

Acute and late effects in children after radiotherapy:

The RiSK Project



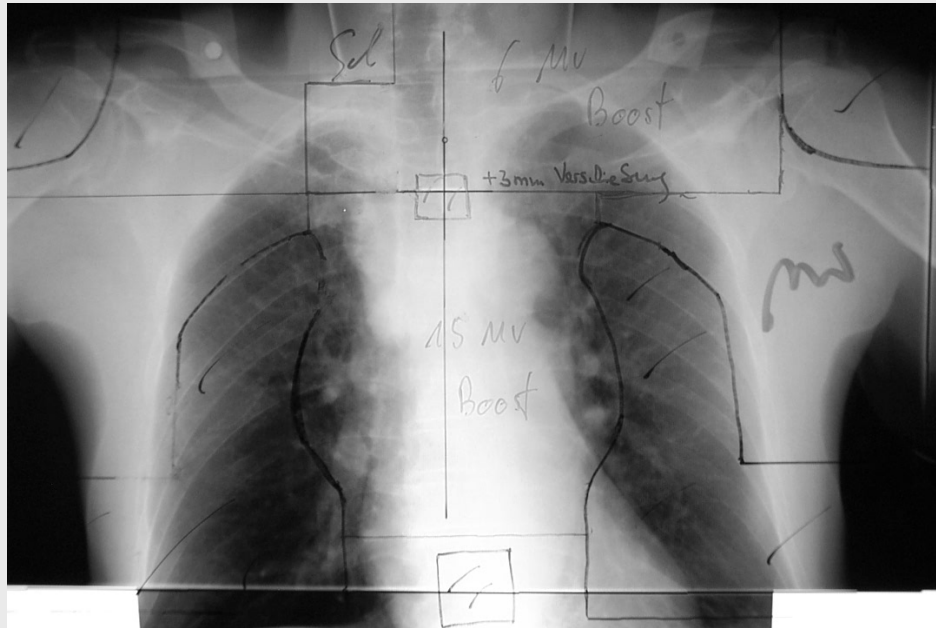
Normann Willich
Dept. of Radiotherapy
University Hospital Münster
Germany



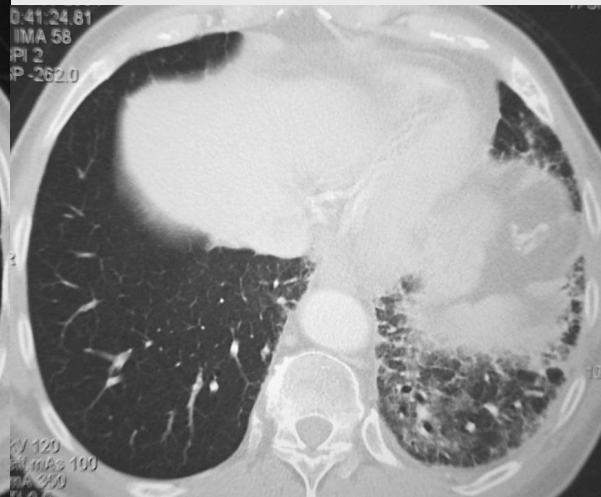
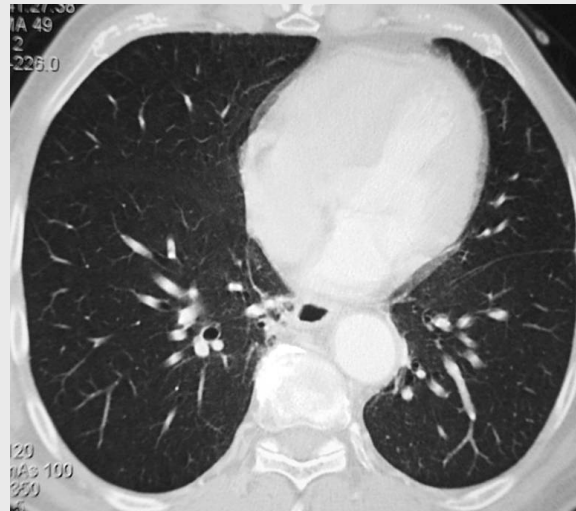
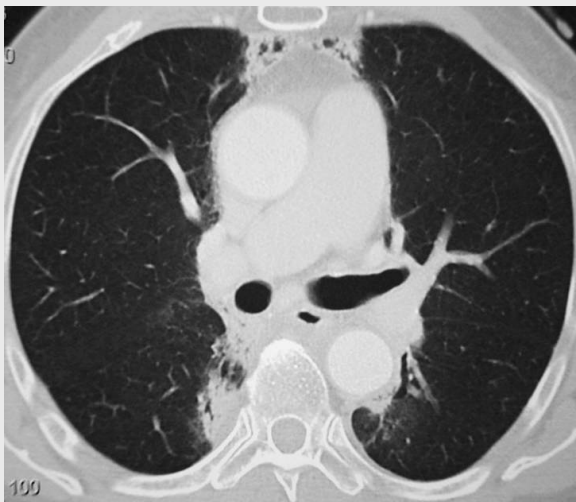
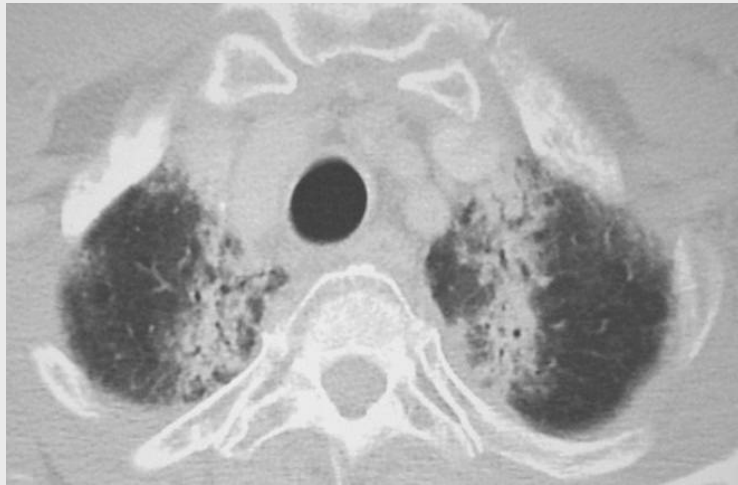
Acute side effects of irradiation

- 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



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

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.





