

## Original Article

# Dosimetric feasibility of hypofractionation for metastatic bone/bone marrow lesions from paediatric solid tumours



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## ABSTRACT

**Background and purpose:** The aim of this study was to determine the feasibility of hypofractionated schedules for metastatic bone/bone marrow lesions in children and to investigate dosimetric differences to the healthy surrounding tissues compared to conventional schedules.

**Methods:** 27 paediatric patients (mean age, 7 years) with 50 metastatic bone/bone marrow lesions ( $n = 26$  cranial,  $n = 24$  extra-cranial) from solid primary tumours (neuroblastoma and sarcoma) were included. The PTV was a 2 mm expansion of the GTV. A prescription dose of 36 and 54 Gy EQD2 $_{\alpha/\beta=10}$  was used for neuroblastoma and sarcoma lesions, respectively. VMAT plans were optimized for each single lesion using different fractionation schedules: conventional (30/20 fractions,  $V_{95\%} \geq 99\%$ ,  $D_{0.1\text{cm}}^3 \leq 107\%$ ) and hypofractionated (15/10/5/3 fractions,  $V_{100\%} \geq 95\%$ ,  $D_{0.1\text{cm}}^3 \leq 120\%$ ). Relative EQD2 differences in OARs  $D_{\text{mean}}$  between the different schedules were compared.

**Results:** PTV coverage was met for all plans independently of the fractionation schedule and for all lesions ( $V_{95\%}$  range 95.5–100%,  $V_{100\%}$  range 95.1–100%), with exception of the vertebrae ( $V_{100\%}$  range 63.5–91.0%). For most OARs, relative mean reduction in the  $D_{\text{mean}}$  was seen for the hypofractionated plans compared to the conventional plans, with largest sparing in the 5 fractions (< 43%) followed by the 3 fractions schedule (< 40%). In case of PTV overlap with an OAR, a significant increase in dose for the OAR was observed with hypofractionation.

**Conclusions:** For the majority of the cases, iso-effective plans with hypofractionation were feasible with similar or less dose in the OARs. The most suitable fractionation schedule should be personalised depending on the spatial relationship between the PTV and OARs and the prescription dose.

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Approximately 20% of the paediatric patients with solid tumours present with distant metastases at diagnosis. Children with metastatic disease generally have a poor prognosis and overall survival rates are on average 35% (range 5–95%), depending on histology and the number of lesions [1–3].

A recent survey across leading European paediatric radiotherapy centres unveiled both consistencies and differences regarding the radiotherapy approach with curative intent on metastatic sites, especially regarding patient selection and treatment characteristics [4]. A growing interest in hypofractionation was noticed, but prescription doses and fractionation schedules are currently mainly based on local experience and institutional protocols [4].

Moreover, in current European paediatric solid tumour protocols, hypofractionation is sporadically recommended [5–8]. Across the respondents of the survey, an urgent need for consensus on the total and fraction dose per site, age group and disease category was expressed [4].

With hypofractionation, a highly conformal dose can be delivered to the target in a limited number of fractions, resulting in steep dose gradients and a potential dose reduction to the organs at risk (OARs) in the vicinity of the target [9]. In adults, the current radiotherapy approach for oligometastatic disease is strongly focused on hypofractionation and outcomes are associated with favourable local tumour control and limited toxicity for lesions within the bone, lymph nodes and soft tissue [10–13]. In contrast, the available literature on hypofractionation in children is mainly limited to retrospective and case studies for both cranial and extra-cranial metastatic disease [14–16]. In these studies, dose and fractionation schedules varied widely (total dose range 20–60 Gy in 1–10 fractions, dose per fraction range 5–20 Gy).

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Nevertheless, high local control rates (> 85%) and no acute or late toxicities of grade 3 or higher were observed.

Between children and adults, the radical radiotherapy approach for metastatic disease differs in several aspects. While radical treatment in adults mostly results in postponing disease progression, treatment of metastatic sites in children intends to cure patients. Moreover, treatment of primary metastatic disease in paediatric patients is often part of the upfront treatment approach, concurrent with conventional irradiation of the primary tumour, while in adults treatment is mostly given in a metachronic setting. Additionally, performing hypofractionation in paediatric patients may be more challenging than in adults due to the developing character of the normal tissues and the risk of asymmetric bone growth caused by the steep dose fall-off of stereotactic plans. In-silico planning feasibility studies can shed some light on these issues.

Therefore, the aim of this dosimetric study was to investigate a range of fractionation schedules and related dose constraints for different metastatic bone/bone marrow lesions in paediatric patients, leading to a better understanding of the feasibility of hypofractionation in children.

## Methods

### Patient data

After institutional review board approval (WAG/mb/17/500028), data from 27 paediatric patients with 50 metastatic bone/bone marrow lesions from solid primary tumours (neuroblastoma,  $n = 21$ ; rhabdomyosarcoma (RMS),  $n = 2$ ; Ewing sarcoma,  $n = 3$ ; osteosarcoma,  $n = 1$ ) who received radiotherapy at the University Medical Centre Utrecht (UMCU) between June 2015 and January 2020 was included. The age of the patients (10 female, 17 male) at the start of treatment was on average 7 years (range, 1–18 years). Cranial metastatic lesions ( $n = 26$ , all neuroblastoma lesions) were located in the orbital bones ( $n = 16$ ) or elsewhere in the skull ( $n = 10$ ) while extra-cranial metastatic lesions ( $n = 24$ , 13 neuroblastoma and 11 sarcoma lesions) were located in the ribs ( $n = 3$ , 2 neuroblastoma and 1 sarcoma lesions), vertebrae ( $n = 6$ , 3 neuroblastoma and 3 sarcoma lesions), pelvis ( $n = 4$ , 3 neuroblastoma and 1 sarcoma lesions) and in the extremities ( $n = 11$ , 5 neuroblastoma and 6 sarcoma lesions).

### Treatment planning

The gross tumour volume (GTV) and OARs, as delineated by the paediatric radiation oncologists, were used in this study. The planning target volume (PTV) in this study was a homogeneous 2 mm expansion of the GTV for all patients, in line with clinical practice in adults undergoing stereotactic body radiation therapy (SBRT) for oligometastatic disease in the bone/bone marrow at our department. The PTV was on average ( $\pm$  standard deviation)  $11.0 \pm 10.4$  cm<sup>3</sup> for the orbita,  $11.6 \pm 11.9$  cm<sup>3</sup> for the skull,  $15.7 \pm 18.9$  cm<sup>3</sup> for the ribs,  $42.5 \pm 45.9$  cm<sup>3</sup> for the vertebrae,  $20.5 \pm 30.3$  cm<sup>3</sup> for the pelvis and  $108.1 \pm 119.7$  cm<sup>3</sup> for the extremities metastatic lesions.

