility due to gametes damage.

Few well-developed options for fertility preservation in young adolescent patients exist nowadays. Oocyte and embryo cryopreservation are the options for fertility preservation in women who have a partner and whose cancer treatment can be delayed. Hormonal ovarian stimulation or collection of immature oocytes has to be carried out. Collecting and cryopreservation of ejaculated, epididimal or testicular sperm should be offered for male patients with ongoing spermatogenesis. Thawed spermatozoa can be used for fertilization of the partner's eggs by intracytoplasmic sperm injection. Ovarian tissue cryopreservation is the only alternative to preserve fertility in young girls. For prepubertal boys, cryopreservation of spermatogonial stem cells within testicular tissue is an option for fertility preservation. In adult life, stored gonadal tissue can be thawed and either transplanted or matured in vitro. The harvested from patients ovarian or testicular tissue should be tested before transplantation for malignant contamination to prevent transmission of tumour cells in the treatment. Possibility for fertility preservation in young cancer patients should be discussed in a multidisciplinary team. The decision has to be made individually in each case, depending on the nature of disease, type of treatment and patient's age. Fertility preservation is important for improving the quality of life in childhood cancer survivors.
Cognition, Psychology and Quality of Life

Cerebrospinal fluid tau protein level and cognitive decline in children with acute lymphoblastic leukemia. [C:01]

Muszyma-Roslan, Katarzyna; Protas, Piotr; Grabowska, Aleksandra; Krawczuk-Rybak, Maryna.
Medical University, Białystok, Poland

Long-term neuropsychological complications, have been described in children after acute lymphoblastic leukemia (ALL) treatment. The aim of the study was to assess the level of cerebrospinal fluid tau protein (a neurodegenerative marker associated with damage of neuronal axons) and to determine whether it is associated with cognitive decline in children with acute lymphoblastic leukemia. We examined 38 patients with ALL at diagnosis, after induction treatment, during consolidation and before maintenance therapy. The reference group consisted of 22 patients with clinical symptoms of cerebrospinal meningitis. In 19 patients we examined the cognitive functioning in median time 3.7 years after diagnosis.

Results: 1. Neither age nor gender had an effect on tau protein levels in both groups. 2. The mean tau protein value at diagnosis was 286.8 ±121.3 pg/ml in the study group and 297.6 ±96.8 in the reference group (norm for adults <300 pg/ml) and showed no correlation with initial leukocytosis, organomegaly at this point. 3. Dynamic analysis revealed a statistically significant increase in tau protein after induction treatment (401.8 ±140.5) as compared to its level at diagnosis [p<0.008] and later during treatment. 4. The levels of tau protein at various points of treatment did not differ statistically significantly between the groups, except for the values obtained after termination of remission induction. 5. The level of tau protein was negatively correlated with verbal abilities measured by intellectual scale.

Conclusion: Changes in tau protein level may indicate that some patients are at a greater risk of central nervous system damage. This results are cross sectional but it still suggest that the treatment may cause increase of tau protein level and decline of some of cognitive functioning. This requires further studies, also in reference to other central nervous system proteins.

Comparison of verbal and practical intelligence quotient in patients treated for childhood acute lymphoblastic leukemia with chemotherapy only. [C:02]

Gavras, Christoforos; Delinikopoulou, Eleni; Adam, Anna; Papageorgiou, Theodotis; Papakonstantinou, Evgenia; Abatzoglou, Grigorios; Koliouskas, Dimitrios; Athanassiadou, Fan; 1Ahepa University Hospital Thessaloniki Greece, Hematology-Oncology Unit, Katerini, Greece; 2Ahepa University Hospital, Thessaloniki, Greece; 3Ippokration University Hospital, Thessaloniki, Greece

Objective: The objective of the current study was to evaluate the long-term neurocognitive effects of chemotherapy in patients treated for childhood acute lymphoblastic leukemia (ALL) after being off treatment for at least two years.

Methods: The total number of participants was 23, 13 male and 10 female, aged from 8 to 24 years old. All had childhood ALL and had completed their treatment with chemotherapy only at least two years before. The intelligence batteries used in our study were WISC III and WAIS-R, which are universally accepted for assessing children (between 6 and 16 years old) and teenagers (above the age of 16) and adults respectively. The intelligence quotient consists of two independent subtypes of intelligence, which are the verbal and the practical one. The participants got a score for each subtype and these two scores underwent comparison in order to prove or not the existence of any statistical significant difference.

Results: The analysis of the data revealed that there is a considerable number of participants who showed a major discrepancy between the scores in the two subtypes. More specifically, 34.8% showed a difference of more than 11 points between the 2 scores which is statistically significant and 4.3% showed a major and rare difference of more than 19 points, which is regarded as abnormal and indicates the need for further research. The 60.9% of the participants showed no statistical significant differences between the scores they got.

Conclusions: From all participants, 39.1% showed a statistical significant difference between the scores they got in the two subtypes of intelligence. The performance of each participant is considered on an individual basis and personal, biological, psychological and other environmental parameters are being taken into account to evaluate the results. Therefore, a different approach is being incorporated by the therapeutic team.
Underlying mechanisms of late neurocognitive sequelae after treatment of childhood ALL

Schuitema, Ilse1; De Sonneville, Leo1; Sanz-Arigita, Ernesto2; Barkhof, Frederik; Van Dijk, Bob1; Stam, Kees1; Buizer, Annemiek1; Veerman, Anja1; Van den Bos, Cor2
1Leiden University, Clinical Child and Adolescent Studies, Leiden, Netherlands; 2VU University Medical Center, Radiology, Amsterdam, Netherlands; 3VU University Medical Center, Clinical Neurophysiology, Amsterdam, Netherlands; 4VU University Medical Center, Pediatric Hematology-Oncology, Amsterdam, Netherlands; 5Academic Medical Center, Pediatric Oncology, Amsterdam, Netherlands

**Objective:** Cognitive functions depend on the integrity of functional networks in the brain. White matter damage can be a cause of disruption of functional networks. We are trying to find the underlying mechanisms of long-term neurocognitive sequelae after childhood ALL by assessment of functional connectivity and quality of the white matter.

**Methods:** Children treated according to two protocols are studied: DCLSG ALL5 (cranial irradiation plus chemotherapy (CRT+CT)) and DCLSG ALL6 (chemotherapy only (CT-only)). In a pilot-study, 14 ALL survivors (7 treated with CRT+CT; 7 treated with CT-only) and 10 healthy controls, were assessed with the Amsterdam Neuropsychological Tasks (ANT) program, structural and functional MRI (n-back task), DTI (diffusion tensor imaging, assessing white matter quality) and MEG (magnetoencephalography, assessing connectivity between brain regions). This pilot-study is being followed by a larger project assessing 175 ALL survivors (2006 - 2010). Quality of life will also be assessed.

**Results pilot-study:** Functional MRI showed different results for each level of the n-back task. On the 1-back level, the CT-only group shows more activity in parietal regions compared to controls. On the 2-back level, the CRT+CT group shows more activation in the dorsolateral prefrontal cortex compared to the CT-only group and controls. The CT-only group makes significantly less use of the premotor cortex than controls. On the 3-back level, the CRT+CT group still shows more activation in the dorsolateral prefrontal cortex compared to controls and not as pervasive as was observed in the historic controls, who also suffered from pronounced motor impairment. Patients who had received fractioned irradiation had a somewhat less favourable outcome compared to the BU group.

**Conclusion:** These results suggest differences in neurocognitive function and functional connectivity in long-term survivors of ALL. Diffuse white matter pathology is suggested to underlie these qualitatively different functional networks.

Neuropsychological development after bone marrow transplantation at 0-3 years of age

Smeder, Ann-Charlotte1; Winianski, Jacek2
1Dept of Psychology, Stockholm, Sweden; 2Karolinska Institute, Huddinge Hospital, Dept of Pediatrics, Stockholm, Sweden

**Background/Objective:** In the face of aggressive forms of childhood leukemia, bone marrow transplantation (BMT) may provide a chance for long-term survival. However, conditioning before transplantation involves potentially neurotoxic treatment modalities, such as total body irradiation (TBI) and cytostatic drugs. Since the immature brain is particularly vulnerable to generalized and diffuse insult, children treated at a very young age are most at risk. We have previously demonstrated that BMT, including TBI of 10 Gy in a single dose, is associated with long-term neuropsychological impairment, particularly in children treated at 3 years of age or younger. The present study investigated whether the impact is less severe when TBI is fractioned (FTBI), or replaced by the cytostatic drug busulfan (BU). Internationally available data are inconsistent and inconclusive, particularly regarding very young patients treated with BU.

**Patients and Methods:** Ten children treated with BMT at 4-3.5 years of age (mean age 2.0 years) according to a BU or FTBI protocol were subject to a neuropsychological assessment, at an average of 7.3 years post therapy. Eight children had received BU, and two had received FTBI. Their results were compared to a group who had received TBI in a single dose (n=10 of which 8 were historic controls; mean age at BMT 2.4 years).

**Results:** Compared to age-based normative data, children treated with BU tended to display deficits in visuo-spatial cognitive functioning, attention, mental speed and working memory. However, the deficits were milder and not as pervasive as was observed in the historic controls, who also suffered from pronounced motor impairment. Patients who had received fractioned irradiation had a somewhat less favourable outcome compared to the BU group.

**Conclusion:** BMT is associated with long-term neuropsychological deficits, calling for routine psychological follow-up and counselling. Busulfan has a less negative impact than irradiation on neuropsychological development after treatment at a very young age.
Long-term Psychosocial Support for Families of Children Who Have Undergone Allogeneic SCT

Forinder, Ulla¹; Edberg Posse, Ebba²
¹Institutionen för socialt arbete, socialt arbete, Stockholm, Sweden; ²Karolinska University Hospital, Huddinge, Department of Social Work, Stockholm, Sweden

Background: Stem cell transplantation (SCT) entails a major strain both on children and their families. The 60-70% of children who make up the group of long-term survivors also have a number of late effects to contend with. These include both somatic and psychological effects that impact on the lives of these families. In an earlier study parents of SCT children expressed both concern for their children and a wish for more information as well as for more support. This knowledge resulted in prolonged psychosocial support to these families. All families attend Karolinska University Hospital, Huddinge Sweden for a yearly post-transplant follow-up were offered an appointment with the social worker at the clinic.

Objective: of this study was to evaluate the prolonged psychosocial support. How many families accepted the offered contact with the social worker? What kind of support did the families ask for? Did the meeting result in any intervention and if so of what kind?

Methods: The data that has been used is the social workers notes in the medical chart. Content analysis was used as research method.

Results: 39 of 46 families accepted the offer to have an appointment with the social worker. By analysing data the participating families were categorized into 5 groups. Each group was characterized by different criteria. The study shows that there is an ongoing need for psychosocial support many years after treatment. Time since treatment doesn’t decline the need for psychosocial support but the content in the support change over time.

Conclusion: There is a need for long term support among both parents and patients after SCT. The study raise the question if the offered prolonged support is enough.

Post-traumatic Stress and Psychosocial Adjustment in Siblings of Paediatric Leukaemia Survivors

Lyons, Shoshanah¹; Brown, Gary²; Melvin, Diane³; Leiper, Alison⁴.
¹Royal Holloway, University of London & Great Ormond Street Childrens Hospital, London, Department of Psychology, Egham, Surrey, TW20 OEX, United Kingdom; ²Royal Holloway, University of London, Department of Psychology, Egham, Surrey, TW20 OEX, United Kingdom; ³Great Ormond Street Childrens Hospital, Department of Psychological Medicine, London, United Kingdom; ⁴Great Ormond Street Childrens Hospital, Department of Haematology and Oncology, London, United Kingdom

Background: Recent research has indicated that a model of post-traumatic stress is applicable to paediatric patients who have a diagnosis of cancer, and their mothers and fathers. However, research on the long-term sequelae of siblings of cancer survivors is limited and inconsistent, and it is not clear whether a model of post-traumatic stress also applies to siblings.

Objectives: To investigate whether siblings of childhood leukaemia survivors experience long-term post-traumatic stress symptoms (PTSS) and poor psychosocial adjustment. To identify risk factors influencing PTSS, and parental perceptions of child post-traumatic stress.

Method: 66 child and adolescent siblings of leukaemia survivors were compared with 70 control participants on measures of PTSS, anxiety, depression and self-esteem. Parents completed a measure of behavioural problems and child PTSS.

Results: 35% of siblings reported mild PTSS, and a further 35% reported moderate-to-severe PTSS, which was significantly higher than the control group. No overall differences were found between groups on measures of general adjustment, however, siblings who did not have PTSS fared better than controls on measures of depression, anxiety and low self-esteem. No demographic, individual or illness variables predicted PTSS. Parents of siblings significantly under-estimated their child’s PTSS, and this was associated with the severity of sibling distress.

Conclusions: Levels of PTSS, but not depression, anxiety, low self-esteem or behavioural problems were elevated in siblings of childhood leukaemia survivors. Furthermore, siblings who did not report PTSS appeared to show ‘post-traumatic growth’ following their experience. Thus, PTSS may be a useful model for understanding siblings’ long-term adjustment to childhood cancer.
Objective: This study was performed during 2003 focusing on health related quality of life among children and adolescents following successful Stem cell transplantation (SCT). The aim was to explore aspects of health related quality of life (HRQoL) both according to diagnosis, the use of a related or unrelated donor.

Methods: A total of 52 children, (age 9-22, m=15) and at least 3 years (median=8) beyond SCT for leukemia (n=31) or nonmalignant diseases, participated in a single center study of health related quality of life (HRQoL) at Karolinska University Hospital, Huddinge. 42 parents participated in the study at the same occasion. With a cross sectional design descriptive statistics, Students T-test and standard multiple regression analyses were used to assess the effect of diagnosis, donor choice, subjective and objective health on HRQoL domains in Swedish Child Health Questionnaire (SCHQ-CF87/ SCHQ-PF50).

Results: As a group we recently reported children having a good HRQoL after SCT, in comparison to a normgroup and other chronically ill children. Most children were also subjectively and objectively in good health. Children with leukemia rated a lower HRQoL score in the psychosocial area (p<0.05) and had a higher degree of objective late effects (p<0.05). Parents rated their children's HRQoL lower in both the psychosocial area and physical area if the child are diagnosed with leukemia compared to non-malignant diagnosis (p<0.01). Late effects are the strongest contributor to the parents HRQoL ratings (p<0.05) and also had an impact on their own (parents) emotional situation. The psychosocial HRQoL area was most affected in recipients of an unrelated donor, according to child (p<0.01) and parent (p<0.05).

Conclusion: Children reason they have a good HRQoL following SCT, but their parents do not agree with this view. When interpreting paediatric HRQoL studies it is crucial to be clear who is responsible for assessing the child's HRQoL. One important clinical conclusion from the study is might be to focus healthcare resources on psychosocial support to both child and parent, especially on the group with more late-effect-related problems.
Background/ Objective: Along with the increasing number of childhood cancer survivors, the late effects of anticancer therapy and the associated quality of survival have got to the forefront of interest. At present, the research in this field is facing methodological problems derived primarily from a paucity of suitable measurement methods and a lack of longitudinal work.

The purpose of the project is to establish a longitudinal study of the quality of life in children surviving cancer in the Czech Republic. The methodological goal of the study is to establish methodology of measuring the quality of life that would reflect changes in the perception of the quality of life throughout the life cycle. The research purpose of the study is to identify the areas in which the quality of life in children with cancer is reduced, both in terms of objective parameters and the subjective perception of contentment.

Methods: The identification of target areas will be based on a comparison of three study populations (healthy children, children with chronic diseases other than cancer and children with cancer). During the duration of the project (4 years), at least 300 childhood cancer survivors can be expected to participate. The results of the research will be analyzed, with the intention to prepare appropriate preventive and interventional strategies that could improve the quality of life in children with cancer.

