



LUND UNIVERSITY

Paediatric radiotherapy. Treatment Planning Aspects

Kristensen, Ingrid

2017

Document Version:

Publisher's PDF, also known as Version of record

[Link to publication](#)

Citation for published version (APA):

Kristensen, I. (2017). *Paediatric radiotherapy. Treatment Planning Aspects*. [Doctoral Thesis (compilation), Tumor microenvironment]. Lund University, Faculty of Medicine.

Total number of authors:

1

General rights

Unless other specific re-use rights are stated the following general rights apply:

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal

Read more about Creative commons licenses: <https://creativecommons.org/licenses/>

Take down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

LUND UNIVERSITY

PO Box 117
221 00 Lund
+46 46-222 00 00

Paediatric radiotherapy

Treatment Planning Aspects

Ingrid Kristensen



LUND
UNIVERSITY

DOCTORAL DISSERTATION

by due permission of the Faculty of Medicine, Lund University, Sweden.
To be defended at Lecture Hall 3rd floor, Klinikgatan 5, Lund, May 22nd, 2017, at
14:00.

Faculty opponent

Michelle Leech, associate professor

Trinity College, Dublin, Ireland

Cover photo by Bent Kristensen

Copyright Ingrid Kristensen

Division of Oncology and Pathology, Clinical Sciences
Faculty of Medicine, Lund University, Sweden

Lund University, Faculty of Medicine Doctoral Dissertation Series 2017:69

ISBN **978-91-7619-449-2**

ISSN **1652-8220**

Printed in Sweden by Media-Tryck, Lund University, Lund 2017



Organization LUND UNIVERSITY Division of Oncology and Pathology, Clinical Sciences Faculty of Medicine, Lund University, Sweden		Document name Doctoral Dissertation	
		Date of issue 2017-05-22	
Author(s) Ingrid Kristensen		Sponsoring organization	
Title and subtitle Paediatric radiotherapy - Treatment Planning Aspects			
<p>Paediatric oncology has made remarkable progress over the years. In the late 1960s the overall survival rate of childhood cancer was ca 25%. This current rate is around 80%. Treatment is usually a combination of surgery, chemotherapy and radiotherapy. Approximately 100 children receive radiotherapy as part of their treatment in Sweden each year. Paediatric treatment is given at six of fifteen radiotherapy centres.</p> <p>The main objective of the work presented in this thesis was to identify areas to improve and optimize paediatric radiotherapy from a treatment planning perspective in a national setting and specifically to:</p> <ul style="list-style-type: none"> - Develop national videoconferences for paediatric radiotherapy for discussion of new cases, collaboration in new settings and maintaining/raising the competence level in paediatric radiotherapy. - Assess inter-observer variations in target delineation and its impact on tumour and normal tissues doses. - Assess the potential gain for a paediatric cohort when changing the treatment modality from photons to protons. <p>Study I describes the initialisation of the national videoconferences for paediatric radiotherapy. Today they are running bi-weekly in clinical routines. The majority of paediatric patients for radiotherapy in Sweden are seen at these conferences.</p> <p>Studies II and III are inter-observer studies on delineation of target volumes and organs at risk. A package containing anonymised patient data for structure segmentation and treatment planning was sent to the participating centres. Returned data were analysed with respect to target volumes and radiation doses to both target volumes and organs at risk. In study II we found considerable variations in target delineations for the four cases sent out. Structure volumes were calculated and the concordance between the participating centres' delineations were assessed using a concordance index; CIgen. The doses to the organs at risk varied considerably as a result of these differences in target volumes. In study III we also found large variations in target segmentation. To further visualise the variation in target delineation we used a mathematically derived consensus volume. The volume was derived in the software package CERR using the STAPLE algorithm. We applied the dose distributions created by each centre to both the original target volumes and the consensus volume. Deriving DVHs in absolute volume for the delineated target volume as well as for the consensus volume adds information on both "compliant" target volumes as well as outliers which are not readily seen when reporting concordance indices only.</p> <p>In study IV a comparison between radiotherapy with photons and protons was investigated. The physical properties of protons can lead to reduced dose to normal tissue compared to photons. It was found, that a majority of patients could benefit from proton treatment. Treatment plan comparisons are often needed to aid in the decision.</p> <p>The studies show that collaboration between centres is beneficial for paediatric radiotherapy. More efforts are needed to assure better uniformity when it comes to target delineation. Workshops and dummy runs on new protocols are useful tools. Radiotherapy with protons will play an increasingly important role in paediatric radiotherapy.</p>			
Key words Paediatric radiotherapy, telemedicine, inter-observer variations, target delineation, treatment planning, proton therapy			
Classification system and/or index terms (if any)			
Supplementary bibliographical information		Language English	
ISSN and key title		ISBN 978-91-7619-449-2	
Recipient's notes		Number of pages	
		Price	
		Security classification	

I, the undersigned, being the copyright owner of the abstract of the above-mentioned dissertation, hereby grant to all reference sources permission to publish and disseminate the abstract of the above-mentioned dissertation.

Signature _____ Date 2017-03-31

Content

Content	5
List of papers	7
Abbreviations	8
Abstract	9
1. Introduction	11
Paediatric cancer	11
Paediatric radiotherapy - the process	13
Target volumes and organs at risk	14
Treatment planning	15
Protocols	19
Radiotherapy collaboration in Sweden	20
2. Aims	21
3. National videoconferences	23
4. Inter-observer studies or dummy runs	25
Target volumes	26
Dosimetric evaluation – dose-volume descriptors	30
Dosimetric evaluation – dose-volume visualisation	31
Organs at risk	36
5. Photons vs. protons	39
6. Discussion	41
National videoconferences	41
Inter-observer studies or dummy runs	42
Photons vs. protons	43
Side effects	44
Conclusions and future work	45

Populärvetenskaplig sammanfattning	47
Bakgrund	47
Nationella videokonferenser	48
”Inter-observer variation – dummy runs”	49
Fotoner jämfört med protoner	49
Biverkningar	50
Slutsatser	50
Acknowledgments	51
References	53

List of papers

This thesis is based on the following papers, which will be referred to in the text by their roman numerals. The papers are appended at the end of the thesis.

- I. Telemedicine as a tool for sharing competence in paediatric radiotherapy – Implementation and initial experiences, Kristensen I, Lindh J, Nilsson P, Bergström P, Björk-Eriksson T, Engellau J, Hjelm-Skog A-L, Malmer B, Martinsson U, Karlsson M, *Acta Oncol* 2009(48)1:146-152
Reprinted with permission; <http://dx.doi.org/10.1080/02841860802409520>
- II. Assessment of volume segmentation in radiotherapy of adolescents; a treatment planning study by the Swedish Workgroup for Paediatric Radiotherapy, Kristensen I, Agrup M, Bergström P, Engellau J, Haugen H, Martinsson U, Nilsson K, Taheri-Kadkhoda Z, Lindh J, Nilsson P. *Acta Oncol*, 2014(53)1:126-133
Reprinted with permission; <http://dx.doi.org/10.3109/0284186X.2013.782104>
- III. A dose based approach to evaluate inter-observer variation in target delineation. Kristensen I, Nilsson K, Agrup M, Belfrage K, Embring A, Haugen H, Svärd A-M, Knöös T, Nilsson P.
In manuscript 2017
- IV. Comparative proton and photon treatment planning in pediatric patients with various diagnoses. Kristensen I, Nilsson K, Nilsson P. *Int J of Particle Therapy* 2015(2)2:367-375

Abbreviations

3DCRT	Three-dimensional conformal radiotherapy
COM	Centre of mass
CT	Computed tomography
HI	Homogeneity index ($D_{2\%}-D_{98\%}/D_{50\%}$)
ICRU	International Commission on Radiation Units and Measurements
IMRT	Intensity-modulated radiotherapy
IPPARCA	International Project on Prospective Analysis of Radiotoxicity in Childhood and Adolescence
MLC	Multi-leaf collimator
MRI	Magnetic resonance imaging
OAR	Organ at risk
PACS	Picture Archiving and Communication System (the digital x-ray archive)
PET	Positron emission tomography
RiSK	Registry of the Evaluation of Side Effects after Radiotherapy in Childhood and Adolescence
RADTOX	Radiation toxicity registry
RBE	Relative biological effectiveness
RT	Radiotherapy
SALUB	Swedish workgroup for long time follow-up after paediatric cancer (Svenska arbetsgruppen för långtidsuppföljning efter barncancer)
SSM	Swedish Radiation Safety Authority (Strålsäkerhetsmyndigheten)
SvBRG	Swedish Workgroup for Paediatric Radiotherapy (Svenska barnradioterapigruppen)
TPS	Treatment Planning System
VMAT	Volumetric Modulated Arc Therapy

Abstract

Paediatric oncology has made remarkable progress over the years. In the late 1960s the overall survival rate of childhood cancer was ca 25%. This current rate is around 80%. Treatment is usually a combination of surgery, chemotherapy and radiotherapy. Approximately 100 children receive radiotherapy as part of their treatment in Sweden each year. Paediatric treatment is given at six of fifteen radiotherapy centres.

The main objective of the work presented in this thesis was to identify areas to improve and optimize paediatric radiotherapy from a treatment planning perspective in a national setting and specifically to:

- Develop national videoconferences for paediatric radiotherapy for discussion of new cases, collaboration in new settings and maintaining/raising the competence level in paediatric radiotherapy.
- Assess inter-observer variations in target delineation and its impact on tumour and normal tissues.
- Assess the potential gain for a paediatric cohort when changing the treatment modality from photons to protons.

Study I describes the initialisation of the national videoconferences for paediatric radiotherapy. Today they are running bi-weekly in clinical routines. The majority of paediatric patients for radiotherapy in Sweden are seen at these conferences.

Studies II and III are inter-observer studies on delineation of target volumes and organs at risk. A package containing anonymised patient data for structure segmentation and treatment planning was sent to the participating centres. Returned data were analysed with respect to target volumes and radiation doses to both target volumes and organs at risk. In study II we found considerable variations in target delineations for the four cases sent out. Structure volumes were calculated and the concordance between the participating centres' delineations were assessed using a concordance index; CI_{gen} . The doses to the organs at risk varied considerably as a result of these differences in target volumes. In study III we also found large variations in target segmentation. To further visualise the variation in target delineation we used a mathematically derived consensus volume. The volume was derived in the software package CERR using the STAPLE algorithm. We applied the dose distributions created by each centre to both the original target volumes and the consensus volume. Deriving DVHs in absolute volume for the delineated target volume as well as for the consensus volume adds information on both "compliant" target volumes as well as outliers which are not readily seen when reporting concordance indices only.

In study IV a comparison between radiotherapy with photons and protons was investigated. The physical properties of protons can lead to reduced dose to normal tissue compared to photons. It was found, that a majority of patients could benefit from proton treatment. Treatment plan comparisons are often needed to aid in the decision.

The studies show that collaboration between centres is beneficial for paediatric radiotherapy. More efforts are needed to assure better uniformity when it comes to target delineation. Workshops and dummy runs on new protocols are useful tools. Radiotherapy with protons will play an increasingly important role in paediatric radiotherapy.

1. Introduction

Paediatric cancer

Approximately 300 children and adolescents (under the age of 18) are diagnosed annually with cancer in Sweden (population of 10 million in 2017) [1]. Paediatric oncology has made remarkable progress in the last 50 years. In the late 1960s the overall survival rate of most childhood cancers was ca 25%. Today this figure is around 80% (figure 1.1).

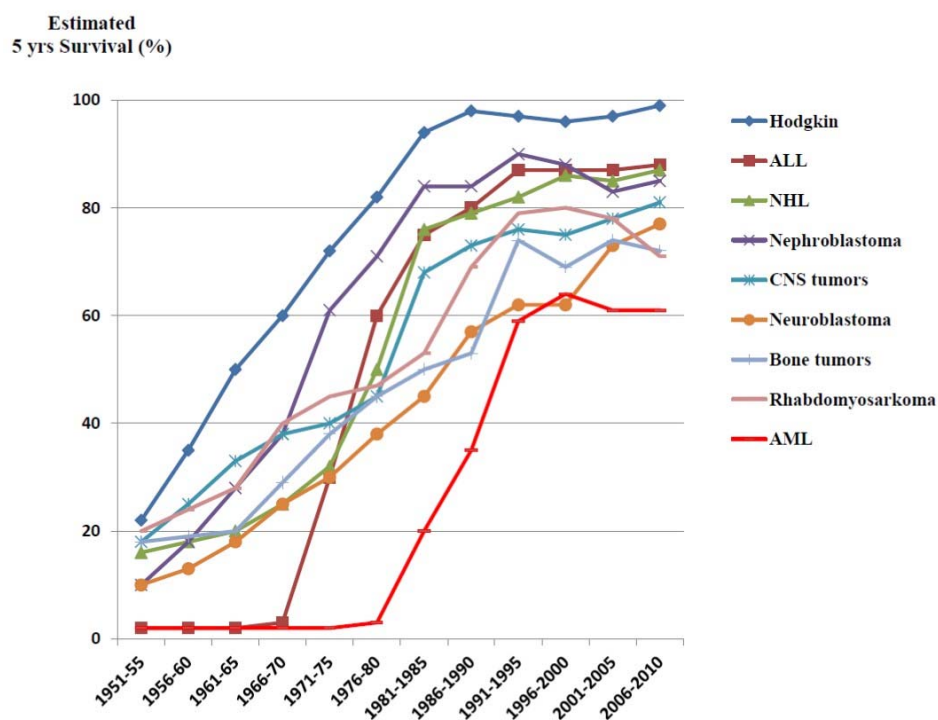


Figure 1.1. Five-year overall survival rates from childhood cancers in Sweden by selected diagnostic groups (Childhood Cancer Epidemiology Group, Karolinska Institute, Stockholm, printed with permission from Göran Gustavsson). ALL – acute lymphatic leukaemia, NHL – Non-Hodgkin's lymphoma, CNS – central nervous system, AML – acute myeloid lymphoma.

