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Background and purpose: The variability in target delineation for similar cases between centres treating paediatric and adolescent patients, and the apparent differences in interpretation of radiotherapy guidelines in the treatment protocols encouraged us to perform a dummy-run study as a part of our quality assurance work. Therefore we performed a dummy-run study as part of our quality assurance work. The aim was to identify and quantify differences in the segmentation of target volumes and organs at risk (OARs) and to analyse the treatment plans and dose distributions.

Materials and methods: Four patient cases were selected: Wilm's tumour, Hodgkin's disease, rhabdomyosarcoma of the prostate and chordoma of the skull base. The five participating centres received the same patient related material. They introduced the cases in their treatment planning system, delineated target volumes and organs at risk and created treatment plans. Dose volume histograms were retrieved for relevant structures and volumes and dose metrics were derived and compared, e.g. target volumes and their concordance, dose homogeneity index (HI), treated and irradiated volumes, remaining volume at risk and relevant V_x and D_x values.

Results: We found significant differences in target segmentation in the majority of the cases. The planning target volumes (PTVs) varied two- to four-fold and conformity indices were in the range of 0.3-0.6. This resulted in large variations in dose distributions to OARs as well as in treated and irradiated volumes even though the treatment plans showed good conformity to the PTVs. Potential reasons for the differences in target delineation were analysed.

Conclusion: Considerations of the growing child and difficulties in interpretation of the radiotherapy information in the treatment protocols were identified as reasons for the variation. As a result, clarified translated detailed radiotherapy guidelines for paediatric/adolescent patients have been recognized as a way to reduce this variation.

Introduction

Target delineation is a crucial and complex task in the radiotherapy process. It requires skill and experience to translate surgical notes, information from diagnostic imaging and pathology reports into a 3D volume in the treatment-planning CT data set. Many studies on inter-physician variability in target delineation for conformal radiotherapy have been presented for adults (1-6). They all show that there is a significant variation between individuals delineating target volumes for various tumour sites. However, paediatric/adolescent diagnoses have been sparsely discussed. Coles et al (7) introduced a new study protocol for medulloblastoma to a group of paediatric radiation oncologists at an educational meeting including a practical target outlining session. This exercise discovered ambiguities in the protocol and highlighted inter-clinician variation in target segmentation. Padovani et al (8) also studied inter-clinician variability in target delineation and its effect on the dose distribution to organs at risk (OARs).

For most paediatric/adolescent tumour sites, treatment study protocols are available. However, they can be difficult to read and interpret correctly because they can be very comprehensive. The chemotherapy part of the protocol is often very detailed while the radiotherapy is often described in more general terms. Other complicating issues may be interference with local practice or sometimes the intention with the treatment (curative or palliative).

Approximately 100 paediatric/adolescent patients receive radiation therapy yearly in Sweden. They are mainly treated according to international treatment protocols. Radiotherapy of paediatric and adolescent patients in Sweden is centralised to six university hospitals (Göteborg, Linköping, Lund, Stockholm, Umeå and Uppsala).

As part of the quality assurance work within the "Swedish Workgroup for Paediatric Radiotherapy" (SWPR), and as a base for future improvements on this matter, the group decided to perform a "dummy-run" on structure segmentation and treatment planning. Four cases with different diagnoses were selected among recently treated patients. The dummy run results were subsequently openly discussed within the group during a two-day workshop.

The primary aim of the present investigation was to identify and quantify the differences between the participating centres in the segmentation of target volumes, and secondarily, to evaluate the resulting differences in the dose distributions to target volumes and OARs. Thirdly, we aimed to identify reasons for any differences found.

Material and Methods

Five of the six centres participated in this study. The cases investigated were: Wilms' tumour, Hodgkin's disease, rhabdomyosarcoma of the prostate, and chordoma of the skull base. The centres who contributed to selection of these cases were instructed to export the necessary data in Dicom-RT format (CT-images, structures, plan and dose) from their treatment planning system and send it together with any relevant diagnostic information (MR- and CT-studies) and medical records including histopathology reports, to the study coordinator (IK). Relevant anonymised medical data and planning CT data sets were then made available to the centres on an FTP server were the cases were organised and stored for easy access.