Results: In 2006 we created the original quality of life assessment (in Czech). Since November 2006 until February 2007 it has been administered to the first 16 childhood cancer survivors (age 7-18) in the framework of a pilot study qolop (Quality Of Life of Oncology Paediatric patients) at the Department of Paediatric Oncology, Brno. We set up the project’s website (http://qolop.eu). Here we present our actual experience obtained from the pilot study.

This research is supported by the Grant Agency of the Czech Republic under No 406/07/1384.
Positive and negative consequences with regard to cancer during adolescence – Experiences two years after diagnosis

Mattsson, Elisabet1; Ringner, Anders; Ljungman, Gustaf2; von Essen, Louise3
1Public Health and Caring Sciences, Psychosocial Oncology, Uppsala, Sweden; 2Dep of Women’s and Children’s Health, Paediatric Oncology, Uppsala, Sweden

Objectives: The purpose was to explore negative and positive consequences of cancer during adolescence experienced two years after diagnosis.

Methods: Two years after diagnosis thirty-eight persons, 15-21 years old, were asked two questions over the telephone: What, if anything, is bad for you due to the cancer disease? and What, if anything, is good for you due to the cancer disease? The answers were analysed by content analysis.

Results: Four categories of negative experiences were identified: a problematic body, unpleasant thoughts and feelings, outside the circle of friends, and difficulties with schoolwork. Six categories of positive experiences were identified: a more positive view of life, good self-esteem, knowledge and experience with regard to disease and hospital care, good relations, broader perspectives, and material gains.

Conclusions: Two years after diagnosis those struck by cancer during adolescence experience not only a number of negative, but also positive, consequences of the cancer disease and its treatment.

Are there any positive consequences related to surviving childhood cancer? A review of the literature

Mattsson, Elisabet1; Lindgren, Björn2; von Essen, Louise1
1Public Health and Caring Sciences, Psychosocial Oncology, Uppsala, Sweden; 2The Vårdal Institute, Lunds University, Lund, Sweden

The aim was to investigate whether there are any positive consequences related to surviving childhood cancer. A review of the literature was performed. In the first step studies with a descriptive design published 1990-2005 reporting at least one positive consequence related to surviving childhood cancer were identified through a search of the databases CINAHL, PsycINFO, and PubMed. Positive consequences were referred to three themes, according to a manifest content analysis: life values, relations to others, and relation to self. Taking these as a starting point a second search was conducted in the databases with the purpose of identifying studies with a comparative design in which variables that could be referred to these themes were investigated. The findings demonstrate that survivors of childhood cancer in most regards are similar to comparison groups with regard to life values, relations to others, and relation to self. However, friendship, marital status, parenthood, and sexuality are areas of concern for survivors of childhood cancer. The major implication for clinical care is that survivors of childhood cancer need to be followed-up by a multi-professional team.
Background/Objectives: The present study sets out to add to knowledge about the development over time of health-related quality of life (HRQL), anxiety, and depression among survivors of adolescent cancer. The aim was to investigate if and how the HRQL, anxiety, and depression of a group of adolescents with cancer differ from those of a reference group shortly after diagnosis, and subsequently at six, twelve, and eighteen months after diagnosis.

Methods: Adolescents diagnosed with cancer and a reference group randomized from the general population completed the Hospital Anxiety and Depression Scale (HADS) and the two subscales Mental Health and Vitality in the Short Form 36 (SF-36) in telephone interviews.

Results: The results indicate a steady increase in psychological well-being from the time of diagnosis when the cancer patients’ ratings were significantly worse than those of the general population, and onwards. The differences gradually disappeared and then were reversed, resulting in the cancer group reporting significantly better HRQL and lower levels of anxiety and depression than the reference group when 1.5 years had passed since diagnosis.

Conclusions: The adolescents faced with cancer show signs of adaptation to trauma which can be understood in relation to the theoretical framework of posttraumatic growth as well as response shift. Future research should continue to follow this development over time, to investigate if the positive effects of the cancer experience will wear off, or if it has facilitated permanent positive outcome.

Objective: The overall aim was to explore whether, and if so in what ways, long-term survivors from childhood cancer experience that their life is influenced by having had cancer.

Methods: All patients diagnosed with childhood cancer between 1985 and 1999 at Astrid Lindgren’s Hospital, Karolinska University Hospital, Stockholm, were invited to participate in the study of which 253 accepted participation (response rate 72 %). Telephone interviews were conducted with participants using an extended version of The Schedule for the Evaluation of Individual Quality of Life-Direct Weighting (SEIQoL-DW). The method uses semi-structured interviews to measure individual quality of life and influence of the former disease on life. The extended version used in this study included a disease-related part. Respondents were asked: ‘If you think about the fact that you have been treated for childhood cancer, what in your life is influenced, both positively and negatively by this? The respondent was allowed to mention as many aspects/areas as wanted. Each aspect/area was subsequently rated regarding how troublesome or satisfying it was perceived today on category scale. The mentioned aspects and areas influencing life today were analysed by means of content analysis.

Results: Preliminary results indicate that approximately 48% of the long-term survivors reported negative consequences and 50% reported positive consequences of having had cancer. The reported negative aspect/areas included a disruption of life, an altered body image, changed interpersonal relationships, disturbing scars and thoughts and worries. The most frequently reported positive aspect/areas were described as a life experience, personal development, improved relationships to other people, a positive outlook on life and increased empathy for others.

Conclusions: Long-term survivors who have experienced childhood cancer report numerous consequences influencing their adult life. Interestingly, positive and negative consequences were reported to the same extent.
Endocrinology, Growth and Metabolism

Thyroid function in children after hematopoietic stem cell transplantation

Niedzielska, Ewa1; Barg, Ewa2; Dorosko, Adrian3; Sego-Pondel, Dorota1; Kazanowska, Bernarda1; Wójcik, Dorota1
1Department of Pediatric Hematology/Oncology and Bone Marrow Transplantation, Wroclaw Medical University, Wroclaw, Poland; 2Department of Endocrinology for Children and Adolescents, Wroclaw Medical University, Wroclaw, Poland; 3Department of Internal Medicine, Occupational Diseases and Hypertension Wroclaw Medical University, Wroclaw, Poland

Background: The success story in transplantation medicine has resulted late effects, e.g. impaired endocrine-, especially abnormal thyroid function. In this study we evaluated the thyroid function in pediatric long-term survivors of hematopoietic stem cell transplantation (HSCT).

Methods: 42 patients (24 girls and 18 boys) aged 2-20 years (median 12.5 years, mean 11.58 ± 4.95) were evaluated prospectively post transplant. The reason for HSCT were: AML (n=10), ALL (n=11), NHL (n=4), CML (n=6), MDS (n=2), carcynoma embryonale (n=2), NBL (n=3) and JMML, RMS, medulloblastoma, Ewing/PNET. These patients underwent autologous HCT (n=15), allogenic MSD-HCT (n=11), MUD-HCT (n=11) and HLA-mismatched related HCT (n=5). In three children two transplants were performed subsequently. The preparative regimens consisted of HDC/T usually BU/MEL (9); BU/CY/VP (6); BU/CY/ATG (5); VP/ATG/TBI (3); BEAM (3). Cranial irradiation (CI) prior grafting received 19 children: auto-HSCT(6) and allo-HSCT(13) and total body irradiation (TBI) in 6 patients. Endocrine function was evaluated from 3 to 104 months (median 24 months) after cessation of steroid therapy. Analysis of TSH, fT3, fT4, aTPO, TRH test was performed.

Results: A) Hypothyroidism was found in 5 pts (2 after auto-HSCT, 3 after allo-HSCT).
B) 2 patients with hypothyroidism underwent CNS radiotherapy prior to the transplant and total body irradiation (TBI) in 1 patient.
C) 3 patients had abnormal aTPO and thyroid hormone substitution was instituted.
D) No case of hyperthyroidism was diagnosed.
E) Time from steroid therapy cessation did not influence the onset of abnormal thyroid function.

Conclusions: Children require standardized endocrine follow-up after HCT, because thyroid metabolism dysfunctions may occur frequently and worsen the quality of life posttransplant.

Abnormalities of the thyroid in long term survivors of Hodgkin’s disease in childhood and adolescence

Vandecruys, Els; Dhooge, Catharina; Benoit, Yves; Laureys, Genevieve
Ghent University Hospital, Pediatric Hemato-Oncology, Ghent, Belgium

Treatment for Hodgkin’s disease (HD) is associated with a variety of thyroid abnormalities, including hypothyroidism, hyperthyroidism and thyroid neoplasms. We retrospectively studied the occurrence of thyroid abnormalities in patients who became a long term survivor after treatment of pediatric Hodgkin Lymphoma at our institution.

From February 1982 until February 2002 the diagnosis of HD has been made in 61 patients, 41 boys and 20 girls, the youngest 3 years(y) 9 months(m) and the oldest 15y6m at diagnosis. Five patients died of disease and 56 became a long term survivor. The duration of follow-up varied between 5 and 25 years.

Results: 18 out of 56 patients (32.1%) developed a thyroid abnormality, 14 subclinical hypothyroidism and 4 thyroid nodules of which 1 thyroid cancer. All patients received neck radiation (dose of radiation to the thyroid 20 Gy in 14, 30 Gy in 1 and 50 Gy in 2 patients who were treated twice) as part of the treatment. Subclinical hypothyroidism was diagnosed in 9 males and 5 females with a mean age at diagnosis of HD of 9y10m (range 4y10m - 15y6m). Hypothyroidism developed a mean of 4y6m (range 1y6m - 11y) after diagnosis of HD. All patients are receiving thyroid hormone replacement therapy. None of these patients developed a clinically apparent thyroid nodule so far. Screening ultrasonography is not routinely performed. Thyroid nodule(s) were diagnosed in 3 males and 1 female with a mean age at diagnosis of HD of 5y10m (range 3y9m - 8y3m). Thyroid nodule(s) developed a mean of 13y1m (range 9y5m - 18y9m) after diagnosis of HD. None of these 4 patients had previously subclinical hypothyroidism. 2 patients had nodular hyperplasia, 1 patient had a thyroid adenoma and 1 patient had a papillary carcinoma. They underwent thyroid surgery (hemi or total thyroidectomy) and are currently receiving thyroid hormone replacement therapy.

Conclusion: 18 out 56 (32.1%) long term survivors of HD in childhood developed a thyroid abnormality, 14 subclinical hypothyroidism and 4 thyroid nodules of which 1 thyroid cancer. The incidence of thyroid nodules may be underestimated since screening ultrasonography is not routinely performed.
Introduction: Having achieved long term survival for pediatric Hodgkin's disease in the range of around 90%, the focus has now shifted on the prevention of therapy related long term complications. Introduction of combined modality protocols in the mid eighties was the first step in this direction. Over the last 2 decades, there has been more and more refinement of these protocols to bring down the incidence of long term toxicity to a minimum level. Even with reduced dose, post radiotherapy (RT) long term complications are still a matter of concern. RT to neck and upper chest can lead to various long term complications including thyroid dysfunction. This could be of serious consequences particularly in growing children. This study was undertaken to find out the incidence of clinical or asymptomatic hypothyroidism in patients who were treated with combined modality therapy, and received RT to neck and upper chest.

Methodology: This is a retrospective analysis of all children with Hodgkin's Lymphoma (age 15 years or less), who were treated at our institute between January 1997 and December 2005.

Results: A total of 50 children were treated. The median age was 10 years (range 3 - 15 years). Majority of children were treated on combined modality protocol, with ABVD chemotherapy and involved field radiotherapy (IFRT). RT was given to 36 patients (72%). The dose of RT ranged from 15 to 30 Grys. Thirty four children (68%) received RT to neck and upper chest. Forty three patients (86%) achieved CR / CRU status at presentation in growing children. This study was undertaken to find out the incidence of clinical or asymptomatic hypothyroidism in patients who were treated with combined modality therapy, and received RT to neck and upper chest. Forty three patients (86%) achieved CR / CRU status at presentation.

Conclusion: A significant number of children developed hypothyroidism after receiving RT to neck and upper chest, which requires replacement therapy for life long. All efforts must be made to find protocols, where RT to the neck and upper chest could be avoided.
Detection of growth hormone deficiency in childhood cancer survivors

Ket, Jan Lucas1; von den Bos, C.1; van der Pal, HJH.1; Fliers, E.2; van Trosenberg, AS.1; Heinen, RC.1; Caron, HN.1; Kremer, LCM.1
1Emma Kinderziekenhuis/AMC, Paediatric Oncology, Amsterdam, Netherlands; 2Academic Medical Center, Endocrinology, Amsterdam, Netherlands; 3Emma Kinderziekenhuis/AMC, Paediatric Endocrinology, Amsterdam, Netherlands

**Background/ Objective:** To determine the prevalence of an abnormal growth hormone (GH) reserve in a cohort of childhood cancer survivors (CCS), and the fraction of GH-deficient CCS on GH-substitution therapy. Furthermore the number of CCS where an abnormal GH-reserve could be detected by a predefined screening protocol was evaluated.

**Methods:** All 387 5-year CCS previously treated at the Emma Children’s Hospital/ Academic Medical Center with craniofacial radiotherapy or surgery to the brain between 1966 and 1999 were retrospectively examined for GH abnormalities as reflected by serum IGF-1 level, GH-stimulation tests and GH-substitution therapy.

**Results:** Interval between diagnosis and last follow-up: mean 19.6 years (range 5-37). Data on GH status were available from 278 of the 387 patients (72%). In the first five years after diagnosis 76 patients underwent a GH assessment, 42 had an abnormal GH-reserve, of whom 26 received GH-substitution. After five years survival 262 of 387 patients underwent GH assessment, 202 of whom for the first time (with a mean of 16.9 years after cancer diagnosis, range 5.0 to 34.4 years). From the other 125 late survivors in follow-up 54 patients died without any GH assessment and 71 surviving patients underwent no GH assessment at all. Of all patients analyzed (n=262) 65 (25%) had an abnormal GH-reserve, 23 of them already receiving GH-substitution. Fifty patients received GH-substitution after five years after cancer diagnosis. These CCS were detected by a screening protocol.

**Conclusions:** For all 387 CCS at risk the prevalence of an abnormal GH-reserve was 25%. GH-substitution therapy was given to n=76 (20%) during a median of 4.7 years (range 0.4-14.3). Fifty were detected by a predefined screening protocol.

---

Endocrine late effects of pediatric cancer and its therapies - a large cohort from a single institution

Modan-Moses, Dalit1; Pinhas-Hamiel, Orit1; Bielorai, Bela2; Waldman, Dalia1; Goldstein, Gal2; Yalon, Michal2; Neumann, Yoram2; Golan, Hanna2; Kaplanisky, Chaim2; Rechavi, Gideon2; Toren, Amos2
1The Edmond and Lily Safra Children’s Hospital, Pediatric Endocrinology, Ramat-Gan, Israel; 2The Edmond and Lily Safra Children’s Hospital, Pediatric Hematology-Oncology and BMT, Ramat-Gan, Israel

**Background:** Disease-free survival from childhood malignancies has improved significantly over the past few decades. Consequently, quality of life and the avoidance of long-term adverse sequelae of treatment have become major foci of interest.

**Objective:** To evaluate the frequency and severity of long-term endocrine sequelae of pediatric cancer and its therapies.

**Methods:** 505 consecutive patients of the Hemato-Oncology clinic were followed for a mean of 4.38±7.6 years. Endocrine evaluation included height and weight measurements, Tanner staging, and measurement of hormone levels.