All treatment plans were optimised for each single lesion using Monte Carlo dose algorithm and a uniform 2 mm grid spacing (Monaco v5.11.02, Elekta AB, Stockholm, Sweden). The volumetric modulated arc therapy (VMAT) plans consisted of two partial non-coplanar arcs for the cranial lesions and two partial co-planar arcs for the extra-cranial lesions, according to our institution's protocol. To prevent treatment planning diversity between patients, a common dose was prescribed for all lesions of the same primary tumour cohort. Thus, a prescription dose of 36 Gy EQD2 $_{\alpha/\beta=10}$  was selected for neuroblastoma metastatic lesions while a pre-

scription dose of 54 Gy EQD2 $_{\alpha/\beta=10}$  was used for sarcoma metastatic lesions. For each neuroblastoma lesion, four fractionation schedules were applied: conventional (20 fractions) and hypofractionated (10/5/3 fractions) (Table 1). For each sarcoma lesion, with exception of the vertebral metastases, three fractionation schedules were used: conventional (30 fractions) and hypofractionated (10/5 fractions) (Table 1). Due to spinal cord and cauda equina dose constraints (Table 2), only two fractionation schedules were applied for the vertebral sarcoma metastases: conventional (30 fractions) and hypofractionated (15 fractions) (Table 1).

Target coverage for the conventional plans was aimed for at least 99% of the PTV to receive 95% of the prescription dose ( $V_{95\%} \geq 99\%$ ). For the hypofractionated plans, at least 95% of the PTV was targeted to receive the total prescription dose ( $V_{100\%} \geq 95\%$ ). The allowed maximum dose ( $D_{0.1\text{cm}^3}^3$ ) in the PTV was 107% for conventional and 120% for hypofractionated schedules. Dose constraints for all OARs were assessed using an  $\alpha/\beta = 3$ , with exception of the spinal cord for which an  $\alpha/\beta = 2$  was used. An overview of the selected dose constraints/objectives for each fractionation schedule is denoted in Table 2. For all lesions with exception of the vertebrae, coverage of the PTV was prioritised. To minimise the risk of bone fracture, a  $D_{0.1\text{cm}^3}^3 < 70$  Gy EQD2 $_{\alpha/\beta=3}$  dose constraint was aimed for all metastatic lesions [17]. For the vertebral lesions, isotoxic planning was performed in order to respect the dose constraints on the spinal cord and cauda equina. In addition, to minimise the risk of asymmetric bone growth, a homogeneous left–right dose gradient (< 3–5 Gy) or alternatively a minimum dose of 36 Gy EQD2 $_{\alpha/\beta=3}$  on the vertebrae primary ossification centres (in case of a prescription dose > 40 Gy) was aimed for all vertebral metastatic lesions [17].

### Plan quality evaluation

Target coverage in the conventional and hypofractionated plans was evaluated as the PTV percentage receiving at least 95% of the prescription dose ( $V_{95\%}$ ) and 100% of the prescription dose ( $V_{100\%}$ ), respectively. Additionally, for the evaluation of the conformity/quality of the hypofractionated plans the following metrics, as described in the NRG-BR001 phase 1 trial [18,19], were used:

$$\text{Homogeneity Index (HI)} = \frac{\text{PD}}{D_{0.1\text{cm}^3}}, \quad 0.6 \leq \text{HI} \leq 0.9, \quad (1)$$

with PD defined as the dose received by 95% of the PTV.

$$\text{Volume ratio of 100\% prescription isodose to PTV (R}_{100\%}) = \frac{V_{\text{PD}}}{V_{\text{PTV}}}, < 1.5, \quad (2)$$

$$\text{Volume ratio of 50\% prescription isodose to PTV (R}_{50\%}) = \frac{V_{\text{PD}/2}}{V_{\text{PTV}}}, < 3.7 - 7.5, \quad (3)$$

$$D_{2\text{cm}} = \frac{\text{maximum dose at 2cm from the PTV}}{\text{PD}}, < 57\% - 94\%, \quad (4)$$

with acceptance values for  $R_{50\%}$  and  $D_{2\text{cm}}$  dependent on the PTV (Supplementary Table 1).

Conventional and hypofractionated plans were considered clinically feasible if all dose constraints/objectives in Table 2 were met. In addition, hypofractionated plans needed to meet all four of the conformity/quality parameters (HI,  $R_{100\%}$ ,  $R_{50\%}$  and  $D_{2\text{cm}}$ ).

For the OARs in close proximity to the PTV, the relative differences in mean dose ( $D_{\text{mean}}$ ) between hypofractionation schedules compared to the conventional were evaluated for each metastatic lesion. For the body, the percentages of the body volume receiving

**Table 1**

Prescription doses used for each fractionation schedule. Dose criteria for 15, 10, 5 and 3 fractions (fx) were calculated using the linear-quadratic (LQ) model with an  $\alpha/\beta = 10$  and without correction for overall treatment time.

Prescription dose	Conventional	15 fx	10 fx	5 fx	3 fx
36 Gy equivalent	$20 \times 1.8 \text{ Gy} = 35.4 \text{ Gy}$ EQD2 $_{\alpha/\beta=10}$	-	$10 \times 3.2 \text{ Gy} = 35.2 \text{ Gy}$ EQD2 $_{\alpha/\beta=10}$	$5 \times 5.5 \text{ Gy} = 35.5 \text{ Gy}$ EQD2 $_{\alpha/\beta=10}$	$3 \times 8 \text{ Gy} = 36.0 \text{ Gy}$ EQD2 $_{\alpha/\beta=10}$
54 Gy equivalent	$30 \times 1.8 \text{ Gy} = 53.1 \text{ Gy}$ EQD2 $_{\alpha/\beta=10}$	$15 \times 3.2 \text{ Gy} = 52.8 \text{ Gy}$ EQD2 $_{\alpha/\beta=10}$	$10 \times 4.5 \text{ Gy} = 54.4 \text{ Gy}$ EQD2 $_{\alpha/\beta=10}$	$5 \times 7.0 \text{ Gy} = 49.6 \text{ Gy}$ EQD2 $_{\alpha/\beta=10}$	-

**Table 2**

Clinical dose criteria used in the optimisation and evaluation of the conventional and hypofractionated treatment plans according to the NRG-BR001 phase 1 trial<sup>a</sup> and in-house<sup>b</sup> guidelines. Dose constraints/objectives were determined for each fractionation schedule using an  $\alpha/\beta = 10$  for the target and an  $\alpha/\beta = 3$  for all OARs, with exception of the spinal cord ( $\alpha/\beta = 2$ ).