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)

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)

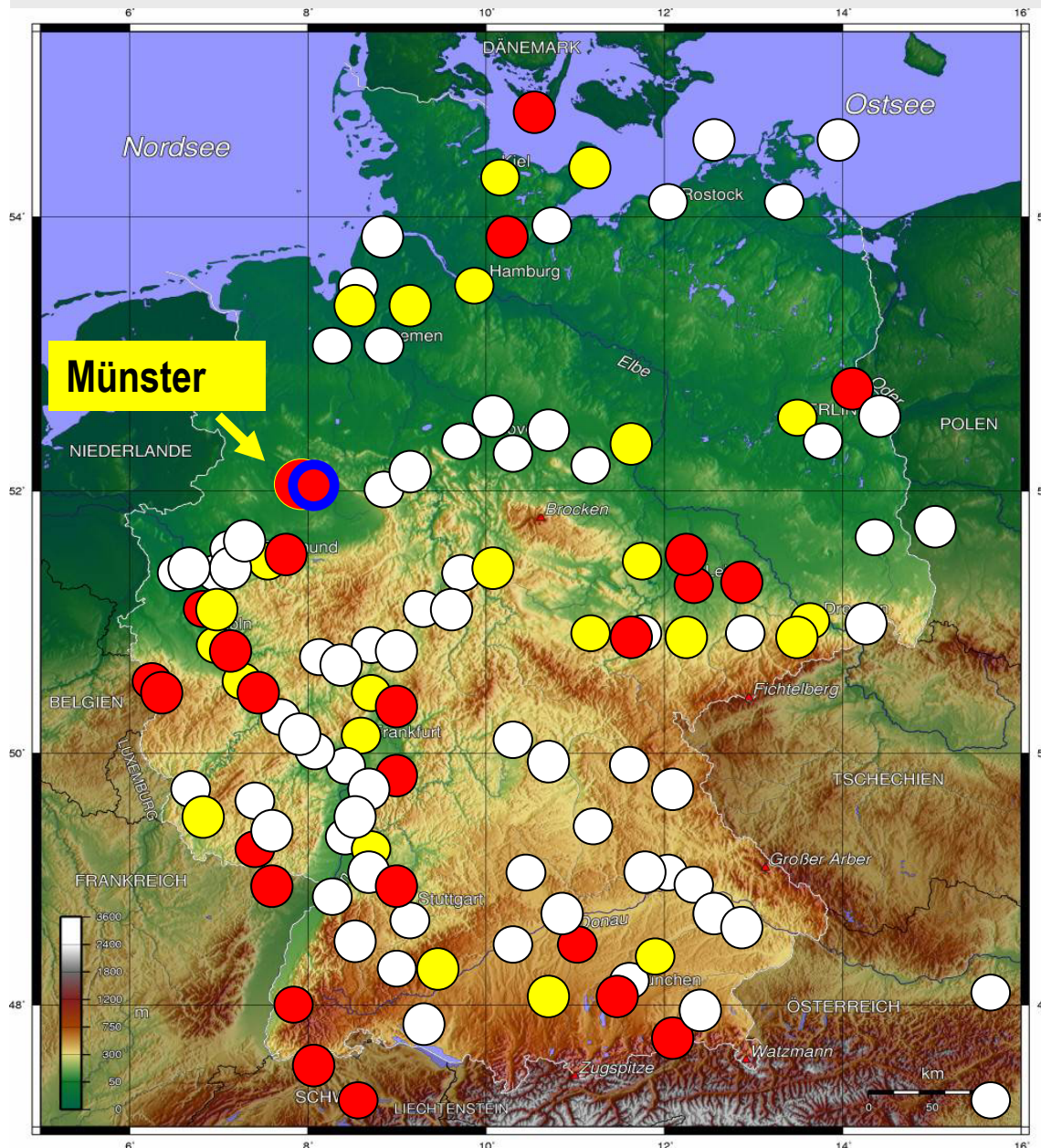
- Use of basis data forms of performed radiotherapy
- Correlation of dose and organ
- 3-D-planning, DVH, dose measurement
- central documentation of basis data
- Follow-up examinations
- Data analyses and establishment of dose/effect relationship per organ

Recruitment (011/2013)



n = 1578

Involved centers:
n=62



Recruitment data (11/2013)

- Patients: n= **1578**
(56% m, 44% f)
including proton treatments n = **262** (**3** with recurrences)