**Results:** 127 (25.1%) of the patients had leukemia (ALL=78, other=49), 84 patients (16.0%) had lymphoma (Hodgkin-61, NHL-23), 145 (28.7%) patients had brain tumors, 93 (18.4%) patients had solid tumors, 15 (3%) patients had Langerhans-cell histiocytosis, and 41 (8.1%) had non-malignant hematologic diseases. 112 patients received radiotherapy either to the CNS or to the head/neck area; 85 patients had bone marrow transplantation (BMT). A total of 169 patients (33.5%) had evidence of at least one endocrinopathy. Sixty-one patients (12.1%) had thyroid malfunction: (hypothyroidism=1, primary hypothyroidism=8, sub-clinical hypothyroidism=31, central hypothyroidism=21). Hypothyroidism was related to radiation to the head/neck area, hypothalamic-pituitary lesions, or specific syndromes. 93 patients (18.4%) had evidence of gonadal dysfunction (hyponadotrophic hypogonadism=68 patients, central hypogonadism=25 patients). 29 patients had proven GH deficiency, while 37 additional patients had a decreased growth rate. As expected, GH deficiency occurred almost exclusively in patients who received cranial irradiation or had hypothalamic-pituitary lesions. Hypocortisolism was found in 12 patients, and hyperprolactinemia in 18.

24% of the patients were overweight (BMI>85th percentile for age). Overweight patients were significantly (p=0.002) younger than normal-weight patients.

**Conclusions:** Our data emphasize the importance of careful follow-up of long-term survivors of pediatric malignancy, aimed at counteracting side effects as early as possible and therefore at minimizing long-term morbidity.
Background: Overweight is frequently diagnosed in acute lymphoblastic leukaemia (ALL) survivors, but less is known about body weight after treatment for a solid tumour. Underweight as well as overweight may be risk factors for cardiovascular disease. As treatment for solid tumours often includes potentially cardiotoxic chemotherapy and/or radiotherapy insight in the prevalence of underweight or overweight in long-term solid tumour survivors is important.

Objective: Assessment of the prevalence of under- and/or overweight after solid tumour treatment in childhood.

Patients and methods: Inclusion criteria: diagnosis of solid tumour between 1972 and 1993, age at diagnosis below 21 years, complete remission more than five years post-treatment. Height and weight for BMI were retrospectively calculated 5, 10 and 15 years post-treatment. The prevalence of overweight and underweight in the survivors was compared with reference groups using the Chi2. The relation between BMI and age at diagnosis and gender was evaluated with regression-analysis.

Results: 337 survivors (198 male) met the inclusion criteria. Cancer diagnoses were: sarcoma (n=74), blastoma (n=65), brain tumour (n=72), malignant lymphoma (n=73), Langerhans Cell Histiocytosis (n=24) and miscellaneous (n=29). The prevalence of overweight was not increased. Compared to normal, the prevalence of underweight was significantly increased in women until 10 years post-treatment, in males until 15 years post-treatment, and in survivors of blastoma, sarcoma or malignant lymphoma. There was no relation between BMI and age at diagnosis and gender was evaluated with regression-analysis.

Conclusion: In long term solid tumour survivors the prevalence of underweight was increased, whereas no increase of overweight was found.

Objective: To determine the prevalence of overweight in childhood acute lymphoblastic leukaemia (ALL) survivors and to assess the relation between overweight and age at diagnosis, gender or treatment with cranial irradiation (CI) and/or corticosteroids.

Patients and Methods: Body mass index (BMI) was assessed in patients in continuous complete remission of ALL who were diagnosed between 1972 and 1993 and who were treated according to the DCLSG protocols ALL 2, 3A, 5-8 or the local ALL high-risk protocol. Patients were divided into three treatment groups. Group 1 included patients who received CI and intermittent corticosteroids for two years (n = 77); group 2 included those who had intermittent corticosteroids for two years (n = 24); group 3 included patients who had two courses of corticosteroids for four weeks each (n = 47). Prevalence in overweight was compared between groups. The relation of overweight and gender or age at diagnosis was assessed by logistic regression analysis. The prevalence of overweight in the entire group was compared with the growth diagrams from the "Fourth Dutch nation-wide Survey 1997".

Results: Until five years post-diagnosis more overweight was demonstrated in group 2 survivors; afterwards we found no differences between groups. The prevalence of overweight in boys surviving more than five years after diagnosis was 17.1% at age 10 and 16.7% at age 15 (Fourth Dutch Nation-wide Survey 7.8%; Chi2 p = 0.01, and 7.7%; p = 0.07). The prevalence of overweight in girls surviving more than five years after diagnosis was 24.4% at age 10 and 28.0% at age 15 (Fourth Dutch Nation-wide Survey resp.11.8%: p = 0.03 and 9.4%: p< 0.01). Overweight correlated with age at diagnosis younger than four years but not with gender.

Conclusion: Survivors of childhood ALL are at high risk for overweight, irrespective of CI and duration of corticosteroid treatment.
Obesity in survivors of childhood malignancies

Modan-Moses, Dalit1; Mazor-Aronovitch, Kineret1; Pinhas-Hamiel, Ori1; Biderai, Bela2; Waldman, Dalia2; Goldstein, Gal2; Neumann, Yoram2; Golan, Hana2; Kaplinsky, Chaim2; Toren, Amos2

1The Edmond and Lily Safra Children’s Hospital, Pediatric Endocrinology, Ramat-Gan, Israel; 2The Edmond and Lily Safra Children’s Hospital, Pediatric Hematology-Oncology and BMT, Ramat-Gan, Israel

Background: Increased incidence of obesity, dyslipidemia, hyperinsulinemia, and impaired glucose tolerance, as well as increased cardiovascular morbidity and mortality have been described in survivors of childhood cancer.

Objective: To evaluate the incidence of overweight and obesity in survivors of childhood cancer followed in our clinic and to identify potential risk factors.

Patients and Methods: Three hundred and forty patients (51.1% males) were prospectively evaluated in our late effects clinic. The mean age at diagnosis was 7.8 years, and the mean age at the time of evaluation was 12.4 years. 25% of our patients were treated for leukemia, 17% were treated for lymphoma, 27% had brain tumors, 21% had solid tumors, and 10% had non-malignant hematologic diseases. Eighty-six patients received radiotherapy to the CNS, and 57 patients had bone marrow transplantation (BMT).

Results: 24% of the patients were overweight (BMI>85th percentile for age), while 10.5% were obese (BMI>95th percentile). These rates are roughly twice as high as the reported rates in the pediatric population in Israel. Cranial irradiation was associated with a significantly increased incidence of obesity in survivors of brain tumors, but not in survivors of leukemia. The rates of overweight and obesity were highest in patients with brain tumors (27.6%), leukemia (29.4%), and optic glioma (38.5%). Overweight and obese patients were significantly (p=0.001) younger than normal-weight patients. This difference may reflect a difference in the distribution of diseases between the different age groups. There was no difference between males and females regarding the risk of obesity.

Conclusions: Obesity is a common sequel of childhood malignancy. Since currently at least 1/1,000 young adults is a survivor of childhood malignancy, it is imperative that healthcare professionals recognize the risk of obesity and the metabolic syndrome in this population and develop strategies to enhance weight control and encourage longitudinal follow-up in order to ensure early prevention of cardiovascular disease.

Association between bone mineral density and history of fractures in childhood cancer survivors

Muszynska-Roslan, Katarzyna; Konstantynowicz, Jerzy; Krawczuk-Rybak, Maryna

Medical University, Bialystok, Poland

Inability to reach peak bone mass is considered as one of causal pathways in survivors of childhood malignancy who develop osteopenia following treatment and are at risk for fractures later in their lives.

To investigate the association between bone mineral density (BMD) and history of fractures in survivors of childhood cancer, dual-energy x-ray absorptiometry was performed twice in 114 patients (70 males) who had been treated for acute lymphoblastic leukemia - ALL (43), Hodgkin disease - HD (35) and solid tumors (36). Median age at diagnosis was 8.4 years; at the consecutive examinations it was 12.8 years and 16.3 years. From 38 subjects (22 males) with a history of fractures, 32 had one whereas six had sustained repeated fractures. All fractures were results of injuries, including low-energy trauma.

Results: For the overall group BMD Z-score for total body (-0.05 ±0.8; -0.07 ±1.0 and lumbar spine (-0.012 ±1.1; 0.03 ±0.9) were not significantly different from reference values in both examinations. In the group reporting fractures, lower BMI, BMD total and Spine Z-score in both examinations were observed in comparison with non-fractured subjects. The analysis in subgroups based on the diagnosis, showed the similar results, except patients treated for ALL. Patients who received treatment for solid tumors had a negative association between both their BMD - total and spine (in Z-scores) and fractures (r= -0.39 p=0.04; r= -0.4 p=0.01). The analysis in subgroups based on the time when the fracture occurred (before, during or after treatment) did not show any differences in BMDs.

Conclusions: Childhood cancer survivors with history of fractures have lower BMD and represent a higher risk of osteoporosis compared with patients without fractures, (especially after treatment for solid tumors).
Follin, Cecilia1; Link, Katarina2; Erfurth, Eva Marie1

1Institution of clinical sciences, Department of Endocrinology, Lund, Sweden; 2Institution of clinical sciences, Department of Endocrinology, Malmö, Sweden

**Background**: Adults with childhood onset GHD have reduced BMD (Bone Mineral Density). Previously, it has been shown that BMD was reduced in young adult survivors treated with cranial radiation (CRT) for childhood ALL. As ALL patients are shorter their bones will have smaller width and also be thinner, i.e. volume corrections, using BMAD is therefore preferable.

**Methods**: 44 former ALL patients (19-31 yr) treated with CRT (18-24 Gy) and chemotherapy with confirmed GHD (91%) or GH insufficiency, and matched controls were studied at baseline. A subgroup of 16 former ALL patients were treated with GH for 4 years and compared with the same controls as from baseline. BMAD and BMD were evaluated by DEXA and markers of bone turnover (crosslaps and osteocalcin) were analysed.

**Results**: Compared with controls, the former ALL patients were significantly shorter (p < 0.001) and had higher BMI (p = 0.005). Serum IGF-1 was significantly lower in the patients (p = 0.004). Compared to controls, BMAD was not reduced in mid radius (p = 0.07), femoral neck (p > 0.3), lumbar spine (p = 0.19), or total body (p = 0.3). A small reduction in BMD of mid radius (p=0.06) and total body (p=0.05) was recorded among the patients, but with no differences in femoral neck, lumbar spine, or in markers of bone turnover (crosslaps and osteocalcin) were analysed.

**Conclusions**: No difference in BMAD at any skeletal sight, or in bone formation markers, was recorded in former ALL patients with GHD. After 4 years of GH treatment, BMAD was unchanged.

---

**Frey, Eva; Hutter, Caroline; Kager, Leo; Helmut, Gadner**
St. Anna Children’s Hospital, Vienna, Austria

**Background**: There is rising concern about skeletal morbidity as a long-term sequela of childhood ALL and NHL. We analyzed bone mineral density (BMD) of survivors of ALL or NHL and tested whether putative risk factors such as age at diagnosis, sex or cranial irradiation had a long-term effect on bone density.

**Method**: We assessed the bone density of 76 patients who had been treated according to BFM protocols for either ALL (N= 67) or NHL (N=9) in the St. Anna Children’s Hospital between 1977 and 1990. DEXA measurement was undertaken in patients who were above 17.5 yrs and had been diagnosed with their condition more than ten years ago. The rationale for this late timepoint was that this group of former patients can be expected to be postpubertal and have already acquired peak bone mass. The mean age at diagnosis was 6.54 years (range: 1.3-15 years) and the mean age at time of DEXA measurement was 21.52 years (range: 17.5-33.5 years).

**Results**: The mean T-Score was -0.94 overall (min -3.3, max 1.13). 8 patients had a T-Score below -2. In contrast to earlier reports we did not find a significant correlation between T Scores (or Z Scores) and age at diagnosis. The mean T-Score in children aged 1-5 at time of diagnosis was -1.08 (SD 1.06), in children aged 6-10 -0.87 (SD 0.95) and those aged 11-15 at time of diagnosis -0.71 (SD 0.73). Furthermore, there was no significant difference in T scores between male and female patients (F: -0.83, SD 1.02; M: -1.02, SD 0.96). We also tested whether cranial irradiation had a negative impact on bone density and found, that there was no correlation between irradiation and bone density 10 years after diagnosis of the initial disease (+ CRX: -1.0, SD 0.89; - CRX: -0.9, SD 1.09).

**Conclusions**: The analysis of this patient population shows no significant correlation between bone density and age at time of diagnosis, sex, or cranial irradiation. Moreover, bone density of patients who had suffered from ALL or NHL normalizes over the years. To our knowledge, the analyzed patient cohort comprises the largest number of patients who are homogeneous regarding time after diagnosis, patient age and treatment protocol.
Occurrence of abnormal glucose metabolism in children treated with hematopoietic stem cell transplantation. Risk factor analysis

Wojcik, Dorota1; Niedzielska, Ewa1; Sega-Pondel, Dorota1; Doroszko, Adrian2; Kazanowska, Bernarda1; Barg, Ewa3

1Department of Pediatric Hematology/Oncology and Bone Marrow Transplantation Wroclaw Medical University, Wroclaw, Poland; 2Department of Internal Medicine, Occupational Diseases and Hypertension. Wroclaw Medical University, Wroclaw, Poland; 3Department of Endocrinology for Children and Adolescents Wroclaw Medical University, Wroclaw, Poland

Background: Endocrine deficiencies are usual complications in children observed after hematopoietic stem cell transplantation(HSCT). This study focuses glucose metabolism in long term survivals.

Methods: In a single transplant centre we investigated: A) 15 patients after auto-HSCT (7 girls, 8 boys) aged 3-20 years (average 11,62 ±5,20) for AML(5), NHL(3), NBL(3), embryonal cancer(2), medulloblastoma, Ewing/PNET; B) 27 patients after allo-HSCT (17 girls, 10 boys) aged 3-17 years (average 11,30 ±4,67). Indication for HSCT was ALL(11), AML(5), CML(6), MDS(2), NHL, JMML, RMS. Allogenic MSD-HSCT underwent(11) patients, MUD-HCT(11) and HLA-mismatched related HSCT(5). Prolonged high steroid doses (at least 28 days) received 18 children: auto-HSCT (4) and allo-HSCT (14) before, and (20) after HSCT . Analysis of IFG - Impaired Fasting Glucose (100-125 mg%), (5,6-6,9 mmol/l); IGT - Impaired Glucose Tolerance (140-199 mg%), (7,8-11 mmol/l); diabetes mellitus, homeostasis model assessment - insulin resistance (HOMA-IR) ≥ 2,5; correct HbA1c (<6,5%) and hiperinsulinemia (>10 mIU/ml), BMI (body mass index) was performed.

Results: 
1) IFG was recognized in 1 pt. Glucose intolerance was found in 7 patients: in 4 treated with auto-HSCT and in 3 after allo-HSCT. All of children had correct HbA1c. 8 pts had incorrect HOMA - index.
2) In none of the children did diabetes mellitus occurred. 
3) There was a statistically significant correlation between of increased HOMA-index and cytostatics: Bu (p=0,0156) and VP (p=0,0046).
4) No correlation was found between IGT and hyperinsulinism and the following parameters: sex, graft type; use of BU, MEL, VP, CY; steroid therapy before and after graft.
5) BMI was 17.80± 2.89 in the analysed group. Positive correlation was found between BMI and hyperinsulinism (p<0,035, R=0,34); BMI and hyperglycemia (p<0,0087, R=0,41); and BMI and increased HOMA-index (p<0,00112, R=0,41). No correlation was found between time from steroid therapy cessation and BMI.