Structure	30 fx	20 fx	15 fx	10 fx	5 fx	3 fx
PTV 36 Gy equivalent <sup>b</sup>	-	$V_{34.2\text{Gy}} \geq 99\%$ $D_{0.1\text{cm}}^3 < 38.5 \text{ Gy}$	-	$V_{32\text{Gy}} \geq 95\%$ $D_{0.1\text{cm}}^3 < 38.4 \text{ Gy}$	$V_{27.5\text{Gy}} \geq 95\%$ $D_{0.1\text{cm}}^3 < 33 \text{ Gy}$	$V_{24\text{Gy}} \geq 95\%$ $D_{0.1\text{cm}}^3 < 28.8 \text{ Gy}$
PTV 54 Gy equivalent <sup>b</sup>	$V_{51.3\text{Gy}} \geq 99\%$ $D_{0.1\text{cm}}^3 < 57.8 \text{ Gy}$	-	$V_{48\text{Gy}} \geq 95\%$ $D_{0.1\text{cm}}^3 < 57.6 \text{ Gy}$	$V_{45\text{Gy}} \geq 95\%$ $D_{0.1\text{cm}}^3 < 54 \text{ Gy}$	$V_{35\text{Gy}} \geq 95\%$ $D_{0.1\text{cm}}^3 < 42 \text{ Gy}$	-
Brainstem <sup>a</sup>	-	$D_{0.1\text{cm}}^3 < 51 \text{ Gy}$	-	$D_{0.1\text{cm}}^3 < 40 \text{ Gy}$	$D_{0.1\text{cm}}^3 < 31 \text{ Gy}$	$D_{0.1\text{cm}}^3 < 23 \text{ Gy}$
Cochlea <sup>b</sup>	-	$D_{\text{mean}} < 24 \text{ Gy}$	-	$D_{\text{mean}} < 20 \text{ Gy}$	$D_{\text{mean}} < 17 \text{ Gy}$	$D_{\text{mean}} < 14 \text{ Gy}$
Eye <sup>b</sup>	-	$D_{0.1\text{cm}}^3 < 44 \text{ Gy}$	-	$D_{0.1\text{cm}}^3 < 35 \text{ Gy}$	$D_{0.1\text{cm}}^3 < 27 \text{ Gy}$	$D_{0.1\text{cm}}^3 < 22 \text{ Gy}$
Lacrimal Gland <sup>b</sup>	-	$D_{0.1\text{cm}}^3 < 40 \text{ Gy}$	-	$D_{0.1\text{cm}}^3 < 32 \text{ Gy}$	$D_{0.1\text{cm}}^3 < 25 \text{ Gy}$	$D_{0.1\text{cm}}^3 < 20 \text{ Gy}$
Lens <sup>b</sup>	-	$D_{0.1\text{cm}}^3 < 10 \text{ Gy}$	-	$D_{0.1\text{cm}}^3 < 9 \text{ Gy}$	$D_{0.1\text{cm}}^3 < 8 \text{ Gy}$	$D_{0.1\text{cm}}^3 < 7 \text{ Gy}$
Optic Nerve <sup>b</sup>	-	$D_{0.1\text{cm}}^3 < 52 \text{ Gy}$	-	$D_{0.1\text{cm}}^3 < 40 \text{ Gy}$	$D_{0.1\text{cm}}^3 < 30 \text{ Gy}$	$D_{0.1\text{cm}}^3 < 25 \text{ Gy}$
Pituitary <sup>b</sup>	-	$D_{\text{mean}} < 22 \text{ Gy}$	-	$D_{\text{mean}} < 19 \text{ Gy}$	$D_{\text{mean}} < 15 \text{ Gy}$	$D_{\text{mean}} < 13 \text{ Gy}$
Oesophagus <sup>a</sup>	$D_{0.5\text{cm}}^3 < 60 \text{ Gy}$	$D_{0.5\text{cm}}^3 < 54 \text{ Gy}$	$D_{0.5\text{cm}}^3 < 48 \text{ Gy}$	$D_{0.5\text{cm}}^3 < 42 \text{ Gy}$	$D_{0.5\text{cm}}^3 < 32 \text{ Gy}$	$D_{0.5\text{cm}}^3 < 25 \text{ Gy}$
Heart <sup>a</sup>	$D_{0.5\text{cm}}^3 < 54 \text{ Gy}$	$D_{0.5\text{cm}}^3 < 48 \text{ Gy}$	$D_{0.5\text{cm}}^3 < 43 \text{ Gy}$	$D_{0.5\text{cm}}^3 < 38 \text{ Gy}$	$D_{0.5\text{cm}}^3 < 29 \text{ Gy}$	$D_{0.5\text{cm}}^3 < 26 \text{ Gy}$
Spinal Cord <sup>b</sup>	$D_{0.1\text{cm}}^3 < 54 \text{ Gy}$	$D_{0.1\text{cm}}^3 < 46 \text{ Gy}$	$D_{0.1\text{cm}}^3 < 42 \text{ Gy}$	$D_{0.1\text{cm}}^3 < 36 \text{ Gy}$	$D_{0.1\text{cm}}^3 < 27 \text{ Gy}$	$D_{0.1\text{cm}}^3 < 22 \text{ Gy}$
Spinal Cord PRV (2 mm) <sup>b</sup>	$D_{0.1\text{cm}}^3 < 60 \text{ Gy}$	$D_{0.1\text{cm}}^3 < 52 \text{ Gy}$	$D_{0.1\text{cm}}^3 < 47 \text{ Gy}$	$D_{0.1\text{cm}}^3 < 40 \text{ Gy}$	$D_{0.1\text{cm}}^3 < 30 \text{ Gy}$	$D_{0.1\text{cm}}^3 < 23 \text{ Gy}$
Liver <sup>b</sup>	$D_{\text{mean}} < 34 \text{ Gy}$	$D_{\text{mean}} < 31 \text{ Gy}$	$D_{\text{mean}} < 29 \text{ Gy}$	$D_{\text{mean}} < 25 \text{ Gy}$	$D_{\text{mean}} < 20 \text{ Gy}$	$D_{\text{mean}} < 17 \text{ Gy}$
Spleen <sup>b</sup>	$D_{\text{mean}} < 15 \text{ Gy}$	$D_{\text{mean}} < 14 \text{ Gy}$	$D_{\text{mean}} < 14 \text{ Gy}$	$D_{\text{mean}} < 12 \text{ Gy}$	$D_{\text{mean}} < 10 \text{ Gy}$	$D_{\text{mean}} < 9 \text{ Gy}$
Contralateral Kidney <sup>a</sup>	$D_{\text{mean}} < 11 \text{ Gy}$	$D_{\text{mean}} < 10 \text{ Gy}$	$D_{\text{mean}} < 10 \text{ Gy}$	$D_{\text{mean}} < 9 \text{ Gy}$	$D_{\text{mean}} < 8 \text{ Gy}$	$D_{\text{mean}} < 7 \text{ Gy}$
Vertebrae <sup>b</sup>	$D_{0.1\text{cm}}^3 < 67 \text{ Gy}$	$D_{0.1\text{cm}}^3 < 59 \text{ Gy}$	$D_{0.1\text{cm}}^3 < 54 \text{ Gy}$	$D_{0.1\text{cm}}^3 < 46 \text{ Gy}$	$D_{0.1\text{cm}}^3 < 35 \text{ Gy}$	$D_{0.1\text{cm}}^3 < 28 \text{ Gy}$
Cauda Equina <sup>a</sup>	$D_{0.1\text{cm}}^3 < 57 \text{ Gy}$	$D_{0.1\text{cm}}^3 < 53 \text{ Gy}$	$D_{0.1\text{cm}}^3 < 48 \text{ Gy}$	$D_{0.1\text{cm}}^3 < 42 \text{ Gy}$	$D_{0.1\text{cm}}^3 < 32 \text{ Gy}$	$D_{0.1\text{cm}}^3 < 24 \text{ Gy}$

