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Guidelines

Management of the vertebrae as an organ at risk in paediatric radiotherapy clinical trials: Initial QUARTET experience

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ABSTRACT

Irradiation of the vertebrae in prepubertal patients, if non-homogenous, can result in future growth deformities including kyphoscoliosis. Vertebral delineation and dosimetry were assessed for 101 paediatric cases reviewed within QUARTET-affiliated trials. Despite the availability of published consensus guidelines, a high variability in vertebral delineation was observed, with impact on dosimetry.

Irradiation of the vertebrae in prepubertal patients can result in growth defects and deformities, related to inhomogeneities in dose distribution[1–4]. In 2019 the SIOPE-ROWG (European Society for Paediatric Oncology- Radiation Oncology Working Group) published a consensus guideline [5] on vertebral delineation and constraints in an effort to standardise practice across Europe. QUARTET [6] (*Quality and Excellence in Radiotherapy and Imaging for Children and Adolescents with Cancer across Europe in Clinical Trials*), a SIOP Europe project for radiotherapy quality assurance (RTQA) in paediatric clinical trials, has developed specific guidelines for each trial, including recommendations on vertebral delineation and dosimetry based on the 2019 ROWG consensus[5].

QUARTET guidelines define VBs_Adj (adjacent vertebrae) as those vertebrae which are in the proximity of the target and cannot be spared, and recommend that these receive more uniform irradiation, to minimize the risk of growth deformities due to dose inhomogeneities and gradients. The VB_NAdj_S/I (non-adjacent superior and inferior vertebrae) are defined as one single vertebra above and below the adjacent ones, which are to be spared where possible. These are dosimetric definitions rather than geometric ones, as they are based on the feasibility to spare the structures. Vertebrae should be contoured using the bone window on the planning CT, including the vertebral body and the posterior (neural) arch, ideally excluding the spinal processes, spinal canal, and intervertebral disks (Fig. 1**A, B**; Supplementary material 1, 2). Slight variations exist in dose requirements for vertebrae across trials, given the different dose prescriptions and are described in Fig. 1 C. The aim of this report is to assess the main challenges in

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vertebral dose management for paediatric patients undergoing radiotherapy within current European clinical trial group studies.

Methods

All cases (152) submitted to QUARTET for review from EpSSG-FaR-RMS (EUDRACT 2018–000515–24), and SIOPEN HR-NBL2 (EUDRACT 2019–001068–31) trials between June 2020 and December 2022 were retrospectively reviewed to identify pre-pubertal patients with vertebrae within proximity of the target volume for inclusion. Initial review outcomes (Per Protocol/Acceptable Variation/ Justified Unacceptable Variation/ Unacceptable Variation requiring resubmission) and reviewers' comments were analysed. [7].

VBs_Adj and VB_NAdj_S/I were assessed for compliance compared to delineation and dosimetry guidelines by a second, independent reviewer, following an independent grading system detailed in Fig. 1**D**, adding additional details regarding the types of variations. Missing or non-compliant structures were manually[2] recontoured using Velocity™ software (Varian Medical Systems, Palo Alto, CA, USA). To determine the magnitude of variation in contouring against the guideline recommendations, the conformality (dice similarity coefficient, with an ideal value of 1) between each structure pair, was computed using the same software.

Dosimetric data was collected for each structure as follows: D2% and D98% for both adjacent and non-adjacent vertebrae; for VBs_Nadj_S/I, specific constraints (D5%/V10Gy and V15Gy) were also noted, and results were compared against the guideline requirements. Gradients were evaluated by calculating the difference between D2% and D98%, followed by a slice-by-slice visual assessment of isodose lines, recording the direction of the gradient (latero-lateral, antero-posterior, supero-inferior). All patients or their parents have given written informed consent for entry into the relevant clinical study including the prospective radiotherapy quality assurance and analysis.

Results

In total, 101 (71 neuroblastoma, 30 rhabdomyosarcoma) prepubertal children with vertebrae in the proximity of the target volume were included in the analysis. Two rhabdomyosarcoma cases had two separate targets proximal to the spine (one primary and one metastasis), and therefore were considered separately for the analysis, resulting in a final number of 103 target-associated vertebral structures. Four cases represent whole lung irradiations[3] and were only considered for delineation and gradient assessment.