Conclusions: Insulin-resistance may occur after HSCT probably due to use of some cytostatic drugs prior to- or during the preparative regimen. Further research is required to make an exact evaluation.
Follow-up

LATER: A nation-wide registry of 5-year survivors of childhood cancer in the Netherlands

Ronckers, CM1; Kremer, LC2; van den Bos, C.1; Jaspers, MWM.2; Hazelfluff, L.1; Agterek, N.3; Postma, A.3; Halvooort-Cammel, FCAJ.4; Bakkenik, JPM.5; van Dulmen-den Broeder, E.5; Versluis, AB.7; Bresters, D.7; van Leeuwen, FE.9

1Emma Children’s Hospital/AMC, Pediatric Oncology, Amsterdam, Netherlands; 2Academic Medical Center, Medical Informatics, Amsterdam, Netherlands; 3UMCG, Pediatric Oncology, Groningen, Netherlands; 4Sophia Children’s Hospital / Erasmus Medical Center, Pediatric Oncology, Rotterdam, Netherlands; 5University Medical Center Nijmegen, Nijmegen, Netherlands; 6Vrije Universiteit Medical Center, Pediatric Oncology, Amsterdam, Netherlands; 7Wilhelmina Children’s Hospital / UMCU, Pediatric Oncology and Hematology, Utrecht, Netherlands; 8Leiden University Medical Center, Leiden, Netherlands; 9Netherlands Cancer Institute, Epidemiology, Amsterdam, Netherlands

Conclusions: Nationwide registries of late adverse treatment effects in CCS are crucial to provide more insight into the full extent of the problem and to provide a solid basis for evidence-based care for long-term survivors.

Background/objective: In view of accumulating evidence of late treatment effects in childhood cancer survivors (CCS), the need for lifelong follow-up is uniformly recognized. However, the full size of the problem has not yet emerged and optimal strategies for follow-up care remain to be determined. The Dutch LATER initiative aims to set up a national registry of 5-year CCS to support scientific research on late effects, and to enable periodic re-evaluation of evidence-based guidelines for patient care.

Methods: Representatives of five paediatric oncology centres, two centres for allogeneic haemopoietic stem cell transplantation and the DCOC, have teamed up to: (1) identify and trace the patient cohort of 5-year CCS since 1960; and (2) design a national registry for uniform data-collection. Furthermore, outpatient clinics have been started where survivors are seen by a multidisciplinary team according to uniform evidence-based guidelines.

Results: Presently, 9500 5yr survivors have been identified. The total retrospective cohort includes approximately 10,12,000 patients with anticipated annual flow-in of 300 new 5-yr survivors. Completeness of the cohort will be achieved by linkage with hospital registries, trial databases, pathology databases, and cancer registries. A computerized national registry system is under development, using a three-phase approach. Phase I has been completed and involves the registration of patient identifiers, medical history, tumour diagnosis and detailed treatment information in a computerized system, locally installed at each participating centre. Phase II will include essential information of physical examination, reproductive history, and health behaviour characteristics. Phase III involves adverse late effects detected at the 7 outpatient clinics. Issues of confidentiality will be addressed as part of this national initiative.

Background: The late effects clinic at Rigshospitalet, Copenhagen, was established in collaboration between pediatric oncologists and endocrinologists in 1995. It is open to children and adults who are at least two years from end of childhood cancer treatment including chemotherapy and/or radiotherapy and with no upper age limit so far. The first year visits include the follow-up investigations relevant to each case and according to the treatment protocol, as well as follow up of growth and pubertal development. Later on, the visits focus on symptomatic or asymptomatic late effects of chemotherapy and/or radiotherapy.

Methods: The clinic is run by pediatric oncologists in close collaboration with the many relevant specialties, e.g. endocrinologists, surgeons, pediatric neurologists or neurologists, ophthalmologists, ENT, gynecologists and fertility clinic. If a late effect is detected, symptomatic or asymptomatic, the patient is referred to the relevant specialty for further investigations and treatment. In case of multiple sequelae, the late effects clinic helps coordinating the multidisciplinary collaboration and keeps up checking for other possible late effects. An individual profile (e.g. cancer diagnosis, treatment received and age at treatment) is written down for each survivor. This profile dictates the follow-up program.

Results: Up to date, app. 650 survivors have been seen at the late effects clinic. Rigshospitalet. Extremely few survivors (less than 1%) drop from follow-up before completed puberty, while after puberty less than 10% express that they don’t wish to visit the clinic or don’t show up. The background and late effects profile of the patients seen at the clinic will be presented.

Conclusions: The late effects clinic represents a model of follow up in places with centralized treatment of childhood cancer and rather short distance to the center. While the group of patients who received whole brain irradiation has heavy and often progressing late effects, the majority of young survivors has no or minor late effects.
Background: Research has shown that many pediatric cancer survivors are unaware of their risk for late effects or the need for follow-up care. Additionally, survivors lack accurate, detailed information about their cancer diagnosis and its treatment, despite exceptional educational efforts by professionals in long term follow-up programs. This knowledge deficit could impact their future health since survivors will “graduate” from their treating institution, potentially incapable of conveying accurate health history information to new providers, thereby limiting interventions for early detection, prevention or amelioration of late effects. Since 1989, the After the Cancer Experience (ACE) Program has provided survivors a cancer treatment summary detailing important aspects of treatment. Clinicians observed that many survivors who were transitioned to adult providers for risk based care lacked significant knowledge about their cancer and unique treatment-related risk factors, even though they had received a detailed document. This observation was especially evident when survivors presented for an evaluation without a parent, and in survivors treated as very young children. In support of the Institute of Medicine’s recommendation to improve awareness of late effects among childhood cancer survivors and their families, a comprehensive educational program was implemented.

Methods:
1. To describe the components of an educational program highlighting an algorithm for educating survivors.
2. To describe a component of the educational package called the ACE Navigator, a computer educational program designed around the developmental milestone of learning to drive a car, featuring the concept of a GPS navigational device to lead survivors through a “map” of their treatment including road stops at the Medical Library, Blood Bank, Laboratory, Hospital Treatment Center, and Clinic.
3. To describe the costs of a comprehensive educational program.

Conclusions: After program implementation, a web-based evaluation of survivor knowledge will be designed.

Development of guidelines for follow-up of childhood cancer survivors

Background/ Objective: Care for childhood cancer survivors (CCS) is recognised as an important health care issue. Survivors form an unique patient group for which specialised care and sharing of knowledge and experience is needed. Until now, guidelines to standardise long-term follow-up care for CCS in The Netherlands were lacking.

Methods: Members of the Dutch Childhood Oncology Group (DCOG), including 7 academic centres, initiated the development of multidisciplinary guidelines for the follow-up of CCS. Based on clinical questions regarding the magnitude of the risk of selected late effects, the efficacy of screening and possible treatments, 16 multidisciplinary teams summarised the evidence presented in existing guidelines, systematic reviews, books, and in articles published in PubMed. Ten nationwide multidisciplinary meetings were held to define the final Dutch recommendations based on the available evidence. The summary of evidence formed the basis for extensive discussions on cost and benefit.

Results: A combined evidence-based and consensus approach was used to formulate recommendations for the optimal screening, prevention, and treatment for possible late effects. Within 2 years, 16 guidelines focused on the follow-up of CCS were developed. These guidelines will be implemented in all participating centres in 2007. In each of the 7 centres dedicated long term follow-up clinics for CCS were started. A national database (LATER) of five-years CCS in The Netherlands was developed.

Conclusion: Development of guidelines for medical follow-up of CCS proved to be feasible on the basis of existing guidelines, available literature and discussion by experts. Because of varying local circumstances, country-specific recommendations have to be developed. Uniform recommendations may lead to standardization and improvement of patient care and will facilitate scientific evaluation of late effects.
Follow-up after childhood cancer: Evaluation of a three-level model

Absalom, Kate1; Eiser, Christine2; Greenfield, Diana3; Glaser, Adam4; Horne, Beverly5; Waite, Heather6; Urquhart, Tanya6; Wallace, W. Hamish B.7; Richard, Ross8; Davies, Helena6
1University of Sheffield, Psychology, Sheffield, United Kingdom; 2University of Sheffield, Psychology, Sheffield, United Kingdom; 3University of Sheffield, Academic Unit of Clinical Oncology, Sheffield, United Kingdom; 4St James University Hospital, Paediatric Oncology, Leeds, United Kingdom; 5St James University Hospital, Paediatric Oncology, Leeds, United Kingdom; 6University of Sheffield, Academic Unit of Child Health, Sheffield, United Kingdom; 7Royal Hospital for Sick Children, Department of Haematology/Oncology, Edinburgh, United Kingdom; 8University of Sheffield, Section of Human Metabolism, Sheffield, United Kingdom

Background: Follow-up for cancer survivors is recommended to detect recurrence; monitor late-effects; record toxicity and provide care and education. We describe our experience with a three-level model developed to guide decisions about intensity and frequency of follow-up (Wallace WHB, Blacklay A, Eiser C, et al. Developing strategies for the long term follow-up of survivors of childhood cancer. BMJ 2001;323:271-274).

Methods: One hundred and ninety eight survivors (52% male) recruited over 12-months: (mean age = 23.8 years, range = 16-39 years; mean time since diagnosis = 16.2 years, range 2.4-32.7 years) reported their number of symptoms and late-effects. Information was taken from the medical records to assign each survivor to the appropriate levels by six clinic staff independently.

Results: The survivors were assigned to level 1 (n = 8), level 2 (n = 97) and level 3 (n = 93). There were seven cases of disagreement. Level 3 survivors self-reported more symptoms and late-effects than level 2 survivors.

Conclusions: Coding was relatively simple for experienced clinic staff, although there were some disagreements for the survivors of ALL. The relationship between assigned level and self-reported symptoms and late-effects provides some evidence for validity of the model. We conclude that it is important to maintain flexibility to allow movement between levels for individual patients and that the default should always be to the higher level.

The needs of general practitioners in the follow-up of adult survivors of childhood cancer

Blaauwbroek, Ria1; Bouma, Martijn1; Zwart, Nienke1; Postma, Aleida1; Kamps, Willem1; Meyboom-de Jong, Betty2
1University Medical Center Groningen, Paediatric Oncology, Groningen, Netherlands; 2University Medical Center Groningen, Department of general practise, Groningen, Netherlands

Background: Long-term follow-up of childhood cancer survivors is mainly organised by paediatric oncologists and until now general practitioners (GPs) are rarely involved. To ensure life-long follow-up for all survivors, a combined effort of paediatric oncologists and general practitioners might be a solution.

We investigated the willingness of GPs, who had followed a postgraduate course on late effects of cancer treatment, to participate in a shared care model for follow-up of adult childhood cancer survivors as well as what their requirements would be in case of participation.

Methods: 358 GPs from the Northern Netherlands participated in a postgraduate course on late effects in paediatric cancer survivors. At completion of the course they were asked to fill in a 10-item questionnaire with questions on motivation to participate, requirements in case of participation and objections to participate.

Results: The response rate was 62%. Ninety six percent of the responders were ready to participate in a shared care model for follow-up and 63% felt that it was their responsibility to be in charge for childhood cancer survivors. The main requirements for participation were the availability of guidelines 63%, sufficient information about the patient’s medical history (36%) and short lines for communication (45%). Fees were important for only 4% of the GPs. The main objections to participate were work burden (16%), lack of knowledge (14%) and poor communication (13%) between GPs and paediatric oncologists. Important issues for communication were easy records for exchange of information and the possibility of returning the results of the screening electronically.

Conclusion: GPs are ready to participate in the long-term follow-up of adult childhood cancer survivors if adequate guidelines and medical information is provided and communication lines are clear.
Background: monitoring people who have completed chemotherapy requires long term, standardized programs in order to identify possible secondary effects related either to primary cancer or to its treatment.

Aim of the study: to tailor the patient’s follow up programs on the basis of their primary tumor and treatment with the help of a computer system.

Methods: we designed specific follow-up programs for each tumor type (oncologic follow up) or system (organ follow-up) on the basis of the available literature and on our personal experience.

Patient’s data were input into the computer system at the first off-therapy visit and included demographics, anamnestic data, cancer type and stage, cumulative doses of chemotherapy and radiotherapy, complications that occurred during treatment. On the basis of the information that was input individual oncologic and organ follow up programs (are individually) were suggested by the computer system. The physician had the option to either accept or reject the tailored programs. If any unexpected results were observed during follow up, rules were defined to propose alternative timing or type of programs.

The system allows remote access via a robust secure protocol (https) according to the international ethical rules and to the severe Italian law regarding password, secure programming and privacy.

Results and conclusion: The Person Prevention Oriented Approach (PPOA) system is available as an internet browser. Security and privacy controls are strongly implemented. A total of 44 oncologic follow-up programs are now in use for patients who had been affected by leukemia, Hodgkin’s and non Hodgkin’s lymphomas, neuroblastoma, soft tissue and bone sarcoma. The organ follow up programs allow us to monitor the heart, thyroid, lungs, liver, kidney, eye, central nervous system and immunological status. At present the system is being used by three Italian centers and has proven its usefulness in providing homogeneous follow-up. It can be shared by multiple institutions in order to collect data even on rare outcomes.
**Gonads and Fertility**

**Inhibin B as a marker of spermatogenesis in young male survivors of solid tumors**

**Objective:** we analyzed the values of serum inhibin B in 24 boys and young men treated for different solid tumors (nephroblastoma-10, neuroblastoma-5, germinal tumors-3, RMS-4, PNET-2) using the different chemotherapy regiments; including alkylating agents (n=12), radiotherapy for abdomen (n=6).

Patients and methods: the values of inhibin B, FSH, LH, testosterone were evaluated in fifteen adolescents (seven of them were treated before puberty) and nine boys - treated and examined before puberty. Three patients diagnosed for testicular tumors, after unilateral orchietomy, were analyzed separately. The control group was performed from 19 prepubertal and 15 pubertal boys.

**Results:** 1/ In 15 patients in puberty, we found lower inhibin B values (116.1 ng/ml ± 64.35) than in control (196.53 ng/ml ± 66.8), p=0.002 and tendency to higher FSH (8.52 IU/ml ± 8.8 vs 3.29 IU/ml ± 1.46) without the differences in LH and testosterone values. 2/ The patients (n=9) treated and examined before puberty, without radiotherapy and alkylating agents, presented normal values of all analyzed parameters. 3/ The patients treated before puberty (and examined during puberty), with chemo- and radiotherapy for abdomen, had lower inhibin B (97.08 ng/ml ± 44.31) than in control (p=0.006). There were no differences in FSH, LH and testosterone values. 4/ In the group treated during puberty, with the use of alkylating agents but without radiotherapy, inhibin B was slightly lowered (138.37 ng/ml ± 91.37, p=0.12). 5/ In all patients treated with radiotherapy for abdomen the mean values of inhibin B were lower (105.06 ng/ml ± 44.2) than in the group without radiotherapy (123.46 ng/ml ± 76.6, p=0.009). 6/ Three patients after unilateral orchietomy presented normal values of inhibin B and elevated values of FSH and LH. One of them achieved paternity three years after the treatment.

**Conclusion:** 1. Radiotherapy for abdomen leads to testicular damage, independently on the time of treatment. 2. Inhibin B is sensitive marker of Sertoli cells function. 3. Leydig cell function rest essentially unaffected by treatment.

---

**Testicular function in young men treated in childhood for Hodgkin lymphoma (HL)**

**Objective:** we investigated the influence of chemo- and radiotherapy for HL during childhood on long-term gonadal function in young men depended on the age of treatment, time after cessation and clinical staging.

Patients and methods: serum concentration of inhibin B (Elsa method), FSH, LH and testosterone (immunoenzymatic methods) were determined in 21 adult patients (mean age 20.03 ± 2.7) treated 5.91 ± 3.7 years before for HL. Eight of them were treated before puberty (mean age 8.39 ± 2.9), thirteen - during puberty (16.02 ± 1.1). Control group was formed from 15 young healthy men.