more than 95% of the prescription dose ( $V_{>95\%}$ ), 80% of the prescription dose ( $V_{>80\%}$ ), 5 Gy EQD2 $_{\alpha/\beta=3}$  ( $V_{>5\text{Gy}}$ ) and 2 Gy EQD2 $_{\alpha/\beta=3}$  ( $V_{>2\text{Gy}}$ ) were evaluated for all fractionation schedules and metastatic lesions.

**Statistical data analysis**

All statistical analysis were performed using R version 1.1.456 (RStudio: Integrated Development for R. RStudio, USA). Since not all data for the plan quality parameters fitted the normal distribution (tested with the Shapiro-Wilk's test for normality), the non-parametric Friedman test was used to assess differences in the plan conformity/quality parameters between the hypofractionation schedules for all metastatic lesions. Since the 15 fractions schedule was used exceptionally for 3 sarcoma lesions, resulting in only three data points for each metric, data was insufficient to include in the statistical test. Therefore, differences in plan conformity/quality parameters were only evaluated between the 10, 5 and 3 fractions schedules.

For the OARs related to the cranial metastatic lesions, as data was normally distributed (tested with the Shapiro-Wilk's test for normality), a one sample t-test was performed to compare the relative differences in  $D_{\text{mean}}$  for each hypofractionation schedule compared to the conventional schedule. For the OARs related to the extra-cranial metastatic lesions, a limited number of data points were available per organ as a result of the large variability in the metastases location. Thus, no statistical tests were performed for these OARs.

For the body dose measurements ( $V_{>95\%}$ ,  $V_{>80\%}$ ,  $V_{>5\text{Gy}}$  and  $V_{>2\text{Gy}}$ ) for all metastases, data did not fit a normal distribution, thus measurements for each hypofractionation schedule (10/5/3 fractions) were compared to the conventional schedule using a non-

parametric paired Wilcoxon test. Similarly to the plan conformity/quality parameters, body dose measurements for the 15 fraction schedule were only available for 3 metastatic lesions and therefore not included in the statistical test. For all statistical tests, p-values < 0.05 were considered significant.