From the 96[4] expert peer-reviewed cases, there was a 23% (n = 22) rejection rate due to unacceptable variations in vertebral delineation (6) or dosimetry (16). Eight cases were considered unacceptable for reasons unrelated to the vertebrae (i.e., target delineation), requiring a total of 30 resubmissions, 17 of which included changes in vertebral delineation or dosimetry; 15/17 (88%) showing improvement after considering reviewer's suggestions. In 59% (57/96) of reviews, at least one acceptable variation in vertebral contouring or dose was identified, 70% (67/96) included comments on the vertebrae, mostly regarding delineation.

The second, independent review of the initial submissions identified an overall guideline compliance in vertebral delineation of 10% for VBs_Adj and 9% for VBs_NAdj_S/I. Major variations such as missing structures (Fig. 1E), incorrect inclusion regarding the target (Fig. 1E) or having more than one single vertebra in the non-adjacent structures (Fig. 1F) were identified in 27% of the VBs_Adj and 56% of VBs_NAdj_S/I structures. For VBs_Adj, minor variations were more frequent, for example, inclusion of the spinal canal (66%) or inclusion of the spinal processes (62%) (Fig. 1H). VBs_Adj were not delineated in 4% of the cases and the volumes were not properly aligned with the PTV in 23% of the cases. Most common variation in VB_NAdj_S/I contours were incomplete structures or misalignment in relation to the body/neural arch (usually observed on sagittal views) (44%), inclusion of spinal canal and processes (42%, 34%), not respecting the space between the adjacent and non-adjacent structures (33%),or including more than one single vertebra in the VB_Nadj_S/I structure (20%) (Fig. 1I).

Average and median conformality between non-compliant and guideline-based, redelineated structures were 0.699/0.687 (SD = 0.124, range 0.363–0.966) for VBs_Adj, 0.702/0.735 (SD = 0.194, range 0.121–0.99) for VB_NAdj_S and 0.66/0.706 (SD = 0.204, range 0.134–0.970) for VB_Nadj_I. Average conformality for VBs_Adj was 0.66 in 2021 and increased to 0.72 in 2022. The lowest average conformality for VB_NAdj_S/I (0.18/0.37) was calculated for the second quartile of 2021, whereas the maximum was in the fourth quartile of 2022 (0.78/0.73).

The D98% constraint was met in 48% of the VBs_Adj structures; 47% of proton cases and 50% of photon cases. Overall, 53% of VB_NAdj_S and 41% of VB_NAdj_I structures were spared. VB_NAdj_S sparing was achieved in 48% of photon cases and 33% of proton cases, whereas VB_NAdj_I were spared in 37% of photon cases and 24% of proton cases. Seventy-six percent of the initially missing and re-delineated superior and inferior non-adjacent vertebrae did not meet the dosimetric requirements.

Dose homogeneity was within the limits in 40% of cases for VBs_Adj (Fig. 2A, C), with acceptable gradients in 50% of photon cases but only 15% of proton cases. Gradients above 5 Gy in patients older than 2 years and 3 Gy in younger patients, were found in 88% and 94% of the cases for VB_NAdj_S and VB_NAdj_I respectively. The visual assessment identified that for most adjacent vertebrae the gradients were in a lateral direction (57%), followed by supero-inferior (23%) and antero-posterior (20%). For non-adjacent vertebrae the gradients were mostly supero-inferior (61.0% VB_NAdj_S/ 57.0% VB_NAdj_I), followed by latero-lateral (28.5%/27.0%) (Fig. 2B, D) and antero-posterior (10.0%/17.4%).

Discussion

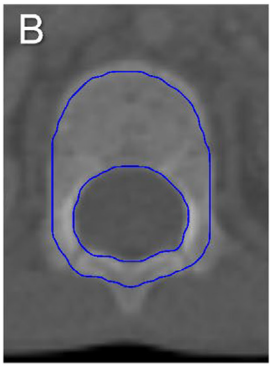
This report describes the patterns of vertebral delineation and dose management for pre-pubertal paediatric radiotherapy patients enrolled in clinical trials in centres across Europe, since the development of the SIOPE ROWG consensus guidelines [5] and the implementation of the QUARTET platform [6] for prospective radiotherapy quality assurance.