**Results:** 1/ In all examined group we found lower values of inhibin B (50.11 ng/ml ± 43.5) than in control (196.53 ng/ml ± 66.8), p=0.0001, higher values of FSH (13.8 IU/ml ± 11.6 vs 3.3 IU/ml ± 1.5), higher LH (4.67 IU/ml ± 3.6 vs 3.6 IU/ml ± 1.5) and normal testosterone values. 2/ We did not observe any differences in analysed parameters between the patients treated before and during puberty. 3/ Inhibin B was lower, whereas FSH and LH was higher in patients in III and IV clinical stage (treated with radiotherapy for abdomen and 3-4 protocols B-DOPA and 3-4 protocols MVPP) than in group in I and II stage (without infradiaphragmatic radiotherapy, 1-2 protocols MVPP and 2- B-DOPA). 4/ Lower inhibin B <-2SD was observed in 15/24, higher FSH - in 8/24 and higher LH - in 5/24.

**Conclusion:** the treatment for HL in high clinical stage causes severe, long-term testicular damage, especially - spermatogenesis, no mater the age of patients at the time of treatment.
**Background:** Overall long term disease free survival in Hodgkin’s is more than 80%. Treatment for Hodgkin’s disease may carry a considerable risk of sterility in male survivors. The aim of this study was to investigate the effect of chemotherapy on gonadal function of young men cured of childhood Hodgkin’s disease.

**Methods:** Adult young males surviving of Hodgkin’s disease who were 17 years old and at least 2 years after off therapy were studied in Ali Asghar Children’s Hospital. Clinical evaluation for secondary sexual characteristics, semen analysis, FSH, LH, testosterone were studied in 33 survivors of Hodgkin’s disease.

**Results:** The age at diagnosis was 5-15 years median 9 years, age at study 17-29 years median 19. The median duration of therapy was 7 years (2-20 years). All 33 patients received chemotherapy as follows: 32 patients received MOPP / ABVD 6-8 cycles, of whom after relapses received other protocols. One received only MOPP. 27 (81.8%) had azoospermia, 2 severe oligospermia, 3 oligospermia and one had normal sperm count (58000,000). All patients had normal secondary sexual characteristics. FSH, and LH in 6/33 patients were above normal. Testosterone in 3/33 was below normal.

**Conclusion:** The study shows that a prepubertal status does not protect the gonads from the harmful effect of chemotherapy.

---

**Background:** The use of powerful therapeutic tools in childhood cancer treatment has increased the survival rates, to date exceeding 70%, and therefore, the life-quality of the survivors plays an important role. Individuals who have received identical treatment may differ in terms of semen quality, some having normal sperm counts whereas approximately 20% develop azoospermia. Sex steroids are of crucial importance for spermatogenesis and polymorphisms in genes encoding for steroids might influence the post-treatment sperm production. The androgen receptor gene (AR) CAG repeat length as well as the polymorphisms in the 5α-reductase type II (SRD5A2) gene have been shown to play a role for sperm production. Interestingly, estrogens also seem to be of importance for testicular function. The estrogen receptor β (ERβ) is expressed in Sertoli as well as in germ cells of human males. Our objective was to investigate whether polymorphisms in the AR, SRD5A2 and ERβ genes play a role for the risk of azoospermia and for the level of sperm counts in men treated for childhood cancer.

**Methods:** In 28 men, 18-45 years of age and diagnosed with cancer in childhood, a semen analysis and genotyping of the AR, SRD5A2 and ERβ genes in leucocyte DNA was performed. In the AR gene the polymorphic CAG and GGN repeats were analysed, whereas regions of interest were the single nucleotide polymorphism V89L in the SRD5A2 gene and the AluI and RsaI in the ERβ gene.

**Results:** Azoospermic men tended to have longer CAG repeats (median [range] 23[18-29] vs. 21[6-28]; p=0.17) and all men (100%) with azoospermia, presented with the ERβ AluI GA genotype, whereas the frequency was 57% in childhood cancer survivors with sperms in the ejaculate (p=0.003). The prevalence in normal population is 45%.

**Conclusions:** This is, to our knowledge, the first report showing a predictive value of a certain genotype for the risk of azoospermia in men treated for childhood cancer. This subgroup of childhood cancer patients could be subjects for cryopreservation of testicular tissue before treatment if our finding is confirmed in a larger study.
1Erasmus MC, Urology/Andrology, Rotterdam, Netherlands; 2Erasmus MC, Department of Pediatric Oncology/Hematology, Rotterdam, Netherlands; 3Erasmus MC, Urology, Rotterdam, Netherlands

Introduction: Cytotoxic chemotherapy and radiotherapy can cause severe gonadal damage depending upon the type and cumulative dosages of drugs administered in pediatric cancer. Inhibin B has been suggested to be the strongest serum marker for spermatogenesis, but it’s role as a possible marker for testicular function in large cohorts of men surviving childhood is not clear.

Material and methods: 261 long-term survivors (median 18 years after completion of therapy), aged more than 18 years (median age 24 years) and treated for childhood cancer in our institute were studied. We assessed testicular size, patient characteristics, disease and treatment modalities, endocrinological parameters (LH, FSH, Inhibin B, SHBG and testosterone) and semen analysis. Inhibin B values are considered normal between 150 and 400 ng/l. Results of sperm analysis and endocrinological evaluation were compared with data from normospermic men (n=74, median age 33) visiting our Andrology clinic.

Results: The median value of Inhibin B in the patient group was 126 ng/l versus 176.5 ng/l in the control group (P<0.01). 151 (66%) of the survivors had Inhibin B levels below 150 ng/l compared to 19 (25%) of the normospermic controls (P<0.01). Inhibin B was strongly correlated with FSH and sperm concentration in the controls as well as in patient (P<0.01). Patients with Hodgkin Lymphoma and Sarcoma had the lowest levels of Inhibin B, respectively, 54 ng/l and 55ng/l compared to the other patient groups (p<0.05). Treatment regimes containing Procarbazine or Cyclophosphamide were significantly correlated with low Inhibin B levels compared to regimens not containing these agents (p<0.01). Age at time of diagnosis in these treatment groups did not correlate with post treatment Inhibin B levels.

Conclusion: Inhibin B can be used to assess post-treatment gonadal function. Inhibin B levels and gonadal function can be severely impaired after gonadotoxic therapy given during childhood especially after treatment for Hodgkin’s lymphoma and sarcoma or regimens containing Procarbazine or Cyclophosphamide. Age at time of diagnosis is no predictor for outcome of post treatment male gonadal function.
Follicular rescue in young girls treated with bone marrow transplantation

Borgström, Birgit1; Hreinsson, Julius2; Keros, Victoria2; Rasmussen, Carsten2; Więckowski, Jacek3; Gustafsson, Britt1; Hovatta, Outi2; Fridström, Margareta2

1Inst for Clinical Science, Karolinska Institutet, Children’s Hospital, Stockholm, Sweden; 2Karolinska Institutet, Dept of Obstetrics and Gynecology, Stockholm, Sweden; 3Karolinska Institutet, Children’s Hospital, Stockholm, Sweden

Background: Bone marrow transplantation (BMT) has over the last 30 years saved the life of many patients suffering from lethal hematological disease. Cytostatic drugs and/or total body irradiation in different combinations and doses has been used as conditioning. Among the inevitable long term side effects infertility is frequent.

Methods: A biopsy from the ovary, taken laparoscopically, was cryopreserved for the future. A small part of the biopsy was prepared for histology to get information about the condition and number of follicles. This method has been used in 17 patients from two groups. One group, 8 girls, had signs of normal ovarian function several years after BMT. Most of these girls had been treated for a non-malignant disease. The biopsy was taken at the age of 13.7-17.6 years. The second group, 9 girls had the biopsy taken shortly before BMT, at the age of 9.2-22 years. Most of these girls suffered from leukemia.

Results: The 8 girls post BMT had a reduced number of follicles in the biopsy. In 2 girls there were no visible follicles and in 6 girls 21-208 follicles/mm³. The 9 girls before BMT all had follicles. In 5 girls the number was normal for age, 350-1519 follicles/mm³ and in 4 there was a reduction, 18-182.

Conclusions: Cryopreservation of follicles for the future offers the possibility for fertility treatment in adult life to girls with a high risk for infertility and premature menopause after BMT. The adolescent girls with mature follicles in the biopsy have a reasonable chance for successful outcome later in life, a few successful cases have been published. In the youngest girls, with only immature primordial follicles, new treatment methods need to be developed. Also, the risk for infiltration of malignant cells in the ovary needs to be considered.

Infertility in Ewing’s sarcoma female patients

Longhi, Alessandra1; Ferrari, Stefano2; Ferrari, Cristina2; Bacci, Gaetano2; Mercuri, Mario2

1Istituto Ortopedico Rizzoli, Chemotherapy, Bologna, Italy; 2Istituto Ortopedico Rizzoli, Bologna, Italy

Background: Infertility in females after chemotherapy in osteosarcoma patients have been investigated in our previous study and the incidence of permanent amenorrhea induced by treatment was 2.1% (2/92) Infertility in Ewing’s sarcoma female patients is the objective of this study

Patients: 112 long term survivors female treated according to 5 different protocols from 1979 to 2005 for localized Ewing’s sarcoma. Treatment was standard chemotherapy with or without Radiotherapy. In the last protocol, ISG-SSG III, poor responders received also High Dose Chemotherapy (HDCT) with PBSCR.

Results: 89 pts were interviewed, 23 couldn’t be reached 29 were prepuberal at the time of chemotherapy and 60 were postpuberal Median age of all group was 15 yrs (range 1-40). Median follow up was 15 yrs (1-27). Prepuberal pts reached menarche at a median age of 13 (range 12.5-15). 17/89 (19%) pts had permanent amenorrhea related to the treatment: 3 were prepuberal at the time of treatment and received HDCT, 2 of them received also RT to pelvis, 14 patients out of 60 postpuberal had permanent amenorrhea: 6 pts received RT to the pelvis, 4 pts received HDCT (two of these had also pelvic RT) and 4 pts received no RT nor HDCT. The age of these latter pts was 28, 30, 35, 40. 20 women delivered 32 normal babies, all except one were full term pregnancy, 1 pt had a voluntary abortion and 2 pts had spontaneous abortions both at the 7th month of gestation: 1 of this premature fetus died of congenital esophageal atresia. Besides 2 patients had 3 Second Malignant Neoplasms: a thyroid cancer and the other pts had a uterus sarcoma and a breast cancer.

Conclusions: The incidence of early menopause is higher in Ewing’s sarcoma female patients (19%) compared to osteosarcoma patients (2.1%) HDCT and RT are confirmed to be the major cause of permanent amenorrhea both in prepuberal and postpuberal patients.
Stillbirth and abortion following radiotherapy for childhood cancer: A population-based cohort study

Winther, Jeanette Falck1; Boice, Jr., John D.2; Svendsen, Anne Louise3; Frederiksen, Kirsten1; Stovall, Marilyn1; Olsen, Jørgen H.1
1Danish Cancer Society, Institute of Cancer Epidemiology, Copenhagen, Denmark; 2International Epidemiology Institute, Rockville, MD, United States; 3The University of Texas M.D. Anderson Cancer Center, Department of Radiation Physics, Houston, United States

Background/Objective: Radiation induces germ-cell mutations in experimental animals. We assessed the risk of abortion and stillbirth in female survivors of childhood cancer in Denmark treated with radiation.

Methods: We identified 1688 female childhood cancer survivors in the national Danish Cancer Registry and 2737 sisters and 16700 women randomly selected from the Central Population Register. Radiation doses to the ovary, uterus and pituitary gland were estimated. Pregnancy outcomes were determined from nationwide health registries, and the proportions of pregnancies among survivors that resulted in a live birth, stillbirth or abortion were compared with the equivalent proportions among the sisters and the population comparison group as proportion ratios (PR), with sisters as referent.

Results: The distributions of live births, abortions and stillbirths among 1479 pregnancies of survivors were remarkably similar to that of the comparison women. Survivors, however, had a 23% excess risk for spontaneous abortion, primarily due to a threefold increase in risk among survivors of Wilms tumour (PR, 3.0; 95% CI, 1.6-5.5) and an excess risk among survivors in general exposed to high-dose radiation to the ovaries and uterus (PR, 2.8; 95% CI 1.7-4.7). The prevalence of other types of procedures during active treatment or follow-up.

Conclusions: An increased risk for spontaneous abortion among survivors who had received abdominal irradiation was likely the result of high-dose radiation uterine damage, a non-mutagenic effect. Among those who were able to become pregnant, there was little evidence that radiation-induced germ-cell mutations led to stillbirths or abortions. These reassuring results are of importance to the cancer survivors and their families, and genetic counsellors.

Are young female cancer patients screened for ovarian dysfunction? An audit of clinical practice

Greenfield, Diana1; Ross, Richard2; Absolom, Kate3; Eiser, Christine3; Coleman, Robert4; Hancock, Barry4; Snowden, John5; Ledger, William6; Davies, Helena7
1University of Sheffield, Academic Unit of Clinical Oncology, Sheffield, United Kingdom; 2University of Sheffield, Endocrine & Reproduction, Sheffield, United Kingdom; 3University of Sheffield, Psychology, Sheffield, United Kingdom; 4University of Sheffield, Academic Unit of Clinical Oncology, Sheffield, United Kingdom; 5Sheffield Teaching Hospitals NHS Trust, Haematology, Sheffield, United Kingdom; 6University of Sheffield, Academic Unit of Reproductive and Developmental Medicine, Sheffield, United Kingdom; 7University of Sheffield, Academic Unit of Child Health, Sheffield, United Kingdom

Background/Objective: Cancer therapy induced ovarian failure in women may lead to a permanent or temporary menopause resulting in menopausal symptoms and risk of osteoporosis. Screening for ovarian dysfunction is straightforward and once identified, can be managed with oestrogen replacement. The aim of this study was to audit clinical case notes of young female cancer patients who had received gonadotoxic therapy for evidence of gonadal function screening and subsequent management during active treatment and follow-up.

Patients and Methods: We audited 288 hospital clinical case notes of young women ages 38.5 years (17.9 to 50.8y, SD 8.1) with haematological cancers (n = 184); carcinomas (n=61); primitive and other cancers (n= 184); carcinomas (n=61); primitive and other cancers (n=184). Women with breast cancer were not included since oestrogen replacement therapy is currently not advised.

Results: The mean age of women at cancer diagnosis was 26.9 y (0.5 to 47y; SD 10.1) and the mean time since diagnosis was 11.1y (2.2 to 34.8y; SD 7.2). 95.1% had received chemotherapy, 68.1% radiotherapy and 63.5% had both. Case note documentation indicated that 43.4% were screened for ovarian function (gonadotrophins and/or oestradiol) at least once during or after cancer treatment. This monitoring was initiated by the: oncologist (62%); haematologist (10%); endocrinologist (14%); gynaecologist (6%); GP (3%); other (5%). Case note documentation indicated that 31.6% had or were taking hormone replacement therapy and a further 15.9% contraceptive medication.