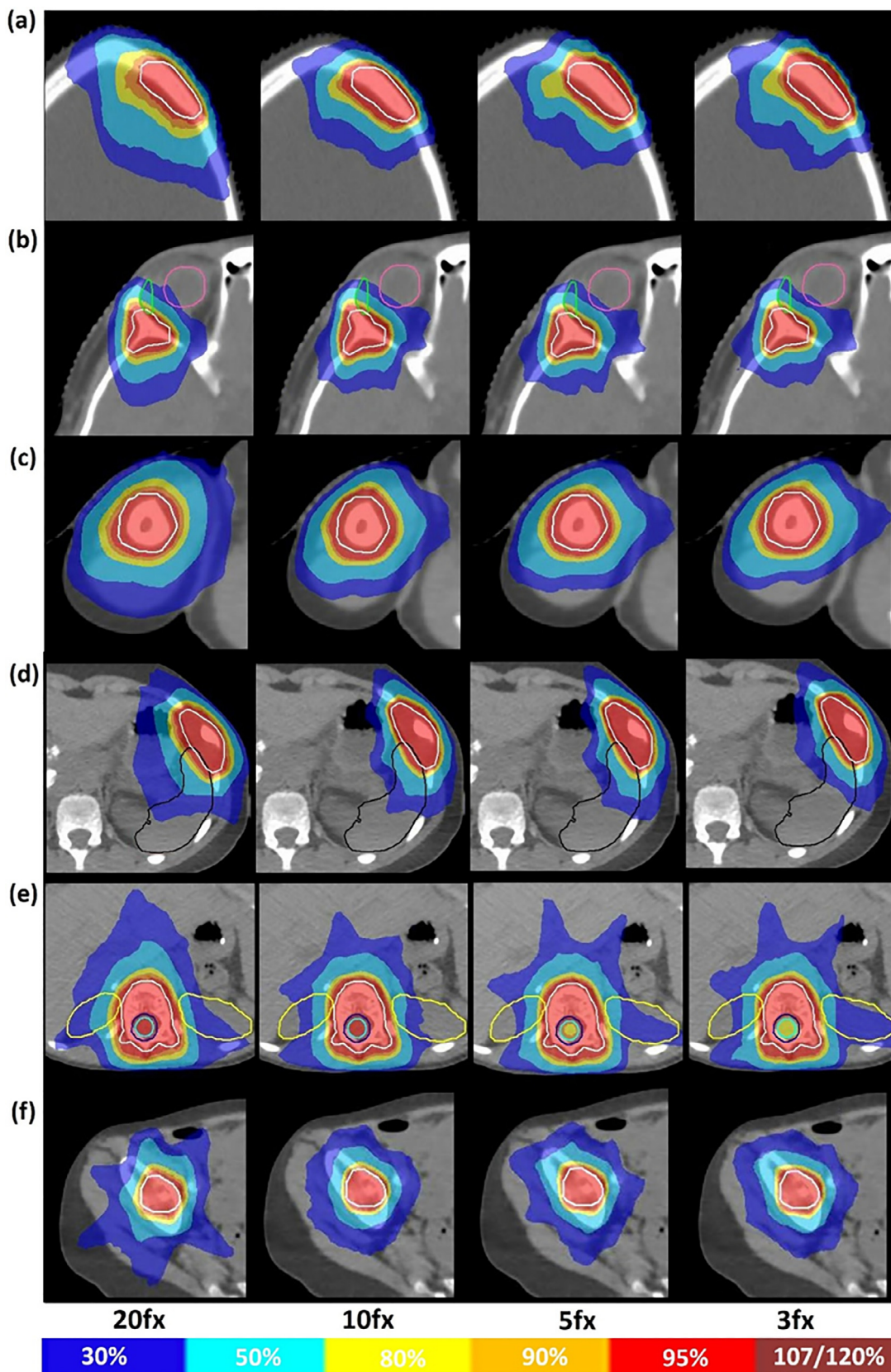
**Results**

For all metastatic lesions with exception of the vertebrae, the PTV coverage was fulfilled for both conventional and hypofractionated plans ( $V_{95\%}$  range 95.5–100%,  $V_{100\%}$  range 95.1–100%). For 5 out of 6 lesions ( $n = 2$  neuroblastoma,  $n = 3$  sarcoma) located in the vertebrae, target coverage was not met ( $V_{100\%}$  range 63.5–91.0%) with hypofractionation (Fig. 1; underdosage even when excluding the spinal cord volume from the PTV).

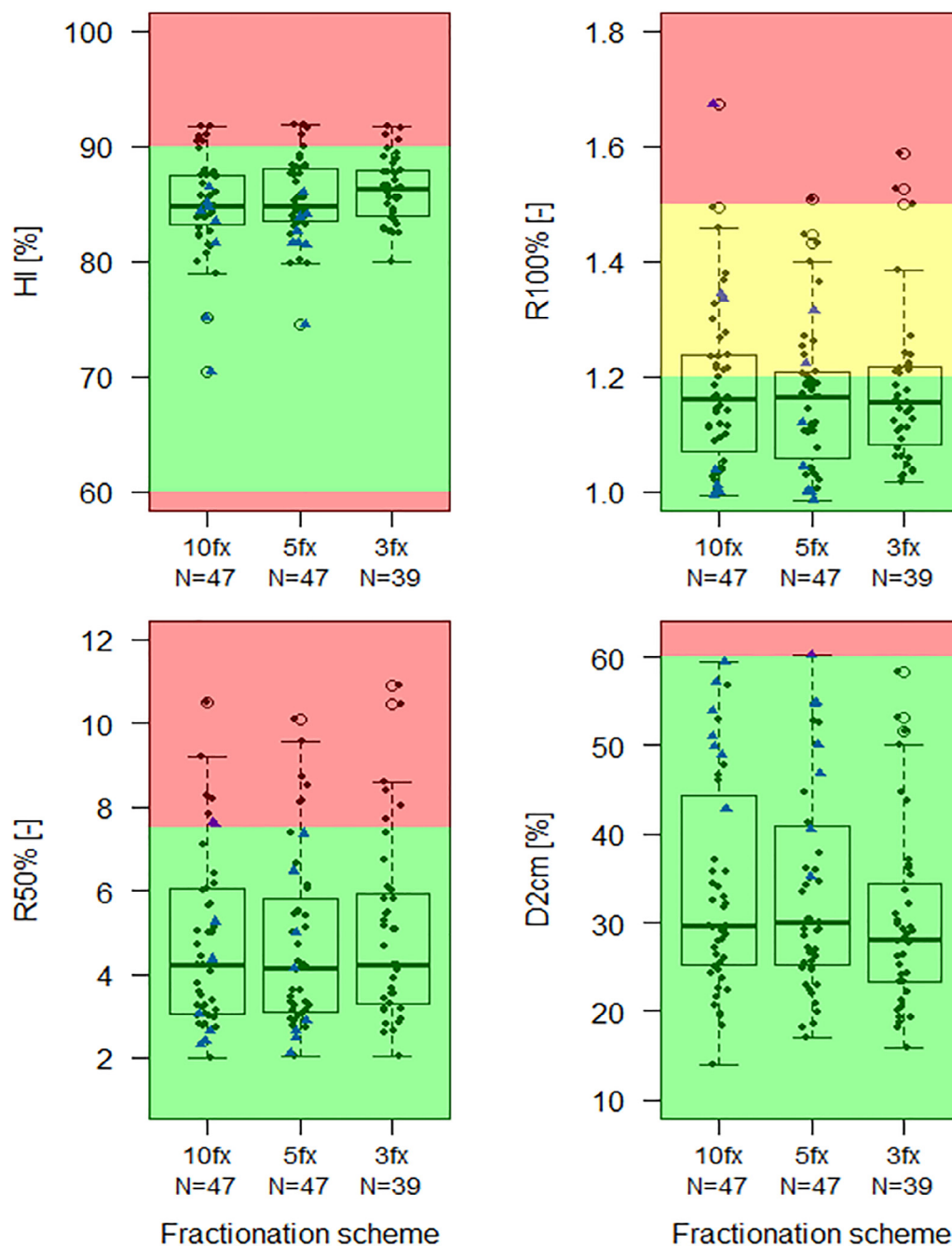
For 39 out of 50 lesions, plans were optimized without violating the OAR dose constrains, with exception of the plans for 11/15 orbital lesions where the lacrimal gland overlapped with the PTV (Fig. 1). Consequently, the  $D_{0.1\text{cm}}^3$  in the lacrimal gland exceeded the allowed dose (Table 2) for 5 out of 15 lesions in the conventional plans and 7, 9 and 11 out of 15 lesions in the 10, 5, 3 fraction schedules, respectively.

An overview of the plan quality parameters is given in Fig. 2. No significant differences were found between the different hypofractionation schedules for any of the considered parameters ( $p > 0.05$ ). For the 36 Gy-equivalent and 54 Gy-equivalent plans, all plan quality parameters for each hypofractionated plan were met for 29/39 and 5/11 lesions, respectively. For the remaining lesions, either one or two parameters were not fulfilled.