- Radiotherapy basis documentation forms n= **1623**

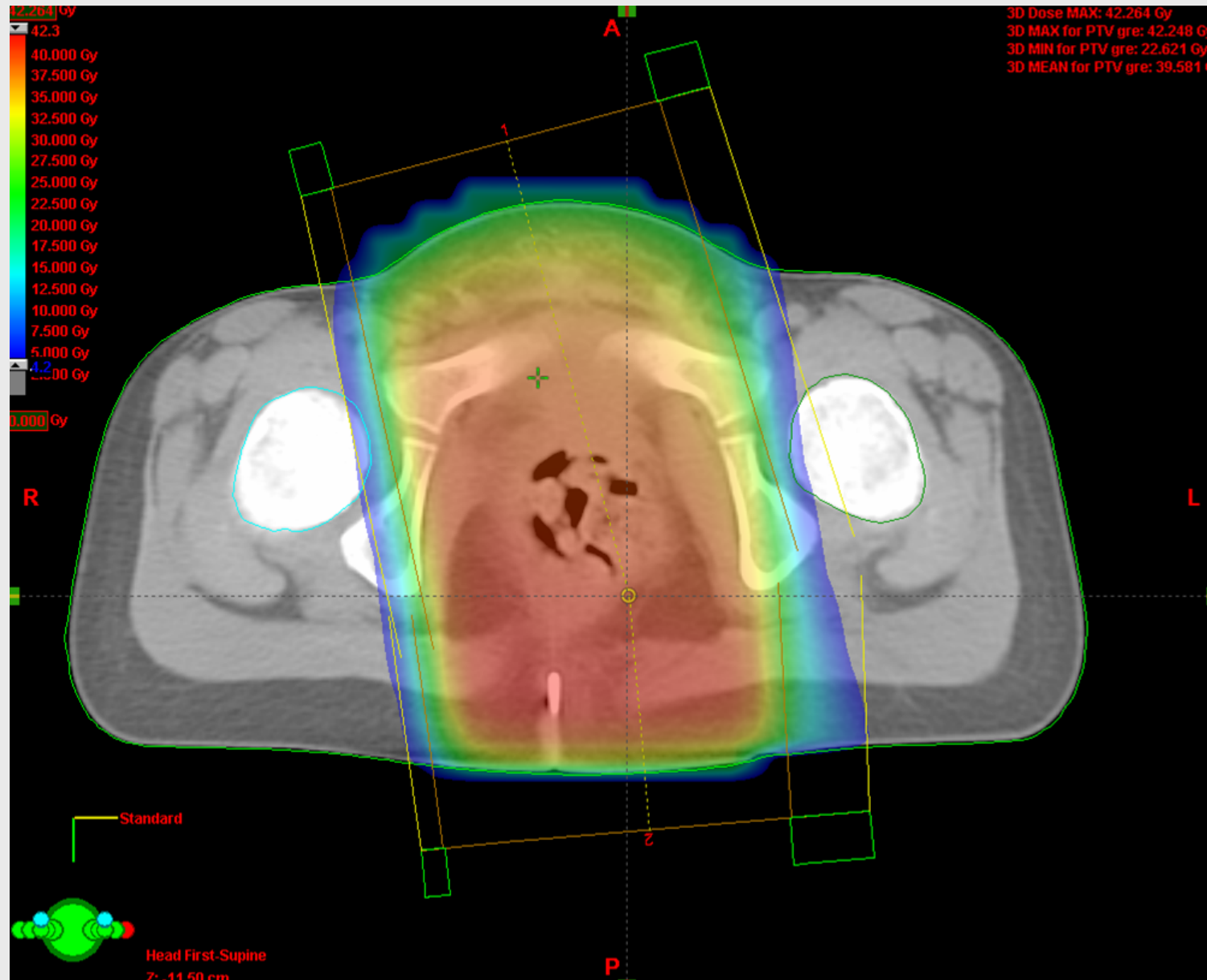
Therapy	%
1st Therapy	~ 90
Recurrence 1	~ 10
Recurrence 2	~ 0.4