Childhood cancer includes a variety of diagnoses (Figure 1.2). About 70% of the diagnoses are leukaemia, lymphomas and brain tumours. Each of the remaining 30% of diagnoses have low incidence. Each case demands different specifications of treatment and care. The Swedish data presented here [1] correlates well with other published international data [2]. Many of the children will receive a combination of surgery, chemotherapy and radiotherapy. For some diagnoses (e.g. leukaemia), chemotherapy will be the first and only choice of treatment, while others will receive all three modalities. Approximately 100 children receive radiotherapy as part of their treatment in Sweden each year.

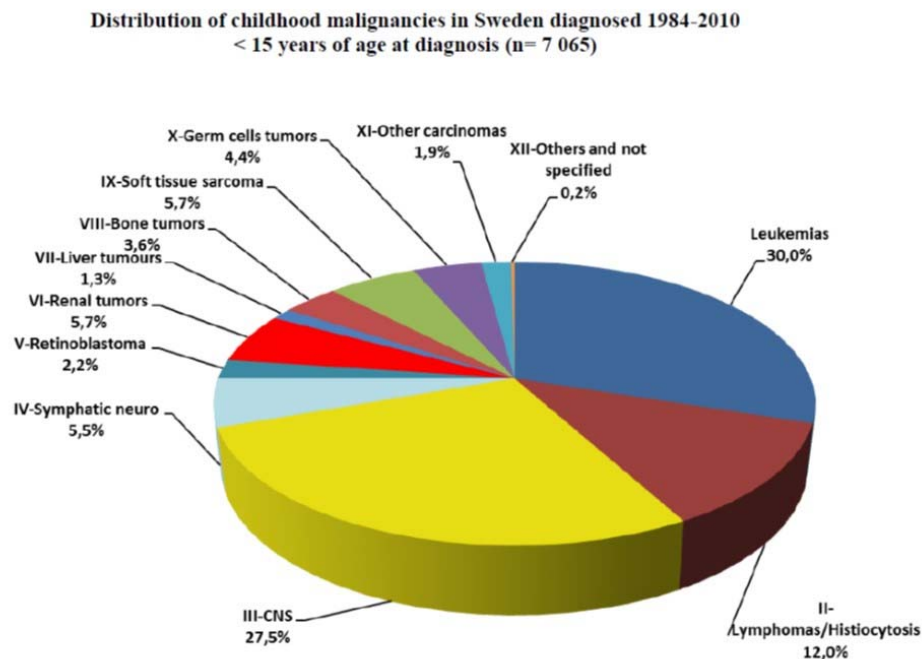


Figure 1.2. Distribution of childhood malignancies in Sweden. Note: children below 15 years of age (Childhood Cancer Epidemiology Group, Karolinska Institute, Stockholm, printed with permission from Göran Gustavsson).

Paediatric radiotherapy - the process

Paediatric radiotherapy has followed the progress made in general radiotherapy. All patients undergo a dedicated computed tomography (CT) examination for radiotherapy. This is necessary in order to obtain a correct volumetric representation of the patient. This means that the patient has to be placed in treatment position, a position that can be accurately recreated during all treatment fractions. To help the patient maintain the same position throughout the entire treatment series, an immobilisation device is often created. This can be, for example, a thermoplastic mask [3]. The CT is used for treatment planning, to give a correct basis for the anatomy (target and organs at risk (OAR) delineation) and for dose calculation. For young children it can be difficult to keep the same position, and many of these patients therefore have to be sedated or anaesthetised (figure 1.3). Older children might manage with some distraction from the treatment process, e.g. by watching a movie or listening to a book. It takes experienced nurses to work with children, to keep them calm and cooperative.



Figure 1.3. Radiotherapy of a young boy (5 years of age) with Hodgkin's disease treated under anaesthesia. Photograph by Ingrid Kristensen, printed with the permission of the child, his parents and the staff.

The CT study used today for geometry representation and for dose calculation purposes may soon be replaced with magnetic resonance imaging (MRI) examinations, thereby discarding the uncertainties in CT-MR image registration and also reducing the radiation to the child during the preparation phase [4]. Using specific MR protocols, the MRI images can be “transformed” to “synthetic” CT images for dose calculation and patient positioning.

Target volumes and organs at risk

Target delineation is an important, as well as a delicate task. It is dependent on a number of different aspects; tumour size and localisation, the RT description in the protocol, other treatments that might affect radiotherapy, the patients’ general health and the knowledge and experience of the individual radiation oncologist [5]. Information on macroscopic and microscopic tumour extension has to be translated from surgical notes, from different diagnostic imaging methods and pathology reports into a three-dimensional (3D) volume in the treatment planning CT dataset. To facilitate the process of target delineation the treatment planning CT is often fused with a diagnostic CT examination, an MRI examination and/or a positron emission tomography (PET) examination.

The International Commission on Radiation Units and Measurements (ICRU) has published a number of reports with the aim to unify the radiotherapy world. In report 50 from 1993 [6], the concept of target volumes in different levels is described (figure 1.4). This has had a great impact in radiotherapy globally.

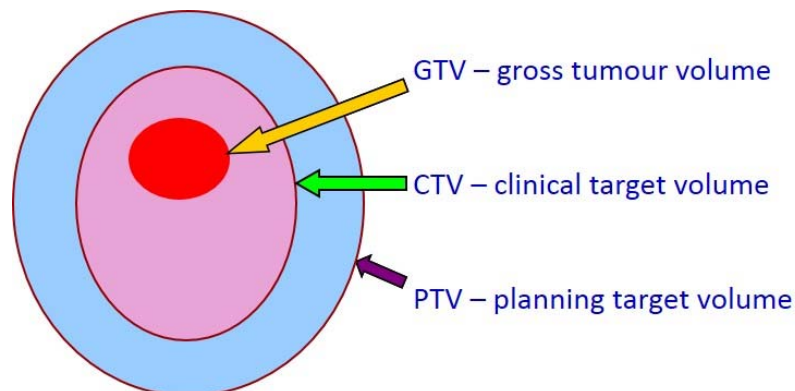


Figure 1.4. Image adapted from ICRU 50 on target volumes to be delineated.

GTV – the gross tumour volume is defined as the visible/demonstrable tumour. The CTV – the clinical target volume contains the GTV and/or volumes with suspected malignant subclinical disease. The PTV – the planning target volume is a geometrical concept. It surrounds the CTV with an additional margin compensating for movements and patient set-up uncertainties. It should ensure that the prescribed dose is actually delivered to the CTV and it is the volume used for treatment planning purposes and reporting.

Normal tissue structures, especially organs at risk (OAR), in close vicinity to the PTV will also impact the treatment planning and the resulting dose distribution.

The ICRU 50 [6] defines OARs as “normal tissues whose radiation sensitivity may significantly influence treatment planning and/or prescribed dose”. The general goal in treatment planning is to keep the doses outside the target volume as low as possible and below specified OAR dose-volume constraints/objectives. When treating children this becomes even more important, due to the increased significance of long term ‘late’ side effects.

Radiation doses to both the delineated target volumes (as described above) and the OARs will have to be assessed in the final treatment plan. Apart from assessing single organs the irradiated normal tissue volume can be assessed by the volume encompassed by a specific isodose surface, e.g. the 95% dose surface (treated volume).

The size and location of the target volume(s) are crucial for the possibilities in sparing OARs. It will have an impact on how the beam arrangement/arcs can be made and thus the resulting dose distribution.

Treatment planning

The goal of treatment planning is to optimise the dose distribution with respect to both target volumes and normal tissues. Treatment planning has seen a tremendous evolution during recent years, from simple dose calculation to a point, to 2D treatment planning on manually created transversal plane(s) and onwards to CT-based 3D dose calculations [7]. This progress has been made possible with the evolution of computers and advanced dedicated software.

What we today call three dimensional conformal radiotherapy (3DCRT) comprises static beams, conformally shaped with multi-leaf collimators (MLC) to the PTV. This is still a common treatment technique. Schematic examples of 3DCRT solutions for the Wilms’ case in paper II are shown in figure 1.5.

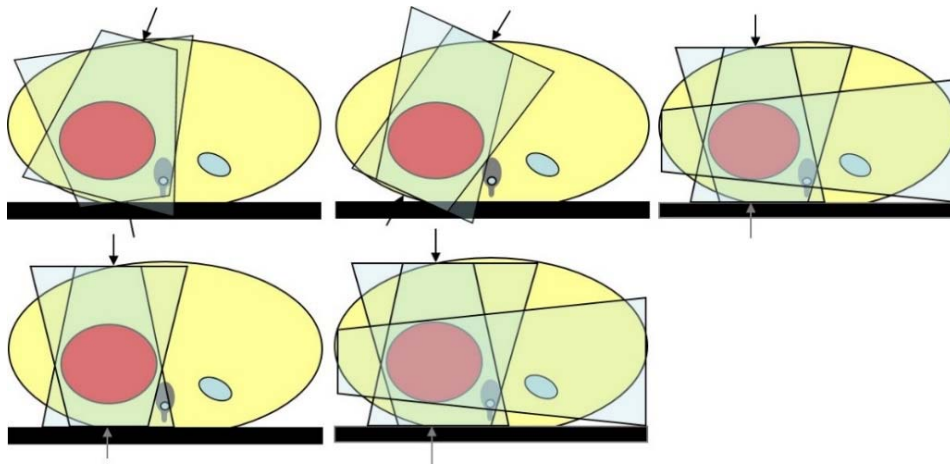


Figure 1.5. Different 3DCRT solutions to the same patient. These are the treatment plans used for the Wilms' case in paper II. The PTV is shown in red and the main OARs in light blue (left kidney and spinal cord).

The next step in the evolution of treatment planning and radiotherapy delivery was the introduction of intensity modulated radiotherapy (IMRT) together with inverse treatment planning techniques. Here static beams are used but each beam is created of a number of segments that together results in an intensity modulated beam. During treatment planning a set of dose volume constraints/objectives are defined for the PTV as well as for the OARs for the calculation of the dose distribution. These values can be interactively changed during treatment planning to reach a final dose distribution that fulfils the goals. The constraints/objectives are a part of the treatment prescription. Several beams work together to deliver the dose distribution wanted. More beams are usually used for IMRT compared to 3DCRT (5-9), leading to a larger spread of “low dose” in the body.

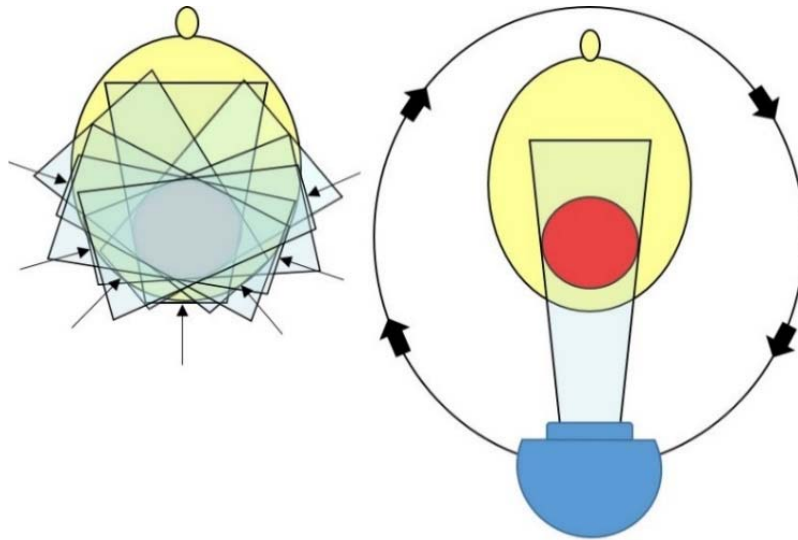


Figure 1.6. Examples of the field arrangement for IMRT (to the left, seven static beams) and VMAT (to the right, one field, (an arc) rotating around the patient).

However, the dose distribution can be better tailored to both cover the target and spare the OARs compared to 3DCRT. This is true also for TomoTherapy® (Accuray Inc®.) and volumetric modulated arc therapy (VMAT) (figure 1.6). While TomoTherapy uses dedicated equipment for rotational treatment, VMAT uses a modern standard C-arm accelerator. The principle is however the same. The radiation delivery is dynamic, with the accelerator (the beam) moving around the patient in an arc with the MLC leaves moving simultaneously. For TomoTherapy the patient table top is moving as well, which makes this treatment modality especially attractive for elongated target volumes.

Rotational RT techniques are currently also used for children. However, due to the increased low dose volume (figure 1.6 and 1.7), it is still applied with some restrictiveness due to the potential increased risk of inducing secondary cancer to these future long time survivors [8, 9].

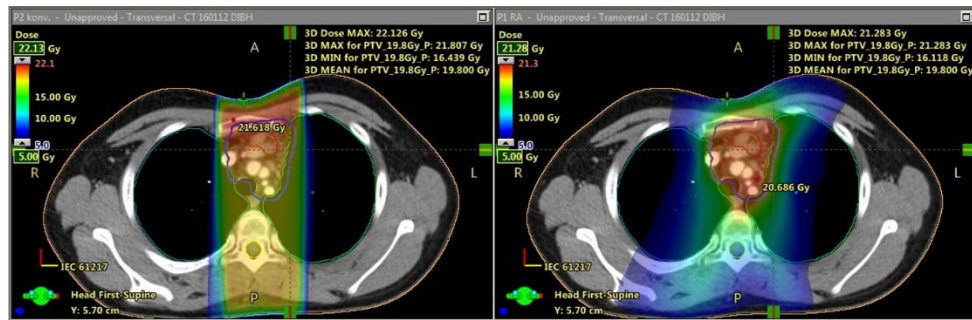


Figure 1.7. Example of 3DCRT (to the left) and VMAT (to the right) for the Hodgkin's case in paper III. The major differences are the OAR sparing (better in VMAT) and low dose spread (higher in VMAT).

Cancer treatment with protons started in the late 50's [10]. The gain with protons compared to photons is primarily due to their physical properties. Protons have a finite range in tissue specific to its energy (figure 1.8).

