

Inter-observer variation in target delineation and dose trade-off for radiotherapy of paediatric ependymoma

Laura Toussaint^a, Petter Brandal^{b,c}, Anna Embring^d, Jacob Engellau^e, Morten Egeberg Evensen^b, Romualdas Griskevicius^f, Jolanta Hansen^g, Henna Hietala^h, Gun Wickart Johansson^d, Morten Jørgensenⁱ, Paul-Heinz Kramer^j, Ingrid Kristensen^e , Kaisa Lehtio^h, Henriette Magelssen^b, Maja Vestmø Maraldoⁱ, Kirsten Marienhagen^k, Ulla Martinsson^l, Kristina Nilsson^m, Sarah Petersⁿ, Sandija Plaude^j, Klaus Seiersen^a, Daiva Sendiulienė^o, Bob Smulders^{a,i}, Tone Edvardsen^k, Johan Martin Søbstad^k, Zarah Taheri^l, Leila Vaalavirta^p, Anne Vestergaard^a, Beate Timmermann^{j,n,q*} and Yasmin Lassen-Ramshad^{a*}; for the NOPHO Radiotherapy Working Group

^aDanish Centre for Particle Therapy, Aarhus University Hospital, Aarhus, Denmark; ^bDepartment of Oncology, Oslo University Hospital, Oslo, Norway; ^cInstitute for Cancer Genetics and Informatics, Oslo University Hospital, Oslo, Norway; ^dDepartment of Oncology, Karolinska University Hospital, Stockholm, Sweden; ^eDepartment of Hematology, Oncology and Radiation Physics, Skane University Hospital, Lund, Sweden; ^fDepartment of Medical Physics, National Cancer Institute, Vilnius, Lithuania; ^gDepartment of Oncology, Aarhus University Hospital, Aarhus, Denmark; ^hDepartment of Oncology and Radiotherapy, Oulu University Hospital, Oulu, Finland; ⁱDepartment of Oncology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark; ^jWest German Proton Therapy Centre Essen, Essen University Hospital, Essen, Germany; ^kDepartment of Oncology, University Hospital of North Norway, Tromsø, Norway; ^lDepartment of Oncology, Uppsala University Hospital, Uppsala, Sweden; ^mDepartment of Immunology, Genetics and Pathology, Experimental and Clinical Oncology, Uppsala University Hospital, Uppsala, Sweden; ⁿDepartment of Particle Therapy, University Hospital Essen, Essen, Germany; ^oDepartment of External Beam Radiotherapy, National Cancer Institute, Vilnius, Lithuania; ^pDepartment of Oncology, Helsinki University Hospital, Helsinki, Finland; ^qWest German Cancer Center (WTZ), German Cancer Consortium (DKTK), Essen, Germany

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Introduction

Postoperative radiotherapy for intracranial paediatric ependymoma is challenging both for target definition and treatment planning [1]. Delineation of the tumour bed is difficult, as structures in prior contact with the tumour will shift back into their original positions after surgery. In infratentorial cases, the target is adjacent to the brainstem and upper spinal cord, therefore the relatively high prescription dose and sparing of surrounding organs at risk (OARs) need to be balanced. Through the radiotherapy working-group of the Nordic Organization of Pediatric Hematology and Oncology (NOPHO) and in collaboration with the Westdeutsches Protonentherapiezentrum Essen (WPE), a study was performed to quantify inter-centre variations in target delineation and treatment plans for these tumours.

Material and methods

After institutional approval, three anonymized cases of previously treated paediatric non-disseminated anaplastic ependymoma were selected. For all cases, planning CT, pre- and post-operative MRIs as well as the medical history, histology and surgery reports were distributed to the participating centres. Case 1 presented as a completely resected frontal tumour. Case 2 was an infratentorial radically resected

tumour. Case 3 presented with a residual tumour anterior to the brainstem, despite second look surgery.

For delineation and treatment planning, guidelines of the European SIOPE Ependymoma II study (NCT02265770) were used. The gross tumour volume (GTV) consisted of the postoperative tumour bed and all measurable pathological tissues after surgery. For the clinical target volume (CTV), a 5-mm margin was added to the GTV, except into the brainstem where a 3-mm margin was used when there was no suspicion of infiltration.

Four paediatric radiation oncologists from different centres independently delineated the CTVs (dCTVs) for the three cases. Their delineations (dCTVs) were afterwards discussed in a video-conference (six participants, including three that had independently delineated) as a basis for defining consensus CTVs (cCTVs), further considered as ground truth.