- No. of toxicity documentation forms:
 - acute: n= **1299**

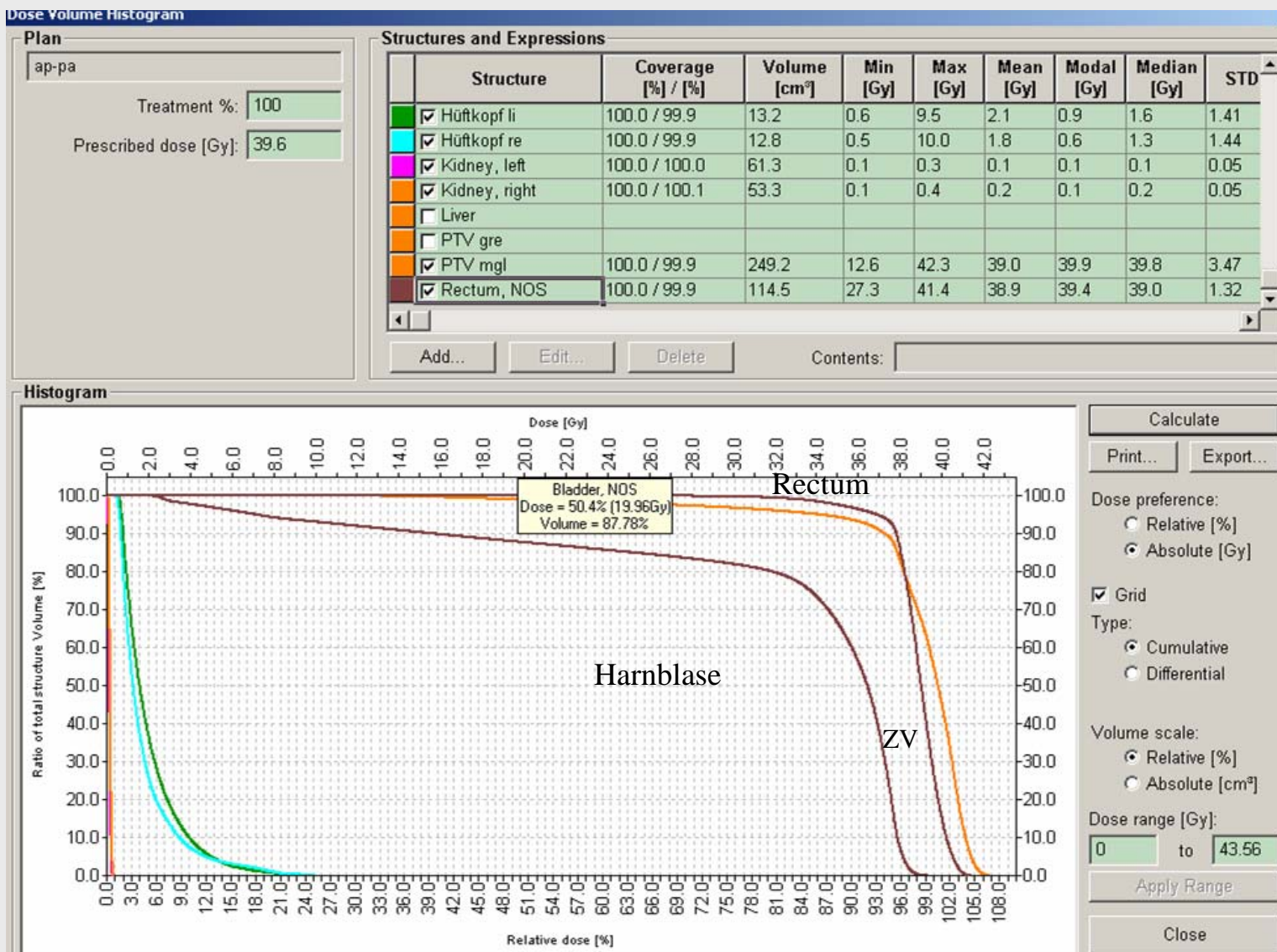
 - late: n= **3296**

- Centers involved: n= **62**

3-D-Planning



Dose-Volume-Histogram



Dose measurement

Organ dose thyroid gland



Documentation forms

- Detail evaluation of acute toxicities (EORT/RTOG)

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

Documentation forms

- Detail evaluation of late toxicities (EORTC/RTOG)

Skin	0 normal	1 Slight atrophy, pigmentation change, some hair loss	2 Patch atrophy, moderate telangiectasia ($\leq 50\%$), total hair loss	3 Marked atrophy, gross telangiectasia ($> 50\%$)	4 ulceration, necrosis, (surgical intervention necessary)
Subcutaneous tissue	0 normal	1 mild asymptomatic fibrosis, without contractures, slight reduced subcutaneous fat	2 moderate asymptomatic fibrosis with $\leq 10\%$ linear contracture, moderate reduced subcutaneous fat	3 severe (symptomatic) fibrosis with $> 10\%$ linear contractures, severe reduced subcutaneous fat	4 ulceration, necrosis, (surgical intervention necessary)
Mucous membrane	0 normal	1 Slight atrophy or dryness	2 moderate atrophy and telangiectasia, reduced production of mucous	3 Marked atrophy and telangiectasia, loss of mucous production	4 ulceration, necrosis, (surgical intervention necessary)
Salivary glands	0 normal	1 Slight dryness, good response on stimulation (normal food possible)	2 moderate dryness of mouth, poor response on stimulation (much fluid, pulpy food)	3 complete dryness of mouth, no response on stimulation (no solid food, fluid food)	4 Fibrosis (complete atrophy) (parenteral nutrition, PEG)
Pharynx/ Esophagus	0 normal	1 mild fibrosis, slight dysphagia regarding solid food, no pain at swallow (normal nutrition)	2 moderate fibrosis, no normal nutrition, pulpy food, perhaps dilatation necessary	3 severe fibrosis (or dysphagia), only fluids possible, dilatation necessary, pain at swallow	4 necrosis, perforation, fistula (surgical intervention necessary or PEG/ parenteral nutrition)
Larynx	0 normal	1 (mild) hoarseness (or cough), mild laryngeal edema	2 moderate hoarseness or cough, moderate laryngeal edema, chondritis (symptomatic therapy)	3 severe hoarseness, severe laryngeal edema, massive chondritis, intensive local therapy, analgesics	4 necrosis, (massive dyspnoea and stridor, ulceration, intubation or tracheotomy)
Lung	0 normal pO ₂ : > 85 ; pCO ₂ < 40	1 no or mild symptoms (dry cough); few radiological signs (mild exercise-induced shortness of breath) pO ₂ : 71-85; pCO ₂ : 41-50	2 moderate symptomatic lung fibrosis or pneumonitis (massive cough); mild fever; radiological signs; (moderate exercise-induced shortness of breath) pO ₂ : 61-70; pCO ₂ : 51-60	3 Severe symptomatic lung fibrosis or pneumonitis, massive radiological signs; (severe shortness of breath) pO ₂ : 51-60; pCO ₂ : 61-70 (intensive medication)	4 Massive respiratory insufficiency; permanent O ₂ -application and controlled ventilation pO ₂ < 50 ; pCO ₂ > 70 (intensive care necessary)