The centres were instructed to introduce the cases in their treatment planning system (TPS), to consider them as "their own" patients and to delineate target volumes based on the data provided and valid study protocols. They were not specifically instructed to delineate GTV (gross target volume), CTV (clinical target volume) or PTV (planning target volume) (9), however, all centres delineated CTV and PTV. They were also asked to delineate OARs and to create treatment plans as they normally would, according to the protocols and their local policies. The treatment planning system Varian Eclipse, versions 8.0 and 8.6, (Varian Medical Systems, Inc. 3100 Hansen Way, Palo Alto, CA, USA) were used at two sites and Nucletron Oncentra MasterPlan, version 3.1 (Nucletron, Waardgelder 13905TH, PO BOX 3900 AX, Veenendaal, The Netherlands) at three sites. Dose calculations were made with pencil beam-based algorithms in both systems.

Patient cases

Case 1 – Wilms' tumour – A 15 year old girl diagnosed with Wilms' tumour in the right kidney, no metastases present at diagnosis. She was treated according to the SIOP 2001 Nephroblastoma protocol preoperatively with chemotherapy. Surgery was considered radical, however, there was a retroperitoneal tumour rupture, but no intra-abdominal macroscopic dissemination and no spread to lymph nodes (no clips marked the resection area). She was assessed as stage III, intermediate risk. For RT planning the pre-operative tumour extent should be localised according to the pre-operative contrast-enhanced CT scan.

According to the protocol the CTV should encompass the extent of post-chemotherapy and pre-operative macroscopic tumour and the kidney according to the surgical and histopathological reports and according to the extent on CT-scan/ ultrasonography with a margin of 1 cm.

Case 2 – Hodgkin's disease – A 15 year old girl with a growing mass in the left supraclavicular lymphatic region. Further examinations revealed a Hodgkin's lymphoma of morphological type nodular sclerosis with involvement of the left supraclavicular fossa, mediastinum, spleen and para-aortic lymph nodes, corresponding to stage IIIA. She was treated with two chemotherapy cycles of OEPA and two COPP according to the GPOH-HD 2002 interim protocol and had a negative PET examination after 2 cycles, after which the protocol indicated radiotherapy to primarily disease-involved sites to 20 Gy. The protocol study centre suggested the treatment to include bilateral supraclavicular fossae, the mediastinum, the spleen and para-aortic lymph nodes extending caudally to the level of L2. This information was included in the patient chart.

Case 3 – Rhabdomyosarcoma – A 17 year old boy, diagnosed with embryonal rhabdomyosarcoma in the prostate 2.5 years earlier. At the time, he had no confirmed dissemination of the disease except for an unspecified solitary lung nodule of 4 mm. Primary treatment was chemotherapy according to CWS 2002p high-risk protocol. After the completion of chemotherapy, there was complete response (biopsy verified). The patient did not receive any radiotherapy or surgery. Local relapse in the prostate with extended growth into the bladder was discovered after 1.5 years and chemotherapy was started according to the CWS 2002p relapse protocol. Pre-operative radiotherapy was planned according to the protocol. According to the patient chart 44.8 Gy twice daily with 1.6 Gy fractions should be given.

Case 4 – Chordoma – A 17 year old boy with a history of cervical pain, stiffness of the neck and increasing neurological deficits including slight, spastic tetraparesis and dysphagia for six years. MR of the brain and cervical spine revealed a large tumour mass with destruction of the skull base including the clivus and C1, and compression of the brainstem, cervical spinal cord, carotid arteries and jugular veins. Primarily, extensive debulking surgery was performed, and biopsy confirmed the chordoma diagnosis. The patient suffered postoperative complications of complete right-sided paralysis, vocal cord paresis and augmentation of his dysphasia. Based on the patient's age, improved neurological condition and the macroscopically evident tumour remaining after surgery, he was offered postoperative radiotherapy. Due to the rarity of the disease and hence, lack of standard treatment protocols for children, no prior recommendation for dose prescription or radiotherapy treatment planning were available.

Protocol excerpts from the protocols SIOP 2001 Nephroblastoma, GPOH-HD 2002 interim and CWS 2002p relapse are given in appendix 1 which can be found online at http://informahealthcare.com.

Data analysis

To facilitate the comparison of data from the different TPSs, treatment plans were analysed with the CERR software package (10). From CERR, data for all volumes, targets as well as OARs, could be retrieved and compared. Dose-volume histograms (DVH) were also extracted.