For all OARs (with exception of the lacrimal gland and spinal cord), a reduction in the  $D_{\text{mean}}$  on average less than 3 Gy EQD2 $_{\alpha/\beta=3}$



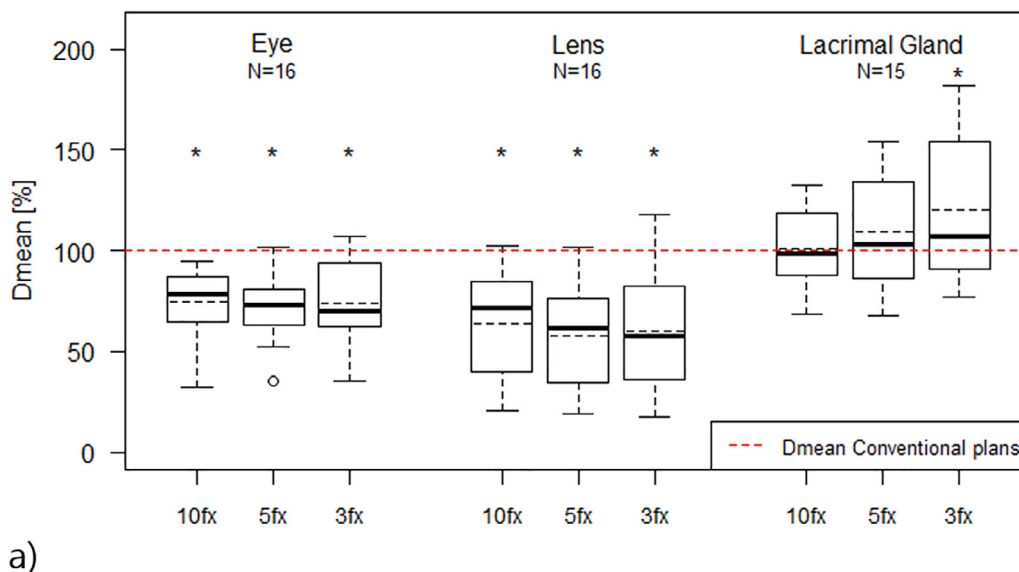
**Fig. 1.** Conventional (20 fractions (fx)) and hypofractionated (10/5/3 fx) transversal dose maps for six metastatic bone/bone marrow lesions from different neuroblastoma patients located in the skull (a), orbita (b), humerus (c), rib (d), vertebra (e) and pelvis (f). The PTV is shown in white, the lacrimal gland in green, the eye in pink, the spleen in black, the kidneys in yellow, the spinal cord in light blue and the spinal cord PRV in dark blue. The allowed maximum dose shown in dark red was 107% for the 20 fx and 120% for the 10/5/3 fx plans.



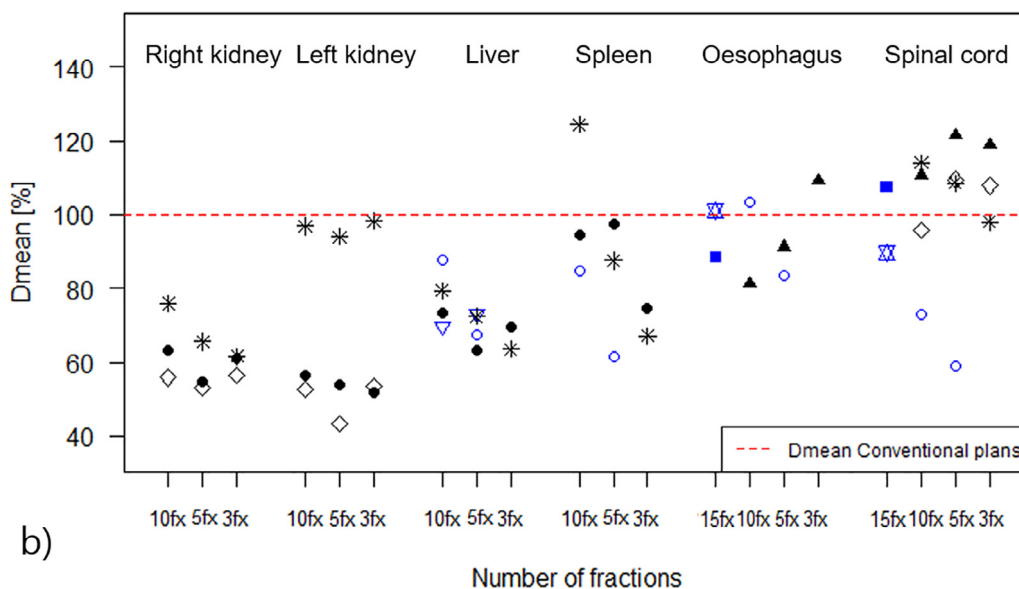
**Fig. 2.** Boxplots of the plan conformity/quality parameters (HI,  $R_{100\%}$ ,  $R_{50\%}$  and  $D_{2cm}$ ) for the hypofractionated plans for cranial ( $n = 26$ ) and extra-cranial ( $n = 21$ ) lesions in paediatric patients. Black dots represent lesions from neuroblastoma patients ( $n = 39$ ) and blue triangles represent lesions from sarcoma patients ( $n = 11$ ). Boxes: median value and upper and lower quartiles; whiskers: lowest and highest data point within 1.5x interquartile range, open circles: outliers. Green indicates preferred values, yellow indicates acceptable values and red indicates values outside of these ranges.  $R_{50\%}$  and  $D_{2cm}$  acceptance range was dependent on the volume of the PTV (Supplementary Table 1).

was seen for the hypofractionated compared to the conventional plans. For cranial lesions located in the orbita, relative differences in doses to the eye ( $n = 16$ ) and lens ( $n = 16$ ) were significantly lower in the majority of the cases ( $> 90\%$ ) for the hypofractionated plans (Fig. 3(a)). Relative differences were largest for the 5 fraction schedule, with a decrease on the  $D_{mean}$  on average of 28% and 43% for the eye and lens, respectively (Supplementary Table 2). In contrast, in 11 out of 15 lesions, where the lacrimal gland was in close proximity to or even overlapped with the PTV, an increased  $D_{mean}$  was noticed for 7 lesions for the 10 fraction schedule and 8 lesions for the 5 and 3 fraction schedules (Fig. 1, Supplementary Table 2).