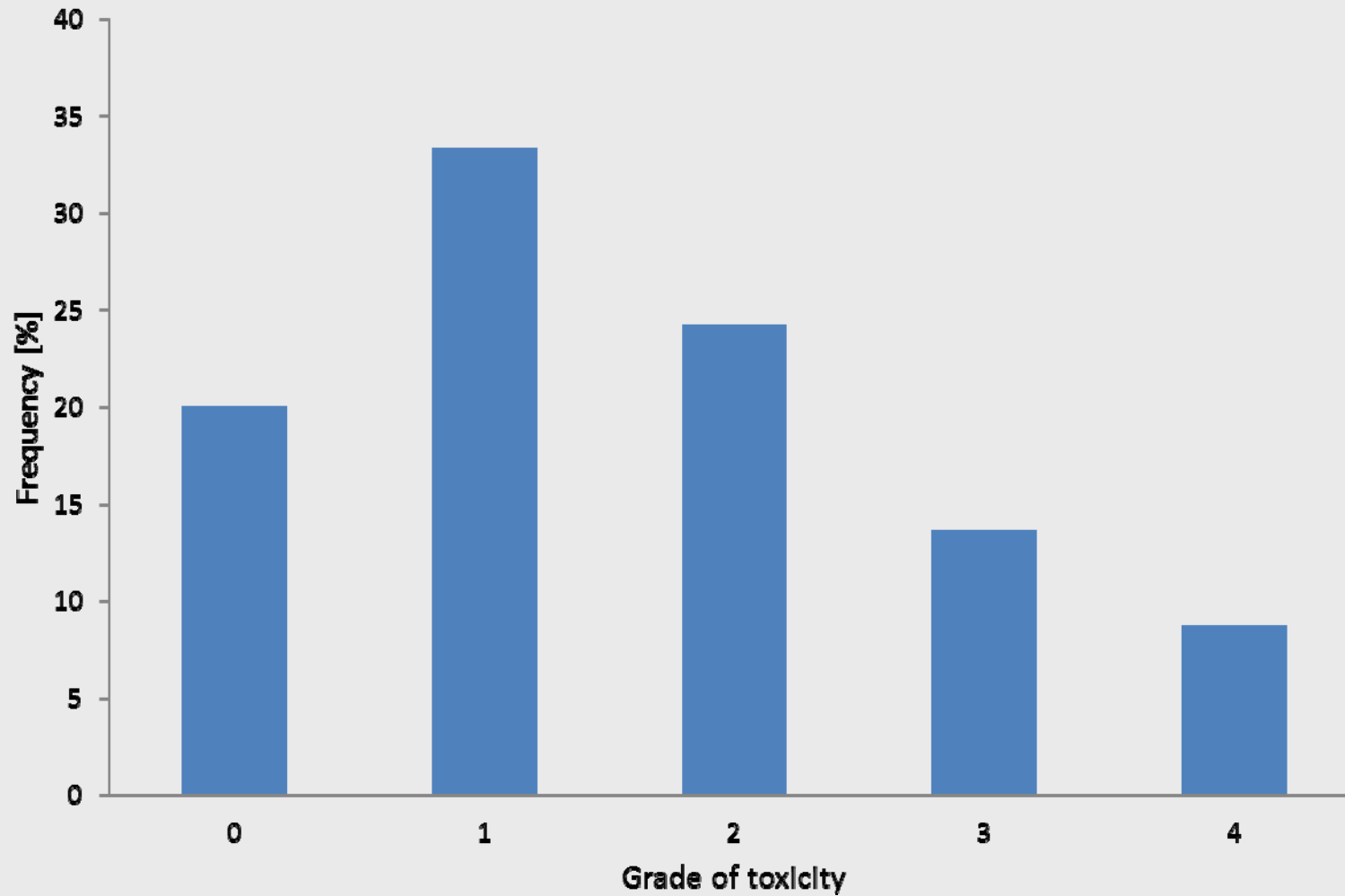
First results

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

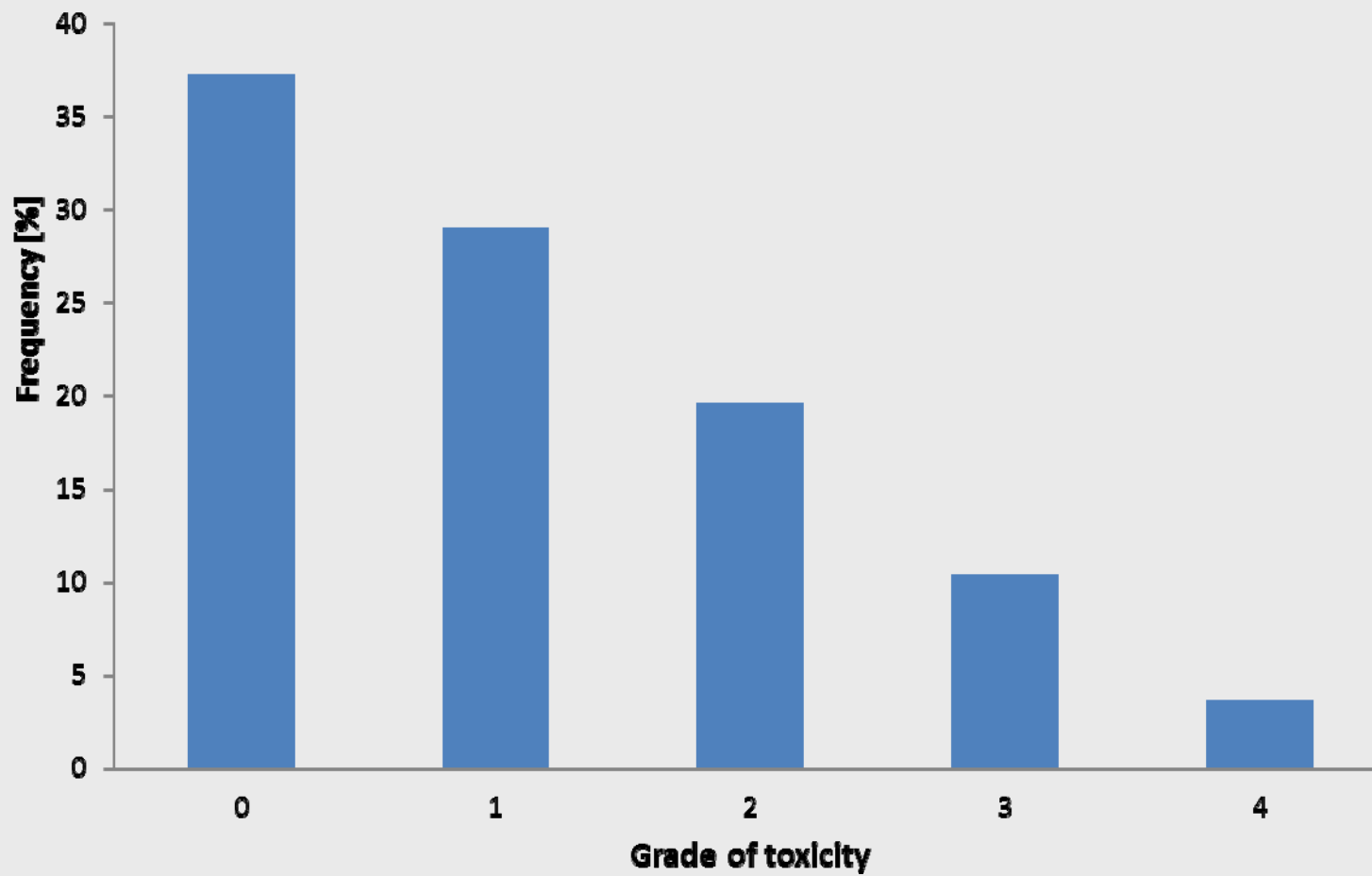
Acute toxicities

Frequency [%] per grade of toxicity (0-4)



Late toxicities

Frequency [%] of grade of toxicity (0-4)