To quantify the variability in target delineation for the five different centres we used the generalized conformity index, CI_{gen}, as derived by Kouwenhoven et al (11) for volume overlap (observers' agreement). This index is useful for simultaneous comparison of any number of delineations and is defined as:

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

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. $CI_{gen} = 1$ indicates a total overlap, while $CI_{gen} = 0$ indicates totally separated volumes.

Target and OAR volumes

At each centre, participating radiation oncologists defined target volumes and OARs according to the available diagnostic images and reports, treatment protocols and their own experience and practice. Thus, five sets of target volumes and OARs were prepared for each case. All target volumes were mutually compared, *i.e.* no "golden standard volume" was set.

Dose distributions

We analysed and compared prescribed doses, $V_{95\%}$, $D_{98\%}$ (near-minimum dose), $D_{50\%}$ (median dose) and $D_{2\%}$ (near-maximum dose) (11) 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 (12) was also calculated.

Results

Prescribed doses

Prescribed doses complied with the existing protocols for cases 1 and 2. Small variations were found for case 3, while major differences were found for case 4 (chordoma) for which no treatment protocol was available. All centres prescribed 14.4 Gy for case 1 as the protocol states. For case 2 the prescription was 19.8/20, also in accordance with the protocol. For case 3 the prescription varied, one centre prescribed 44.8 (1.6 Gy/fraction), three prescribed 45.0 Gy (1.8 Gy/fraction) and finally, one centre prescribed 50.4 Gy (1.8 Gy/fraction). The largest variation in prescribed dose was found for case 4 where the centres prescribed 46.8 Gy, 50.4 Gy, 54 Gy (two centres) or 70.2 Gy, all in 1.8 Gy/fraction.

Delineated volumes

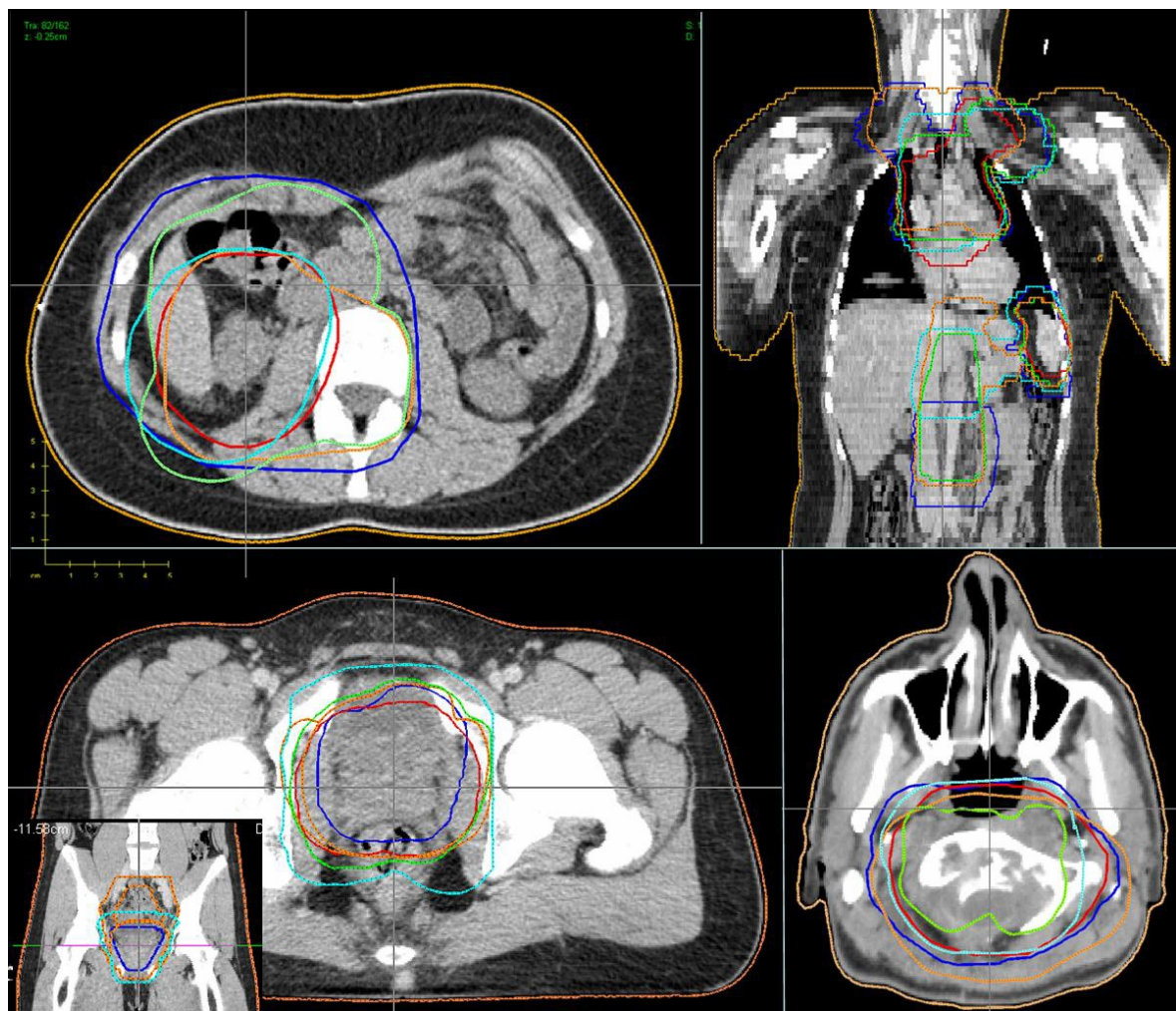A large variation in target segmentation was found for the majority of the cases (Figure 1).