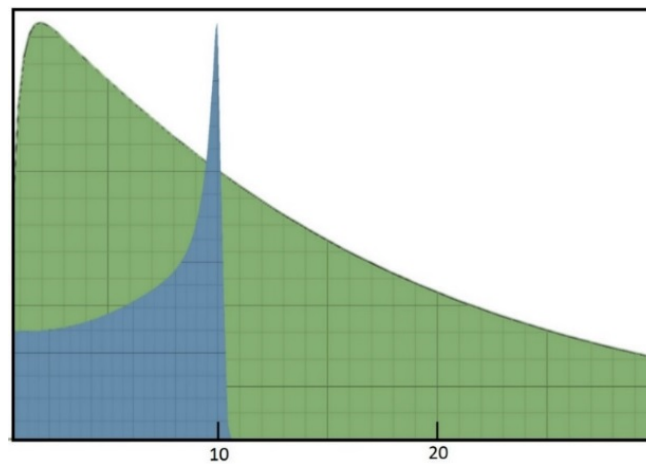


Figure 1.8. The depth dose curves of 6 MV photons (green) and 115 MeV protons (blue).

Compared to photons, the protons deliver their energy primarily in the so called Bragg peak, just before they stop in the tissue. This means that normal tissue behind the target volume in the beam direction will receive almost no dose at all. However, the proton dose distributions have usually a wider penumbra than photons, leading to situations where, in a comparison, treatment plans will be more advantageous for photons. The physical properties of protons also make them more sensitive to motion, such as target and/or organ motion as well as daily variations in set-up. Figure 1.9 shows a practical example of the difference between photons and protons. The protons have a relative biological effectiveness (RBE) of 1.1 compared to 1.0 for high energy photons and this is used clinically. It is known, however, that the RBE varies, especially in the Bragg peak [11].

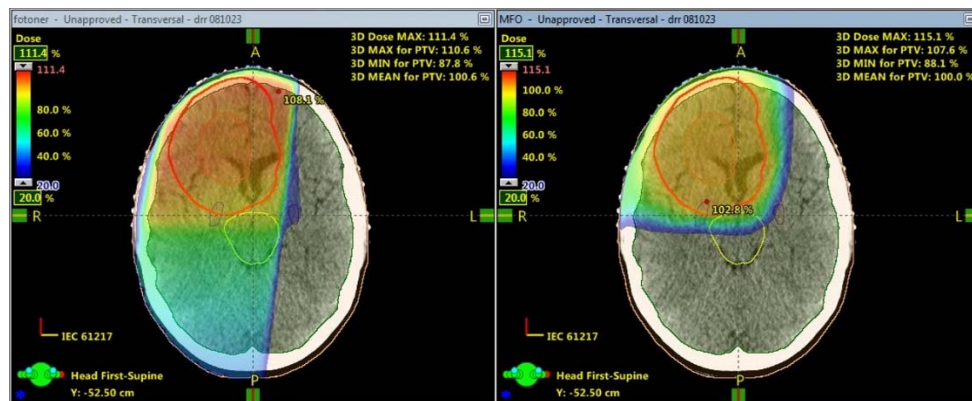


Figure 1.9. Comparison between 3DCRT to the right and intensity modulated proton therapy (IMPT) to the left. Note the sparing of normal tissue for the proton plan compared to the photon plan.

Technical achievements have made it possible to plan and treat in the same fashion as done with photons. The national proton facility Skandionkliniken offers all of these new possibilities with protons, and many of the paediatric patients will be able to receive their radiotherapy there. The absorbed dose to normal tissue can often be reduced more with protons compared to photons. The risk for secondary malignancies can be decreased compared to photons and especially with the spot scanning technique used at Skandionkliniken, since the production of neutrons are lower with this technique compared to the more common passive scattering technique [12, 13].

Protocols

Most of the paediatric cancer patients in Sweden are treated according to specific national or international study/treatment protocols.

The protocols stipulate the timing of different events – when chemotherapy shall be given, which drugs and dosage are used, when surgery shall be performed and/or/if/when radiotherapy shall be given.

The radiotherapy part in study/treatment protocols is often sparsely described, especially in protocols with combined treatment regimens. However, it is important to assure unity in the way e.g. target volumes are delineated, since ambiguities leave room for local variations which might jeopardize the outcome. For radiotherapy, it is also important that radiation doses both to target volumes as well as dose-volume constraints/objectives to OARs are clearly specified.

Well defined protocols facilitate target delineation, the optimisation process and the evaluation of the treatment plan and can shorten the radiotherapy process as well as improving overall outcome and safety.

Radiotherapy collaboration in Sweden

The Swedish Workgroup for Paediatric Radiotherapy (SvBRG) was established in 2000. It was formed by the radiation oncologists and physicists working especially with paediatric radiotherapy. The group's main task is to obtain and distribute knowledge in paediatric radiotherapy. The members of the group are also radiotherapy representatives in other Swedish paediatric oncology groups, as well as in international paediatric societies.

The group initiated a research project in 2005 to explore the use of telemedicine tools in paediatric radiotherapy.

2. Aims

The main objective of the work presented in this doctoral thesis was to identify topics which might improve and optimise paediatric radiotherapy from a treatment planning perspective in a national setting, and specifically to:

- Develop a system of national videoconferences for discussion of new paediatric radiotherapy cases, collaboration in new settings and maintaining/raising the competence level in paediatric radiotherapy. This is described in detail in paper I and summarised in chapter 3.
- Assess inter-observer variations in target delineation and its impact on dose to normal tissues. Two studies, separated in time, were performed with four and two cases, respectively. The studies are described in papers II and III and are summarised in chapter 4.
 - Evaluate and quantify the volumetric variation in target delineation.
 - Evaluate the use of a calculated consensus volume to visualise and quantify the dosimetric impact of inter-observer variations in target delineation.
- Assess the potential gain for a paediatric cohort when changing the treatment modality from photons to protons. This study is described in paper IV and summarised in chapter 5.

3. National videoconferences

Telemedicine can be defined as “the use of telecommunication and information technologies to provide health care services to individuals who are at a distance from the health care provider” [14]. The research project to connect the six university centres treating children started in 2005. At that time similar systems for radiotherapy collaboration had already been introduced in different parts of the world [15-22]. The use of telemedicine has since expanded, and is used today in various fields of oncology and radiotherapy; e.g. palliative care, remote treatment planning, oncology training and follow-up [23-25].

SvBRG uses the tools of telemedicine combined with videoconferencing to discuss and review all paediatric patients referred to radiotherapy in Sweden. The telemedicine project described in paper I has evolved to be a part of the current clinical routine in each of the six Swedish university hospitals treating paediatric patients (figure 3.1). In late 2010 Århus, Denmark, also joined.

The initiative for videoconferences came from the members of SvBRG. The previous biannual physical meetings were considered not sufficient to cover all items on the agenda. The aim of the research project presented in paper I was to maintain and/or raise the competence level within the group of specialists as well as to distribute this competence more widely in the participating centres as they see more cases and to act as discussion partners and support in difficult clinical decisions.

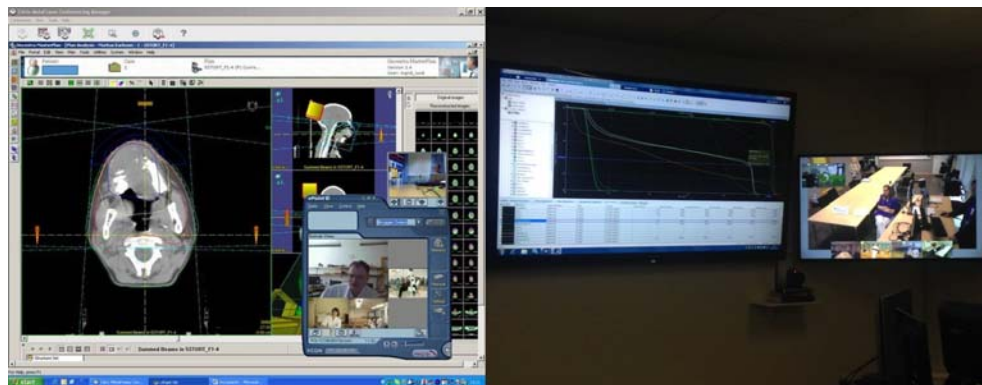


Figure 3.1. Paediatric telemedicine conferences. To the left an early picture with a mix of video conference systems and personal videoconference systems. To the right a conference in Dec 2016 with modern video conference systems.

Conferences are presently scheduled bi-weekly for approximately 30-45 minutes. On average 20 conferences are held each year, including a summer break. Since the start in November 2005 until December 2016, 718 children have been seen at 211 conferences. On average five hospitals (of seven possible) have participated in each conference (figure 3.2).

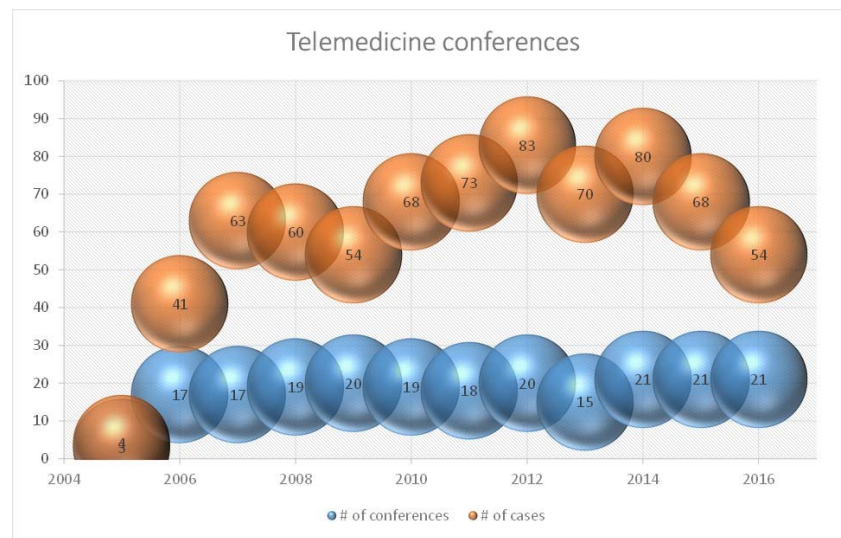


Figure 3.2. The number of conferences and presented cases over the years since the start in 2005.

At these conferences final treatment plans are reviewed and discussed, and also diagnostic imaging for pre-treatment discussions. Paediatric oncologists take an active part when reviewing especially complicated cases. An Australian paediatric group has also shown interest in the arrangement and participated with the aim of eventually copying it. Lectures have been given this way, and the group has regular meetings using the same system. Other groups have followed; the national lymphoma group meets bi-weekly to discuss patients with Hodgkin's disease and routine monthly national meetings for gyno-oncology has just started as well as for gastro-intestinal oncology. Many local multi-disciplinary tumour boards now use the same platform for their frequent meetings as well as the national proton treatment rounds.

4. Inter-observer studies or dummy runs

Inter-observer studies or dummy runs are a tool to assure and assess the quality in the radiotherapy process. It can be applied to the whole process or as in this case only to specific parts. How well does a group of individuals comply with the specifications in a protocol? Is the protocol unambiguous or are there parts which can be misunderstood? Here we have looked at the interpretation of study protocols specifically regarding target delineation and treatment planning.

A “patient package” is distributed to the participants in the study. Each patient package includes anonymised diagnostic imaging, patient charts, treatment planning CT and other patient related information needed for the task. The package for each patient also includes the treatment protocol intended to be applied. Each participant delineates and plan according to the protocol and the result is then collected and analysed.

Target delineation comparisons can be done in several ways. The literature presents a variety of different indices for this purpose. A clear consensus regarding which indices to use has not yet been reached. Fotina et al. [26] published a review where they explored a large number of published inter-observer studies. They divided the studies into three categories. The *first* category is based on descriptive statistics; volume size, standard deviation, range, ratio, and COV (coefficient of variation), the dispersion of the distribution in one single number. The *second* category deals with approaches to quantify overlapping volumes. The use of a “golden standard” delineation is often applied. All observer segmentations are compared to this volume in terms of various similarity coefficients/indices, e.g. the Dice similarity coefficient [27] or the Jaccard similarity index [28]. These are useful when comparing single structure pairs (the golden standard vs. single-observer delineation). A perfect match in size and position will result in an index numerically equal to 1. An overlap measure that is appropriate when comparing several observers simultaneously is the generalized conformity index [29]. The centre of mass (COM) [30] is sometimes calculated to evaluate the displacement of volumes in space. In the *third* category statistical measures are applied for structure comparisons.

When comparing treatment plans (dose distributions) a number of dose-volume descriptors are analysed and compared for both target volumes and relevant organs at risk (OAR) [31, 32].

In papers II and III dummy runs were specifically performed in order to evaluate inter-observer target delineations. We used the generalized CI (CI_{gen}) [29] as well as measures of volumes and dose distributions. The definition of this index is:

$$CI_{\text{gen}} = \frac{\sum_{\text{pairs } i,j} (A_i \cap B_j)}{\sum_{\text{pairs } i,j} (A_i \cup B_j)}$$

where the numerator is the sum of all pairs (i,j) of volume intersections and the denominator is the sum of all pairs of volume unions. $CI_{\text{gen}} = 1$ indicates a total overlap, while $CI_{\text{gen}} = 0$ indicates totally separated volumes.

The use of a “golden standard” target delineation is common. This volume can be derived in different ways, e.g. a selected expert delineation or a volume decided in agreement by a group of experts. Another method is to use a mathematical algorithm to calculate the consensus volume from all delineated volumes. A probabilistic estimate of true volume is the expectation-maximization (EM) algorithm for simultaneous truth and performance level estimation (STAPLE) [33]. This method was used in paper III together with evaluation of dose volume histograms (DVH) for estimating the quality of inter-observer target delineations. Kappa-statistics (K) for strength of agreement was calculated as well.