Our results show that there is still significant variability in how the vertebrae are managed, despite these consensus recommendations and trial specific RTQA guidelines. Both the expert peer review and our second, independent audit identified several major variations in vertebral delineation, which could have an impact on dosimetry and ultimately on long term outcome and toxicities. While the inclusion of spinal processes is common in some centres, this practice of homogenously covering the vertebrae including the lateral processes could result in the dose to the lungs or kidneys being unnecessarily increased. The inclusion of the posterior processes may be less likely to have detrimental effects but could result in more growth-related issues with paraspinal muscles also receiving a higher dose. In some cases, the exclusion of the spinal canal could help achieve more optimal dosimetry or sparing the

[2] Both the second independent review and the manual redelineation were performed by a radiation oncologist, research fellow, under the supervision of the RTQA manager and one of the reviewers/radiotherapy lead for one of the trials.

[3] Prescribed dose was 15Gy; homogenous coverage and gradient avoidance is recommended.

[4] 5 cases were not reviewed at the time of analysis.

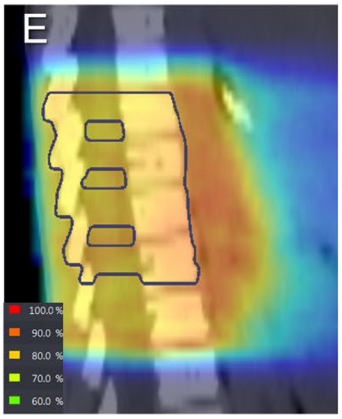


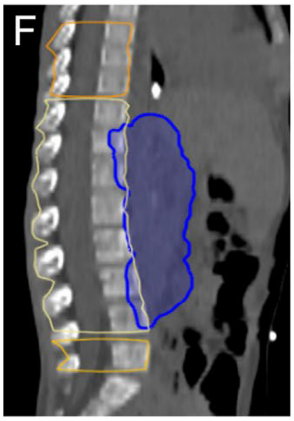
C

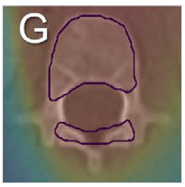
	VBs_Adj	VB_NAdj_S/I
FaR-RMS (prescribed doses 41.4-59.4Gy)	D98% ≥ 36Gy	V15Gy ≤ 2% V10Gy ≤ 10%
HRNBL2 (prescribed doses 21.6-36Gy)	*Gradient requirements*	D5% ≤ 15Gy children aged >2 years D5% ≤ 10Gy children aged <2 years
Gradient (FaR-RMS and HRNBL2)		< 5Gy- children aged >2 years < 3Gy- children aged <2 years

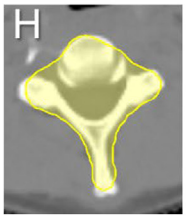
D

Major contouring variations	Minor contouring variations
Missing structures (not delineated) *(E)*	Spinal canal included *(H)*
Incorrect inclusion related to the target/prescription dose *(E)*	Spinal processes included *(H)*
Delineating more than 1 vertebra as VB_NAdj_S/I *(F)*	Neural arch and vertebral body misaligned (sagittal view) *(E,F,I)*
	Incomplete contour *(G)*
	No space left between VBs_Adj and VB_NAdj_S/I *(F,I)*









