RiSK:
Prospective data collection in modern paediatric radiation oncology for radiation doses, acute and late effects

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Acute side effects of irradiation

- occurrence during treatment until 90 days after end of treatment
- classification after RTOG/EORTC
- radiogenous inflammation
- dependent on dose at organ, fractionation, type of organ, volume of irradiation, combined modalities (drug therapy, operation), earlier damage to organs, individual disposition (morbidity, intrinsic radiation sensitivity)
- may disappear completely after end of irradiation
- may precede late side effects
- may compromise organ function
- may compromise the well being
- may require supportive care
Mantle Field 36 Gy (30 Gy + 6 Gy)
Pneumonitis 42 days after end of irradiation
Classification for oral mucositis (RTOG/EORTC, acute)

- **Grade I**
  Injection/may experience mild pain not requiring analgesic.

- **Grade II**
  Patchy mucositis that may produce an inflammatory sero-sanguinous discharge/may experience moderate pain requiring analgesia

- **Grade III**
  Confluent fibrinous mucositis/may include severe pain requiring narcotic

- **Grade IV**
  Ulceration, hemorrhage or necrosis
Late deterministic side effects of irradiation

- occurrence **later than 90 days after end** of treatment
- classification after RTOG/EORTC
- radiogenous chronic inflammation, scarification, impairment or loss of organ function
- may persist after end of irradiation
- may compromise organ function
- may compromise the well being
- may require supportive care
Late effect dependency

- **patient dependent factors:**
  - age, growth status, gender
  - type of organ
  - earlier damage to organs
  - individual disposition (morbidity, intrinsic radiation sensitivity)

- **therapy dependent factors:**
  - organ doses
  - volume of irradiation
  - volume parts of irradiated organs
  - fractionation and total dose
  - combined modalities (drug therapy, operation)
Example of Radiation late effect

**Figure 15.** Scoliosis in a 17-year-old patient who underwent resection of and radiation therapy for a left adrenal neuroblastoma in infancy. Radiograph depicts scoliosis, as well as the surgical clips from the previous resection.

Parisi et al., RadioGraphics 1999
Limitations of retrospective analyses of late effects:

- Long time interval between treatment and analysis
- No general availability of modern treatment planning tools
- Poor documentation of the real treatment
- No strict control of real administered doses in TOS
- Obsolete treatment techniques

- No well established dose effect relationship in children
Situation at the outset (1998)

- Broad experience regarding anti-tumour efficacy of radiotherapy
- No systematic evaluation of radiation associated toxicities in paediatric clinical trials
- No detailed correlation between organ dose levels and side effects
German working group paediatric radiation oncology (APRO):

• Concept for prospective, multicentric and therapy trial independent evaluation of early and late toxicities of radiotherapy 

("Registry for the Detection of Late Sequelae after Radiotherapy in Childhood and Adolescence" (RiSK))

• Aim:
Optimizing treatment recommendations in future clinical trials regarding radiotherapy and its interactions with other therapy modalities.
("Registry for the Detection of Late Sequelae after Radiotherapy in Childhood and Adolescence" (RiSK))

Aims

• Optimizing treatment recommendations in future clinical trials regarding radiotherapy and its interactions with other therapy modalities particularly for future GPOH-studies

• Correlation of dose and organ

• Therapy study - independent prospective multicentric evaluation of early and late toxicities of radiotherapy in the framework of GPOH-studies

• Establishing organ tolerance doses dependent on age and therapy modalities (operation, drug therapy).