Discussion: Evidence suggests that despite receiving gonadotoxic cancer treatment, less than half these young women were screened for ovarian failure. We advocate routine gonadal function screening for all young women receiving gonadotoxic cancer treatment.
Amh and inhibin B are valuable new markers for gonadal damage after the treatment of pediatric hodgkins lymphoma(HL) without radiotherapy

cite { van den Heuvel-Eibrink, Marry M.1; van Beek, Robert2; Weber, Rob3; Laven, Joop5; de Jong, Frank4; Hakkoot-Cammel, Friederike G.A.J.3; van der Bos, Cor7; Peters, Rob1; de Muinck Keizer-Schrama, Sabine M.P.F.6 Erasmus MC - Sophia Childrens Hospital, Pediatric Oncology, Rotterdam, Netherlands; 2Erasmus MC, Andrology, Rotterdam, Netherlands; 3Erasmus MC, Gynaecology and Obstetrics, Rotterdam, Netherlands; 4Erasmus MC, Internal Medicine, Rotterdam, Netherlands; 5AMC - Emma Childrens Hospital, Pediatric Oncology, Amsterdam, Netherlands; 6Erasmus MC - Sophia Childrens Hospital, Pediatric Endocrinology, Rotterdam, Netherlands

An important long-term effect of chemotherapy is gonadal dysfunction. The aim of this study is to evaluate the gonadal long-term effects of the treatment for childhood HL with combination chemotherapy (ABVD or EBVD with/without MOPP) and to identify markers for long-term gonadal function. Eighty-six pediatric HL patients treated between 1974-1998 were included in a protocol in which RT was avoided because of the risk of serious long-term side effects. All patients were in complete remission. Median follow-up was 15.5 yr. (range 5.6-30.2 yr.), median age at follow-up was 27.0 yr. (range 17.7-42.6 yr.). Follicle stimulating hormone (FSH), luteinizing hormone (LH) and inhibin B were determined in all patients.

Additionally, in men testosterone and sex hormone binding globulin (SHBG) and in women 17β-estradiol and anti-Müllerian hormone (AMH) were determined. In 20 men semen analyses were performed. In men treated with MOPP, median FSH (16.6 U/l vs 2.4 U/l; p<0.001) and LH (5.7 U/l vs. 2.5 U/l; p<0.001) were increased and Inhibin B (17.5 ng/l vs. 143 ng/l; p<0.001) and semen concentration (1.1*10^6/ml vs.49.5*10^6/ml; p<0.05) were decreased as compared with patients treated without MOPP. Inhibin B was strongly correlated with semen concentration (r=0.83; p<0.001). LH (r=-0.68; p<0.001) and inhibin B (r=-0.68; p<0.001) were correlated with cumulative dose procarbazine.

In women no significant differences in LH, FSH, inhibin B or estradiol between patients treated with or without MOPP were found, but AMH was significantly lower in patients treated with MOPP as compared to patients treated without MOPP (0.39 µg/l vs. 1.40 µg/l; p<0.01). AMH levels were correlated with cumulative dose procarbazine (r=0.54; p<0.01). This study shows that AMH and inhibin B are valuable new serum markers for gonadal damage after chemotherapy for pediatric HL. In men inhibin B is strongly correlated with semen concentration, whereas in women AMH detects early gonadal damage even in cases with normal LH/FSH levels.

Xenografting as an approach for fertility preservation and exploration of cancer cell contamination of testicular grafts

cite { Jahnukainen, King1; Hou, Mi1; Ehmcke, Jens2; Schlatt, Stefan2; Söder, Olle1 Karolinska Institutet, Department of Woman and Child Health, Stockholm, Sweden; 2University of Pittsburgh, Pittsburgh, United States

Background/ Objective: Xeno-grafting of fresh immature primate testicular tissue into nude mice leads to establishment of spermatogenesis. It therefore presents a beneficial tool for prepubertal cancer patients generating fertility options without risk of a cancer relapse. However, it is unknown whether cryopreservation maintains spermatogonial potential in primate testicular tissue or if cancer cells in the testicular graft affect the success rate of testicular tissue transplantation.

Methods: Male nude mice received eight subcutaneous grafts of either fresh juvenile rhesus monkey testicular tissue or cryopreserved tissue (24h of cryopreservation time; two concentrations of DMSO [1.4M and 0.7M], using slow uncontrolled cooling (0.5°C/min). In another experiment, Rat T-cell leukemia was employed as the source of leukemic testicular grafts which were transplanted subcutaneously into nude mice. Graft number, weight and histology were examined 5 months later or when signs of leukemia developed.

Results: Control primate grafts showed pubertal induction of spermatogenesis to the level of B-spermatogonia and spermatocytes. Spermatogenic stem cells in juvenile testicular tissue survived cryopreservation and were able to initiate spermatogenesis when DMSO 1.4M was used as cryopreservative agent. Only few grafts with SCO tubules survived cryopreservation with DMSO 0.7M. In the second set of experiments, all mice carrying either fresh or cryopreserved testicular tissue from leukemic donors, developed generalized leukemia and/or local tumors. Rat spermatogenesis in the retrieved grafts was destroyed and leukemic infiltration was detected.

Conclusions: Our observations suggest that cryopreservation of immature primate testes is a feasible approach to maintain spermatogonial stem cells and may serve as a promising tool for fertility preservation of prepubertal boys. Grafting testicular tissue contaminated with leukemic cells results in tumor growth at the injection site. Xenografting may provide a novel strategy for simultaneous detection of malignant cell contamination and spermatogonial potential of testicular xenografts collected for fertility preservation.
Background: Infertility is one of severe late side effects of cancer treatment in boys surviving from childhood cancer. Autologous germ cell transplantation may be an efficient way to restore their fertility. The risk of reseeding contaminated tumor cells to cured patient has made germ cell purging a crucial step for preventing disease relapse.

Methods: PVG rats carrying Roser’s leukemia, that resembles human acute lymphoblastic leukemia, were used as a source of testicular cells and healthy PVG rats as recipients. Ep-CAM and CD4/ MHC-Cl I were identified as specific surface markers of germ cells and leukemic cells, respectively. Testicular cells were labeled with Ep-CAM or CD4/MHC-Cl I or Ep-CAM+CD4/MHC-Cl I. This allowed flow cytometry to positively select germ cells or negatively deplete cancer cells simultaneously. The efficiency of FACS sorting was determined by intratesticular injection of 0.1x10⁶ purged germ cells to recipients followed by FACS analysis. Aggregation of germ cells and leukemic cells was studied.

Results: Positive selection based on Ep-CAM expression reduced leukemic cell contamination and one of three recipients survived. The reduction in malignant cell contamination achieved by deletion was less pronounced. After positive selection and negative depletion leukemic cells were shown to aggregate with germ cells and resulted in contamination of the germ cell preparation. A combination of positive and negative selection prevented the transmission of leukaemia in association with transplantation, but 99.5% of cells were lost during the 4-hour sorting procedure.

Conclusions: Combined positive and negative FACS sorting allows purification of germ cells from leukemic rats. However, problems with phenotypic variations of surface markers on leukemic cells, poor cell recovery, lengthy sorting procedures and aggregation of leukemic and testicular cells limit the efficacy and safety of this approach for clinical use.
Breast cancer risk in 5-year survivors of childhood and adolescent Hodgkin’s lymphoma, the influence of treatment and premature menopause

Amoroso, Loredana1; Grill, Jacques1; Sakiroglu, O.1; Raquin, Marie-Anne1; Habrand, JL2; Sainte-Rose, Christain3; Lemerle, Jean1; Hartmann, Olivier2; Kalifa, Chantal1
1Institute Gustave Roussy, Paediatrics, Villejuif, France; 2Institute Gustave Roussy, Department of Radiation Oncology, Villejuif, France; 3Necker Sick Children’s Hospital, Department of Neurosurgery, Paris, France

The risk of second tumor after brain tumor is increased compared to the normal population. Little is known about the incidence and the risk factors of second tumors in patients with medulloblastoma. We undertook a retrospective survey in all first 100 children who survived more than 5 years after the diagnosis in our institution. They were treated between 1964 and 1991 with a combination of surgery and craniospinal irradiation plus posterior fossa boost. Seventy eight children also received chemotherapy containing alkylating drugs.

All seven patients who experienced a relapse died. Forty second tumors occured in 29 patients eight to 34 years from initial diagnosis (median 21 years). Fifteen years cumulated acturial risk was 45%. Thirty-three tumors were located within the radiation field, mostly in the CNS (13 patients) and in the skin (8 patients). The interval was shorter for malignant tumors (7 years) than for benign tumors (10 years). Cancer predisposition was evidenced in 6 patients (5 Gorlin et one Li-Fraumeni syndromes). The risk of second tumor was not increased in younger children, patients receiving growth hormone replacement or higher doses of craniospinal irradiation. After treatment of their second tumor, nineteen patients were in complete remission; nine died from the second tumor and one in a car accident.

As survival of medulloblastoma patients improves, long-term surveillance for second tumors is required especially in the brain and on the skin. Cancer predisposition syndrome seems to be the most important predictor for second tumour in this population.

Background: Female Hodgkin’s lymphoma (HL) survivors are at increased risk of breast cancer (BC), especially those irradiated to the breast area at young ages. In adult HL-patients, chemotherapy (CT) decreases the high risk of breast cancer after radiotherapy (RT). We assessed the influence of gonadotoxic therapy on the risk of BC in survivors of childhood and adolescent HL.

Methods: We performed a cohort study in 310 women, treated for HL in the period 1965-1995 before age 21 (31% (RT), 9% CT, 60% RT+CT). We compared the incidence of BC with the general population and calculated standardized incidence ratios (SIRs) and absolute excess risks (AERs). Cox regression analyses was performed to study therapy-effects in relation to gonadotoxicity.

Results: During follow-up (median 17.5 years), 33 women developed BC (SIR 16.9 [95%CI 11.7-23.8], AER 72 per 10,000 patients per year). The risk remained high after prolonged follow-up (>25 years after treatment SIR 13.5 [6.7-24.1]). All BC’s occurred among patients irradiated to the breast area. Although a trend is observed, neither CT (HR 0.8 [0.4-1.7]), nor RT to the ovaries (HR 0.3 [0.04-2.2], nor onset of menopause before age 40 (HR 0.5 [0.2-1.5]) decreased the risk of BC significantly among these patients. However, patients with <10 years of intact ovarian function after irradiation to the breast, experienced a more than 10-fold significantly lower risk of subsequent BC compared to those with >20 years of intact ovarian function (HR 0.09 [0.01-0.8]). Smoking, overweight and the use of oral contraceptives were not associated with BC.

Conclusion: The risk of BC in young survivors of HL remains elevated up to more than 25 years after treatment. Gonadotoxic therapy lowers the increased risk of BC in patients irradiated in the breast area only when menopause is induced relatively shortly after treatment.
Background/Objective: Dutch recommendations regarding screening for skin cancer in childhood cancer survivors (CCS) are not available. We determine the scientific and clinical relevance of screening for skin cancer in CCS and formulate recommendations.

Methods: A literature search was accomplished on magnitude of the risk of skin cancer in CCS and associated risk factors and the efficiency of skin cancer screening methods. Because of the high cure rates of basal cell carcinoma, we only focus on melanoma (for the Late Effect Task Force strategy of the Dutch Childhood Oncology Group, see the abstract of L.C.M. Kremer et al.).

Results: After childhood cancer the risk of skin cancer is increased. General risk factors for melanoma are: ≥50 naevi (≤20 years old), ≥4 dysplastic naevi, naevi on soles, buttocks, anterior scalp, or iris. For melanoma an odds ratio of 16.1 is observed when someone has three or more risk factors, combined with an age younger than forty. After chemotherapy CCS have an increased number of melanocytic naevi or atypical naevi compared to healthy controls. In all studies significantly more naevi were seen on palms and soles in CCS. Also radiotherapy above 15 Gray may contribute to an increased risk for malignant melanoma. Randomized- or case-control studies on screening programs have shown that routine screening for melanoma does not reduce morbidity or mortality.

Conclusions: Despite an increased risk for developing melanomas in CCS, we do not recommend special visits for screening on skin cancer during follow-up without evidence for the effectiveness of screening. Furthermore, we advise physicians to educate patients on the increased risk for melanoma.

Late Treatment Sequelae of Hodgkin Disease and Its Treatment in a Cohort of Long-Term Survivors Treated at a Single Center between 1980 and 1999

Background/Objective: The aim of the study was to evaluate a wide spectrum of impairments in patients in remission for more than five years. We conducted a cross-sectional study to evaluate sequelae in patients treated between 1980 and 1999 by one of four different treatment protocols. 347 patients with Hodgkin Disease diagnosed prior to the age of 19 were treated. In 2003, 270 of them were in remission for at least 5 y. The mean age at the time of enrollment in the study was 23.9 (SD +/- 4.9) y., and the mean time in remission was 10.6 (SD +/- 3.9) y.

Methods: All patients received physical examination + immunologic, endocrine, pulmonary function and exercise testing. Mammological examination was offered to women.

Results: 32% of patients had sub-clinical hypothyroidism. Increased IgE in 29.9 % was found. Lower total T lymphocyte counts in 18.8 %, lower proportion of T-helper cells in 13.6% and a decreased CD4/CD8 ratio in 26.2 % were found. Total cholesterol, triglycerides, HDL and LDL were checked, and 47.4% had at least one pathology. Mammogram and/or breast ultrasonography was performed in 68 women. We did not detect any case of carcinoma of the breast. Abnormal pulmonary function at least in one parameter was found in 49.7% out of 153 patients examined. Exercise stress testing did not reveal any signs of myocardial ischemia on ECG, maximal aerobic capacity was decreased more than two standard deviations of reference values in 18.9% out of 224 patients examined. Echocardiographic examination revealed hemodynamically significant heart valvular pathology in 1% of the cohort. No impairment in LVEF and no cases of cardiomyopathy were found.

Conclusions: We found a wide variety of late sequelae and yet a small incidence of serious sequelae in patients with Hodgkin Disease treated during childhood or adolescence. The potential for significant longevity in these patients emphasizes the importance of identifying and minimizing late sequelae of the treatment regimen.
Subclinical cardiac dysfunction in young adult survivors of childhood ALL revealed by exercise echocardiography

M:06

Jarfelt, Marianne1; Kujacic, Vuk2; Holmgren, Daniel1; Bjarnason, Ragnar3; Lannering, Birgitta1

1Institute of Clinical Sciences, Department of Pediatrics, Göteborg, Sweden; 2Institute of Medicine, Cardiovascular Institute, Div. of Clinical Phys, Göteborg, Sweden; 3Institute of Clinical Sciences, Göteborg Pediatric Growth Research Center, Göteborg, Sweden

Background: Anthracyclines (AC) have highly contributed to the increased survival rate in ALL. The risk of late cardiotoxicity is probably multifactorial but total dose is a strong prognostic factor. Can patients without symptoms of cardiac disease who have received low doses of AC in early childhood be excluded from further cardiac surveillance in adulthood?

Methods: Basal evaluation with two-dimensional (2D), M-mode echocardiography and Doppler examination was performed. Thereafter echocardiography was done at maximal exercise stress and after recovery. Twenty-three young adult ALL patients in first remission treated with median 120 (120-400) mg AC/m² before the onset of puberty and 12 healthy controls were examined. Median patient age 27 (20-31) years and median follow-up time after remission was 21 (17-27) years. Eleven patients had received cranial radiotherapy and 25% had low spontaneous GH secretion.

Results: We found highly significant differences between patients and controls in systolic function at maximal stress. The most pronounced difference was in ejection fraction at stress 59.5 (32.6-81.1) % and 77.3 (66.2-85.3) % in patients and controls respectively (p<0.00006). Ten out of 23 patients reduced their ejection fraction at stress compared to at rest; this was not found in any of the controls. There was also a pronounced difference in cardiac output 4.0(1.6-5.1) and 6.8(4.5-8.0) in patients and controls respectively despite no difference in heart rate (p= 0.0002). Systolic function was not correlated to cumulative dose of AC. Cardiovascular risk factors such as GH deficiency and a high proportion of trunk fat did not have an impact on cardiac function in this study.