We used the following dose-volume descriptors for treatment plan quality evaluations; $V_{95\%}$, $D_{98\%}$ (near-minimum dose), $D_{50\%}$ (median dose) and $D_{2\%}$ (near-maximum dose) for PTVs. In addition, the homogeneity index [$HI = (D_{2\%} - D_{98\%})/D_{50\%}$] for PTV, treated volume ($V_{95\%}$ for the body) and irradiated volume ($V_{50\%}$ for the body) were calculated for each treatment plan. The mean dose to the remaining volume at risk (RVR), i.e. the total body volume minus CTV(s) and OARs was also calculated [31, 32].

Target volumes

In paper II the first study of inter-observer variability is described. Four cases had been selected for this purpose: Wilms’ tumour (case 1, figure 4.1), Hodgkin’s disease (case 2, figure 4.2), rhabdomyosarcoma (case 3, figure 4.3) and chordoma (case 4, figure 4.4).

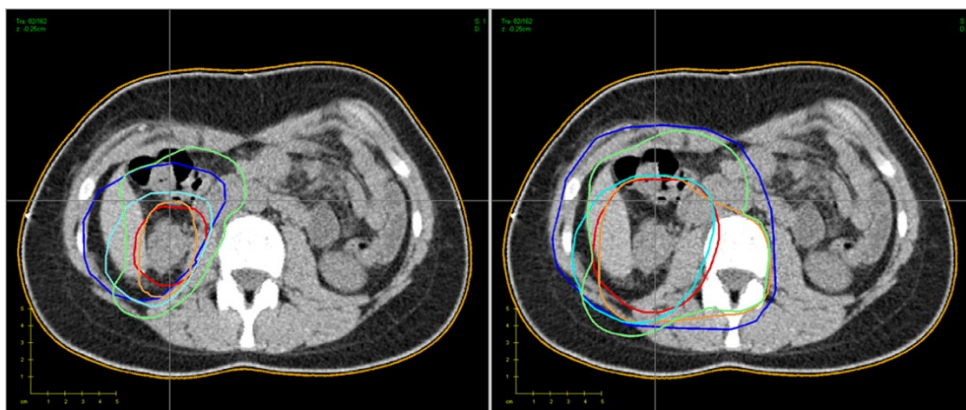


Figure 4.1. Case 1; patient with Wilms' tumour with observer delineations of CTV (left) and PTV (right). The major difference is in including the vertebrae body or not.

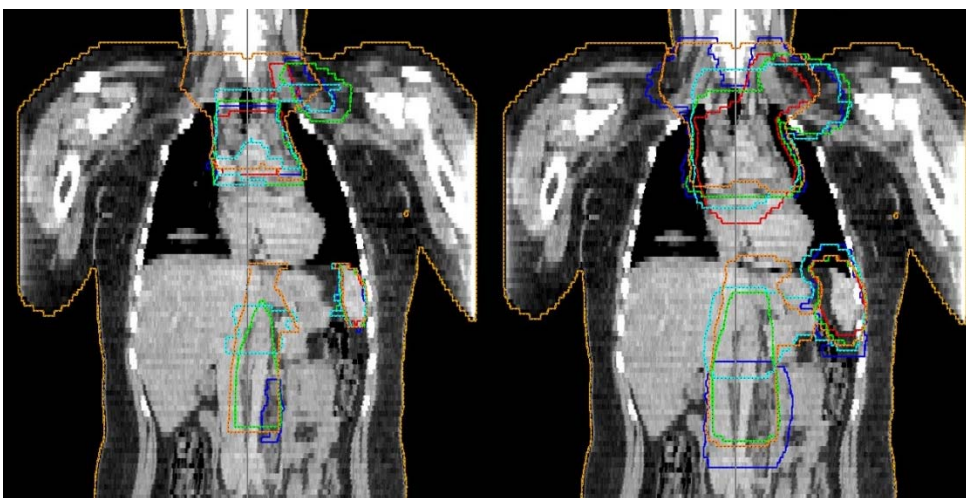


Figure 4.2. Case 2; patient with Hodgkin's disease with observer delineations of CTV (left) and PTV (right). Large variations are observed in target length and width of the mediastinal target as well as for the abdominal target.

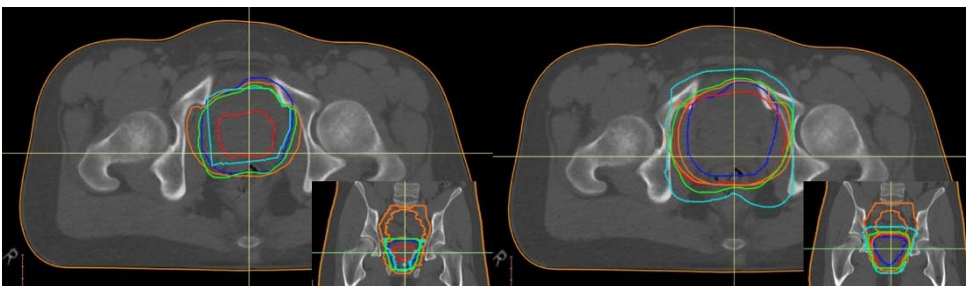


Figure 4.3. Case 3, patient with rhabdomyosarcoma with observer delineations of CTV (left) and PTV (right). Note the difference in the cranial extension. One centre included the iliac lymph nodes for part of the treatment.

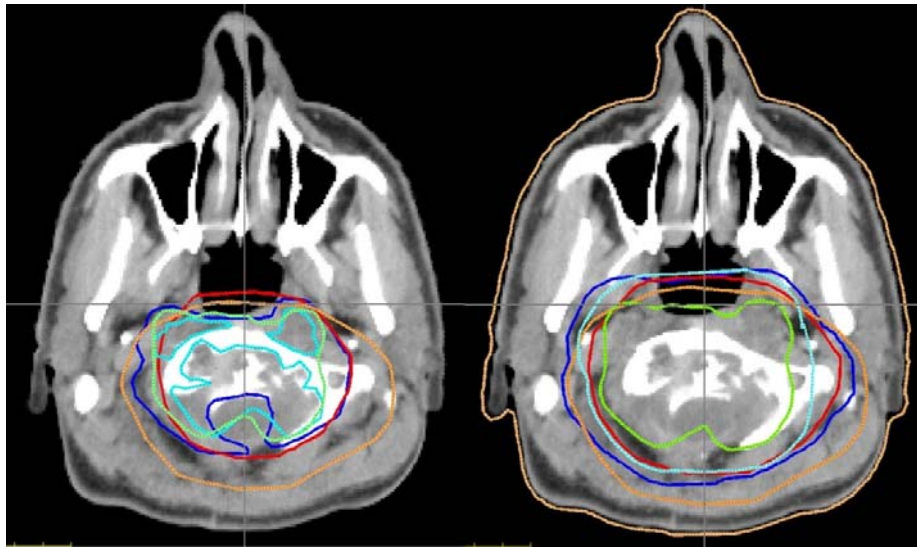


Figure 4.4. Case 4, patient with chordoma of the skull base with observer delineations of CTV (left) and PTV (right).

Large variations in the delineated target volumes (figure 4.7) were identified in this inter-observer study (paper II). The CI_{gen} for CTV for the four cases were 0.32 (case 1; Wilms'), 0.43 (case 2; Hodgkin's mediastinal), 0.42 (case 3; rhabdomyosarcoma) and 0.47 (case 4; chordoma). The quotients of the largest to the smallest CTV volumes were 5.2, 2.1, 5.8 and 3.5 for cases 1, 2, 3 and 4, respectively.

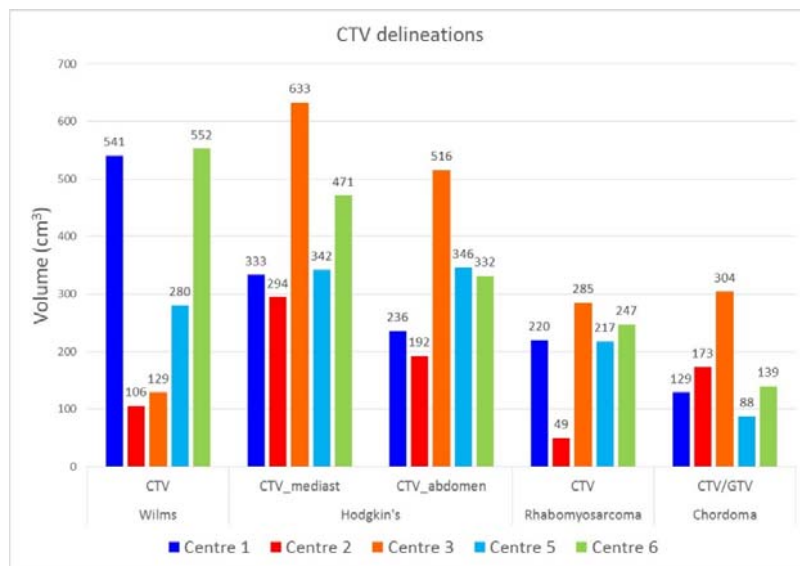


Figure 4.7. CTV volumes for all four cases.

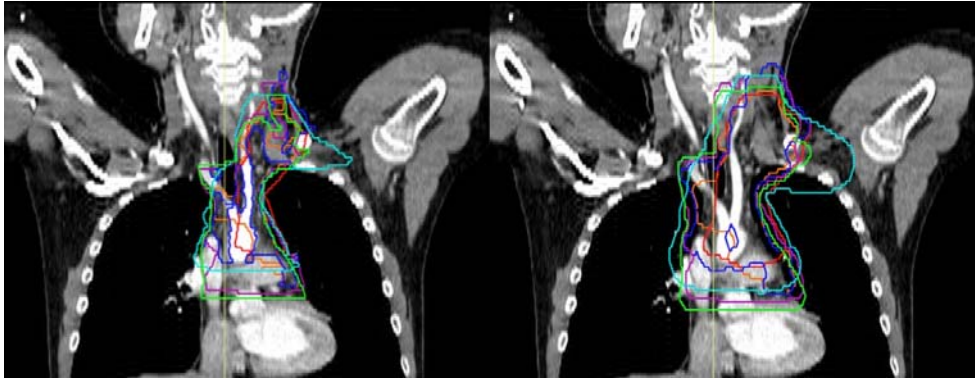


Figure 4.5. Case 5; patient with Hodgkin's disease with observer delineations of CTV (left) and PTV (right). Note the difference in delineations of the supraclavicular fossae and caudally over the heart.

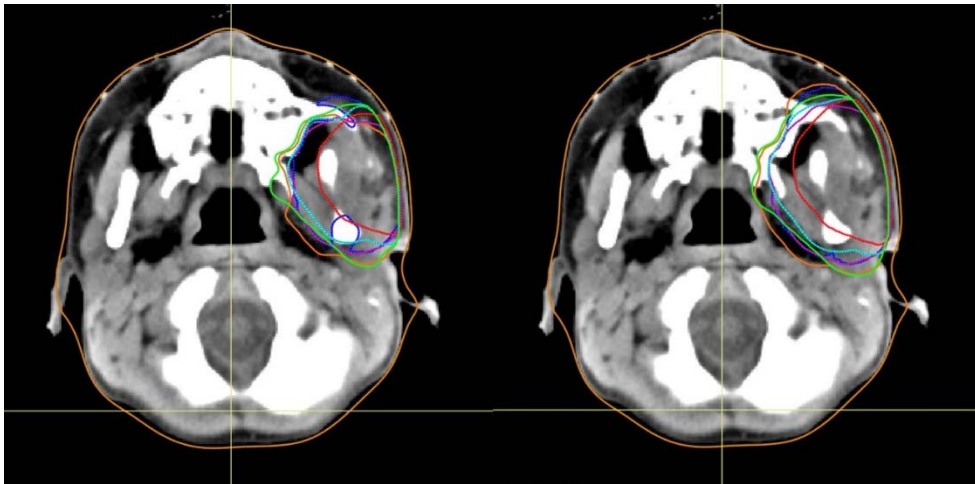


Figure 4.6. Case 6; patient with rhabdomyosarcoma of the parotid gland with observer delineations of CTV (left) and PTV (right).

In the second delineation study (paper III) two cases were selected; one patient with Hodgkin's disease (case 5, figure 4.5) and one patient with rhabdomyosarcoma of the parotid gland (figure 4.6).

Based on CI_{gen} and quotients of the largest to smallest target volume, the second inter-observer study (paper III) indicated less inter-observer variation compared to the first study (figure 4.8). Any stringent comparison between the two studies cannot be performed due to the differences in diagnoses/target extensions studied. The CTV CI_{gen} for the two cases were 0.48 (case 5; Hodgkin's) and 0.62 (case 6; rhabdomyosarcoma). The quotients of the largest to smallest CTV were 2.3 and 1.8, respectively.

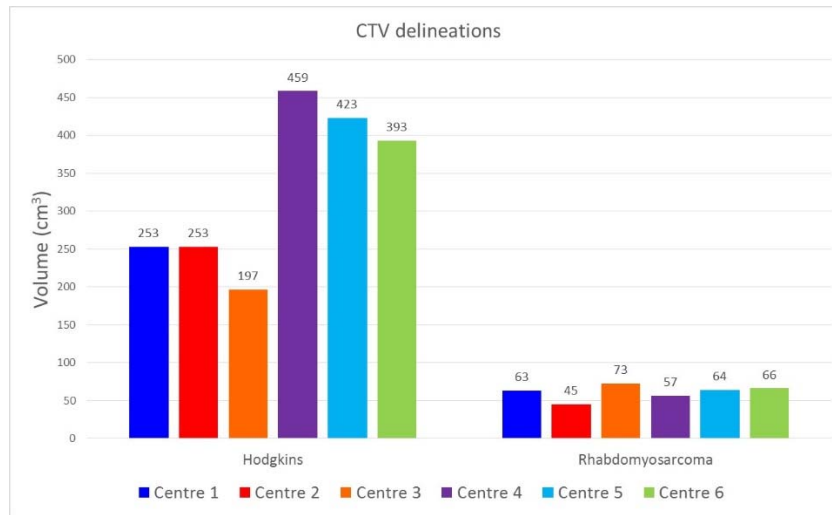


Figure 4.8. Variation in delineated CTV volumes in the second inter-observer study (paper III).