• Individual alerts
RiSK – Concept

"Registry for the Detection of Late Sequelae after Radiotherapy in Childhood and Adolescence" (RiSK)

- Use of basis data forms of performed radiotherapy
- Correlation of dose and organ
- 3-D-planning, DVH, dose measurement
- Central documentation of basis data
- Follow-up examinations
- Data analyses and establishment of dose/effect relationship per organ
Phases / Grants

- **Brainstorming APRC 1998**

- **Pilot phase** June 2001 – January 2004: Involvement of few centers, Establishment of documentation forms, first recruitment of patients. Integration into all GPOH trials. Support by Elternverein

- **Feasibility phase** February 2004 till July 2005: Grant from the „Deutsche Kinderkrebsstiftung“ for 1.5 years, multicentric use, establishment and intensification of contacts

- **Study phase** since December 2005: Grant of the „Deutsche Kinderkrebsstiftung“ for further 2 years until 12/07, increase of patient numbers and prolongation of follow-up, first data analysis

- **Prolongation of study phase** 12/2007 – 5/2011 by grant of „Deutsche Kinderkrebsstiftung“

- **Prolongation of study phase** 6/2011 – 5/2014 by grant of „Deutsche Kinderkrebsstiftung“
Agreement of Cooperation

The German
Registry for the Evaluation of Late Side Effects after Radiotherapy in Childhood and Adolescence (RiSK)

and the
Swedish Working Group for Paediatric Radiotherapy

decided to enter into an Agreement of Cooperation

in the

"International Project on Prospective Analysis of Radiotoxicity in Childhood and Adolescence (IPPARCH)"

Münster, Umeå, 6th May 2009

Prof. Dr. Normann Willich
RiSK study chairman

Ass Prof. Dr. Jack Lindh
Swedish Working Group for Paediatric Radiotherapy

Department of Radiotherapy
University Hospital of Münster
Germany

Department of Oncology
University Hospital of Umeå
Sweden
RiSK: Internationalisation

Europeanizing:
Faster increase of patient numbers
Symposia:

Symposium Tumorthherapie-assoziierte Nebenwirkungen bei Kindern und Jugendlichen. Münster, 28./29.01.2005


1st IPPARCA Bilateral Meeting Sweden – Germany, Stockholm, May 2008

3rd Münster Symposium on Late Effects after Tumour Therapy in Childhood and Adolescence, 13.-15.02.2009, Münster

2nd IPPARCA Meeting, Münster, February 2010

3rd IPPARCA Meeting, Stockholm, May 2011

4th Münster Symposium on Late Effects after tumour Therapy in Childhood and Adolescence, July, 15th – 16th, 2011

4th IPPARCA Meeting, Münster, April, 19th – 20th, 2012

5th IPPARCA Meeting, Häckeberga, Sweden, April, 18th – 19th, 2013
Recruitment (04/2013)  
n = 1528  

Involved centers:  
n=62
No. of patients from study trials (4/2013)

- ALL: n= 217
- EWING: n= 218
- Soft Tissue Sarcomas: n= 268
- Neurological Tumors: n= 278
- Hodgkin: n= 208
- AML n= 139
- Nephroblastoma n= 55
- Others n= 220
# Recruitment data (4/2013)

- **Patients:**
  - \( n = 1528 \)
  - 56% m, 44% f

- **Radiotherapy basis documentation forms:**
  - \( n = 1576 \)

## Therapy

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st Therapy</td>
<td>~ 90</td>
</tr>
<tr>
<td>Recurrence 1</td>
<td>~ 10</td>
</tr>
<tr>
<td>Recurrence 2</td>
<td>~ 0.4</td>
</tr>
</tbody>
</table>

- **No. of toxicity documentation forms:**
  - acute:
    - \( n = 1259 \)
  - late:
    - \( n = 3151 \)