Conclusions: In this study with very long follow up in a homogenous cohort of ALL survivors we found subclinical cardiac dysfunction even after low doses of AC. This motivates future follow-up of these patients.
Hypertension and prehypertension evaluation in long-term survivors of childhood and adolescent cancer: a new approach

Background: Childhood cancer, which occurs in approximately 1 out of 350-400 children and adolescents, is no longer an almost uniformly fatal disease. It has been estimated that approximately 1 of 500 young adults (20-35 years of age) having had a diagnosis of cancer as children or adolescents. Unfortunately, two-thirds of these survivors have at least one late effect, mostly from treatment. Hypertension as a late effect following childhood and adolescent cancer (CAAC) has received little attention and the risk of hypertension is considered to be either questionable or no more frequent than for the general population. Nevertheless, an increased incidence between these patients has been observed in some recent studies. It is now widely accepted that cardiovascular health originates in childhood. So, the blood pressure (BP) control became essential in long-term survivors of CAAC.

Methods: Diagnosis of hypertension is critically dependent on accurate BP measurement. Systolic and diastolic BP are usually measured by an occasionally auscultatory measurement, with a properly calibrated and validated aneroid sphygmomanometers with an appropriately-sized cuff that fits the patient’s arm. Nevertheless, this method has many limits. To date automated BP measurement is the only one accurate method and offers multiple advantages in achieving high-quality BP determinations by reducing observer errors. The most commonly used form is 24-h ambulatory BP measurement (ABPM) but in literature there aren’t any works that have used this method in long-term survivors of childhood and adolescent cancer. ABPM has been the primary tool to identify the deficiencies of office BP determination in the diagnosis of hypertension and prehypertension. ABPM showed that there were patients with white-coat hypertension and more recently patients with masked hypertension (normal office blood pressure and elevated 24-h ABPM).

Conclusion: To minimize observer and subject errors that commonly occur in clinical BP measurement and to improve the diagnosis of this important late effect of cancer therapy we suggest that ABPM should be used in all survivor of CAAC.

Cardiac damage after treatment of childhood cancer

The purpose of the study was to determine the frequency of late effect on the heart of childhood cancer survivors in Slovenia and to identify groups at the highest and lowest risk.

Included in the study were 211 survivors, treated 1968 - 1998 at ages of less than 18 years. All were over 18 years and at least 5 years after end of treatment. The observation time was 5 - 32, average 16 years. Fifty-nine had been treated surgically, 191 had received chemotherapy, 166 radiation, in 56 of whom the heart had been within the field of radiation. The total radiation dose with the area of the heart was between 10-42 Gy, average 28 Gy. Chemotherapy with anthracyclines had been given to 146 patients, to the total dose of 50-620 mg/m², average 247 mg/m². Anthracyclines together with alkylating agents had been given to 136 patients. Thirty-three children had been treated with anthracyclines and radiation to the heart area. The pathological diagnostic methods included history, physical examination, electrocardiogram (ECG), electrocardiographic exercise testing on a bicycle ergometer and echocardiography. Descriptive and univariate analysis (chi square test) as well as multivariate analysis (decision tree) were used for data analysis.

Our analysis showed abnormalities in the structure and function of the heart in 53% of survivors. They were all asymptomatic. However, in 2 of these, cardiac death occurred.

The period of treatment (1989-1998) emerged as an important risk factor for any injury to the heart (73% of survivors). Among survivors treated earlier are at the highest risk those with Hodgkin’s lymphoma treated with radiation above 30 Gy and those treated for sarcoma. At the lowest risk for injury of the heart are those treated for brain tumors and those with other malignancies treated with low total dose of anthracyclines. Among specific forms of heart injury, patients treated with large doses of anthracyclines or concomitant alkylating agents are at highest risk of systolic function defect and enlarged heart chambers and those treated with anthracyclines are at highest risk of diastolic function defect. Radiation to the heart area correlated to the valve injury.

References:
Frenos, Stefano; Pollini, Iva; Calabri, Giovanni; Tondo, Annalisa; Tamburini, Angela; Tucci, Fabio; Sardi, Iscopo; Farina, Silvia; Caresi, Tommaso; Veltroni, Mar面板ella; Lippi, Alma; Bernini, Gabriella
Anna Meyer Childrens Hospital, Onco-hematology, Florence, Italy; Anna Meyer Childrens Hospital, Cardiology Unit, Florence, Italy

Velensek Prestor, Veronica1; Mazic, Uros2; Jereb, Berta3; Zaletel Zadravec, Lorna3
1 University Children Hospital, Div. of Pediatric Hematology and Oncology, Ljubljana, Slovenia; 2 University Medical Center, Pediatric Cardiology, Ljubljana, Slovenia; 3 Oncology Institute, Ljubljana, Slovenia

1
2
3
Tetanus and diphtheria antibody levels in patients after sarcoma treatment: A report from the Late Effects Surveillance System

Paulides, Maria1; Stohr, Wolfgang1; Bielack, Stefan2; Klingebiel, Thomas1; Jurgens, Heribert4; Beck, Jorn-Dirk1; Langer, Thorsten7
1Late Effects Surveillance System, University Hospital for Children and Adolescents, Erlangen, Germany; 2COSS/EURAMOS Trial Centre, Olghospital Department of Pediatrics 5, Stuttgart, Germany; JCWS Trial Centre, University Hospital for Pediatrics III, Frankfurt, Germany; EEURO-E.W.I.N.G. Trial Centre, University Hospital for Children and Adolescents, Munster, Germany

Background: It is known that antineoplastic treatment may induce secondary immunodeficiency. However, there has been a lack of prospective studies after childhood cancer treatment. Aim of this study is to investigate lack of immunity against vaccine-preventable diseases after childhood sarcoma treatment.

Methods: Since 1998, the Late Effects Surveillance System (LESS) of the German Society for Paediatric Oncology and Haematology (GPOH) prospectively registers late effects in soft tissue-, osteo- and Ewing's sarcoma patients of all ages treated within the therapy trials EICESS-92/ EURO-E.W.I.N.G.-99, CWS-96/CWS-2002P, COSS-96 in Austria, Germany and Switzerland. The follow-up is conducted locally in accordance with the LESS guidelines. According to these guidelines, antibody levels are to be examined at four weeks and six months after end of anti-neoplastic treatment to determine immunity against vaccine-preventable diseases. Ten hospitals within the LESS network participated in data collection for this analysis, for which antibody levels against diphtheria and tetanus were used, as there are well-defined guidelines by the Robert-Koch Institute for protective antibody level values.

Results: There were 47 eligible relapse-free patients <21 years of age (31 male, 16 female), of whom 10 had been treated for osteosarcoma, 12 for Ewing's and 25 for soft tissue sarcoma. Median age at diagnosis was 9.6 (interquartile range: 4.4-14.7) years. In 27.6% (13/47) of patients there were no protective antibody levels (<0.1 IU/ml) against diphtheria and/or tetanus. In multivariate analysis, treatment had no effect on antibody levels, similar to tumour type and time of examination after treatment end. Younger patients had significantly lower antibody levels against tetanus (p=0.0132) and girls had significantly lower antibody levels against diphtheria (p=0.0421).

Conclusions: Lack of protective antibody levels against tetanus and/or diphtheria is frequent after childhood sarcoma treatment. Prospective surveillance of immunity and, if indicated, re-immunization is necessary in patients treated for childhood cancer.

Serum Cystatin C as a screening method in follow-up for late effects of malignancy on renal function

Braam, K.I.1; Laarman, C.1; Stoefel-Wagner, B.2; Bouman, A.3; Kon, W.A.4; Kaspers, G.J.L.1; Bökenkamp, A.1
1vU university medical center, Pediatrics, Amsterdam, Netherlands; 2University of Bonn, Clinical biochemistry, Bonn, Germany; 3vU university medical center, Clinical biochemistry, Amsterdam, Netherlands

Background: In screening for childhood cancer late effects serum creatinine and 51CrEDTA are commonly used markers for estimating glomerular filtration rate (GFR). However, serum creatinine lacks diagnostic sensitivity for the detection of mild to moderate renal failure and 51CrEDTA clearance is too cumbersome for daily practice. Cystatin C has been shown to be a simple and robust endogenous marker of GFR, which is particularly useful in the detection of incipient renal failure.

Aim of the study: To compare serum cystatin C with the creatinine-based Schwartz-formula in children in the follow-up of renal disease and/or malignancy.

Methods: 84 children (median age 10.5, range 0.2 to 21; gender 30f, 54m) who needed assessment of renal function for malignancy (n=33) or kidney disease (n=51) participated in this study. Serum cystatin C was measured using a particle-enhanced immunonephelometric assay, creatinine by modified kinetic Jaffé reaction. From these measurements, cystatin C-based (GFRcys - calculated according to Filler et al) and creatinine-based (GFRSchwartz) estimates of GFR were calculated. Single injection inulin clearance was done as the gold standard.

Results: Mean (±SD) cystatin C was 1.13 ± 0.5 mg/l, creatinine 83 ± 38 µmol/l. GFR was 74 ± 26 ml/min/1.73m², GFRcys 94 ± 33 ml/min/1.73m², GFRSchwartz 90 ± 29 ml/min/1.73m². 46% of the patients had mildly reduced GFR (i.e. 60 - 90 ml/min/1.73m²). GFRcys detected these patients with 33% sensitivity, 89% specificity. The positive predictive value was 72%, the negative predictive value 61%. For GFRSchwartz, the respective values were lower (i.e. 28%, 64%, 41% and 51%).

Conclusions: These data suggest that in daily practice, a cystatin C-based equation for the calculation of GFR is superior to the commonly used Schwartz-GFR, in particular in patients with mild-moderate renal failure. Therefore, cystatin C should complement creatinine measurements in the follow-up for late effects of malignancy on renal function.
Elevated liver enzymes two years after hematopoietic stem cell transplantation in children: prevalence and etiology

**Background:** In previous studies the prevalence of elevated liver enzymes late after hematopoetic stem cell transplantation (SCT) varied from 40 to 58%. Etiology includes viral hepatitis, iron overload, auto-immune hepatitis and/or chronic graft versus host disease (cGvHD) in a majority of these patients, but in some etiology remains unclear.

**Aim of the study:** was to establish the prevalence and etiology of elevated liver enzymes in children surviving long term after SCT in a country with a low prevalence of HBV and HCV among blood donors.

**Methods:** This is a single center retrospective study. AST and ALT values from before SCT until 2 years after SCT, age, sex, diagnosis, type of transplant, conditioning regimen and post-transplant complications involving the liver (veno-occlusive disease, acute/chronic GvHD, viral reactivation) were collected in all children transplanted between 1980 and 2002.

**Results:** 290 of 455 patients who underwent SCT were alive at least 2 years after SCT. Median age in survivors was 7.1 years and the majority were transplanted for a hematological malignancy (57.6%) with bone marrow (95.5%) of a matched sibling donor (66.6%). The conditioning regimen included TBI in 58.5% of the patients.

AST and ALT were assessed at 2 years after SCT in 216 patients and values were above normal in 53 (24.5%). In 17 patients (7.9%) AST and/or ALT value was at least twice the upper limit of normal. In 13 of 17 patients etiology could be established and included iron overload in 6, chronic hepatitis C in 2 and cGvHD in 4. HCV seropositivity (tested after 1992) occurred in 3 patients, but chronic hepatitis B was not present in any of our patients.

**Conclusions:** The prevalence of abnormal liver enzymes after SCT in children surviving longer than two years was 24.5%, with 7.9% having significantly elevated enzymes. Chronic hepatitis C was found in only 5.7% of patients with elevated liver enzymes. Longer follow-up is needed to establish the clinical relevance of elevated liver enzymes late after SCT.

---

Continuing recovery of neurologic symptoms even after very long term follow-up in Kinsbourne syndrome

**Introduction:** Kinsbourne syndrome, also known as ‘dancing eyes-elevating feet syndrome’ or ‘opsoclonus-myoclonus syndrome’ (OMS) is a well described but rare neurologic syndrome, which is highly associated with neuroblastoma. The characteristic symptoms are rapid, involuntary, irregular conjugate eye movements (opsoclonus), myoclonic jerking of the limbs and trunk, ataxia and behavioral disturbance and the disease has a sub acute onset. The exact etiology and pathogenesis of OMS is not yet clear, but the current suggestion is that it is immune-mediated. Data on long-term follow-up of these patients is not available so far.

**Patients and methods.** The purpose of our study was to investigate the course of recovery and very long-term outcome (med. > 10 years) in all 9 patients treated for OMS from 1989 until 2000 in our institute. The results include data on medical, neurological and oncologic follow up, as well as radiological evaluation and a Quality of Life assessment (TacqOL) in a longitudinally survey.

**Results.** In 4 out of 9 patients in this study a NBL was found. Five children showed signs of bulbar dysfunction, including dysarthria. Two children lost speech completely. All children had behavioural problems. All children were treated with either Prednison, ACTH, gammaglobulines or a combination. During follow up we saw a very slow continuing improvement of neurologic symptoms in all patients. Especially the three main symptoms, ataxia, opsoclonus and myoclonus improved after starting therapy and rather strikingly, kept improving even 10 years of follow-up. 7/9 children had a severe mental retardation at the latest point of evaluation. At follow-up, a significant improvement of motor skills (p=0.043) and the autonomy scale was found all still below the normal population average. Physical function, positive emotions and negative emotions however were, although low, within the range of the normal population.
Background/objective: Hair loss is a feared side effect of cancer treatment. Hair is expected to regrow after chemotherapy but after radiotherapy areas of permanent hair loss are common. This is a continuing cause of concern for children, adolescents and adults. The radiosensitive scalp hair follicles lie 0.5 to 1 mm below the skin surface and are irradiated as the radiation beam enters and leaves the head. We investigated the relationship between the total dose of radiation (in small daily amounts) and permanent hair loss. We could not find this information in the literature.

Methods: We developed a visually graded scoring system for hair loss. All patients known to us who had received radiotherapy involving scalp hair more than 6 months before the study were invited for assessment (Oxford Ethics study no A99.001). Photographs and diagrams indicated the pattern of hair loss. This was then related to scalp radiation dose which was estimated from review of treatment plans.

Results: From the 50 patients assessed ninety nine areas of scalp were scored. No clinically detectable permanent hair loss was seen when the total dose to the scalp was below 20 Gy (in 2 Gy fractions). Between 30 and 40 Gy, permanent loss became more likely, hair was present but thinned. After doses of 50 Gy or above, 80% had easily detectable and 50% total or virtually total, hair loss. The relationship between dose and permanent hair loss was highly significant (p=0.0001).

Conclusion: Children and young adults surviving brain tumours are at risk of hair loss after radiotherapy areas of permanent hair loss are common. This is a continuing cause of concern for children, adolescents and adults. The radiosensitive scalp hair follicles lie 0.5 to 1 mm below the skin surface and are irradiated as the radiation beam enters and leaves the head. We investigated the relationship between the total dose of radiation (in small daily amounts) and permanent hair loss. We could not find this information in the literature.

Methods: We developed a visually graded scoring system for hair loss. All patients known to us who had received radiotherapy involving scalp hair more than 6 months before the study were invited for assessment (Oxford Ethics study no A99.001). Photographs and diagrams indicated the pattern of hair loss. This was then related to scalp radiation dose which was estimated from review of treatment plans.

Results: From the 50 patients assessed ninety nine areas of scalp were scored. No clinically detectable permanent hair loss was seen when the total dose to the scalp was below 20 Gy (in 2 Gy fractions). Between 30 and 40 Gy, permanent loss became more likely, hair was present but thinned. After doses of 50 Gy or above, 80% had easily detectable and 50% total or virtually total, hair loss. The relationship between dose and permanent hair loss was highly significant (p=0.0001).

Conclusion: Children and young adults surviving brain tumours are at risk of hair loss after radiotherapy areas of permanent hair loss are common. This is a continuing cause of concern for children, adolescents and adults. The radiosensitive scalp hair follicles lie 0.5 to 1 mm below the skin surface and are irradiated as the radiation beam enters and leaves the head. We investigated the relationship between the total dose of radiation (in small daily amounts) and permanent hair loss. We could not find this information in the literature.