For extra-cranial lesions located in or near the vertebrae, relative differences in  $D_{mean}$  to the kidneys ( $n = 6$ ), liver ( $n = 4$ ), spleen ( $n = 3$ ), oesophagus ( $n = 4$ ) and the spinal cord ( $n = 6$ ) were evaluated for the hypofractionated plans and compared to the conventional plan (Fig. 3(b)). For the kidneys, liver and spleen, a larger dosimetric sparing was achieved by reducing the number of fractions (on average 30% reduction in  $D_{mean}$  compared to the conventional plan). In contrast, the  $D_{mean}$  of the spinal cord was larger when using less fractions for 8 out of 13 lesions (Fig. 3 (b)). Nevertheless, constraints to the spinal cord were met in all cases ( $D_{0.1cm}^3 < \text{physical dose constraints listed in Table 2}$ ).



**Fig. 3.** Relative EQD2 differences (y-axis) in  $D_{\text{mean}}$  of the OARs in close proximity to the target for the different hypofractionation schedules (x-axis) compared to the conventional fractionation schedules (red dotted line) for cranial (a) and extra-cranial (b) metastatic lesions. Dose criteria for 15, 10 and 5 fractions were calculated using the linear-quadratic (LQ) model with an  $\alpha/\beta = 3$  for all OARs, with exception of the spinal cord ( $\alpha/\beta = 2$ ). In (a), \* indicates significance difference ( $p < 0.05$ ). Boxes: median value and upper and lower quartiles; whiskers: lowest and highest data point within  $1.5 \times$  interquartile range, circles: outliers, diamonds: averages. In (b), each symbol represents a different patient and symbols in black represent neuroblastoma and in blue sarcoma patients. No statistical test was performed for the extra-cranial lesions due to the limited number of data points per hypofractionation schedule.



**Fig. 3 (continued)**

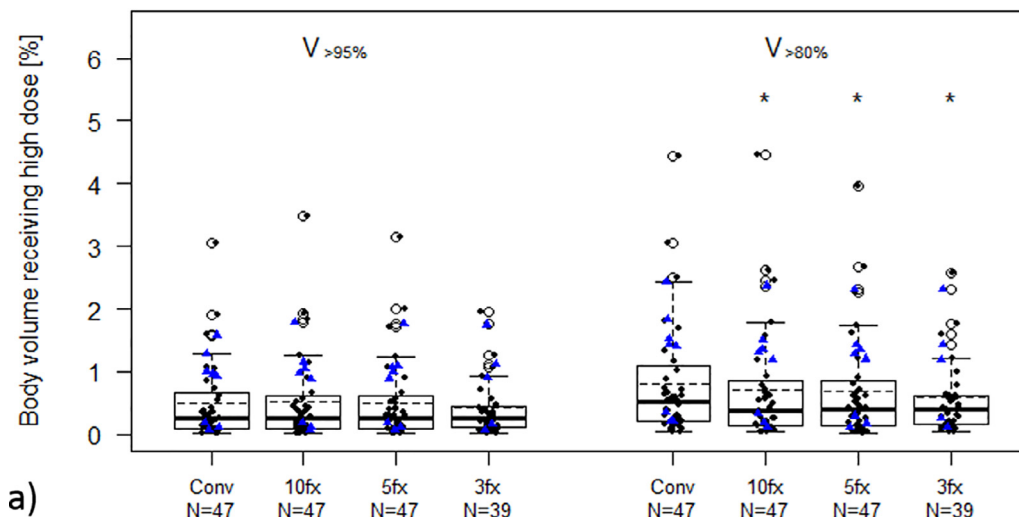
For the  $V_{>80\%}$ ,  $V_{>5\text{Gy}}$  and  $V_{>2\text{Gy}}$  body dose measurements, a significant larger dosimetric sparing was achieved with all hypofractionated compared to the conventional plans ( $p < 0.05$ ) (Fig. 4). For the  $V_{>95\%}$ , no significant differences were found between the hypofractionated and the conventional plans ( $p > 0.05$ ).

**Discussion**

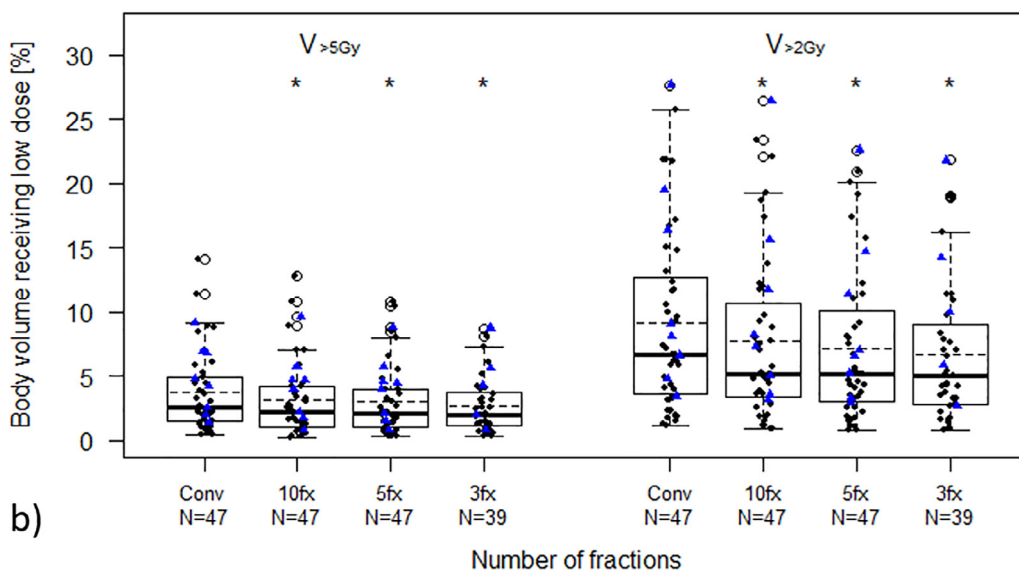
In this study, the feasibility of hypofractionated compared to conventional radiotherapy schedules for metastatic bone/bone marrow lesions in neuroblastoma and sarcoma patients was evaluated with focus on the target coverage and dose to the healthy surrounding tissues. Results demonstrated that for the majority of the paediatric metastases, iso-effective plans with less fractions

could be generated with similar or even significantly less dose deposition in the surrounding tissues. For cases in which the dose criteria were not met, the limiting factor was often the presence of OARs in close proximity or overlapping with the target. Consequently, the most suitable fractionation schedule should be personalised depending on the spatial relationship between the PTV-OARs and the prescription dose.