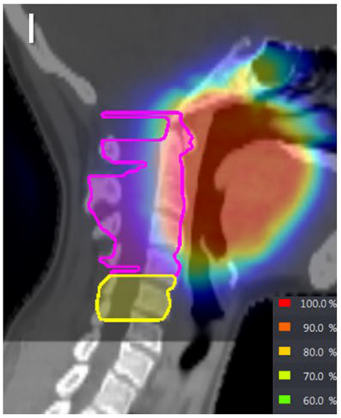


Fig. 1. A: Sagittal view of a planning CT in a neuroblastoma case with vertebrae delineated as per the RTQA guidelines (Purple- VB_NAdj_S, Blue- VBs_Adj, Pink- VB_NAdj_I, Red- PTV); B: Axial view of a single vertebrae delineated as per the RTQA guidelines- including the vertebral body, lateral pedicles and posterior arch (covering the location of the bone growth centres) and excluding the spinal canal, lateral and posterior processes. C. Table showing the different dosimetric requirements in the trial-specific RTQA guidelines; D. Independent grading system used for evaluating the delineation compliance; E,F- Two planning CT scans (sagittal views) of neuroblastoma cases showing major and minor delineation variations (E-dark blue- VBs_Adj; F- orange- VB_NAdj_S/I, blue- PTV); G,H- Axial images of a single vertebra, showing minor variations in delineation; I: Sagittal view of a H&N rhabdomyosarcoma patient with several minor vertebral delineation variations (pink- VBs_Adj, yellow- VB_NAdj_I); VBs_Adj- adjacent vertebrae, VB_NAdj_S/I- superior and inferior non-adjacent vertebrae; D98%= dose near-minimum, Gy = Gray;

spinal cord (Fig. 2C) and by leaving the intervertebral disc space between the adjacent and the non-adjacent structures can help achieve a steep dose-falloff and reduce the supero-inferior gradient within the non-adjacent vertebrae (Fig. 2 G,H). Failure to delineate the required vertebral structures, and so not including them in the optimisation process, will inevitably lead to unmet dosimetric constraints, as was highlighted in the data reported here.

These guidelines were developed acknowledging the limited scientific evidence, the literature being based on historic data[8–12], old radiotherapy techniques[13–15] or preclinical studies [16–19]. Therefore, it is essential that long-term follow-up of these patients includes clinical assessment of late effects, in order to clinically validate these recommendations and understand the impact radiotherapy dose delivered by highly conformal photon or proton techniques[20–23].

Our data highlights how vertebral sparing and homogeneity can be more challenging with protons, mainly due to the larger penumbra (Fig. 2F, H), with more significant gradients observed particularly within the non-adjacent vertebrae (Fig. 2D). These indicate the need to adapt the current recommendations, which are based on photon practice, and develop proton-specific approaches. Already we are seeing proton centres developing novel ways to mitigate these challenges, such as introducing an intermediate vertebral structure between VBs_Adj and VB_NAdj_S/I to produce a 2-step dose de-escalation or introducing an aperture while using pencil beam scanning, thus resulting in a sharper lateral dose fall-off[24]. We will look to evaluate and incorporate these approaches going forward.

Important aspects to consider include the time required to undertake vertebral contouring, likely a limiting factor for guidance adherence. The use of automatic delineation tools can also introduce errors when not closely monitored. Presently there is no robust and reproducible method for the assessment of intra-vertebral gradients, which means that interobserver variability can potentially be a factor. The challenge of guideline compliance is highlighted in the presented data but is shown to be slowly improving. Ongoing monitoring and audits such as this will remain an objective of QUARTET, to enable continual improvements in clarity and standardisation for normal tissue delineation guidelines and dose objectives. The QUARTET trial specific RTQA guidelines are dynamic, with adaptions aiming towards harmonization of paediatric radiotherapy practice across all trials. As a new initiative