Methods: We developed a visually graded scoring system for hair loss. All patients known to us who had received radiotherapy involving scalp hair more than 6 months before the study were invited for assessment (Oxford Ethics study no A99.001). Photographs and diagrams indicated the pattern of hair loss. This was then related to scalp radiation dose which was estimated from review of treatment plans.

Results: From the 50 patients assessed ninety nine areas of scalp were scored. No clinically detectable permanent hair loss was seen when the total dose to the scalp was below 20 Gy (in 2 Gy fractions). Between 30 and 40 Gy, permanent loss became more likely, hair was present but thinned. After doses of 50 Gy or above, 80% had easily detectable and 50% total or virtually total, hair loss. The relationship between dose and permanent hair loss was highly significant (p=0.0001).

Conclusion: Children and young adults surviving brain tumours are at risk of hair loss after radiotherapy areas of permanent hair loss are common. This is a continuing cause of concern for children, adolescents and adults. The radiosensitive scalp hair follicles lie 0.5 to 1 mm below the skin surface and are irradiated as the radiation beam enters and leaves the head. We investigated the relationship between the total dose of radiation (in small daily amounts) and permanent hair loss. We could not find this information in the literature.

Methods: We developed a visually graded scoring system for hair loss. All patients known to us who had received radiotherapy involving scalp hair more than 6 months before the study were invited for assessment (Oxford Ethics study no A99.001). Photographs and diagrams indicated the pattern of hair loss. This was then related to scalp radiation dose which was estimated from review of treatment plans.

Results: From the 50 patients assessed ninety nine areas of scalp were scored. No clinically detectable permanent hair loss was seen when the total dose to the scalp was below 20 Gy (in 2 Gy fractions). Between 30 and 40 Gy, permanent loss became more likely, hair was present but thinned. After doses of 50 Gy or above, 80% had easily detectable and 50% total or virtually total, hair loss. The relationship between dose and permanent hair loss was highly significant (p=0.0001).

Conclusion: Children and young adults surviving brain tumours are at risk of hair loss after radiotherapy areas of permanent hair loss are common. This is a continuing cause of concern for children, adolescents and adults. The radiosensitive scalp hair follicles lie 0.5 to 1 mm below the skin surface and are irradiated as the radiation beam enters and leaves the head. We investigated the relationship between the total dose of radiation (in small daily amounts) and permanent hair loss. We could not find this information in the literature.
Treatment-induced ototoxicity in pediatric medulloblastoma patients

Lafay-Cousin, Lucie1; Mabbott, Don1; Druker, Susan2; Bartels, Ute1; Hu-ang, Annie1; Forte, Vito3; Bouffet, Eric3

1Hospital for Sick Children, Pediatric Brain Tumor program, Toronto, Canada; 2Hospital for Sick Children, Audiology, Toronto, Canada; 3Hospital for Sick Children, ENT, Toronto, Canada

Purpose: To report on the kinetic of cisplatinum(CDDP) induced ototoxicity and to correlate the need for hearing assistance in pediatric medulloblastoma patients.

Patients and Method: Clinical records of 37 children (older than 3 yrs) with medulloblastoma were reviewed. Results of serial pre-chemotherapy audiograms and during follow-up as well as use of hearing aids were recorded.

Results: 24 patients were treated according to average risk (AR) protocol including reduced dose of CSI and intended CDDP cumulative dose of 600mg/m2 in 8 cycles. 13 high risk (HR) patients were intended to received conventional CSI and 3 cycles of CDDP (cumulative dose of 270 mg/m2). High frequencies hearing loss (greater than 55db) occured very early on therapy in up to 54% of the AR patients after 2 cycles and 90% after 4cycles. In HR patients high frequencies HL raised from 53.8% to 100% between cycle 1 to 3, 21% of the AR patients had HL (greater than 55db) between 2000 and 4000Hz frequencies after 5 cycle of CDDP. After completion of chemotherapy, 15.8% of AR patients and 25% of the HR patients had HL greater than 25db below 2000Hz. 45.9% of the patients required 50% CDDP dose reduction at a median of 4 cycles (2-8) The median cumulative dose of CDDP administred was 412.5 mg/m2, (intended cumulative dose of 600mg/m2) in AR patients and 270mg/m2 in HR patients(intended cumulative dose of 270mg/m2). CDDP was discontinued in 6/37 patients. 6/37 required either hearing aids. Interestingly 5/6 developed moderate HL (median=50db) early on therapy(cycle 3).

Discussion/Conclusion: High frequencies HL occured early on therapy. AR patients showed greater HL between 2000-4000Hz frequencies compare to HR patients. In AR patients, ototoxicity led to early dose adjustment (cycle 4) and limited the delivered dose by 2/3 of the intended dose in AR patients. Early HL below 4000 Hz might predicte further need for hearing support. Correlation between hearing loss and academic achievement are under investigation
# Index of Authors

<table>
<thead>
<tr>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aarsen, FK</td>
<td>de Sonneville, Leo</td>
<td>Calabri, Giovanni</td>
<td>D'Angio, Giulio</td>
</tr>
<tr>
<td>Abatzoglou, Grigorios</td>
<td>de Vos, M.J.</td>
<td>Camnasio, R.</td>
<td>Daghofer, Fedor</td>
</tr>
<tr>
<td>Absolum, Kate</td>
<td>Dekker, Friedo</td>
<td>Calabri, Giovanni</td>
<td>Davies, Helena</td>
</tr>
<tr>
<td>Adam, Anna</td>
<td>Dehlinkopodoup, Eleini</td>
<td>Caron, HN.</td>
<td>de Bruin, Mariëtte</td>
</tr>
<tr>
<td>Ageerickx, N</td>
<td>Dhooge, Catharina</td>
<td>Caruso, Sara</td>
<td>de Jong, Frank</td>
</tr>
<tr>
<td>Aknes, Liv Høge</td>
<td>Donathela, Francesca</td>
<td>Casini, Tommaso</td>
<td>de Meijer, Frank</td>
</tr>
<tr>
<td>Altawi, Shadiia</td>
<td>Dohle, G.R.</td>
<td>Casini, Tommaso</td>
<td>de Meijer, Frank</td>
</tr>
<tr>
<td>Albanece, Assunta</td>
<td>Donatela, Francesca</td>
<td>Casini, Tommaso</td>
<td>de Meijer, Frank</td>
</tr>
<tr>
<td>Aleman, Berthe</td>
<td>Dorosiko, Adram</td>
<td>Casini, Tommaso</td>
<td>de Meijer, Frank</td>
</tr>
<tr>
<td>Allen, Carin</td>
<td>Drucker, Susan</td>
<td>Catharina, Jos</td>
<td>de Meijer, Frank</td>
</tr>
<tr>
<td>Amoroso, Loredana</td>
<td>Ehrfurh, Eva Marie</td>
<td>de Meijer, Frank</td>
<td>de Meijer, Frank</td>
</tr>
<tr>
<td>Anderson, Margaretta</td>
<td>Eshelman, Debra</td>
<td>de Meijer, Frank</td>
<td>de Meijer, Frank</td>
</tr>
<tr>
<td>Arjmandi Rafsanjani, Khadijeh</td>
<td>Erfurh, Eva Marie</td>
<td>de Meijer, Frank</td>
<td>de Meijer, Frank</td>
</tr>
<tr>
<td>Arjmandi Rafsanjani, Khadijeh</td>
<td>Erfurh, Eva Marie</td>
<td>de Meijer, Frank</td>
<td>de Meijer, Frank</td>
</tr>
<tr>
<td>Arjmandi Rafsanjani, Khadijeh</td>
<td>Erfurh, Eva Marie</td>
<td>de Meijer, Frank</td>
<td>de Meijer, Frank</td>
</tr>
</tbody>
</table>

* Presenting author

---

<table>
<thead>
<tr>
<th>E</th>
<th>F</th>
<th>G</th>
<th>H</th>
</tr>
</thead>
<tbody>
<tr>
<td>de Ridder-Sluiter, Hanneke</td>
<td>Faranousoh, Mohammad</td>
<td>Gadomski, Artur</td>
<td>Habrand, J.L.</td>
</tr>
<tr>
<td>de Ridder-Sluiter, Hanneke</td>
<td>Fatma, Sûlia</td>
<td>Gavazza, Stanislao</td>
<td>Hallsten, K.</td>
</tr>
<tr>
<td>de Ridder-Sluiter, Hanneke</td>
<td>Ferrari, Cristina</td>
<td>Gavras, Christoforos</td>
<td>Hancock, Barry</td>
</tr>
<tr>
<td>de Ridder-Sluiter, Hanneke</td>
<td>Ferrari, Stefano</td>
<td>Gibson, Faith</td>
<td>Hartmann, Olivier</td>
</tr>
<tr>
<td>de Ridder-Sluiter, Hanneke</td>
<td>Fioredda, Francesca</td>
<td>Giwercman, Aleksander</td>
<td>Hazeldine, Oliver</td>
</tr>
<tr>
<td>de Ridder-Sluiter, Hanneke</td>
<td>Fliers, E.</td>
<td>Giwercman, Yvonne L.</td>
<td>Hazeldine, Oliver</td>
</tr>
<tr>
<td>de Ridder-Sluiter, Hanneke</td>
<td>Follin, Cecilia</td>
<td>Glaser, Adam</td>
<td>Hazeldine, Oliver</td>
</tr>
<tr>
<td>de Ridder-Sluiter, Hanneke</td>
<td>Fonti, Ulla</td>
<td>Golan, Hana</td>
<td>Hazeldine, Oliver</td>
</tr>
<tr>
<td>de Ridder-Sluiter, Hanneke</td>
<td>Forte, Vito</td>
<td>Goldstein, Gal</td>
<td>Hazeldine, Oliver</td>
</tr>
<tr>
<td>de Ridder-Sluiter, Hanneke</td>
<td>Francesca, Gióiasl</td>
<td>Grabowska, Aleksandra</td>
<td>Hazeldine, Oliver</td>
</tr>
<tr>
<td>de Ridder-Sluiter, Hanneke</td>
<td>Fredriksen, Kirsten</td>
<td>Graham, Andrew</td>
<td>Hazeldine, Oliver</td>
</tr>
<tr>
<td>de Ridder-Sluiter, Hanneke</td>
<td>Frenos, Stefano</td>
<td>Green, Daniel M.</td>
<td>Hazeldine, Oliver</td>
</tr>
<tr>
<td>de Ridder-Sluiter, Hanneke</td>
<td>Frey, Eva</td>
<td>Greenfield, Diana</td>
<td>Hazeldine, Oliver</td>
</tr>
<tr>
<td>de Ridder-Sluiter, Hanneke</td>
<td>Frijns, Jeroen</td>
<td>Guia, Hanau</td>
<td>Hazeldine, Oliver</td>
</tr>
<tr>
<td>de Ridder-Sluiter, Hanneke</td>
<td>Frisvold, Britte</td>
<td>Guia, Hanau</td>
<td>Hazeldine, Oliver</td>
</tr>
</tbody>
</table>

---

<table>
<thead>
<tr>
<th>J</th>
<th>K</th>
<th>L</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>de Ridder-Sluiter, Hanneke</td>
<td>de Ridder-Sluiter, Hanneke</td>
<td>Laarmann, C.</td>
<td>Mahbott, Don</td>
</tr>
<tr>
<td>de Ridder-Sluiter, Hanneke</td>
<td>de Ridder-Sluiter, Hanneke</td>
<td>Lackner, Herwig</td>
<td>Mahmoud, Saieddine</td>
</tr>
<tr>
<td>de Ridder-Sluiter, Hanneke</td>
<td>de Ridder-Sluiter, Hanneke</td>
<td>Lafay-Cousin, Lucie</td>
<td>Marra, Pillon</td>
</tr>
<tr>
<td>de Ridder-Sluiter, Hanneke</td>
<td>de Ridder-Sluiter, Hanneke</td>
<td>Lambrecht, B.C.</td>
<td>Mattison, Elisabet</td>
</tr>
<tr>
<td>de Ridder-Sluiter, Hanneke</td>
<td>de Ridder-Sluiter, Hanneke</td>
<td>Langer, Thorsten</td>
<td>Matusiyak, Michal</td>
</tr>
<tr>
<td>de Ridder-Sluiter, Hanneke</td>
<td>de Ridder-Sluiter, Hanneke</td>
<td>Lambrichts, J.M.</td>
<td>Maura, Faraci</td>
</tr>
<tr>
<td>de Ridder-Sluiter, Hanneke</td>
<td>de Ridder-Sluiter, Hanneke</td>
<td>Lamy, Joel</td>
<td>Mazanek, Pavel</td>
</tr>
<tr>
<td>de Ridder-Sluiter, Hanneke</td>
<td>de Ridder-Sluiter, Hanneke</td>
<td>Langer, Thorsten</td>
<td>Mazur, Urszula</td>
</tr>
<tr>
<td>de Ridder-Sluiter, Hanneke</td>
<td>de Ridder-Sluiter, Hanneke</td>
<td>Landau, Yehuda</td>
<td>Mazzaro-Aronovich, Kimon</td>
</tr>
<tr>
<td>de Ridder-Sluiter, Hanneke</td>
<td>de Ridder-Sluiter, Hanneke</td>
<td>Lanksa, Bart</td>
<td>McElhinney, Danielle</td>
</tr>
<tr>
<td>de Ridder-Sluiter, Hanneke</td>
<td>de Ridder-Sluiter, Hanneke</td>
<td>Langer, Thorsten</td>
<td>McElhinney, Danielle</td>
</tr>
<tr>
<td>de Ridder-Sluiter, Hanneke</td>
<td>de Ridder-Sluiter, Hanneke</td>
<td>Landau, Yehuda</td>
<td>McElhinney, Danielle</td>
</tr>
<tr>
<td>de Ridder-Sluiter, Hanneke</td>
<td>de Ridder-Sluiter, Hanneke</td>
<td>Langer, Thorsten</td>
<td>McElhinney, Danielle</td>
</tr>
<tr>
<td>de Ridder-Sluiter, Hanneke</td>
<td>de Ridder-Sluiter, Hanneke</td>
<td>Landau, Yehuda</td>
<td>McElhinney, Danielle</td>
</tr>
<tr>
<td>de Ridder-Sluiter, Hanneke</td>
<td>de Ridder-Sluiter, Hanneke</td>
<td>Langer, Thorsten</td>
<td>McElhinney, Danielle</td>
</tr>
<tr>
<td>de Ridder-Sluiter, Hanneke</td>
<td>de Ridder-Sluiter, Hanneke</td>
<td>Landau, Yehuda</td>
<td>McElhinney, Danielle</td>
</tr>
<tr>
<td>de Ridder-Sluiter, Hanneke</td>
<td>de Ridder-Sluiter, Hanneke</td>
<td>Langer, Thorsten</td>
<td>McElhinney, Danielle</td>
</tr>
<tr>
<td>de Ridder-Sluiter, Hanneke</td>
<td>de Ridder-Sluiter, Hanneke</td>
<td>Langer, Thorsten</td>
<td>McElhinney, Danielle</td>
</tr>
<tr>
<td>de Ridder-Sluiter, Hanneke</td>
<td>de Ridder-Sluiter, Hanneke</td>
<td>Langer, Thorsten</td>
<td>McElhinney, Danielle</td>
</tr>
<tr>
<td>de Ridder-Sluiter, Hanneke</td>
<td>de Ridder-Sluiter, Hanneke</td>
<td>Langer, Thorsten</td>
<td>McElhinney, Danielle</td>
</tr>
</tbody>
</table>

---

* Presenting author
Map of Lundagård

LUNCH

VENUE
PALAESTRA

WELCOME
RECEPTION