In paper III the concept of an algorithm based consensus volume was applied. This volume is calculated from the observers' delineations using an expectation-maximization (EM) algorithm for simultaneous truth and performance level estimation (STAPLE) [33]. Kappa-statistics (K) for the segmentation by the participants was also determined. K for the CTVs was 0.60 and 0.76 for case 5 (Hodgkin's) and case 6 (rhabdomyosarcoma), respectively. For the PTV the corresponding values were 0.63 and 0.78, respectively. A *moderate* kappa-value is considered to be between 0.41-0.60 and a *good* kappa-value from 0.61-0.8. For a perfect match the value should be 1 (according to Landis and Koch) [34]. The "strength of agreement" was good to moderate for these two cases.

Dosimetric evaluation – dose-volume descriptors

In papers II and III, the dose volume descriptors $V_{95\%}$, $D_{98\%}$ (near-minimum dose), $D_{50\%}$ (median dose), $D_{2\%}$ (near maximum dose) and the homogeneity index (HI) as recommended by the ICRU [32] were investigated.

In paper II one treatment plan was VMAT (for the chordoma case) while all others were 3DCRT. In paper III all plans were VMAT plans, and for the rhabdomyosarcoma case three additional plans with protons were included. In paper IV all photon plans were 3DCRT while all proton plans created were intensity modulated (IMPT).

In both delineation studies PTV- $V_{95\%}$ were generally kept within clinically acceptable dose values. The lowest coverage (65% of the prescribed dose) was for the chordoma case, where one of the plans was created to keep the spinal cord at tolerance level, thereby accepting a lower dose to the PTV closest to the spine. All other treatment plans in both delineation studies present PTV- $V_{95\%}$ levels between 76% and 100% of the prescribed dose. The near-minimum dose ($D_{98\%}$) is also the lowest for the chordoma case, otherwise it is never below 90% and the near-maximum dose ($D_{2\%}$) is never above 108%. The HI varies between 0.06-0.19. A truly homogenous plan would have a HI of 0. The chordoma plan is again an outlier with a HI of 0.64.

Dosimetric evaluation – dose-volume visualisation

In paper III a novel method was presented where DVHs (with the volume in absolute units) were used together with a consensus volume for exploring inter-observer target delineation variations in dosimetric terms in addition to conventional geometrically based volume concordance indices. Dose distributions for photon plans were used for exploring the concept introduced in paper III.

Companion proton plans were also generated in this study and the results when applying these rather than the photon plans are presented here. DVHs for the treatment plans applied to their corresponding PTV volumes are shown in figure 4.9. The DVH with volume in relative units (upper panel) can be used for plan quality evaluation. The DVH with the volume in absolute units (lower panel) adds visual information on the difference in target delineation which accomplishes the identification of segmentations leading to over and under dosage. The yellow dashed line indicates the consensus volume.

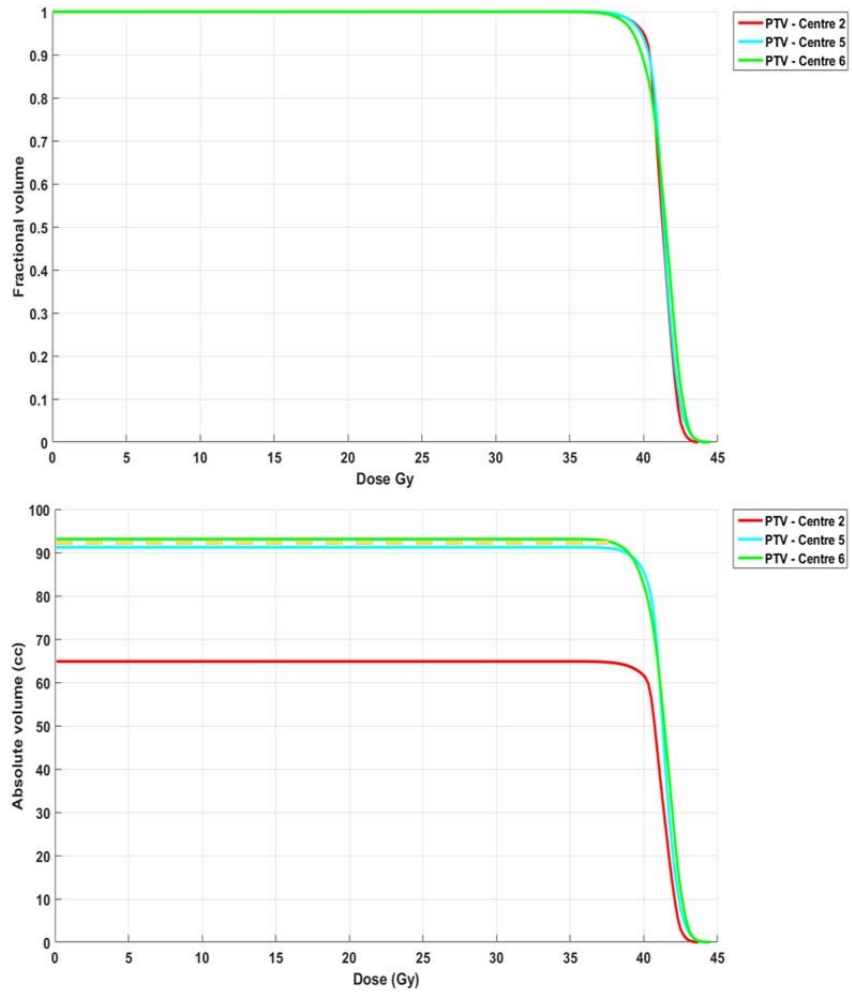


Figure 4.9. DVH for case 2 from paper III. In the upper panel, a DVH in relative volume and absolute dose, in the lower panel, a DVH with absolute volume and dose. Yellow dashed line represents the consensus volume.

In figure 4.10 this variation is displayed in DVHs where the plan of each centre is applied to both its target ($DVH_{PTV,i}$) as well as to the consensus volume ($DVH_{con,i}$). The $DVH_{PTV,i}$ and $DVH_{con,i}$ in figure 4.10a indicates that the consensus volume is under-dosed while for b and c the consensus volume is well covered. It also shows that the volumes not only are of the same size but also congruent.

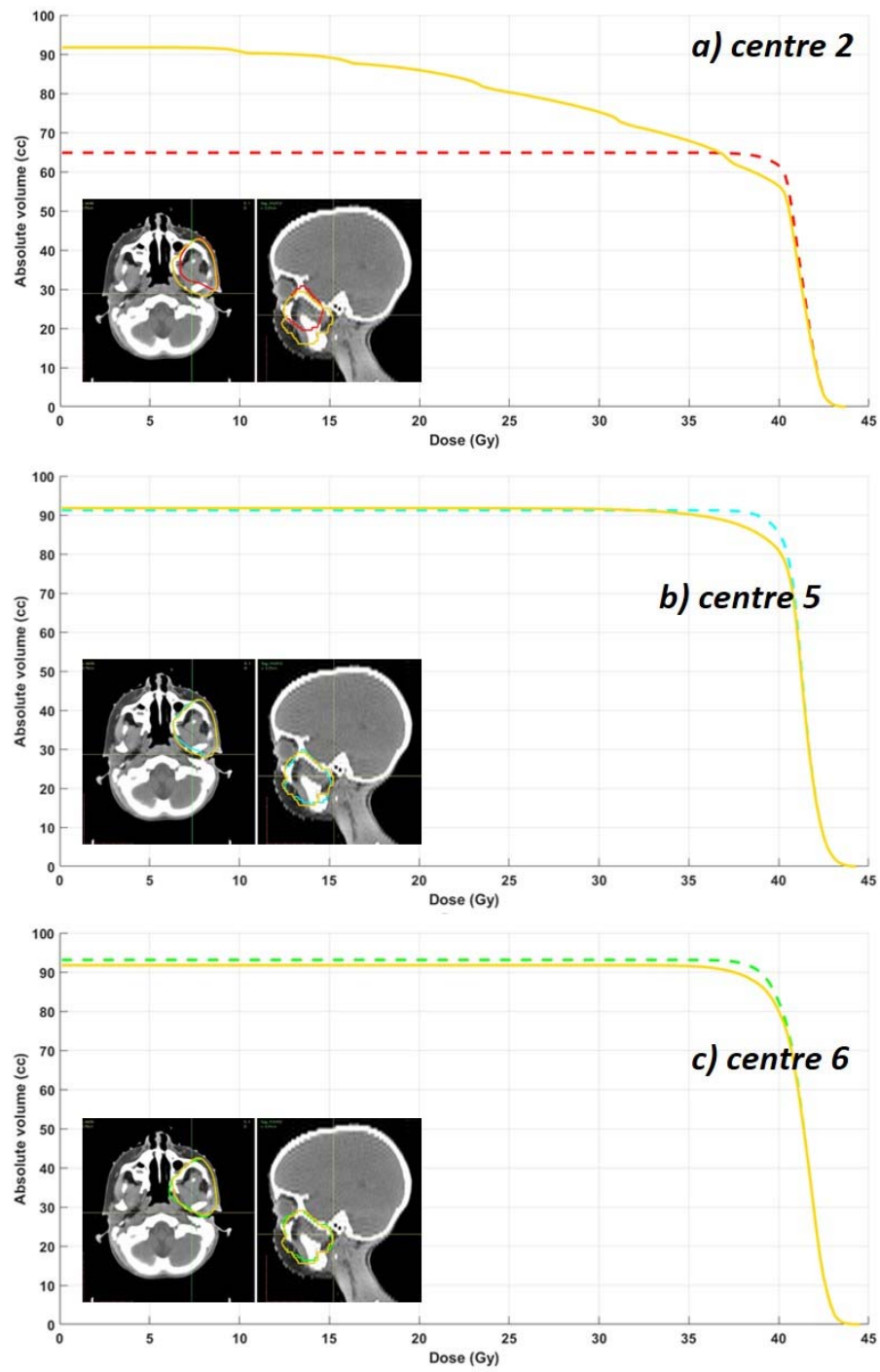


Figure 4.10. The individual DVHs for all target volumes (dashed lines) compared to the consensus volume (yellow).

To further explore the concept, a consensus volume was calculated for the Wilms' case from paper II. Figure 4.11 presents the DVHs for target coverage (upper panel) as well as the variation in delineated volume in comparison with the consensus volume (lower panel).

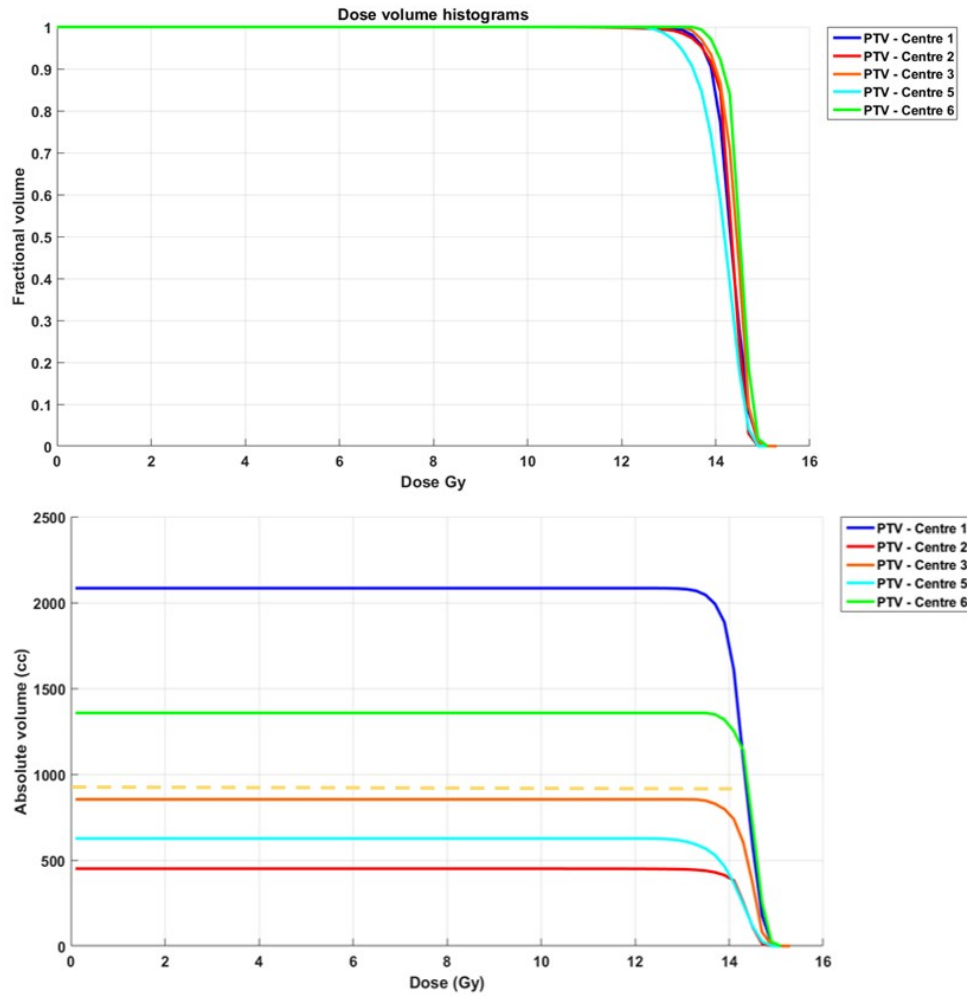


Figure 4.11. DVH for case 2 from paper II. In the upper panel, a DVH in relative volume and absolute dose, in the lower panel, a DVH with absolute volume and dose. Yellow dashed line represents the consensus volume.

In figure 4.12 $DVH_{PTV,i}$ and $DVH_{con,i}$ for centre 1 it is obvious that volumes outside the consensus volume are over-dosed. This is also noted for centre 6. For centres 2, 3 and 5, the consensus volume is under-dosed to varying degrees.