Figure 1. Representative CT images with PTV delineation for the four patient cases and the five centres. Upper left: case 1 - Wilms' tumour. Upper right: case 2 - Hodgkin's disease. Lower left: case 3 – rhabdomyosarcoma. Lower right: case 4 - chordoma.

Case 1 – Wilm's tumour. The major PTV differences were dependent on whether or not the whole width of vertebral bodies and/or retroperitoneal space were included in the PTV.

Case 2 – Hodgkin's disease. The prescribed treatment region from the protocol study centre included the supraclavicular fossae and the mediastinum as well as an abdominal target. The largest variation was observed in the width of the delineated supraclavicular fossae and in the cranio-caudal extensions of the mediastinal targets. The largest variation in the abdominal target volumes was in their cranio-caudal extensions.

Case 3 – Rhabdomyosarcoma. For three of the centres the target segmentation was rather similar while one centre included the iliacal lymph nodes and one centre delineated a significantly larger PTV than the others.

Case 4 – Chordoma. This case showed the best PTV concordance, despite the lack of a study protocol.

Altogether, a substantial variation in PTV volumes was found for all cases (Figure 2).
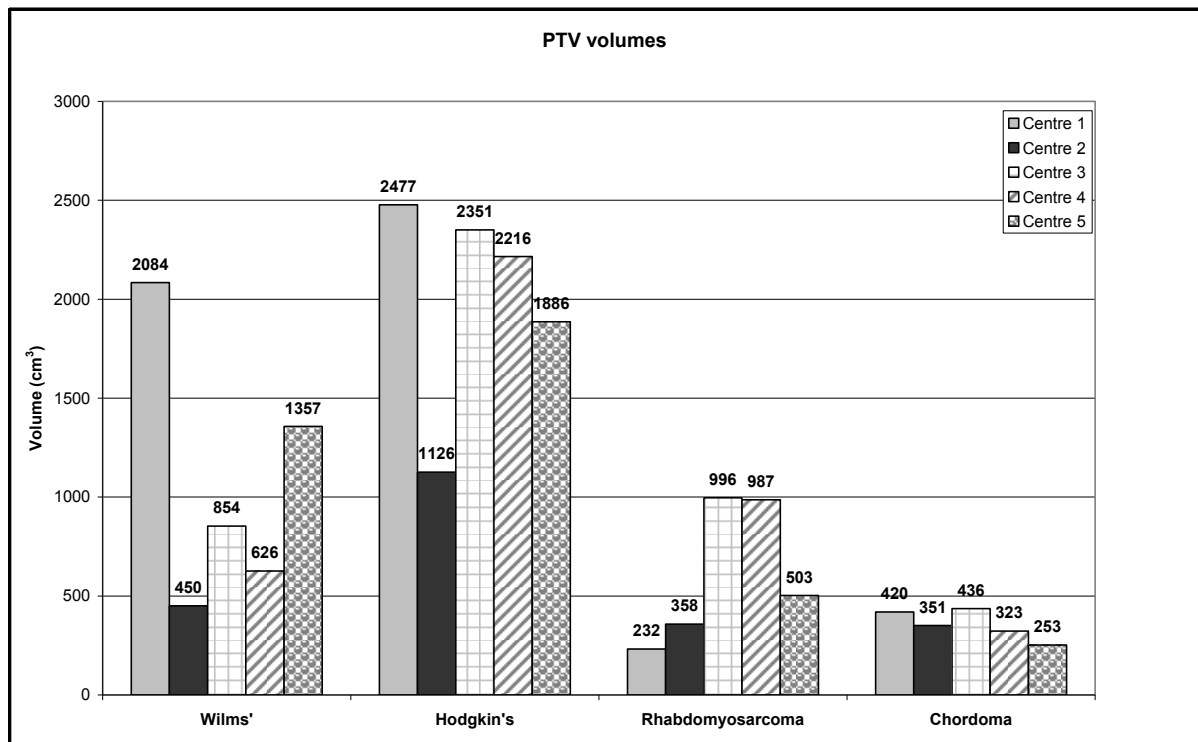