- **Centers involved:**
  - \( n = 62 \)
<table>
<thead>
<tr>
<th>Organ</th>
<th>Dosisbeschränkung</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knochenmuskulatur</td>
<td>mehr als 30 % des KM mit ≥ 15 Gy belastet</td>
</tr>
<tr>
<td>Knochen, Gelenke,</td>
<td>≥ 20 Gy</td>
</tr>
<tr>
<td>Weichteile</td>
<td></td>
</tr>
<tr>
<td>Ganzschädel</td>
<td>jede eingestrahlte Dosis</td>
</tr>
<tr>
<td>Teilhörrbestrahlung</td>
<td>≥ 20 Gy</td>
</tr>
<tr>
<td>Myelon</td>
<td>≥ 20 Gy</td>
</tr>
<tr>
<td>Auge</td>
<td>jede eingestrahlte Dosis</td>
</tr>
<tr>
<td>Ohr</td>
<td>jede eingestrahlte Dosis</td>
</tr>
<tr>
<td>Speicheldrüse</td>
<td>≥ 20 Gy</td>
</tr>
<tr>
<td>Zähne/Kiefer</td>
<td>jede eingestrahlte Dosis</td>
</tr>
<tr>
<td>Schilddrüse</td>
<td>jede eingestrahlte Dosis</td>
</tr>
<tr>
<td>Kehlkopf</td>
<td>≥ 20 Gy</td>
</tr>
<tr>
<td>Mamma</td>
<td>jede eingestrahlte Dosis</td>
</tr>
<tr>
<td>Ösophagus</td>
<td>≥ 40 Gy</td>
</tr>
<tr>
<td>Lunge</td>
<td>Ganzlunge ≥ 10 Gy&lt;br&gt;Teillungendosis ≥ 18 Gy</td>
</tr>
<tr>
<td>Herz</td>
<td>≥ 15 Gy</td>
</tr>
<tr>
<td>Leber</td>
<td>jede Dosis bei Radiatio &gt; 1/3 des Organs&lt;br&gt;Teilleberdosis &gt; 20 Gy</td>
</tr>
<tr>
<td>Nieren</td>
<td>jede Dosis wenn ≥ 1/2 Niere bestrahlt&lt;br&gt;Teilnierendosis ≥ 12 Gy</td>
</tr>
<tr>
<td>Pankreas</td>
<td>≥ 20 Gy</td>
</tr>
<tr>
<td>Dünn-/Dickdarm</td>
<td>≥ 10 Gy</td>
</tr>
<tr>
<td>Harnblase</td>
<td>falls im Zielvolumen</td>
</tr>
<tr>
<td>Vagina/Uterus</td>
<td>falls im Zielvolumen</td>
</tr>
<tr>
<td>Ovarien</td>
<td>jede eingestrahlte Dosis</td>
</tr>
<tr>
<td>Hoden</td>
<td>jede eingestrahlte Dosis</td>
</tr>
</tbody>
</table>
3-D-Planning
Dose-Volume-Histogram

- Rectum
- Harnblase
- ZV
### Documentation forms

- **Example: Dose-Volume-Histograms**

<table>
<thead>
<tr>
<th>Dose</th>
<th>Heart</th>
<th>Lung left</th>
<th>Lung right</th>
<th>Whole lung</th>
<th>Liver</th>
<th>Kidney left</th>
<th>Kidney right</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 5 Gy</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>&gt;10 Gy</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>&gt;15 Gy</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>&gt;20 Gy</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>&gt;30 Gy</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>&gt;40 Gy</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>&gt;50 Gy</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>&gt;60 Gy</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
</tbody>
</table>
Dose measurement