RiSK data base: Lung irradiation

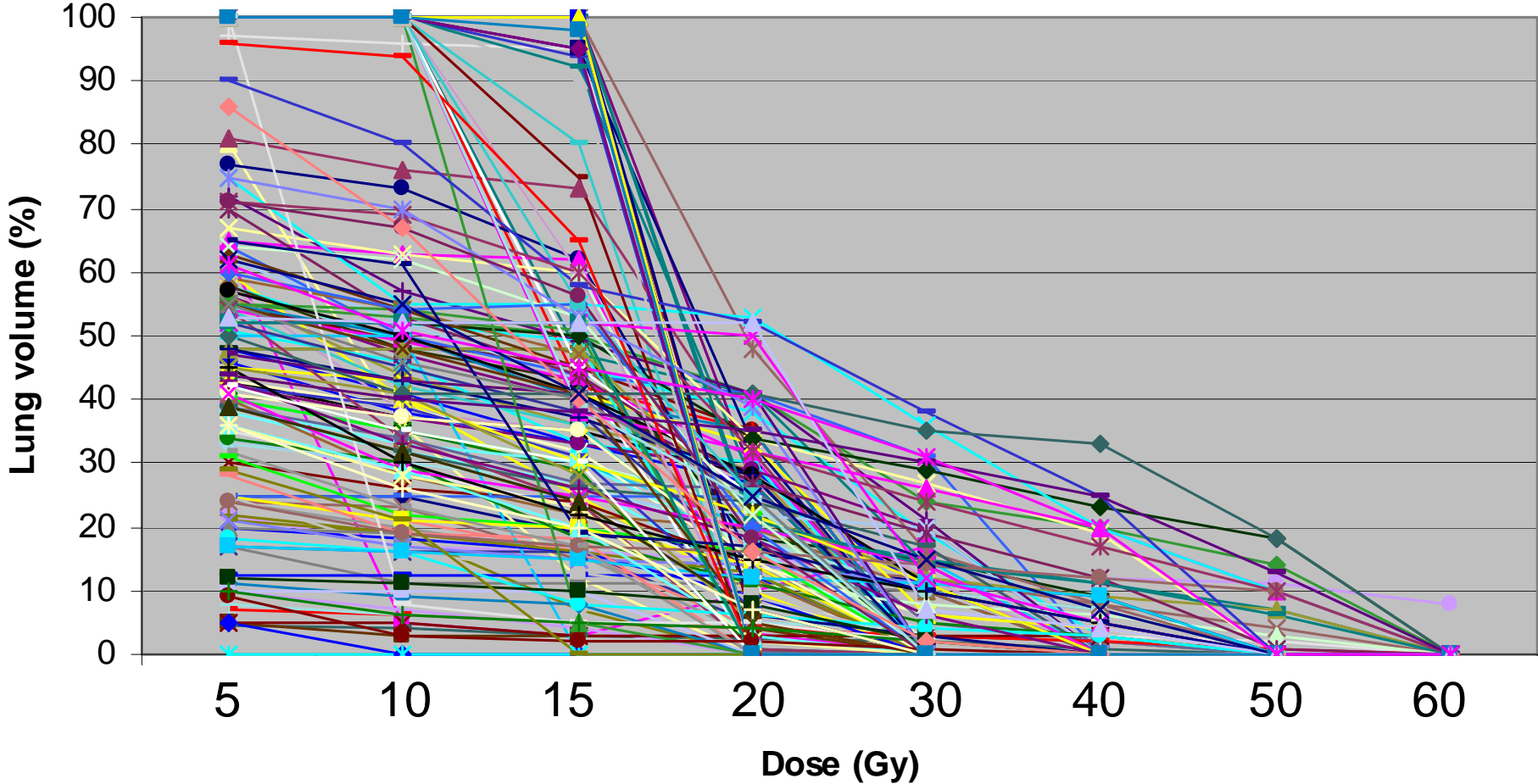
Database of 1050 registered patients from 62 centres
(05.09)

- 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



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:

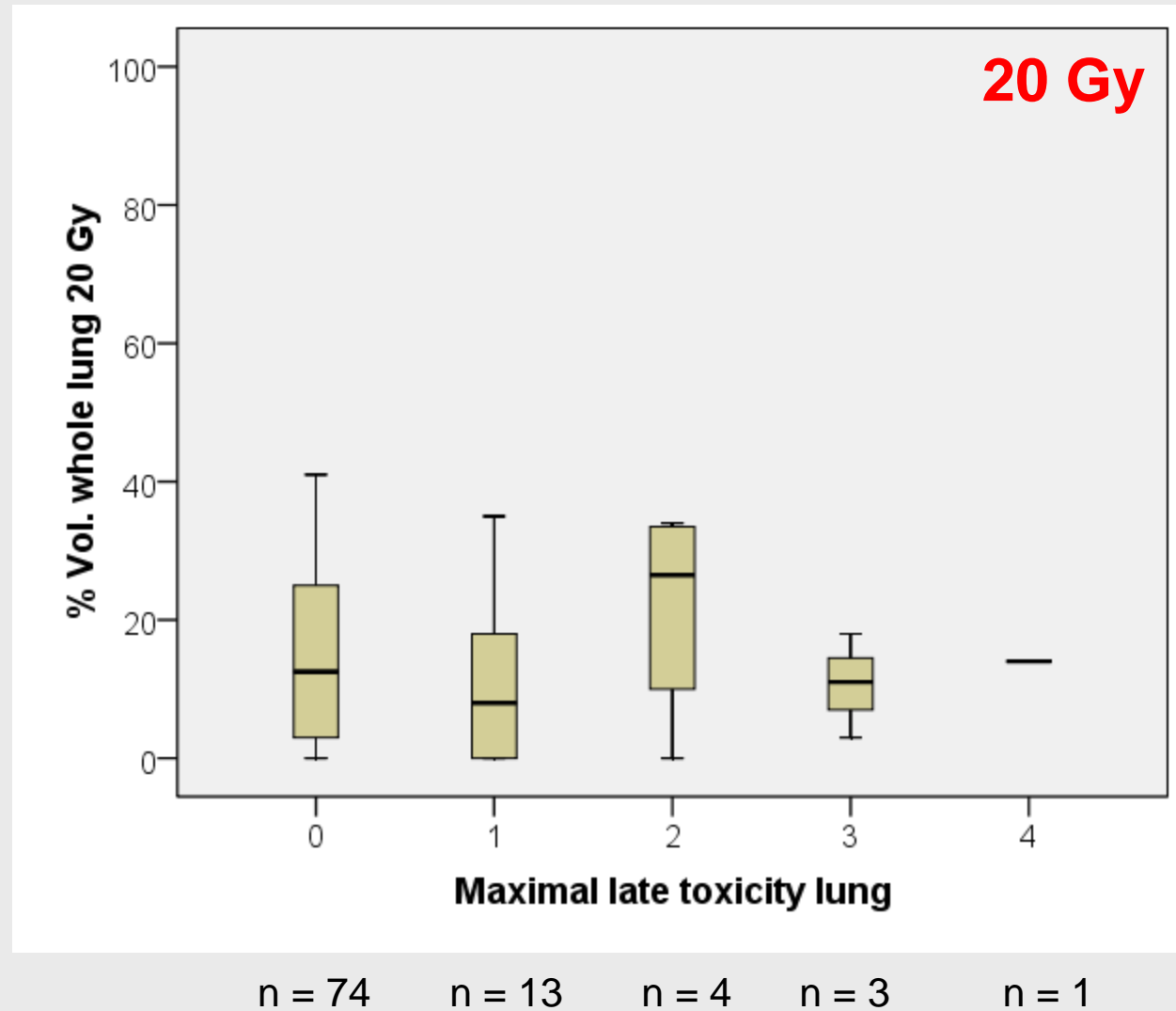
- **120 Pat.** with documentation of **acute-toxicity** of the lungs
- **95 Pat.** with documentation of **late effects** of the lungs

- 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:

Tox-grade	0°	1°	2°	3°	4°
acute	100	16	4	0	0
late	74	14	4	3	1

DVH-based analysis



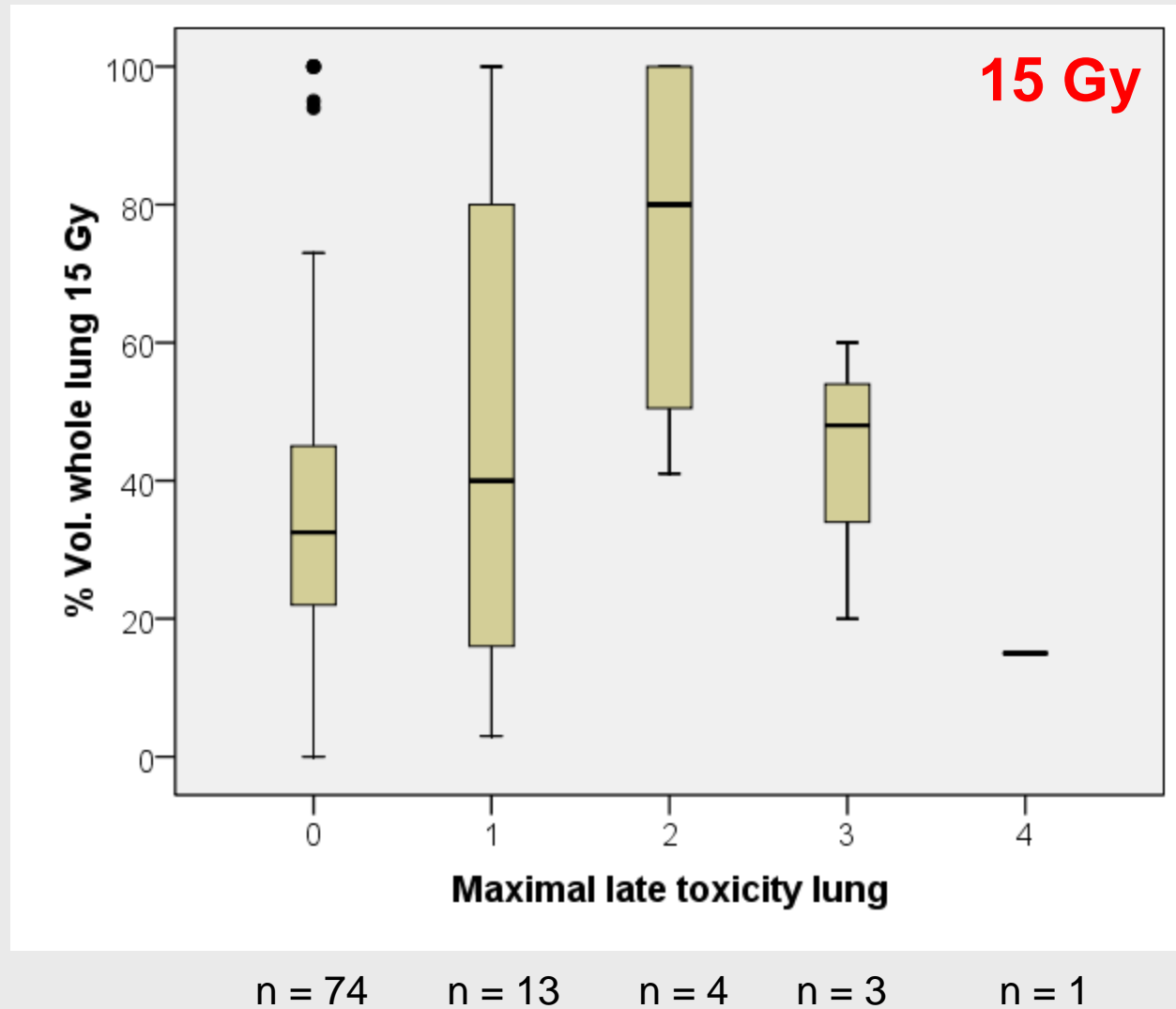
**dose -
volume -
toxicity
correlation.**