Figure 2. PTV volumes for the four cases studied.

The quotients of the largest to the smallest PTV volumes were 4.6, 2.1, 4.3 and 1.7 for cases 1, 2, 3 and 4, respectively. The calculated conformity indices (CI_{gen}) are shown in Table 1 for CTV and PTV.

Table 1. Target conformity indices, CI$_{gen}$.

Patients	CI$_{gen}$ CTV	CI$_{gen}$ PTV
Case 1	0.32	0.40
Case 2 - mediastinum	0.43	0.59
Case 2 - abdomen	--	0.50
Case 3	0.42	0.46
Case 4	0.47	0.61

Treatment planning and dose distributions

The majority of the cases where planned with 3D-CRT technique. IMRT was only used by one centre for case 4. Variations in target coverage were mainly due to variation in target volumes. However, the variation in target volume considerably affected the doses to the OARs, especially those close to the tumour volumes. PTV dose-volume data are given in Table 2 for all cases.

Table 2. Dose-volume data (average values, range within parentheses) for the PTV. The numbers (except for HI) are in % of the prescribed dose for each individual case.

Centre	Case 1 Wilms'	Case 2 Hodgkin's mediastinum	Case 2 Hodgkin's abdomen	Case 3 Rhabdomyo-sarcoma	Case 4 Chordoma
$V_{95\%}$	95% (86-100)	95% (93-98)	97% (94-99)	98% (96-100)	87% (65-100)
$D_{98\%}$	94% (91-97)	95% (94-96)	95% (94-96)	95% (94-97)	77% (29-98)
$D_{50\%}$	100% (99-101)	101% (99-105)	104% (103-105)	101% (100-102)	99% (65-103)
$D_{2\%}$	103% (103-104)	107% (105-108)	106% (105-107)	102% (101-105)	104% (69-107)
HI	0.09 (0.07-0.12)	0.11 (0.10-0.13)	0.10 (0.08-0.13)	0.07 (0.06-0.07)	0.28 (0.06-0.64)

Dose distributions in OARs were analysed, and the results for the most relevant OARs, treated volumes and irradiated volumes are shown in Table 3.

In general the extension, shape and position of the PTV are the main contributors to the variation of dose distributions in the OARs. The inclusion of vertebrae in the volume to treat also affected the dose distributions in the OARs. Vertebrae inclusion had a large impact on the size of the treated and irradiated volumes (see Table 3). The SIOP 2001 protocol and the GPOH-HD 2002 interim protocol include information on allowed doses to critical organs (included in Table 3).

Table 3. Mean doses (range) for all organs at risk except for spinal cord and brainstem where maximum absorbed doses are given (italics in the table). Dose constraints relate to the information given in protocols SIOP 2001 (case 1) and GPOH-HD 2002 interim (case 2). Treated and irradiated volumes (mean vales and range) are also presented.