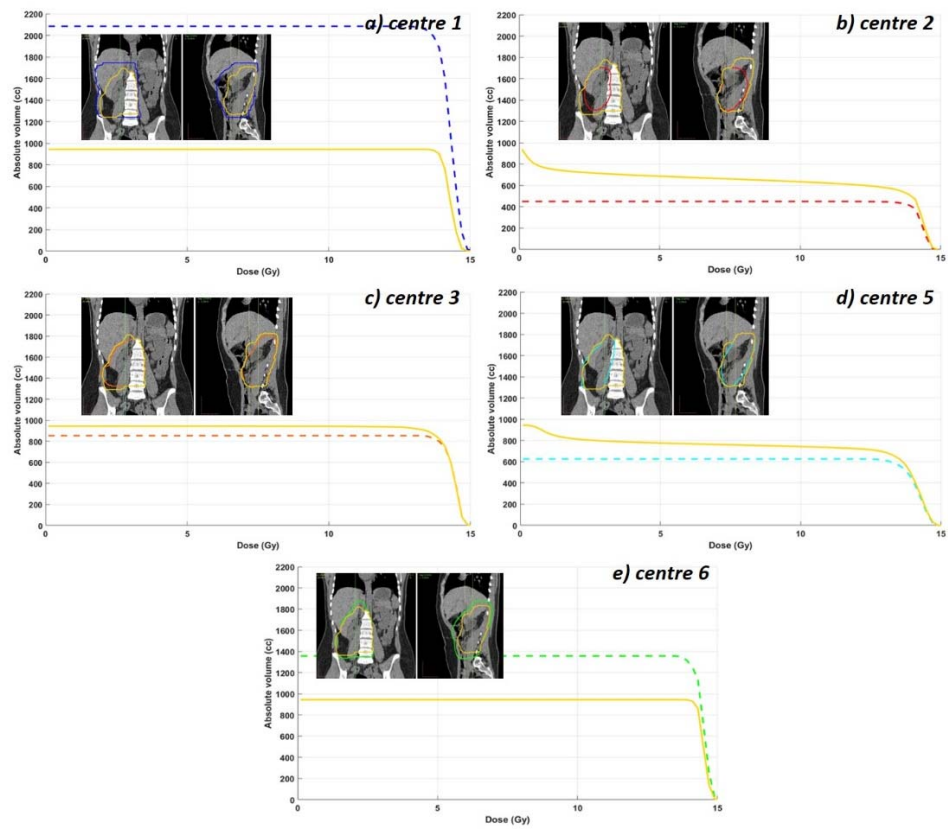


Figure 4.12. Case 2 from paper II. The individual DVHs for all target volumes (dashed lines) compared to the consensus volume (yellow).

Organs at risk

All plans kept doses to the OARs below those stated in the protocols. In figure 4.13 the difference in irradiated volume is clearly visible.

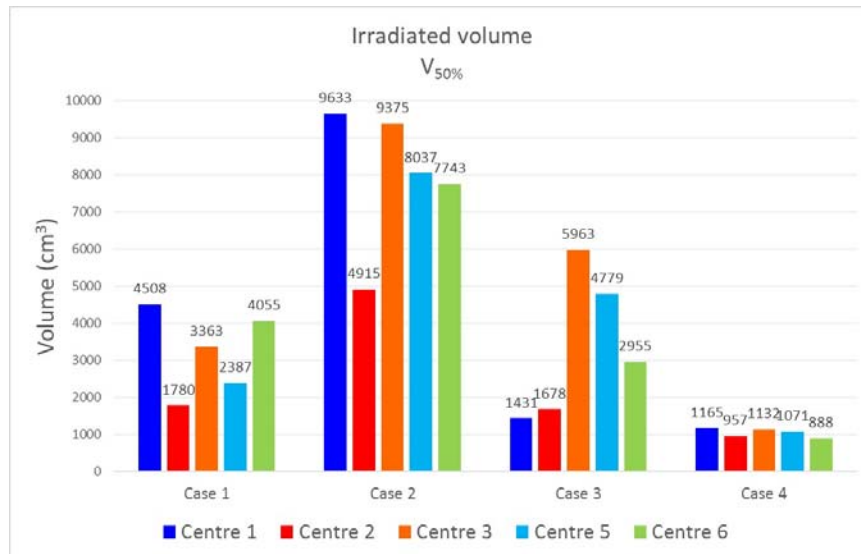


Figure 4.13. Irradiated volume for the four cases from paper II. For cases 1-3 there is an obvious variation, for case 4 there is almost no variation.

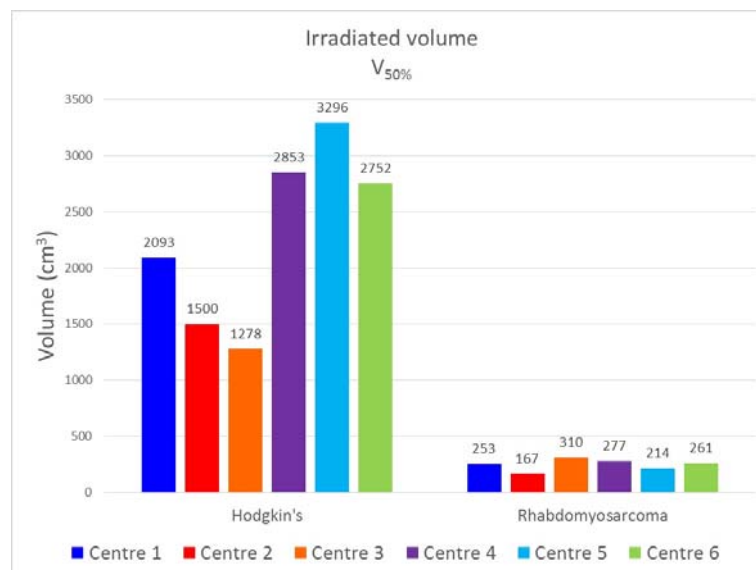


Figure 4.14 Irradiated volume for the two cases from paper III.

For the two cases in paper III the variation is larger for the Hodgkin's case than the rhabdomyosarcoma case (figure 4.14). The variation in target volume were larger for the Hodgkin's case. All centres created VMAT plans. If this patient were a young woman instead of a young man, the centres would probably have chosen a 3DCRT technique to avoid the low dose volume from the VMAT technique to the mammary glands. For the rhabdomyosarcoma case there is less difference between the photon plan, as well as the protons plans.

5. Photons vs. protons

In paper IV plans for a number of paediatric and adolescent patients were compared for photons and protons. All paediatric patients receiving radiotherapy with photons during one year in Sweden were selected for re-planning with protons. Of 93 patients treated, proton plans could be created for 45 patients and compared to the photon radiotherapy that they already had received. The 45 patients were all treated with 3DCRT technique and were re-planned with intensity modulated proton therapy (IMPT) (figure 1.9) for comparison. The same dose-volume descriptors as described in chapter 4 were used for the comparison.

There were very small differences between the photon and proton plans regarding target coverage. The largest differences in target coverage were found in patients with superficial targets. The HI was similar or better for protons in all cases.

The irradiated volume was significantly lower, on average 38%, for protons than for photons ($p < 0.0001$) (figure 5.1).

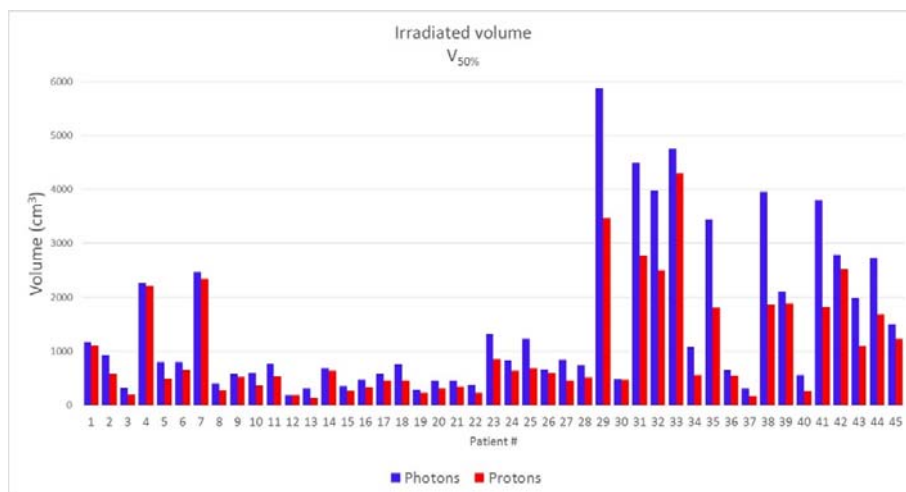


Figure 5.1. Irradiated volume for the 45 cases comparing photons and protons.

However, proton therapy will not be suitable for all paediatric patients. It depends on the target volumes size and localisation as discussed in paper IV. Comparing photon and proton plans will aid in the decision.

6. Discussion

National videoconferences

Telemedicine is a broad concept used in many different and varied situations, from the collaboration between two or more specialist nodes exchanging information to the interaction between the hospital and patients in their home. Originally it was simply a way of communicating between two nodes until it evolved to “tele-healthcare” and “e-health” involving all aspects in communication between the healthcare system and the patient. [35]. The telemedicine collaboration between the hospitals treating children with radiotherapy in Sweden (paper I) has become very successful. This is mainly due to the active interaction between the participants during the conferences, their willingness to share their experience and to discuss the more difficult cases. Paediatric oncologists are called upon when considered to be needed. In addition to patient related issues, such as target delineation and/or treatment plans, new protocols and how to interpret them are discussed. Since there is also a national collaboration within the group on long-term side-effects after radiotherapy, discussions around these matters are also frequent during the bi-weekly conferences. The national conferences for paediatric radiotherapy have also served as a framework and layout for the development of other national oncology videoconferences, e.g. for the collaboration between the university clinics and the proton facility (Skandionkliniken) in Sweden. This national facility is built on “distributed competence” and relies on the technological progress made in telemedicine applications. For Skandionkliniken all patient preparations; CT, fixation, target delineation and treatment planning are performed at the “home centre” (one of seven university hospitals) [36]. Patients and their treatment plans are then discussed at national teleconferences in the same fashion as the paediatric radiotherapy conferences. In other parts of the world this technology is used in similar ways; to aid and to perform quality assurance in international studies [19] or consult and/or perform treatment planning tasks remotely [37].

Inter-observer studies or dummy runs

As seen in the studies described in papers II and III it is difficult even for a small group as the SvBRG to be completely homogeneous in target delineation. Delineating a volume that is too small might end up in a local recurrence while too large a volume might instead increase the side-effects of the treatment.

Delineation protocols exist locally, nationally and internationally for different diagnoses. A number of delineation atlases also exist to aid the clinicians in this task [38]. Inter-observer studies are useful tools when testing a new delineation concept [39] for example, as might be the case when a new study protocol is brought into use or in an attempt to unify target delineation in a collaboration between centres [40] or to unify treatment planning within a group.

The first delineation study (paper II) showed large differences in target delineation, both in size, but also in geometrical concordance. In the second delineation study (paper III) this variation seemed to be smaller. There might be several reasons for the difference in delineation. In both studies diagnostic imaging were included in the distributed “patient package”. However, it would be up to each centre to actually import also this material into the TPS and register the diagnostic images with the treatment planning CT to enhance target delineation. In a recent review, Vinod et al. [41] identified a number of scientific papers on the subject of inter-observer variability (IOV) and target delineation. Their conclusion was that IOV could be reduced and they recommended several actions for this; the use of guidelines and atlases, the possibility to co-register PET and/or MR with treatment planning CT and to attend delineation workshops.

In 2012 Fairchild et al. published a paper describing which information should be included in a study protocol in general [42]. The scientific council on ionizing radiation within oncology created by The Swedish Radiation Safety Authority (SSM) published a report with a focus on the radiotherapy part of a study protocol [43] as well as a template for the radiotherapy description [44]. These papers will hopefully lay the framework for improved study protocols in the future.

A consensus volume for target delineation inter-comparisons was used in paper III. This could actually be any volume that could be considered the “truth” or “expert delineation”. The consensus volume was used to visualize the variation in target delineation by use of the dose distribution for each target volume. A DVH is an “easy-to-interpret” way of presenting the results of a target delineation study and its dosimetric impact compared to just using a concordance index.

As the target volumes vary in size and localization, this will affect the treatment planning. As seen in paper II there were a variety of treatment solutions to solve the same problem. This is in part dependent on the target volume, but also on the OARs

close to the target. From the study described in paper III it became apparent that we do not have commonly agreed upon dose-volume constraints for children. They are not very detailed in the study protocols, or in compliance with the more advanced treatment techniques of today. This variation is illustrated by the DVH for the heart for the Hodgkin's case from paper III (figure 6.1). With common dose-volume constraints the variation would probably have been smaller. This could be of importance in studies where it is of interest to evaluate dose to OARs and draw conclusions from it.

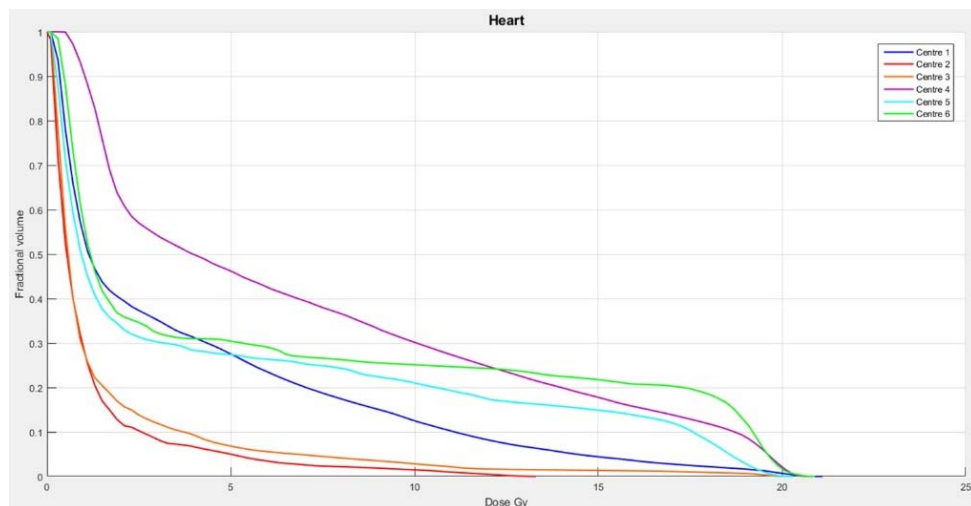


Figure 6.1. DVH for the heart for case I, paper III.