Organ dose thyroid gland
Dose measurement

Organ dose testicles
# Documentation forms

- **Detail evaluation of acute toxicities (EORT/RTOG)**

<table>
<thead>
<tr>
<th>Skin / Subcutis</th>
<th>0 normal</th>
<th>1. Follicular, faint or dull erythema/edema/dry desquamation/decreased sweating</th>
<th>2. Tender or bright erythema, patchy moist desquamation/moderate edema, (local therapy necessary)</th>
<th>3. Confluent, moist desquamation other than skin folds, pitting edema (intensive therapy necessary)</th>
<th>4. Ulceration, hemorrhage or necrosis, (operative therapy necessary)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucous membrane</td>
<td>0 normal</td>
<td>1. Injection/may experience mild pain not requiring analgesic.</td>
<td>2. Patchy mucositis that may produce an inflammatory serosanguinous discharge/may experience moderate pain requiring analgesia</td>
<td>3. Confluent fibrinous mucositis/may include severe pain requiring narcotic</td>
<td>4. Ulceration, hemorrhage or necrosis</td>
</tr>
<tr>
<td>Salivary glands</td>
<td>0 normal</td>
<td>1. Mild mouth dryness/ slightly thickened saliva/may have slightly altered taste</td>
<td>2. Moderate to complete dryness/hick, sticky saliva / markedly altered taste.</td>
<td>3. Complete dryness</td>
<td>4. Acute salivary gland necrosis</td>
</tr>
<tr>
<td>Pharynx/ Esophagus</td>
<td>0 normal</td>
<td>1. Mild dysphagia or odynophagia/may require topical anesthetic or non-narcotic analgesics/may require soft diet</td>
<td>2. Moderate dysphagia or odynophagia/may require narcotic analgesics/may require puree or liquid diet</td>
<td>3. Severe dysphagia or odynophagia with dehydration or weight loss &gt;15% from pre-treatment baseline, requiring NG feeding tube, i.v. fluids or hyperalimentation</td>
<td>4. Complete obstruction, ulceration, perforation, fistula</td>
</tr>
<tr>
<td>Larynx</td>
<td>0 normal</td>
<td>1. Mild or intermittent hoarseness/cough not requiring antitussive / erythema of mucosa</td>
<td>2. Persistent hoarseness but able to vocalize, sore throat, patchy fibrinous exudates or mild arytenoids edema not requiring narcotic/cough requiring antitussive</td>
<td>3. Whispered speech, throat pain requiring narcotic / confluent fibrinous exudates, marked arytenoids edema</td>
<td>4. Marked dyspnea, stridor or hemoptysis with tracheostomy or intubation necessary</td>
</tr>
<tr>
<td>Lung</td>
<td>0 no change</td>
<td>1. Mild symptoms of dry cough or dyspnea on exertion</td>
<td>2. Persistent cough requiring narcotic, antitussive agents / dyspnea with minimal effort but not at rest</td>
<td>3. Severe cough unresponsive to narcotic antitussive agent or dyspnea at rest / clinical or radiological evidence of acute pneumonitis/intermittent oxygen or steroids may be required</td>
<td>4. Severe respiratory insufficiency / continuous oxygen or assisted ventilation</td>
</tr>
</tbody>
</table>
Documentation forms  

- Detail evaluation of late toxicities (EORT/RTOG)