		Dose (Gy)	Dose constraints* (protocol)	Treated volume $V_{95\%}$ (litres)	Irradiated volume $V_{50\%}$ (litres)

	Organ	Value	Constraint		
Case 1	*Liver*	**5.8 (2.3-9.7)**	**<20 Gy**		
	Left kidney	**1.4 (0.1-3.8)**	**<12 Gy**		
	Spinal cord	**11.9 (2.2-15.1)**			
	Body			**1.76 (1.11-2.88)**	**3.22 (1.78-4.51)**
Case 2	*Right lung*	**6.5 (5-7.6)**	**-**		
	Left lung	**12.4 (9.5-14.2)**	**-**		
	Heart	**8.4 (5.4-10.6)**	**<35 Gy**		
	Right kidney	**2.5 (0.1-4.6)**	**<12 Gy**		
	Left kidney	**7.0 (1.8-9.2)**	**<12 Gy**		
	Body			**4.41 (3.22-5.01)**	**7.94 (4.92-9.63)**
Case 3	*Bladder*	**43.6 (37.2-51.7)**	**-**		
	Rectum	**33.2 (24.6-48.2)**	**-**		
	Body			**0.48 (0.20-1.11)**	**3.20 (1.43-5.96)**
Case 4	*Right parotid gland*	**30.6 (19.5 - 41.8)**	**-**		
	Left parotid gland	**33 (30 - 46.8)**	**-**		
	Brainstem	**53.2 (47.7 - 57.9)**	**-**		
	Spinal cord	**34.7 (23.6 - 38.2)**			
	Body			**0.34 (0.23-0.50)**	**1.04 (0.89-1.17)**

*It's not stated in the study protocols which dose concepts (D_{mean}, D_{max}, etc.) are referred to.

Dose volume histograms for the "remaining volume at risk" (RVR) are shown in Figure 3. The variations were mainly due to the size of the PTV volume.
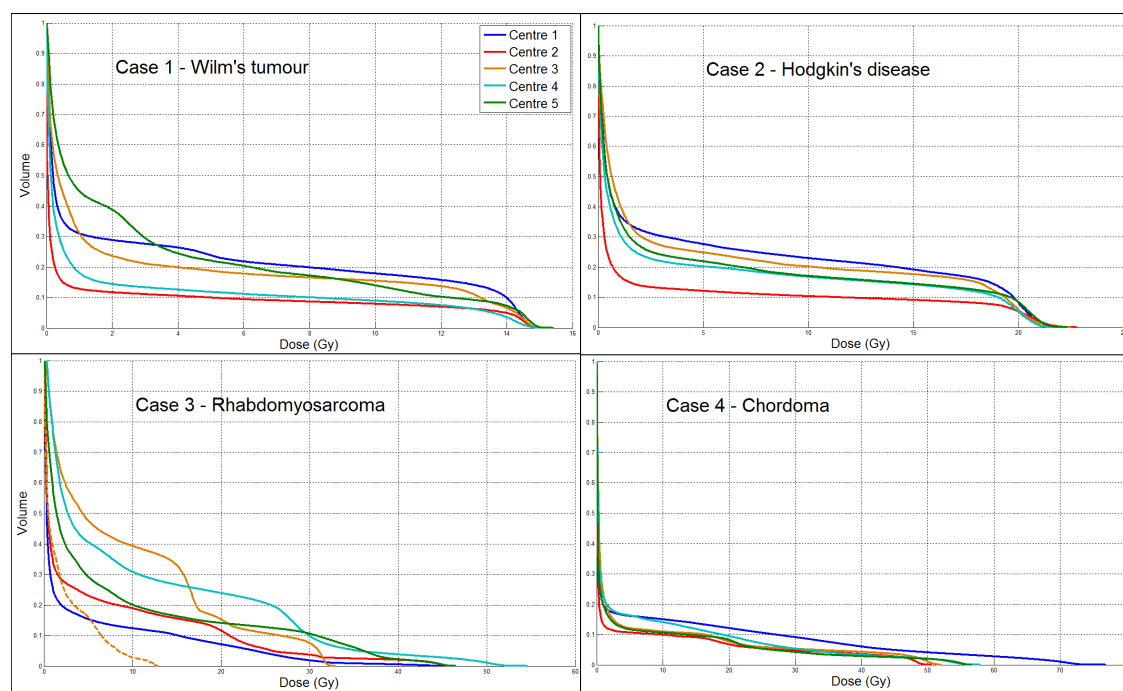

Figure 3. DVHs for the "remaining volume at risk". The dashed line for Case 3 (Rhabdomyosarcoma) represents the boost volume from Centre 3.