In adults, the current radiotherapy approach for oligometastatic disease has a strong focus on stereotactic techniques with hypofractionation [12,13,20]. For the evaluation of hypofractionated schedules, plan conformity/quality parameters (i.e. HI,  $R_{100\%}$ ,  $R_{50\%}$  and  $D_{2\text{cm}}$ ) were designed as described in [18,19]. Although these criteria were developed for adults, in this study the same parameters were pragmatically used for the evaluation of paediatric hypofraction-



**Fig. 4.** Boxplots denoting the body volume receiving more than 95% and 80% of the prescription dose (high dose) (a) and more than 5 and 2 Gy EQD<sub>2,  $\alpha/\beta=3$</sub>  (low dose) (b) for hypofractionated (10/5/3 fractions (fx)) and conventional (Conv) fractionation schedules for all cranial and extra-cranial metastatic lesions. Black dots represent lesions from neuroblastoma patients and blue triangles represent lesions from sarcoma patients. Boxes: median value (solid line), average value (dashed line) and upper and lower quartiles; whiskers: lowest and highest data point within 1.5x interquartile range, circles: outliers. \* indicate significant differences between the hypofractionated and the conventional plans.



**Fig. 4 (continued)**

ated plans. The guidelines however state that for small gross target volumes ( $< 1.8 \text{ cm}^3$ ) and/or volumes within 2 cm of the skin, which was the case for the majority of the metastatic lesions in this study (43/50 lesions), it may be challenging to meet the criteria for all plan conformity/quality parameters [19]. Nevertheless, all parameters were fulfilled in all hypofractionated schedules for the majority of the lesions (34/50 lesions). No significant differences in the plan quality parameters were noticed between the different fractionation schedules, indicating that similar iso-effective plans can be generated either with 10, 5 and/or 3 fractions. In addition, target and OARs dose constraints/objectives were met for all hypofractionated plans with exception of lesions in the orbita ( $n = 11$ , neuroblastoma) and vertebrae ( $n = 5$ , 2 neuroblastoma and 3 sarcoma). For the orbital lesions, where in several cases the PTV overlapped with the lacrimal gland, a significant dose increase for this OAR was observed in at least one of the hypofractionated plans compared to the conventional plan. For the vertebral lesions, since the maximum dose constraint to the spinal cord could not be violated,

an underdosage of the PTV was unavoidable in all hypofractionated schedules. Thus, when adhering to the spinal cord constraints, performing hypofractionation for these metastases is not feasible for both neuroblastoma (with 10 fractions and a prescription dose of 36 Gy EQD<sub>2,  $\alpha/\beta=10$</sub> ) and sarcoma patients (with 15 fractions and a prescription dose of 54 Gy EQD<sub>2,  $\alpha/\beta=10$</sub> ). For the remaining lesions, a significant dose reduction to the surrounding OARs and body was achieved with all hypofractionation schedules compared to the conventional schedule. It is clear that the expected benefit of hypofractionation for the OARs decreases with increasing PTV margins. Nevertheless, the use of a homogeneous 2 mm GTV-PTV margin in this in-silico study was in accordance with clinical residual set-up errors after online patient position correction recorded during hypofractionated treatments of oligometastatic bone/bone marrow disease in literature [21,22].

In paediatrics, literature on hypofractionated radiotherapy and the radiobiological effect of a higher dose per fraction on the normal tissue is lacking. Also, as normal tissue complication probability

(NTCP) models for hypofractionation and especially for children still have to be developed, dose constraints in this study were based on the known tolerance doses for 2 Gy fractionation schedules. Dose criteria were calculated with an  $\alpha/\beta$  of 3 for most OARs, with exception of the spinal cord ( $\alpha/\beta = 2$ ) and with an  $\alpha/\beta$  of 10 for the target. For metastatic bone/bone marrow lesions, it is however debatable which  $\alpha/\beta$  is appropriate to use in case of a target volume and/or an OAR, since for certain lesions the use of hypofractionation could lead to a higher risk of bone fracture [23]. Nevertheless, all conventional and hypofractionated plans in this study met the dose constraint  $D_{0.1\text{cm}}^3 < 70 \text{ Gy EQD2}_{\alpha/\beta=3}$  to bony structures to minimise the risk of fracture as suggested by Hoeben et al. [17].

Stereotactic radiotherapy with hypofractionation can be especially beneficial for the irradiation of patients with multiple metastases within an acceptable overall treatment time. Compared to a conventional schedule, using hypofractionation can reduce the treatment time for metastases from approximately 4 weeks (20 fractions, 5 fractions/week) to 1–2 weeks (3–5 fractions, 3 fractions/week) in neuroblastoma patients and from 6 weeks (30 fractions, 5 fractions/week) to 2–3 weeks (5–10 fractions, 3 fractions/week) in sarcoma patients. Moreover, with an increasing sensitivity/specificity of imaging techniques, a larger number of metastases will be detected, making irradiation of the primary tumour together with the metastatic lesions more challenging regarding to child compliance and machine capacity. Therefore, combining a hypofractionation schedule to treat multiple metastases while simultaneously irradiating the primary tumour in a conventional manner, could be an attractive alternative to conventional radiotherapy alone.

In addition, caution regarding the combination of hypofractionated schedules with systemic therapies is needed. Specific chemotherapy or targeted therapy might increase radiotherapy side-effects, so timing between treatment modalities as well as relevant constraints for critical OARs in the vicinity of the tumour during treatment should be carefully considered. In literature, limited data is available on the effectiveness and toxicity of hypofractionated treatments, either by radiotherapy alone or by a combination with chemo/targeted therapy. To find a consensus on hypofractionation regimens (taking site, histology, number of lesions and the age group in mind) and to register toxicity from radiotherapy whether or not combined with systemic agents, a SIOPE endorsed working group has been established recently. Given the potential advantages of hypofractionation in daily practice, this working group will not only focus on paediatric patients presenting with stage 4 disease treated with a curative intent, but also on patients referred for radiotherapy with palliative intent. Performing hypofractionation in children would not only simplify the treatment logistics for the clinicians and family but also allow for increased child comfort with patients in a reduced time under general anaesthesia.

In conclusion, the results from this study show that iso-effective hypofractionated plans, yielding similar target coverage and potential dose sparing to the surrounding tissues compared to conventional plans, could be generated for the majority of the patients with neuroblastoma or sarcoma and metastatic lesions in the bone/bone marrow. In practice, the most suitable fractionation schedules should be personalised per tumour type and site depending on the spatial relationship between the target and surrounding critical structures and the prescription dose.

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#### 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.

#### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.radonc.2021.04.020>.

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