<table>
<thead>
<tr>
<th>Skin</th>
<th>0 normal</th>
<th>1 Slight atrophy, pigmentation change, some hair loss</th>
<th>2 Patch atrophy, moderate telangiectasia (&lt; 50%), total hair loss</th>
<th>3 Marked atrophy, gross telangiectasia (&gt; 50%)</th>
<th>4 ulceration, necrosis, (surgical intervention necessary)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subcutaneous tissue</td>
<td>0 normal</td>
<td>1 mild asymptomatic fibrosis, without contractures, slight reduced subcutaneous fat</td>
<td>2 moderate asymptomatic fibrosis with ≤ 10% linear contracture, moderate reduced subcutaneous fat</td>
<td>3 severe (symptomatic) fibrosis with &gt;20% linear contracture, severe reduced subcutaneous fat</td>
<td>4 ulceration, necrosis, (surgical intervention necessary)</td>
</tr>
<tr>
<td>Mucous membrane</td>
<td>0 normal</td>
<td>1 Slight atrophy or dryness</td>
<td>2 moderate atrophy and telangiectasia, reduced production of mucus</td>
<td>3 Marked atrophy and telangiectasia, loss of mucus production</td>
<td>4 ulceration, necrosis, (surgical intervention necessary)</td>
</tr>
<tr>
<td>Salivary glands</td>
<td>0 normal</td>
<td>1 Slight dryness, good response on stimulation (normal food possible)</td>
<td>2 moderate dryness of mouth, poor response on stimulation (much fluid, pulpy food)</td>
<td>3 complete dryness of mouth, no response on stimulation (no solid food, fluid food)</td>
<td>4 Fibrosis (complete atrophy) (parenteral nutrition, PEG)</td>
</tr>
<tr>
<td>Pharynx/Esophagus</td>
<td>0 normal</td>
<td>1 mild fibrosis, slight dysphagia regarding solid food, no pain at swallow (normal nutrition)</td>
<td>2 moderate fibrosis, no normal nutrition, pulpy food, perhaps dilatation necessary</td>
<td>3 severe fibrosis (or dysphagia), only fluids possible, dilatation necessary, pain at swallow</td>
<td>4 necrosis, perforation, fistula (surgical intervention necessary or PEG/parenteral nutrition)</td>
</tr>
<tr>
<td>Larynx</td>
<td>0 normal</td>
<td>1 (mild) hoarseness (or cough), mild laryngeal edema</td>
<td>2 moderate hoarseness or cough, moderate laryngeal edema, chondritis (symptomatic therapy)</td>
<td>3 severe hoarseness, severe laryngeal edema, massive chondritis, intensive local therapy, analgesics</td>
<td>4 necrosis, (massive dyspnoea and stridor, ulceration, Intubation or tracheotomy)</td>
</tr>
<tr>
<td>Lung</td>
<td>0 normal pO2 &gt; 85; pCO2 &lt; 40</td>
<td>1 no or mild symptoms (dry cough), few radiological signs (mild exercise-induced shortness of breath) pO2:71-85; pCO2: 41-50</td>
<td>2 moderate symptomatic lung fibrosis or pneumonitis (massive cough), mild fever, radiological signs; (moderate exercise-induced shortness of breath) pO2:61-70; pCO2: 51-60</td>
<td>3 Severe symptomatic lung fibrosis or pneumonitis, massive radiological signs; (severe shortness of breath) pO2:51-60; pCO2: 61-70 (intensive medication)</td>
<td>4 Massive respiratory Insufficiency; permanent O2-application and controlled ventilation pO2 &lt; 50; pCO2 &gt; 70 (intensive care necessary)</td>
</tr>
</tbody>
</table>
HYPOTHYROIDISM AFTER HEAD-AND-NECK RADIOTHERAPY IN CHILDREN AND ADOLESCENTS: PRELIMINARY RESULTS OF THE “REGISTRY FOR THE EVALUATION OF SIDE EFFECTS AFTER RADIOTHERAPY IN CHILDHOOD AND ADOLESCENCE” (RiSK)

Tobias Bölling, M.D., a, b, c, d, e, f, g, h; Alina Osenhers, e, f, g, h; Hildegard Pape, M.D., a, b, c, d, e, f, g, h; Carmen Martini, M.D., f, g, h; Christian Rübe, M.D., a, b, c, d, e, f, g, h; Beate Timmermann, M.D., a, b, c, d, e, f, g, h; Karin Fischedick, M.D., a, b, c, d, e, f, g, h; Rolf-Dieter Kortmann, M.D., a, b, c, d, e, f, g, h; Joachim Gerß, f, g, h; Raphael Koch, f, g, h; Normann Willich, M.D.; a, b, c, d, e, f, g, h

Department of Radiation Oncology, University Hospital of Münster, Germany; Department of Radiation Oncology, University Hospital of Düsseldorf, Germany; Department of Radiation Oncology, University Hospital of Erlangen, Germany; Department of Radiation Oncology, University Hospital of Freiburg, Germany; Department of Radiation Oncology, University Hospital of Heidelberg, Germany; Department of Radiation Oncology, University Hospital of Hamburg, Germany; Department of Radiation Oncology, University Hospital of Homburg/Saar, Germany; Department of Radiation Oncology, University Hospital of Munich, Germany; Department of Radiation Oncology, University Hospital of Munich, Germany; Department of Radiation Oncology, University Hospital of Munich, Germany