Discussion

We analysed the inter-physician variability in CTV/PTV delineation and found large variation in segmented volumes and in their concordance. We chose the CI_{gen} to compare the conformity between target volumes. This parameter has been shown by Kuwenhoven et al (11), and confirmed by Fotina et al (14), to be easily derived and is directly applicable to comparisons of any number of pair-wise delineations, contrary to the commonly used Dice index (15).

It was unfortunately not possible to study the variability in GTV delineation since these structures were not segmented by all centres. One reason for this might be that the ICRU volume concepts are not specified in the study protocols with the exception of SIOP 2002. Neither the GPOH-HD 2002 nor the CWS protocols use these volume concepts.

PTV dose coverage was adequate for all cases with only small differences between the centres. Therefore, the variation in HI was small for all cases except for case 4. The IMRT plan for this case was optimized to keep the dose to the brainstem and spinal cord at their tolerance levels at the expense of delivering a lower dose to the adjacent target volume while keeping a higher dose to other parts of the PTV.

The inter-clinician variability in target volume delineation affected doses to the nearby OARs and normal tissues to a large extent as previously shown by Padovani et al (8). In addition, it had a large effect on the treated volume, the irradiated volume, and the remaining volume at risk. The latter volume is applicable for estimating and comparing risk of late effects, such as carcinogenesis (13).

Dose constraints to OARs are only given to some extent in two of the protocols, i.e. SIOP 2002 and GPOH-HD 2002. However, the constraints are often only stated as a single upper dose value not to be exceeded but without any specification of which dose concept is intended (e.g. D_{mean}, D_{max}, etc.). Constraints/objectives for OARs in terms of composite dose-volume quantities (D_V and V_D), as recommended by ICRU (13) and as required for optimization of treatment plans when using 3D-CRT/IMRT, are totally lacking in the study protocols. Therefore there is a need to update them with this information in order to further harmonize the radiotherapy for children/adolescents. A recent summary of organ-specific dose-volume objectives for different endpoints in children can be found in Brodin et al. (16).

During the two-day workshop a number of case-specific questions were raised which affect the inter-clinician target variability to a large extent. For case 1 the discussion within the

group was whether to include the whole vertebrae in the volume to be treated to a therapeutic dose level or not. Some centres argued that the patient was 15 years old at the time of treatment and almost fully grown. Therefore it would be more beneficial for her to minimize the irradiated volume. There is no age-related information on bone irradiation stated in the protocol. An additional discrepancy for this case was the inclusion of the retroperitoneal space. Since there was a rupture of the tumour it should be included in the target volume. The surgeon should (according to protocol) have placed markers to aid the target delineation which was not done. For case 2 the pictogram from the study centre was not included in the material sent out to the participants. However, this information was in the patient notes that were distributed and might explain part of the target variability in this case. For case 3 one centre chose to include the nodes along the pelvic wall which the others did not. This is probably due to different interpretation of the protocol, which is difficult in this case due to recurrent disease. The large variation in prescribed doses for case 4 was due to different opinions regarding the intent (palliative or curative) with the treatment. Moreover, there was a variation between the centres in dose constraints to the brainstem (54-60 Gy) and spinal cord (46-48Gy), which further added to the variation.

Other general reasons for the variability in target segmentation could have been varying experience of physicians as described by Jeanneret-Sozzi et al. (17). Although the participating physicians in this group have had a long experience of radiotherapy for adults, adolescents and children, the small number of paediatric/adolescent cases that are presented annually at each centre might actually be one of the limiting factors for gaining broader experience in the field. Moreover, variations in standard procedures established locally, might influence the process of radiotherapy for each individual patient.

Establishing detailed radiotherapy protocols, guidelines and templates for target delineation and treatment planning is of great value (18, 19). Accordingly, it is important that the radiotherapy guidelines in parallel to the medical treatment recommendations of the established protocols, especially in paediatric oncology, are of such quality that they are interpreted unequivocally even though individual tailoring of the treatments might become necessary. Consequently, it is necessary for the radiotherapy guidelines of the protocols to be as explicit as possible concerning the delineations of the target volumes (GTV, CTV and PTV) and OARs. In addition, guidelines should include up-to-date dose-volume constraints/objectives for OARs, preferably including a priority list. Uniform interpretation of the protocols may influence the probability of cure and reduce long-term side effects of the

treatment in children. In a recent publication by Fairchild et al (20), recommendations are given for the writing of a clinical trial protocol, including radiotherapy. In Sweden, the Scientific Council of the Swedish Radiation Safety Authority has pointed out the need for guidelines for the radiotherapy-specific part of a study protocol (21).