p:

0 vs. 1: 0.170

0 vs. 2: 0.841

DVH-based analysis



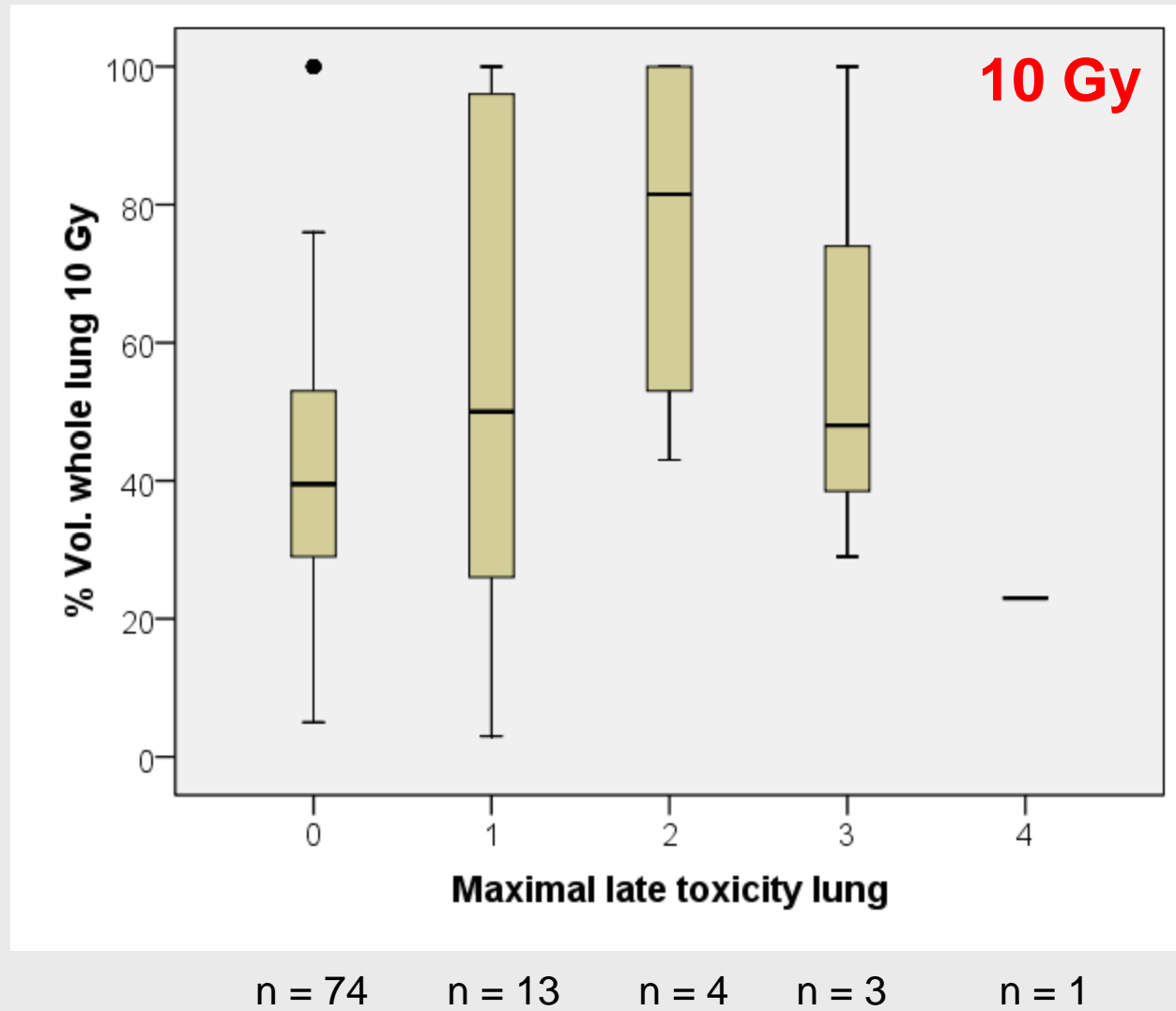
**dose -
volume -
toxicity
correlation.**

p:

0 vs. 1: 0.937

0 vs. 2: 0.027

DVH-based analysis



**dose -
volume -
toxicity
correlation.**

p:

0 vs. 1: 0.926

0 vs. 2: 0.117

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

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, dose rate
- 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.