Prospective Evaluation of Radiotherapy-associated Late Effects in Children

a report by

Prospective Evaluation of Radiotherapy-associated Late Effects in Children

a report by

Tobias Bölling1 and Normann Willich2

DOSE–VOLUME ANALYSIS OF RADIATION NEPHROPATHY IN CHILDREN: PRELIMINARY REPORT OF THE RiSK CONSORTIUM

Tobias Bölling, M.D., a, b, d, e, f, g, h; Irina Ernst, M.D., a, b, d, e, f, g, h; Hildegard Pape, M.D., a, b, c, d, e, f, g, h; Carmen Martini, M.D., a, b, c, d, e, f, g, h; Christian Rübe, M.D., a, b, c, d, e, f, g, h; Beate Timmermann, M.D., a, b, c, d, e, f, g, h; Karin Fischedick, M.D., a, b, c, d, e, f, g, h; Rolf-Dieter Kortmann, M.D., a, b, c, d, e, f, g, h; and Normann Willich, M.D., a, b, c, d, e, f, g, h

Original article

Acute toxicity profile of radiotherapy in 690 children and adolescents: RiSK data

Nadja Selo, Tobias Bölling, Iris Ernst, Hildegard Pape, Carmen Martini, Christian Rübe, Beate Timmermann, Karin Fischedick, Rolf-Dieter Kortmann, Joachim Gerß, Raphael Koch, Normann Willich

Behaviorassoziierte Spätfolgen nach Strahlen-Therapie maligner Erkrankungen im Kindes- und Jugendalter

Machbarkeitsanalyse einer prospektiven multizentrischen Registerstudie


Evaluation of Side Effects After Radiotherapy in Childhood and Adolescence: From Retrospective Case Reports to a Prospective, Multicentric and Transnational Approach

Normann Willich1, Iris Ernst1, Hildegard Pape2, Christian Rübe2, Beate Timmermann2, Branka Asadpour2, Rolf-Dieter Kortmann2, Tobias Bölling1

Register zur Erfassung von Spätfolgen nach Strahlentherapie im Kindes- und Jugendalter – erste Ergebnisse

Register for the Evaluation of Side Effects in Childhood and Adolescence – First Results

Klin Pädiatr 2007; 219: 139–145

German Register for Detection of Late Sequelae after Radiotherapy for Children and Adolescents (RiSK): Present Status and First Results

Tobias Bölling1, Andreas Schuck1, Hildegard Pape2, Christian Rübe2, Frank-Michael Meyer2, Carmen Martini2, Beate Timmermann2, Branka Asadpour2, Rolf-Dieter Kortmann2, Jörn D. Beck1, Thorsten Langer1, Marios Paulides1, Normann Willich1
First results

First (preliminary) analyses were performed on:

- Acute and late effects lung (preliminary)
- Acute toxicity Liver
- Acute toxicity salivary glands
- Acute and late effects bowel
- Late effects kidney
- Late effects thyroid gland
Examples for different organs
Radiation dose: Breast

right

left
Example of dose documentation

Patients with dose at thyroid gland

Patients with lung volume > 20 Gy

Thyroid gland in PTV: n=164
Acute toxicities
Frequency [%] per grade of toxicity (0-4)
Late toxicities

Frequency [%] of grade of toxicity (0-4)
**RiSK data base:**
**Lung irradiation**

Database of 1050 registered patients from 62 centres (05.09)

- 167 pat. with thoracic irradiation and DVH of lungs:
  - 80 pat. with M. Hodgkin
  - 55 pat. with Ewingsarcoma
  - 17 pat. with soft tissue sa.
  - 6 pat. with nephroblastoma
  - 9 others
Irradiated lung volumes

DVH whole lung

Lung volume (%) vs. Dose (Gy)
DVH-based analysis

- Comparison of patients with and without pulmonary function impairment
  - Acute side effects
  - Maximal late side effects
  - Last side effects, i.e. side effects at last information

- Calculation with whole lung volume, no separation left / right lung
Follow up of 167 patients with thoracic irradiation:

- 120 Pat. with documentation of acute-toxicity of the lungs
- 95 Pat. with documentation of late effects of the lungs

- median age (RT): 14.7 years (2.3-25.5 years) (9 pat. >18 years)
- median follow-up: 23.5 months (4-84 months)

Recorded toxicities after RTOG/EORTC:

<table>
<thead>
<tr>
<th>Tox-grade</th>
<th>0°</th>
<th>1°</th>
<th>2°</th>
<th>3°</th>
<th>4°</th>
</tr>
</thead>
<tbody>
<tr>
<td>acute</td>
<td>100</td>
<td>16</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>late</td>
<td>74</td>
<td>14</td>
<td>4</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>
DVH-based analysis

dose-volume – toxicity correlation.

\[ p:\]
\[ 0 \text{ vs. } 1: 0.442 \]
\[ 0 \text{ vs. } 2: 0.103 \]
DVH-based analysis

dose - volume – toxicity correlation.

p:
0 vs. 1: 0.372
0 vs. 2: 0.209
DVH-based analysis

dose - volume – toxicity correlation.

p:
0 vs. 1: 0.170
0 vs. 2: 0.841

n = 74     n = 13     n = 4     n = 3     n = 1
DVH-based analysis

dose-volume – toxicity correlation.

p:

0 vs. 1: 0.937
0 vs. 2: 0.027

n = 74   n = 13   n = 4   n = 3   n = 1
DVH-based analysis

Dose-volume–toxicity correlation.

\[
p:
0 \text{ vs. } 1: 0.926 \\
0 \text{ vs. } 2: 0.117
\]
DVH-based analysis

- 5 Gy
- 1 pat. with phrenic paresis
- 1 pat. with recurrent lung tumour + 2nd RT

p:
- 0 vs. 1: 0.833
- 0 vs. 2: 0.218

n = 74       n = 13       n = 4      n = 3          n = 1

p: 0 vs. 1: 0.833
0 vs. 2: 0.218

- 1 pat. with phrenic paresis
- 1 pat. with recurrent lung tumour + 2nd RT
DVH-based analysis

Dose-volume-toxicity correlation.

\[ \text{p:} \]

- 0 vs. 1: 0.833
- 0 vs. 2: 0.218

1 pat. mit severe post-OP scarrings

\[ n = 74 \quad n = 13 \quad n = 4 \quad n = 3 \quad n = 1 \]
Selo et al.: acute toxicity in relation to DVHs

Selo et al., Radiother Oncol, 2010
Results: acute toxicity in relation to DVHs

Stoppel et al., unpublished data
Results lung:

- reduced lung function after thoracic irradiation is not rare
- up to now no data regarding organ dose / volume relationship
- First indications of relevance of organ volumes also in the low dose area (<20 Gy) (IMRT?)

Correlations of organ dose / volume / toxicity relationships become possible.
Acute toxicities in 690 patients

Recruited patients till 5/2009 \( n = 1086 \)

Acute toxicity rate documented \( n = 747 \)

Excluded (reirradiation) \( n = 57 \)

Analysed patients \( n = 690 \)

with toxicities \( n = 506 \) (73%)

age 1 – 19 years old

male 55.9% (median age 11.0 years)

female 43.9% (median age 11.3 years)
No. of acute side effects for 6 organs (n = 1088) according to RTOG guidelines

mainly blood parameters under ongoing chemotherapy, skin, mucosa
## Toxicity classification

**Max. acute side effects after radiotherapy in childhood (adapted from RTOG/EORTC)**

<table>
<thead>
<tr>
<th>Liver</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>normal</td>
<td>Mild lassitude; nausea, dyspepsia, slightly abnormal liver function,</td>
<td>Moderate symptoms; some abnormal liver function tests; serum albumin normal</td>
<td>Disabling hepatic insufficiency; liver function tests grossly abnormal; low albumin; edema or ascites</td>
<td>Necrosis / Hepatic coma or encephalopathy</td>
</tr>
</tbody>
</table>
Irradiated liver volumes