The cCTVs volumes were compared to the median (range) volume dCTVs, and the inclusion of cCTV in dCTV was assessed. For the infratentorial cases, the overlap between brainstem and CTVs was calculated. DICE coefficients were calculated relative to the cCTV [2].

Eight centres participated in the treatment planning part of this study. Four proton and four photon plans were generated for all three cases using cCTVs. To assess inter-centre variations in the treatment planning process, no common set of objectives/optimization criteria were shared across centres.

CONTACT Laura Toussaint  laura.toussaint@clin.au.dk  Danish Centre for Particle Therapy, Aarhus University Hospital, Aarhus, Denmark

*Shared last authorship.

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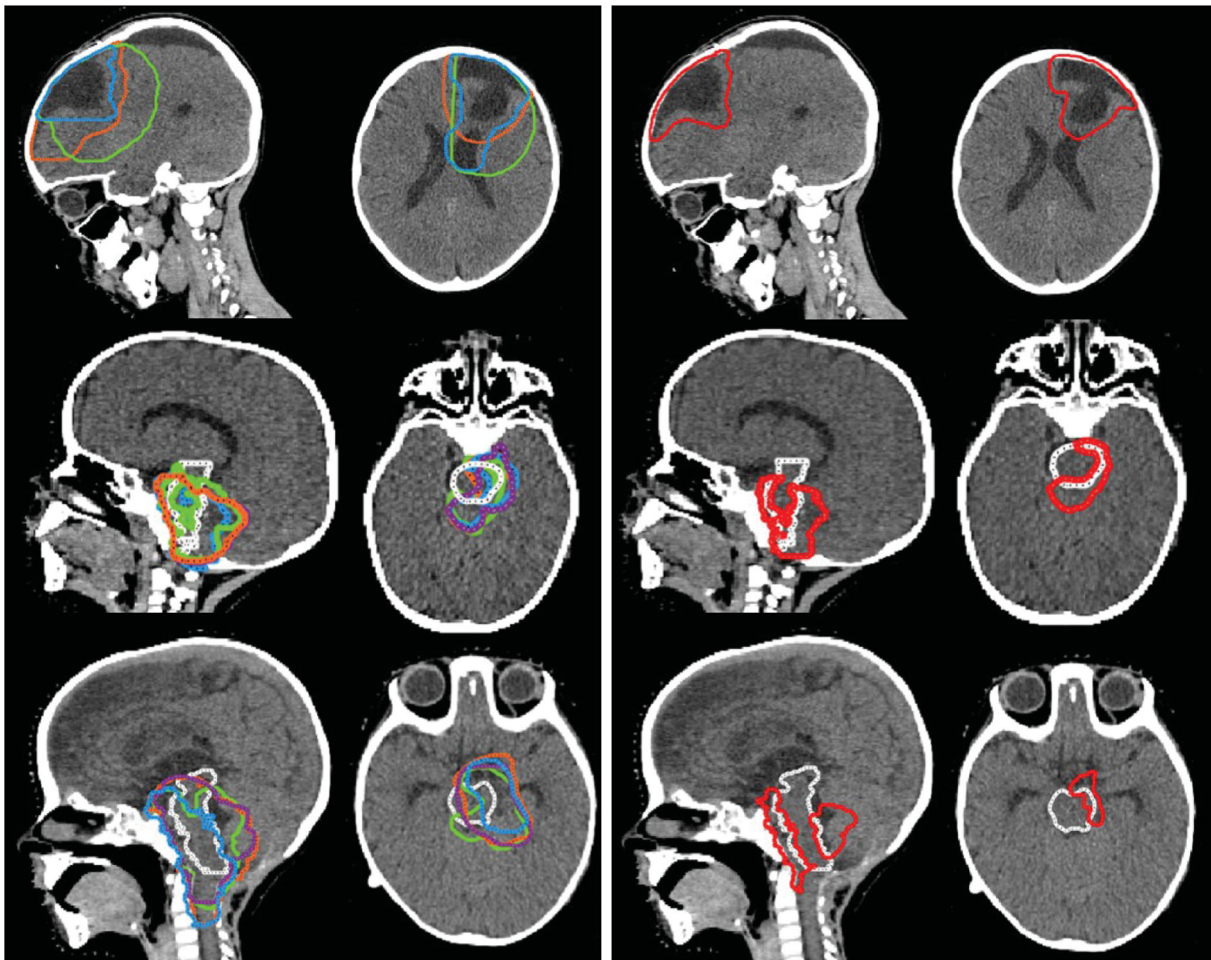


Figure 1. Illustration of the differences in CTV delineations (transversal/sagittal views) for the three cases (Case 1 upper row, Case 2 middle row, Case 3 lower row). The box to the left presents the independent delineations (Center C1 blue, Center C2 green, Center C3 orange, Center C4 purple) while the consensus CTV is presented in red in the box to the right. The brainstem is delineated in white. Note that for Case 1, only three paediatric radiation oncologists delineated the CTV.