Photons vs. protons

In our studies we have seen a shift from 3DCRT (paper II), to rotational treatments (paper III) and protons (paper IV). However, the decision on treating with 3DCRT or VMAT has to be made on an individual case basis where dose-sparing of specific OARs have to be balanced against the risk of inducing a second cancer later in life.

The results of the study comparing photons to protons confirm other studies on the same subject [45-48]. These have been performed on small and selected patient groups while our study includes all patients seen during a year with a variety of diagnoses. Proton treatment will be greatly advantageous for most children, but not all. This is highly dependent on the target volume, i.e. size and localization. In many cases this will have to be decided on an individual basis comparing treatment plans created for both modalities. The gain for the patients is the lower dose outside the

target volume, which in most cases can be reduced substantially, and thereby reducing side-effects [49].

Side effects

There is an increased risk in childhood cancer survivors for different types of long term treatment induced side effects. These are not only related to the radiotherapy but also to the chemotherapy and surgery that have been part of the total treatment. The long-term side-effects of the combination of radiotherapy and chemotherapy are not yet fully understood. The children have an increased risk of complications associated with almost any organ system compared to the normal population. A majority of the children/adolescents will have at least one chronic health condition at 40 years of age related to the cancer treatment they received early in life [50]. There is also an increased risk of developing secondary cancers due to previous treatments [8].

It is therefore important to monitor the children after their cancer treatment and register the side effects to the knowledge base needed to further improve paediatric treatments. In Sweden all patients under 18 years of age are registered in the Radtox database. Germany started registration [51] in 2004 (pilot from 2001), Sweden followed in 2008 and recently both Norway and Denmark joined. Radiotherapy data is registered, and side-effects are monitored for at least ten years. In 2016 the first paper on acute side effects from the collaboration was published [52].

Today radiotherapy data for 745 patients have been entered into the Radtox database. There are follow-up data for acute toxicity for just over 500 patients and late effect data for 400 patients.

Although late effects data are not available for all patients entered in the Radtox database, a survey made in 2014 showed that most side-effects diminish over time. However, it is an area that needs more attention, and several initiatives are ongoing, nationally and internationally. In 2015 the “Pediatric Normal Tissue Effects in the Clinic” (PENTEC) group, consisting of physicians, physicists and epidemiologists, was formed. Their specific aims are to improve outcome for survivors of radiation therapy for childhood cancers, to describe relevant physics issues specific to paediatric radiotherapy, and to propose dose-volume-outcome reporting standards to systematically inform future treatment guidelines [53].

International collaboration groups such as the American Childhood Cancer Survivor Study [54], British Childhood Cancer Survivor Study [55] and the Pan-European Network for Care of Survivors after Childhood and Adolescent Cancer [56, 57] are active in addressing questions on late-effects and quality of life, and frequently

publish data based on their databases. These databases contain mostly patient-reported quality of life data.

The Swedish workgroup for long time follow-up after paediatric cancer (SALUB) is a working group within the Swedish Paediatric Oncology and Haematology group. They have produced a national protocol for long-term follow-up which is available from the websites of both the Swedish Paediatric Oncology and Haematology group and the regional cancer centres [58]. The aim of their work is to aid the survivors in awareness of possible side-effects. It is also a guide for the general practitioner (or specialist) in what might be needed when it comes to follow-up procedures.

Conclusions and future work

The aim of all cancer treatment is to cure with a minimal level of side effects. This is the main reason behind the studies in this thesis.

Collaboration will aid in unifying the treatment in the country and telemedicine has improved paediatric radiotherapy at a national level.

Inter-observer studies can aid in many ways in the clinic, as well as finding those areas still in need of improvement. The SvBRG has decided to make an increased use of “dummy-runs” for target delineation in order to reach consensus on how to delineate according to and interpreting a new study/treatment protocol as well as workshops on the delineation of specific organs at risk.

Protons will play an increasingly important role in the radiation treatment of children in Sweden. Comparing different treatment modalities as well as comparing photons to protons will also aid the improvement of treatment.

The SvBRG has also decided to finalise and implement a national dose-volume constraints list for paediatric/adolescent patients.

Populärvetenskaplig sammanfattning

svensk sammanfattning/summary in Swedish

Målet med innehållet i denna avhandling var att identifiera områden för förbättring och optimering av strålbehandling av barn/ungdomar ur ett dosplaneringsperspektiv i en nationell miljö. Vi har utvecklat nationella videokonferenser för kommunikation kring nya fall, samarbete och upprätthållande av kompetensnivån i pediatrik strålbehandling. Vi har undersökt hur olika experter utlinjerar målvolym och hur skillnader inverkar på stråldosen till normal vävnad. Vi har visat på en metod att visualisera dessa skillnader som ett komplement till gängse metoder. Vi har även undersökt den potentiella vinsten för gruppen barn/ungdomar vid byte av behandlingsform från fotoner till protoner.

Bakgrund

Ca 300 barn får cancer varje år i Sverige. Enastående framsteg har gjorts inom barnonkologin; från 60-talets totala långtidsöverlevnad på ca 25 % till dagens totala långtidsöverlevnad på ca 80 %. De flesta behandlas med en kombination av kirurgi, cellgiftsbehandling och strålbehandling. Ca 100 barn får varje år strålbehandling i Sverige. Sex universitetssjukhus ger strålbehandling till barn/ungdomar i Sverige. Inför sin strålbehandling genomgår alla patienter en datortomografiundersökning (CT) i behandlingsläge. Den används både för att återge korrekt anatomisk geometri, för beräkningarna vid dosplaneringen samt för positionering under behandlingen. Under strålbehandlingen måste patienten ligga stilla i samma position vid varje behandling. För att underlätta detta, görs ofta någon form av fixation, t.ex. en termoplastisk mask. Yngre barn är ofta sövda eller lätt sederade för att kunna ligga stilla, medan äldre barn kan distraheras med en film eller ljudbok.

Utlinjering av målvolym är en viktig del av förberedelserna inför strålbehandlingen. Hur den slutgiltiga målvolymen ser ut beror bl.a. på; tumörens storlek och utbredning, utformningen av behandlingsprotokollet, patientens andra behandlingar, det allmänna hälsotillståndet och kunskapen/erfarenheten hos den som ansvarar för uppgiften. All information om tumören och dess utbredning ska översättas från utlåtanden från andra undersökningar till en tre-dimensionell målvolym i CT-undersökningen. Den normala vävnad (strukturer/organ) som kan påverka dosplaneringen kallas riskorgan och även denna utlinjeras i CT-

undersökningen. Detta underlag utgör grund för dosplaneringen (beräkningen) av patientens strålbehandling.

Vid dosplaneringen optimeras dosfördelningen både med avseende på målvolymer men också på att minimera dosen till omkringliggande vävnad. För barn/ungdomar kan det finnas en vinst med protoner. Deras fysikaliska egenskaper gör att dosen till normalvävnaden kan minskas jämfört med den som erhålls vid användning av fotonstrålning.

Svenska Barnradioterapigruppen (SvBRG) samarbetar sedan år 2000 i frågor som rör strålbehandling av barn. Gruppen bildades för att öka och sprida kunskap kring strålbehandling av barn.

De flesta barnen/ungdomarna följer ett studie/behandlingsprotokoll. Protokollen innehåller som regel information om den specifika sjukdomen, om tidigare studier och dess resultat. De ger också information om vilken behandling som ska ges, när i tiden och förhållandet till andra behandlingar. Strålbehandlingsdelen i protokollen är ofta undermåligt beskriven. Det ger ett stort utrymme för lokala variationer. För en adekvat strålbehandling är det viktigt att alla stråldoser till målvolymer är tydliga liksom dosbegränsningar till riskorganen. Välskrivna protokoll underlättar hela dosplaneringsprocessen, förbättrar följsamheten och ökar därmed patientsäkerheten.

Nationella videokonferenser

2005 initierade SvBRG ett forskningsprojekt för att oftare kunna ”ses” och diskutera strålbehandlingen av enskilda fall (granska strålmål och dosplaner), lära av varandra och på så sätt sprida och upprätthålla kompetensen inom ett område med få patientfall per år (beskrivet i studie I).

Idag är videokonferenserna varannan vecka en del av den kliniska vardagen. Ca 20 konferenser hålls årligen, med uppehåll över sommaren. Från starten i november 2005 till december 2016 har 718 fall visats på 211 konferenser. Utöver representanter från de sex svenska sjukhus som ger strålbehandling till barn/ungdomar i Sverige deltar även representanter från Århus i Danmark.

Arbetsättet har inspirerat till att starta fler grupper; till exempel nationella hodgkin-gruppen, gyn-onkologigruppen liksom gastro-intestinal gruppen. Ett flertal multidisciplinära tumörrounder använder sig av samma plattform för sina möten. Barnrounderna har även fungerat som ”testbädd” för de nationella protonrounderna, som startades i samband med att det nationella protoncentrat Skandionkliniken i Uppsala togs i bruk.

”Inter-observer variation – dummy runs”

Att använda sig av s.k. ”dummy-runs” för att studera hur enhetligt målvolymen utlinjeras eller hur olika sjukhus löser ett dosplanproblem är vanligt. Man kan också använda sig också av dummy-runs för att testa nya studie/behandlingsprotokoll, i syfte att ta reda på hur väl protokollet beskriver hur målvolymen ska utlinjeras.

Vi har gjort två studier där vi studerat hur målvolymen utlinjeras. I den första studien (beskriven i studie II) undersöktes fyra fall. I den andra (beskriven i studie III) undersöktes två fall. Deltagarna fick alla samma underlag – dosplanerings-CT, andra diagnostiska undersökningar, patientjournal innehållande all information om patienten och hans sjukdom samt studie/behandlingsprotokoll i de fall det var aktuellt. All patientdata var anonym. Deltagarna utlinjerade målvolymen, ordinerade stråldos och skapade dosplaner.

Data analyserades och jämfördes. Vid jämförelsen av målvolymerna beräknas dels volymerna, dels ett index för de inbördes skillnaderna. För jämförelse av dosfördelningen studerades olika dos-volym-variabler.

Stora skillnader sågs mellan de olika målvolymerna för varje fall i studie II. Alla dosfördelningarna visar god täckning av det enskilda centrets målvolym. Målvolymernas olika storlek och till viss del olika lokalisering påverkade doserna till riskorganen, som även de varierade. I studie III sågs också en viss variation mellan utlinjeringarna. Dosfördelningarna visar även i denna studie god täckning av den egna målvolymen. I studie III skapades en matematiskt beräknad expertutlinjering (konsensus) av målvolymen. Den matematiska algoritmen utgår från de redan utlinjerade målvolymerna. Den användes för att grafiskt visa skillnaderna mellan de olika målvolymerna. Varje enskild dosfördelning applicerades på både den ”egna” målvolymen och konsensusvolymen. I ett dosvolym-histogram (DVH) får man då en uppfattning om hur väl dosfördelningen täcker både den ”egna” målvolymen och konsensusvolymen. Det grafiska DVHt blir ett bra komplement till de gängse index som används som mått på överensstämmelse.

Fotoner jämfört med protoner

Protoner har fysikaliska fördelar som gör att det kan vara mer attraktivt att behandla barn/ungdomar med protoner än med fotoner. Man kan i större grad undvika bestrålning av normalvävnad med protoner. I studie IV utgick vi från de barn/ungdomar som fått strålbehandling under ett år (totalt 93 fall). Av dem omplanerades 45 fall. De planerades om med den moderna teknik som idag finns för protonplanering och behandling. Resultatet av denna studie visar att majoriteten

av denna grupp gagnas av protonbehandling. Protonernas fysikaliska egenskaper kan dock ibland också bli till en nackdel, t.ex. i fall av yttre eller inre rörelser inom strålområdet. Om det finns en vinst, liksom hur stor denna vinst är, avgörs till stor del av tumörens läge och storlek. Att jämföra dosplaner med fotoner och protoner är därför också viktigt för valet av slutlig strålbehandlingsmodalitet.

Biverkningar

Det finns en ökad risk för långtidsöverlevare att få någon form av behandlingsrelaterad biverkan senare i livet. De är inte enbart relaterade till strålbehandlingen utan även till kirurgin och cellgiftsbehandlingen.

I Sverige följs alla barnen efter sin behandling. Den givna strålbehandlingen registreras i ett gemensamt register (Radtox), därefter följs patienterna med jämna mellanrum och deras ev. biverkningar registreras. Ett flertal grupper arbetar med att följa, stödja och undersöka långtidsöverlevarna. Dels i syfte att ge dem ett gott liv efter sjukdomen, dels för att vi ska lära oss hur vi sammantaget kan minska på de bekymmer som kan uppstå framgent.

Slutsatser

Målet för all cancerbehandling är att bota med så få biverkningar som möjligt.

Samarbete kan leda till att vi ”gör mer lika”. Videokonferenser har förbättrat barnradioterapi i landet genom att experterna ser fler barn, kan diskutera sina erfarenheter och ta råd av varandra. Det har gått från att vara ett forskningsprojekt till att vara en del av den kliniska vardagen.

Dummy-runs är användbara för att skapa enighet – tolkning av behandlingsprotokoll blir mer lika, vilket kan leda till bättre studieresultat. Fler dummy-runs är önskvärt liksom ”workshops” för att gemensamt utlinjera både målvolym och riskorgan samt diskutera resultatet.

Protoner kommer att användas i allt större utsträckning för barn/ungdomar i Sverige. Jämförande planer är ett viktigt verktyg för att individanpassa vård och behandling.

Acknowledgments

Who would have thought....?