Moreover, performing dummy runs when introducing new study protocols is an important part of treatment development. This may facilitate identification of subsequent differences in interpretation of treatment guidelines and the clinical and practical impacts of possible and unwanted radiotherapy treatment variations for individual cases before the patients are actually treated. Since the outset of the work presented here was a workshop for the specialists, the results indicate that radiotherapy guidelines can be interpreted differently.

Future work within the group will be to follow-up this study and to see whether more frequent target discussions within the group have had any influence on standardisation of the target delineation.

In conclusion, interactive collaboration between radiotherapy centres is an important step to establish new or revised radiotherapy treatment protocols in children and adolescents and to provide continuous peer-based support in day-to-day practice. For our group this "dummy-run" has resulted in several changes. The most common study protocols or guidelines have been translated into Swedish. More effort is put into discussing the extension of the target volumes and doses to OARs during our regular telemedicine meetings (22). These meetings may be a quick method for quality control (QC) of the treatment or may be a step towards a more advanced QC system as suggested by Carrie et al (23). Hopefully this will lead to an improved clinical quality for paediatric and adolescents patients on a multi-institutional level, and it can be a way for future harmonization of the process for children undergoing radiotherapy.

Conflict of interest statement

The authors of this manuscript have no actual or potential conflicts of interest to disclose.

Acknowledgements

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Appendix

The appendix consists of except from the three protocols, according to which the children were treated.

Case 1 –SIOP 2001 Nephroblastoma

"The boundaries of the tumour and kidney during surgery must be marked with clips and in the case of areas suspicious of incompletely resected disease these should be marked with clips (material which does not interfere with CT or MR imaging) as well. A margin of one cm should be taken superior, lateral and inferior of these clips. The medial border always encompasses the full width of the vertebral bodies. In the case of pre-operative or intra-operative rupture the anatomic location and the intra-abdominal space (intra/retro-peritoneal) should be clearly indicated in the surgical note and drawing. Infiltration into the peri-renal fat, involved lymph nodes, macroscopic incomplete resection, microscopic or macroscopic ruptures have to be stated clearly.

Flank RT

*CTV: This encompasses the extent of post-chemotherapy and pre-operative macroscopic tumour and the kidney according to the surgical and histopathological reports and according to the extent on CT-scan/ ultrasonography. The margin for CTV is 1 cm. If there is no pre-operative CT-scan CTV is delineated by clips at the boundaries of the tumour and kidney placed by the surgeon during surgery. The margin for CTV is 1 cm beyond the clips. The **treated volume** should extend across the midline to achieve homogeneous irradiation of the full width of the vertebral bodies."*

Case 2 – GPOH-HD 2002 interim protocol

"Radiation therapy to all primary infected lymphatic regions for all patients of therapy group 2 + 3 and for therapy group1 patients who are not in complete remission after chemotherapy. The standard dose is 20 Gy."

Case 3 – CWS 2002p high-risk protocol

"Patients with favourable histology (RME [N0&N1]) with a measurable response of <2/3 >1/3 tumour volume reduction (poor responders) as well as patients with unfavourable histology and a response of >2/3 tumour volume reduction (good/complete responders) at week 9 at which time the conditions for a successful second-look-surgery by a pre-operative irradiation could be improved (for example by volume reduction of residual tumour), will be irradiated pre-operatively with 44.8 Gy. For patients with unfavourable histology and tumour response of <2/3 >1/3 the order of local secondary measures must be decided on an individual basis. The total dose will be administered through accelerated hyperfractionation using two treatment sessions per day five days per week. The fraction dose is 1.6 Gy, the daily dose is .,2 Gy, the weekly dose is 16 Gy. The time between the two daily fractions must be at least 6 hours. The standard target includes the documented or presumed primary tumour region with a margin of at least 2 cm. It is of particular importance, when irradiating soft tissue sarcoma in the pelvic region, that the growth zones in the pelvic bones and/or hips is spared to avoid growth impairment by keeping the dose to these areas as low as possible. This may, however, not lead to an insufficient margin (2cm) to the tumour."[4]

Case 4 –no standard treatment protocol was available