Cases 1 and 2 had a prescription dose of 59.4Gy, while case 3 was planned to three different dose levels – 54Gy to cCTV1, 5.4Gy to cCTV2 (cCTV1 minus spinal cord) and a stereotactic boost of 8Gy/2 fractions to the tumour residue (cCTVboost) [3]. For plan summation, the hypofractionated boost was recalculated to EQD_{1.8Gy} dose ($\alpha/\beta=3$ Gy) [4]. Treatment technique and dose/volume metrics for targets and OARs were compared across the eight centres. Proton doses are reported for a relative biological effectiveness (RBE) of 1.1.

Results

Inter-observer variations in target delineation

In case 1, cCTV was 79cm³ vs. 131cm³ for median dCTVs. In case 2, cCTV was 19.2cm³ vs. 28.4cm³ for median dCTVs and the overlap between brainstem and CTV was reduced from 3.5cm³ for median dCTVs to 1.8cm³ in cCTV. In case 3, cCTV1 was 31.5cm³ vs. 62.2cm³ for median dCTVs, and the overlap between the brainstem and CTV1 was reduced from 10.9cm³ in median dCTV1s to 2.5cm³ for cCTV1. For case 1, a median of 13.2cm³ of cCTV was not included in the individual dCTV delineations, 0.6cm³ for case 2 and 3.7cm³ for case 3 (CTV1). Median CTV DICE coefficient was 0.69 for case 1, 0.77 for case 2 and 0.57 for CTV1 in case 3 (Figure 1, Supplementary Table 1).

Treatment technique

Coplanar volumetric modulated arc therapy (VMAT) was in most cases used for photon plans, while for proton plans a non-coplanar pencil beam scanning (PBS) technique was used (Supplementary Table 2). In case 3, one of the proton plans was a hybrid plan, consisting of PBS plans for cCTV1/cCTV2 and a VMAT plan for cCTVboost.

Comparison of dose/volume metrics

Target coverage V95% > 98% was achieved for all treatment plans for cases 1 and 2. In case 3, target coverage was compromised for most individual plans, then restored in the composite plans for all photon plans, but not all proton plans: median V95% of 95.1% (88.6%–100%) (protons) vs. 100% (100%–100%) (photons) (Figure 2, Supplementary Table 3).

For case 1, protons reduced the irradiated whole brain volume, with a median brain Dmean of 8.9Gy vs. 16.8Gy for photons. This was less pronounced in the infratentorial cases, with a median brain Dmean of 8.7Gy with protons vs. 10.7Gy for photons (case 2)/10.5Gy vs. 12.5Gy (case 3) (Figure 2, Supplementary Table 3).