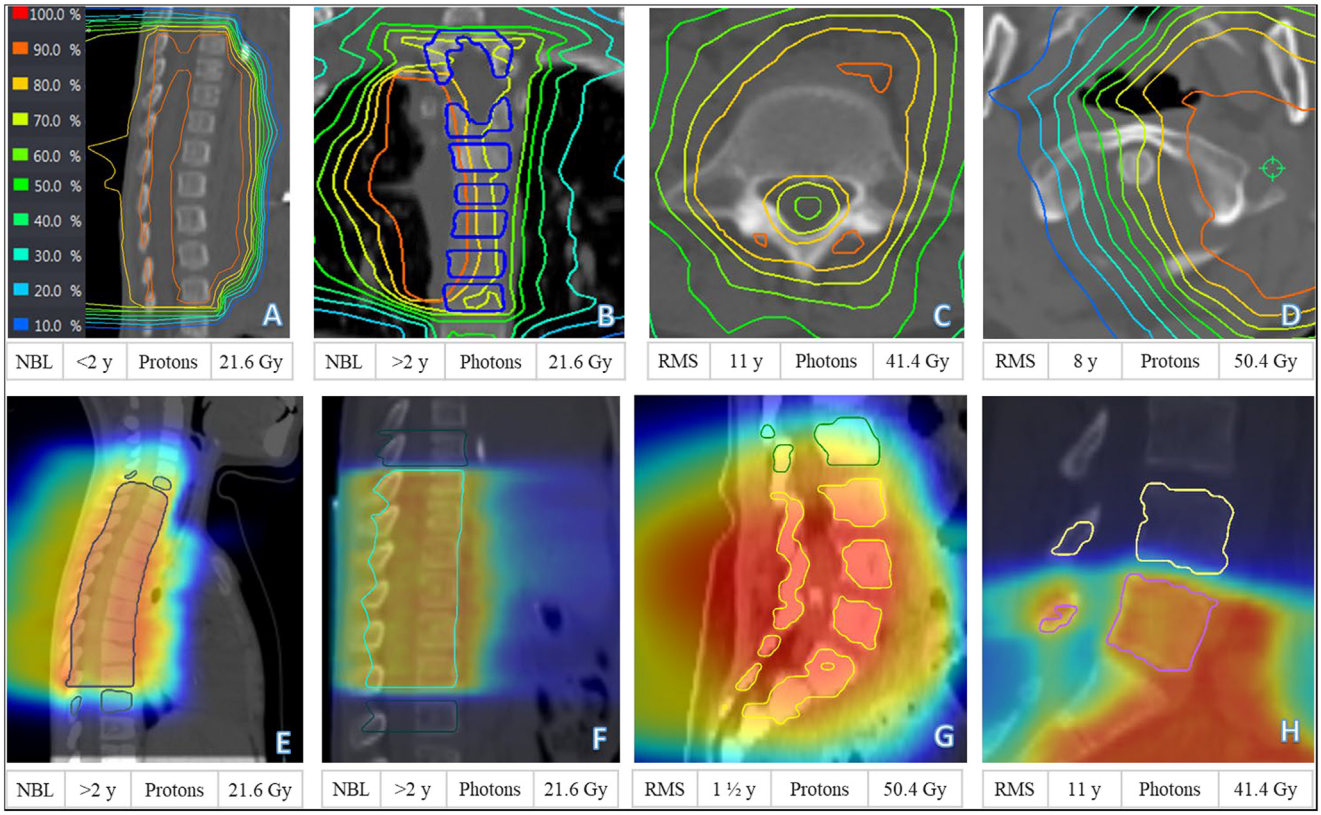


Fig. 2. Example images of vertebral dosimetry. A. Sagittal view of a neuroblastoma proton case with homogenous coverage of the adjacent vertebrae, with steep supero-inferior gradients in both superior and inferior non-adjacent vertebrae; B. Coronal view of a VMAT neuroblastoma case showing a left to right gradient within the adjacent vertebrae; C. Axial view of a homogenously covered vertebrae with additional sparing of the spinal cord; D. Axial view of a steep left to right gradient within a cervical vertebra (each line representing 5 Gy difference); E. Sagittal view of a neuroblastoma case planned with protons with effects on VBs_NAdj from large penumbra; F. Sagittal view of a neuroblastoma case planned with VMAT achieving sharper fall off of dose beyond VBs_Adj; G. Sagittal view of a pelvic rhabdomyosarcoma case planned with protons with effects on VB_NAdj_S from large penumbra; H. Sagittal view of a pelvic rhabdomyosarcoma case planned with VMAT achieving sharper fall off of dose beyond VBs_Adj. NBL- Neuroblastoma, y = years, Gy = Gray, RMS = Rhabdomyosarcoma.

to provide prospective RTQA internationally across all participating countries, there is ongoing training of reviewers to strive to reduce inter-observer variability for vertebrae, targets, and other OARs.

Conclusions

This initial analysis of vertebra management within QUARTET affiliated trials has demonstrated high variability, despite the availability of consensus guidelines. Variations in delineation often have a dosimetric impact and vertebral sparing is more challenging with protons. Evaluation of dosimetric impact on vertebral growth defects using long-term follow-up is needed for clinical validation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

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