This has certainly been a work to which many has contributed in different ways. For all discussions, all good humour and support – thank you! It has been, and certainly still is, great to work with SvBRG – thank you all! There are so many more that deserves my sincere gratitude;

- my main supervisor, Per Nilsson, without him, his scientific skills and his believe in me this wouldn't have happened.
- my scientific supervisor, Tommy Knöös, who actually got me started “once upon a time”, comparing treatment planning systems, from there on to indices and dosimetry.
- my scientific supervisor, Kristina Nilsson, who with her deep knowledge in both paediatric radiotherapy and proton therapy so willingly have shared her knowledge and friendship.
- my early tutor Crister Ceberg who supervised my “C-uppsats” so many years ago, thereby introducing me to a new world.
- Karin Belfrage for her knowledge, friendship and support at all times.
- Elinore Wieslander for her knowledge, friendship and for always being there!
- Lee Ambolt for making sure my writing is in understandable English.
- Mikael Karlsson and Jack Lindh in Umeå, for giving me the chance to set up our national videoconferences for paediatric radiotherapy and for their believe in my abilities for further work.
- all my friends and colleagues, current and former, in Radiation Physics, Lund as well as friends and colleagues in the radiotherapy community in Umeå, Uppsala, Stockholm, Linköping, Göteborg, Örebro and Skandionkliniken. Always there with a cheer, encouraging words and/or a beer ☺
- my very best friends outside my work, none mentioned by name, but all remembered – always there, just being very good friends in any situation!
- my friends, all ages, at Torns scoutkår –for the joy of scouting.
- last but not least – my extended family, for being there, supporting but never pushing! And Bent, my husband and our wonderful sons for outstanding love and encouragement.

References

1. Childhood cancer incidence and survival in Sweden, 1984-2010. Report 2013 <http://www.cceg.ki.se>, Accessed Mar 14, 2017
2. Howlader N, Noone AM, Krapcho M, Miller D, Bishop K, *et al.* SEER Cancer Statistics Review, 1975-2013, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2013/, based on November 2015 SEER data submission, posted to the SEER web site, April 2016. Accessed Nov 28 2016
3. Leech M, Coffey M, Mast M, Moura F, Osztavics A, *et al.* ESTRO ACROP guidelines for positioning, immobilisation and position verification of head and neck patients for radiation therapists. *Technical Innov Pat Support Radiother Oncol* 2016, available at <http://dx.doi.org/10.1016/j.tipsro.2016.12.001>
4. Jonsson J, Karlsson MG, Karlsson M, Nyholm T. Treatment planning using MRI data: an analysis of the dose calculation accuracy for different treatment regions. *Radiation Oncology* 2010;5:62
5. Jeanneret-Sozzi W, Moeckli R, Valley J-F, Zouhair A, Ozsahin E M, *et al.* The reasons for discrepancies in target volume delineation. A SASRO study on head and neck and prostate cancers. *Strahlenther Oncol* 2006; 182:450-457
6. Prescribing, recording and reporting photon beam therapy, ICRU Report 50. Bethesda, USA. ICRU; 1993
7. Thariat J, Hannoun-Levi J-M, Sun Myint A, Vount T, Gérard J-P. Past, present, and future of radiotherapy for the benefits of patients. *Nature Reviews Clinical Oncology* 2013;10: 52-60
8. Bathia S, Sklar C. Second cancers in survivors of childhood cancer. *Nature reviews cancer* 2002;2:124-132
9. Newhauser WD, Durante M. Assessing the risk of second malignancies after modern radiotherapy. *Nature Reviews Cancer* 2011;11:438-448
10. Montelius A, Blomquist E, Naeser P, Brahme A, Carlsson J, *et al.* The narrow proton beam therapy unit at the The Svedberg laboratory in Uppsala. *Acta Oncol* 1991;30:739-745
11. Tilly N, Johansson J, Isacson U, Medin J, Blomquist E, *et al.* The influence of RBE variations in a clinical proton treatment plan for hypopharynx cancer. *Phys.Med.Biol.* 2005;50:2765-2777
12. Schneider U, Agosteo S, Pedroni E, Besserer J. Secondary neutron dose during proton therapy using spot scanning. *Int J Radiation Oncology Biol Phys* 2002;53:244-251
13. Paganetti H, van Luijk P. Biological considerations when comparing proton therapy with photon therapy. *Semin Radiat Oncol* 2013;23:77-87

14. Roine R, Ohinmaa A, Hailey D. Assessing telemedicine: a systematic review of the literature. *CMAJ* 2001;165:765-771
15. Norum J, Bruland ØS, Spanne O, Bergmo T, Green T, *et al.* Telemedicine in radiotherapy: A study exploring remote treatment planning, supervision and economics. *J Telemed Telecare* 2005;11:245-50
16. Olsen DR, Bruland ØS, Davis BJ. Telemedicine in radiotherapy treatment planning: requirements and applications. *Radiother Oncol* 2000;54:255-259
17. Björelund A, Blomquist M, Säterberg A, Bergström P, Karlsson M, *et al.* Joint Center - samarbetsprojekt för optimal strålbehandling i närmiljö. *Läkartidningen* 2004;101:472-475. (In Swedish)
18. Gomez A, Fernandez Sanchez C, Mouriño Gallego JC, González Castaño FJ, Rodríguez-Silva D, *et al.* Remote radiotherapy planning: The eIMRT project. *Stud Health Technol Inform* 2006;120:330-335.
19. Eich HT, Müller RP, Schneeweiss A, Hansemann K, Semrau R, *et al.* Initiation of a teleradiotherapeutic network for patients in German lymphoma studies. *Int J Radiat Oncol Biol Phys* 2004;58:805-808.
20. Huh SJ, Shirato H, Hashimoto S, Shimizu S, Kim DY, *et al.* An integrated service digital network (ISDN)-based international telecommunication between Samsung Medical Center and Hokkaido University using telecommunication helped radiotherapy planning and information system (THERAPIS). *Radiother Oncol* 2000;56:121-123.
21. Datta NR, Rajasekar D. Improvement of radiotherapy facilities in developing countries: A three-tier system with a teleradiotherapy network. *Lancet Oncol* 2004;5:695-698.
22. McAleer JJ, O'Loan D, Hollywood DP. Broadcast quality teleconferencing for oncology. *The Oncologist* 2001;6:459-462
23. Watanbe S, Fairchild A, Pituskin E, Borgersen P, Hanson J, *et al.* Improving access to specialist multidisciplinary palliative care consultation for rural cancer patients by videoconferencing: report of a pilot project. *Support Care Cancer* 2013;21:1201-1207
24. Belard A, Dolney D, Zelig T, McDonough J, O'Connell J. Improving proton therapy accessibility through seamless electronic integration of remote treatment planning sites. *Telemedicine and e-health* 2011;17:370-375
25. Agrawal S, Kumar Maurya A, Shrivastava K, Kumar S, Pant MC, *et al.* Training the trainees in radiation oncology with telemedicine as a tool in a developing country: a two-year audit. *Int J Telemed Appl* 2011, available at <http://dx.doi.org/10.1155/2011/230670>
26. Fotina I, Lütgendorf-Caucig C, Stock M, Pötter R, Georg D. Critical discussion of evaluation parameters for inter-observer variability in target definition for radiation therapy. *Strahlenther Onkol* 2012;188:160-167.
27. Dice LR. Measures of the amount of ecologic association between species. *Ecology* 1945;26:297-302.
28. Jaccard P. Distribution florale dans une portion des Alpes et du Jura. *Bull Soc Vaud Sc Nat.* 1901;142:547-579

29. Kouwenhoven E, Giezen M, Struikmans H. Measuring the similarity of target delineations independent of the number of observers. *Phys Med Biol* 2009;54:2863–2873
30. Lütgendorf-Causig C, Fotina I, Stock M, Pötter R, Goldner G, *et al.* Feasibility of CBCT-based target and normal structure delineation in prostate cancer radiotherapy: Multi-observer and image multi-modality study. *Radiother Oncol* 2011;98:154-161
31. Prescribing, recording, and reporting proton-beam therapy ICRU Report 78. Bethesda, USA. ICRU; 2007
32. Prescribing, Recording, and Reporting Photon-Beam Intensity-Modulated Radiation Therapy (IMRT), ICRU Report 83, Bethesda, USA. 2010
33. Warfield SK, Zou KH, Wells M, Simultaneous Truth and Performance Level Estimation (STAPLE), an algorithm for the validation of image segmentation. *IEEE Trans Med Imaging* 2004;23:903-21
34. Landis JR, Koch GG, The measurement of observer agreement for categorical data. *Biometrics* 1977;33:159-74
35. Reith A, Olsen DR, Teleradiology with satellite units – six years experience at the Norwegian Radium Hospital. *Stud Health Technol Inform.* 2008;134:209-16.
36. Karlsson M, Björk-Eriksson T, Mattson O, Mattson S, Montelius A, *et al.* “‘Distributed proton radiation therapy’” - A new concept for advanced competence support. *Acta Oncol* 2006;45:1094-1101
37. Datta N, Heuser M, Samiei M, Shah R, Lutters G. *et al.* Applications and feasibility for providing cost-effective comprehensive radiotherapy care in low- and middle-income group countries for cancer patients. *Telemedicine and e-health.* 2015;21:523-532
38. Quality guidelines for volume delineation in radiation oncology. The Royal Australian and New Zealand college of radiologists. <http://www.ranzcr.edu.au/resources/professional-documents/guidelines>. Accessed Mar 09, 2017
39. Lütgendorf-Causig C, Fotina I, Gallop-Evans E, Claude L, Lindh J. *et al.* Multicenter evaluation of different target volume delineation concepts in pediatric Hodgkin’s lymphoma. *Strahlenther Onkol.* 2012;188:1025–1030
40. Pasquier D, Boutard de la Combe-Chossiere L, Carlier D, Darloy F, Degrendel-Courtchuisse A C, *et al.* Harmonization of the volume of interest delineation among all eleven radiotherapy centres in the north of France. *PLoS ONE* 11(3): e0150917. doi:10.1371/journal.pone.0150917
41. Vinod S, Jameson MG, Min M, Holloway LC. Uncertainties in volume delineation in radiation oncology. A systematic review and recommendations for future studies. *Radiother Oncol* 2016;121:169-179
42. Fairchild A, Bar-Deroma R, Colette L, Haustermans K, Hurkmans C, *et al.* Development of clinical trial protocols involving advanced radiation therapy techniques: The European Organisation for Research and Treatment of Cancer Radiation Oncology Group approach. *Eur J Cancer* 2012;48:1048-1054
43. Report from SSM’s scientific council on ionizing radiation within oncology, 2011, Swedish Radiation Safety Authority 2012:20. Available from: <http://www.stralsakerhetsmyndigheten.se>, Accessed Dec 2, 2016

44. Report from SSM's scientific council on ionizing radiation within oncology, 2011, Swedish Radiation Safety Authority 2014:03.
Available from: <http://www.stralsakerhetsmyndigheten.se>, Accessed Dec 2, 2016
45. Lee CT, Bilton SD, Famiglietti RM, Riley BA, Mahajan A. *et al.* Treatment planning with protons for pediatric retinoblastoma, medulloblastoma, and pelvic sarcoma: How do protons compare with other conformal techniques? *Int J Radiat Oncol Biol Phys* 2005;63:362-372
46. St.Clair WH, Adams JA, Bues M, Fullerton BC, La Shell S. *et al.* Advantage of protons compared to conventional X-ray or IMRT in the treatment of a pediatric patient with medulloblastoma. *Int J Radiat Oncol Biol Phys* 2004;58:727-734
47. MacDonald SM, Safai S, Trofimov A, Wolfgang J, Fullerton B, *et al.* Proton radiotherapy for childhood ependymoma: initial clinical outcomes and dose comparisons. *Int J Radiat Oncol Biol Phys* 2008;71:979-986
48. Beltran C, Roca M, Merchant TE. On the benefits and risks of proton therapy in pediatric craniopharyngioma. *Int J Radiat Oncol Biol Phys* 2012;82:e271-e287
49. Indelicato DJ, Merchant T, Laperriere N, Lassen Y, Vennarini S, *et al.* Consensus report from the Stockholm Pediatric Proton Therapy Conference. *Int J Radiat Oncol Biol Phys* 2016;96:387-392
50. Oeffinger KC, Mertens AC, Sklar CA, Kawashima T, Hudson MM, *et al.* Chronic health conditions in adult survivors after childhood cancer. *N Engl J Med* 2006;355:1572-1582
51. Bölling T, Schuck A, Pape H, Rübe C, Meyer F-M, *et al.* German register for detection of late sequelae after radiotherapy for children and adolescents (RiSK): Present status and first results. *Strahlenther Onkol* 2007;183:7-8
52. Pixberg C, Koch R, Eich H-T, Martinsson U, Kristensen I, *et al.* Acute toxicity grade 3 and 4 after irradiation in children and adolescents: results from the IPPARCA collaboration. *Int J of Particle Ther* 2016;94:792-799
53. <http://www.pentecradiation.org/>. Accessed Mar 09, 2017
54. Robison LL, Armstrong GT, Boice JD, Chow EJ, Davies SM, *et al.* The Childhood Cancer Survivor Study: A national cancer institute-supported resource for outcome and intervention. *J Clin Oncol* 2009;27:2308-2318
55. Hawkins MM, Lancashire ER, Winter DL, Frobisher C, Reulen RC, *et al.* The British Childhood Cancer Survivor Study: Objectives, methods, population, structure, response rate and initial descriptive information. *Pediatr Blood Cancer* 2008;50:1018-1025
56. <http://www.pancare.eu/en/>. Accessed Mar 09, 2017
57. Hjorth L, Haupt R, Skinner R, Grabow D, Byrne J, *et al.* Survivorship after childhood cancer: PanCare: A European Network to promote optimal long-term care. *EJC* 2015;51:1203-1211
58. <http://www.blf.net/onko/page6/index.html> and <http://www.cancercentrum.se/samverkan/cancerdiagnoser/barn/vardprogram/>. Accessed Mar 09, 2017