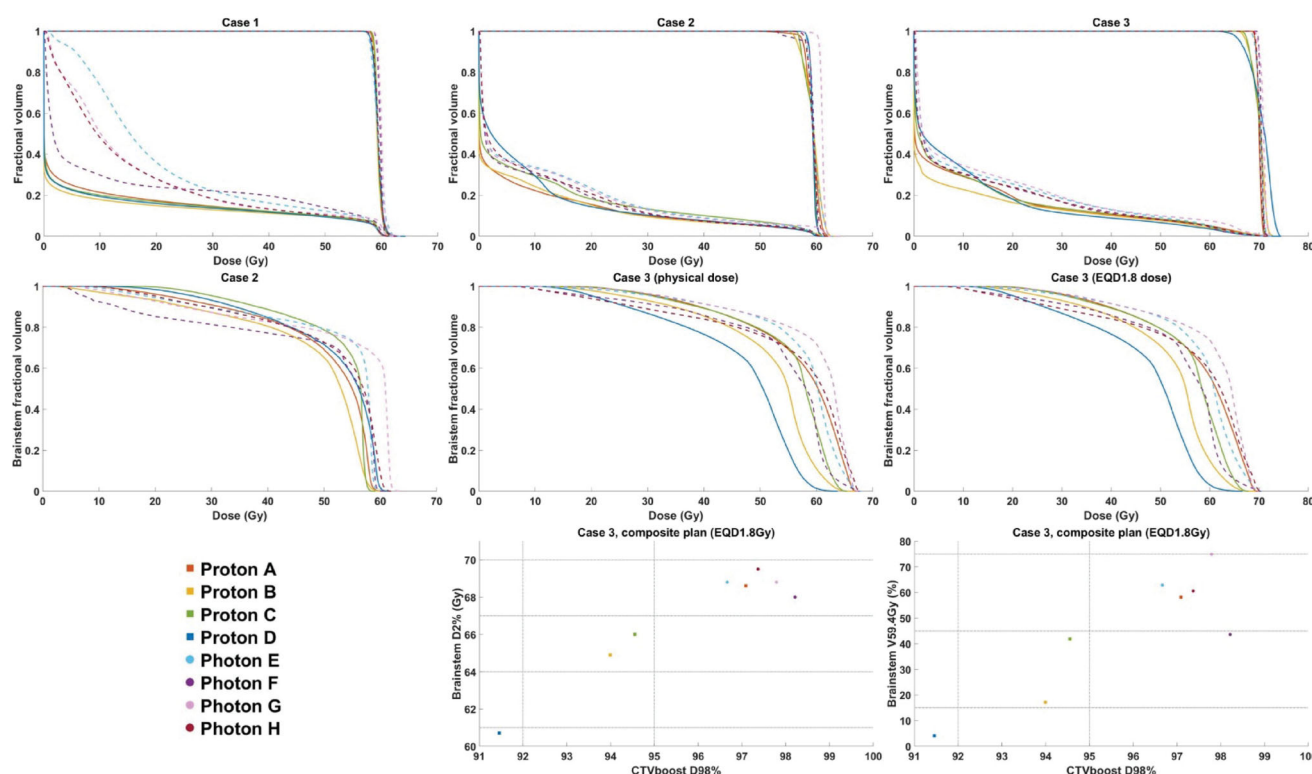


Figure 2. Upper row – dose-volume histograms (DVHs) for the CTV and whole brain for the three cases. Middle row – brainstem’s dose-volume histograms for the two infratentorial cases. The composite plans for Case 3 were calculated for both the physical dose (middle panel) and the EQD_{1.8Gy} dose (right panel). Lower row – Scatter-plot of brainstem dose metrics (left: D2%, right: V59.4Gy) as a function of CTVboost coverage for the composite plan, for Case 3 (EQD_{1.8Gy}). Square markers represent proton centres, while circles represent photon centres. Note: Each centre is associated with a specific colour and for the DVHs, full lines represent proton plans, and dotted lines photon plans. For Case 3, Proton D is the hybrid plan.

Brainstem metrics (V59.4Gy, D2%) for the infratentorial cases were in general lower in the proton plans, but with a large range for both modalities (Supplementary Table 3). Trade-offs between brainstem sparing and target coverage were separately examined for case 3: the plans could be separated in three groups independent of modality. Group 1 (three photon/one proton plan) had satisfactory target coverage (D98% > 95%) and high brainstem doses (V59.4Gy of 45–75%; D2% of 67–70 Gy). Group 2 (two proton plans) had lower target coverage (D98% of 92–95%) and lower brainstem doses (V59.4Gy of 15–45%; D2% of 64–67Gy). Group 3 (the hybrid plan) had the lowest target coverage (D98% < 92%) and brainstem doses (V59.4Gy < 5%; D2% < 61Gy). The fourth photon plan belonged to group 1 for target coverage and to group 1/2 for brainstem doses (Figure 2).

Discussion

In this study, we explored variations in CTV delineations of intracranial paediatric ependymoma cases and investigated the impact of performing peer-review on the resulting consensus CTV. Treatment plans were then compared in terms of target coverage and dose to OARs. We observed that peer-review consistently resulted in reduction of target volume size as well as overlap with surrounding OARs compared to individual delineations. For supratentorial ependymoma, protons demonstrated an obvious advantage for normal tissue sparing. This effect was less apparent for infratentorial cases, where

doses to OARs varied between centres independent of modality, but based on individual trade-off strategies.

For delineation of the post-surgical tumour bed, the biggest challenge was to identify brain tissue in contact with the tumour before structures shifted back to their original position following resection. In Case 1, variations were mainly seen in the superior/inferior extent of the target (ventricles and cerebral parenchyma inclusion), whereas variations in overlap with the brainstem and inclusion of cerebellar parenchyma were seen for the infratentorial cases. In all cases, the observed variations resulted in large volume differences. For case 1 in particular, parts of the cCTV (mostly adjacent to the skull) were not included in the individual dCTVs, which could be of concern regarding potential under-dosage of malignant cells in addition to over-dosage of normal tissues.