DVH Liver

Dose (Gy)
Liver volume (%)
Liver acute toxicity

15 Gy

100
80
60
40
20
0

p=0.167

Acute toxicity liver

% Vol. liver 15 Gy

20 Gy

100
80
60
40
20
0

p=0.64

Acute toxicity liver

% Vol. liver 20 Gy
Liver acute toxicity

5 Gy

p=0.157

10 Gy

p=0.044
Dose-volume analysis of radiation nephropathy in children

Table 1. Definitions for late radiation toxicity grades for the kidney

<table>
<thead>
<tr>
<th>Definition</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine</td>
<td>Age norm (N)</td>
<td>&gt;N to 1.5 × N</td>
<td>&gt;1.5 × N to 3 × N</td>
<td>&gt;3 × N to 6 × N</td>
<td>&gt;6 × N</td>
</tr>
<tr>
<td>Creatinine clearance (mL/min)</td>
<td>≥90</td>
<td>60–89</td>
<td>40–59</td>
<td>20–39</td>
<td>≤19</td>
</tr>
<tr>
<td>Proteinuria (g/L)</td>
<td>None</td>
<td>&lt;3</td>
<td>3–10</td>
<td>&gt;10</td>
<td>Nephrotic syndrome</td>
</tr>
<tr>
<td>Hematuria</td>
<td>None</td>
<td>Microscopic</td>
<td>Macroscopic without clot passage</td>
<td>Macroscopic with clot passage</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Patients with acute, maximal late, and last late toxicity differentiated according to grades 0, 1, and 2

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>0</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute toxicity</td>
<td>82 (92)</td>
<td>6 (7)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Maximal late toxicity</td>
<td>65 (88)</td>
<td>7 (9)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Last late toxicity</td>
<td>69 (94)</td>
<td>4 (5)</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

Values are number (percentage).

Bölling et al., Int J Radiat Oncol Biol Phys. 2011
Dose-volume analysis of radiation nephropathy in children

Fig. 1. Whole kidney volumes exposed to 20 and 30 Gy (V20, V30) differentiated for patients with and without Grade 1 or 2 maximal late effects. A statistically significant difference was seen in patients with and without Grade 1 toxicity (V20: \( p = 0.031 \); V30: \( p = 0.003 \)).

Bölling et al., Int J Radiat Oncol Biol Phys. 2011
Hypothyroidism after head-and-neck radiotherapy in children and adolescents

Thyroidea and/or hypophysis were completely or partially located in the target volume of 404 patients

- Development of pathological thyroidea gland values
  - Hazard ratio: 15-25 Gy SD vs. PCI: 3.072 (p=0.002)
  - Hazard ratio: >25 Gy SD vs. PCI: 3.768 (p=0.009)
  - Hazard ratio: CSA vs. PCI: 5.674 (p=0.000)

Bölling et al., Int J Radiat Oncol Biol Phys. 2011
Conclusions for organs

• **Liver**: Low toxicity rates and a small number of patients with grade 3 or 4 toxicity. In consequence dose- / volume-response curves due to acute or late toxicity cannot be created. In cases, in which better tumor control is necessary, the dose or the irradiated liver volume perhaps could be enhanced.

• **Lung**: Acute toxicity seems to be dependent on organ volumes irradiated with lower doses. Simultaneous chemotherapy influences late effects.
Conclusions for organs

• **Kidney**: radiation-induced kidney function impairment is rare in current pediatric multimodal treatment approaches.

• **Hypothyreodism**: Radiation-induced thyroid function impairment, including damage to the thyroid gland and/or hypophysis, can frequently be observed after radiotherapy in children. A structured follow-up examination is advised.

In the future, RiSK will be able to provide further detailed data regarding dose–volume effect relationships of radiation-associated side effects in pediatric oncology patients.
General conclusions:

Dose-volume-effect-relationships regarding acute and side effects of irradiation in children and adolescents can be established by means of prospectively collected planning data using 3-D-planning, DVH, dose measurements and their correlation with observed side effects.

Further aims:
More detailed analyses are required regarding
• age,
• fractionation,
• combined modalities with chemotherapy and/or surgery,
• time of appearance and
• course of side effects.

Information to affected children and parents is improved.

The registry will contribute to optimised treatment recommendations in future clinical trials regarding radiotherapy and its interactions with other therapy modalities.

The RiSK project focusses mainly on late effects of irradiation.
Many thanks to all participating institutions and to the Deutsche Kinderkrebsstiftung

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Liver (Doctorate candidate Pascal Rösler), Hannover

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