Similarly to our results, previously published studies of inter-observer variations for paediatric cases consistently reported a large range in the delineated target volume, for a variety of treatment sites [4–6]. Discussion of target delineations was shown to consistently reduce the target volume and the overlap with surrounding OARs. Therefore, a peer-review process could be advised for increased delineation quality in complex paediatric tumour cases, as also concluded elsewhere [6].

In terms of treatment technique for the photon plans, the field configuration in the infratentorial cases were similar with regards to selected modality (VMAT) and angles, mainly based on full arcs. For case 1, more custom choices were made in the rotation span, and one centre chose to use IMRT. Dose/volume metrics to the whole brain and OARs

were substantially different between the four centres, despite similar target coverage. For the proton plans, even though PBS was preferred by all centres, more variations were seen in the selection of gantry and couch angles, in particular for the infratentorial cases where this resulted in a large span of OAR and whole brain doses. This highlights the impact of the planning and optimization process, as well as the clinical trade-offs unique to each centre [4].

VMAT plans could in general spare OARs superior to the infratentorial targets (e.g., chiasm) better than proton plans, due to the choice of the beam arrangement in the proton plans. To limit the concerns of RBE [7], most of the proton centres were opting to minimize the use of beams stopping directly towards the brainstem [8] and therefore had to use more superior directions than what was done with VMAT. However, the fine-tuning of proton beam entry directions allowed better sparing of some of the bilateral structures such as the cochlea or hippocampi. When comparing both treatment modalities for the supratentorial case 1, the physical advantages of protons in terms of normal tissue dose sparing was clearly apparent.

Overall, case 3 (the plan with the highest prescription dose) necessitated the largest compromises between target coverage and brainstem sparing. As the aim of this study was to investigate inter-centre variations in the treatment planning process and clinical decisions, we did not share a common set of objectives/optimization criteria, nor did we suggest any clinical compromises for target coverage vs. brainstem sparing to the planners. In both infratentorial cases, and for Case 3 in particular, target coverage could only be achieved at the expense of delivering high doses to the brainstem and spinal cord. It appeared that proton planners were consistently more conservative toward brainstem preservation compared to photon planners, due to the previously mentioned concerns of increased RBE at the distal edge of the beam [7]. By having restrictions in the choice of beam directions and being cautious with the spot location in the brainstem to lessen RBE concerns, the advantages of protons might not be fully exploited in infratentorial ependymoma cases.

The evaluation of target coverage between photon and proton plans represented a weakness in this study. We assessed target coverage based on the CTV on nominal plans for both modalities, in order to compare the exact same volume. Indeed, proton plans were robustly optimized and evaluated with each individual centres' clinical parameters, and similarly, the PTV margins used for photon plans optimization were also centre specific. It therefore appeared that a comparison based on a common volume would offer a fairer assessment of coverage differences, and the robustness aspect of all plans was therefore neglected. For future studies, a more consistent approach for photon vs. proton target coverage should be explored [9].

Another point of discussion is the evaluation of dose metrics in case 3, where different fractionation schemes were used. CTV1 and CTV2 were treated at 1.8 Gy/fraction, whereas the boost was hypofractionated to 4 Gy/fraction. The composite plan was therefore calculated using the EQD_{1.8 Gy} dose, in order to have a radiobiologically more accurate

summation, but it is difficult to estimate how to best handle fractionation differences regarding dose constraints throughout the same radiation course. However, it appeared relevant to include the effect of increased fraction dose on the total plan despite the underlying uncertainties, in particular in the sensitive paediatric population and at such close vicinity to the brainstem and spinal cord. As the concern was mainly toward OARs, the EQD_{1.8 Gy} dose was calculated for a homogeneous $\alpha/\beta = 3$ Gy throughout the whole volume. A more complex scenario could be investigated, using a larger α/β (e.g., 10 Gy) for the tumour volume [10].

In summary, it is advised to perform peer-review for discussing target delineations in complex paediatric brain tumour cases, in order to ensure consistency and quality of target volumes, and to minimize overlap with surrounding OARs. For treatment planning, despite following some common guidelines, the clinical trade-offs necessary for target coverage vs. OARs sparing were dependent on individual centres more than the treatment modality used.

Disclosure statement

No potential conflict of interest was reported by the authors.

ORCID

Ingrid Kristensen  <http://orcid.org/0000-0002-2742-0887>

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