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Published in:
Radiotherapy and Oncology

DOI:
10.1016/j.radonc.2014.01.020

2014

Haematological toxicity in adult patients receiving craniospinal irradiation - indication of a dose-bath effect

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Keywords: Dose bath, Haematological toxicity, Helical tomotherapy, Craniospinal Irradiation.

Abstract

Background and Purpose

The purpose of this study was to investigate the correlation between the haematological toxicity observed in patients treated with craniospinal irradiation, and the dose distribution in normal tissue, specifically the occurrence of large volumes exposed to low dose.

Material and Methods

Twenty adult male patients were included in this study; eight treated with helical tomotherapy (HT), and twelve with three-dimensional conformal radiation therapy. The relative volume of red bone marrow and body that was exposed to low dose (*i.e.* the so-called dose bath) was evaluated and correlated with nadir blood values during treatment, *i.e.* the severity of anaemia, leukopenia, and thrombocytopenia. The correlation was tested for different dose levels representing the dose bath using the Pearson product-moment correlation method.

Results

We found a significant correlation between the volume of red bone marrow exposed to low dose and the severity of thrombocytopenia during treatment. Furthermore, for the HT patients, a significant correlation was found between the relative volume of the body exposed to low dose and the severity of anaemia and leukopenia.

Conclusions

The severity of haematological toxicity correlated with the fraction of red bone marrow or body that was exposed to low dose.

Introduction

Craniospinal irradiation (CSI) is used as part of the curative treatment of central nervous system (CNS) tumours having a high risk of cerebrospinal fluid (CSF) dissemination [1], *e.g.* primitive neuroectodermal tumours (PNETs), medulloblastomas, and pineoblastomas. CSI is commonly delivered with a three-dimensional conformal radiation therapy (3DCRT) technique. With the patient in prone position, CSI is usually given with two laterally opposed fields for the brain and cervical cord, and one or two abutting posterior fields for the rest of the spinal cord, depending on the length of the target [1]. This technique results in field junctions where the delivered absorbed dose is very uncertain [2], an inhomogeneous dose distribution in the planning target volume (PTV), and a high absorbed dose to some organs at risk (OARs), *e.g.* the thyroid gland, heart, and sternum [3]. The unique geometry of helical tomotherapy (HT) enables the possibility of treating the entire craniospinal axis without any field junctions or field matching [4]. This feature and other positive characteristics of HT compared to 3DCRT delivery of CSI, such as superior target coverage and a more homogenous target dose, have been reported in the literature [4-6], making it an attractive modality for CSI. The disadvantage of CSI with HT is that almost the entire patient is irradiated to some extent, with large volumes of normal tissue exposed to low dose (relative to the target dose). This so-called dose bath may be associated with acute and late adverse effects, *e.g.* haematological toxicity and secondary cancers [3, 5, 7-12]. Thus, even if a HT plan can fulfil typical normal tissue tolerance criteria better than a 3DCRT plan, it does not necessarily mean that the therapeutic result is better as a different spectrum of side-effects might become apparent. Haematological toxicity may exclude the patient from concomitant chemotherapy, thereby having important implications for treatment outcome.

This study was initiated after the introduction of HT as the treatment modality for CSI treatment in our clinic, as it had resulted in haematological toxicity of unexpected severity for the first two patients treated. The purpose of this study was to compare acute haematological effects for adult male patients treated with CSI using either HT or a 3DCRT technique, and if possible, correlate the haematological toxicity with the dose distribution in normal tissue, specifically the dose bath. Such information can be used to optimise plans with a lower risk of severe haematological toxicity occurring during treatment.

Material and Methods

Twenty adult male patients were included in this study. Eight patients received CSI with HT, and twelve patients with 3DCRT technique. Patient and radiotherapy data are given in the Supplementary Appendix. The whole brain, including meninges and the entire spinal cord along with its tecal sac were defined as the clinical target volume (CTV). The PTV was defined as the CTV with a 5 mm margin. Thermoplastic masks, standard head supports, and full-body vacuum cushions were used for immobilization. 3DCRT patients were treated in prone position while HT patients were treated in supine position. Positional verification was performed with EPID in the case of 3DCRT and with megavoltage computed tomography (MVCT) for daily image-guidance of the HT treatments. Six of the eight patients treated with HT and seven of the twelve treated with 3DCRT received concomitant chemotherapy: Vincristine 1.5 mg/m^2/week via intravenous infusion (maximum dosage: 2 mg/week). All HT plans but the plans for the first two patients treated were generated and optimised according to a revised treatment planning protocol for CSI with HT (See Supplementary Appendix).

Acute haematological toxicities were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03 [13]. Bone was delineated and the red bone marrow content was quantified for every patient according to Ellis [14].
The mean absorbed dose to breast bone, pelvic bone, spleen, kidneys, lungs, heart, thyroid gland, red bone marrow, and entire body, *i.e.* OARs which were considered as potentially important with regards to acute haematological toxicity, and also with regards to late side effects, were evaluated and compared for the different treatment techniques. Student's *t*-tests (normally distributed data) and Mann-Whitney U-tests (not normally distributed data) were performed to test the statistical significance of differences found. All statistical tests performed were two-sided with a chosen significance level of 5% ($\alpha = 0.05$).
The relative volume of the red bone marrow and the body that was exposed to the low dose was evaluated and correlated with nadir blood values during treatment, *i.e.* the severity of anaemia, leukopenia, and thrombocytopenia. The correlation was tested for different threshold dose levels defining the dose bath using the Pearson product-moment correlation method, which summarises the direction and degree (closeness) of linear relations between two variables. The correlation coefficient (r) can take values between -1 (perfect negative correlation) through 0 (no correlation) to +1 (perfect positive correlation.

Results

The type and grade of acute haematological toxicity experienced by the patients during treatment are presented in Table 1.The majority of patients (15 of 20) did not suffer from any kind of haematological toxicity at the start of their radiotherapy treatment. However, four of the 3DCRT patients already suffered from a grade 1 anaemia, two of which also suffered from a grade 1 thrombocytopenia. One of the HT patients also suffered from a grade 1 thrombocytopenia at the start of treatment. During radiotherapy treatment; chemotherapy was interrupted for four of the HT patients and one of the 3DCRT patients due to the severity of their thrombocytopenia. Two of these HT patients, the 3DCRT patient, and two other 3DCRT patients suffering from grade 2 anaemia, all received blood transfusions. Furthermore, one of the 3DCRT patients and two of the HT patients developed infections during or shortly after their radiotherapy treatment, which might have affected their blood values. One of these HT patients discontinued his treatment due to the severity of his infection.

The mean absorbed doses for OARs and relative volumes of red bone marrow and entire body that received 3 Gy or more, for the treatment plans generated for CSI with HT or 3DCRT, are displayed in Figure 1. The figure also shows whether the differences found between treatment techniques were significant or not. The average dose-volume relationships of the PTV, body and red bone marrow, for the HT patients and the 3DCRT patients, are displayed in Figure 2. Examples of typical dose distributions for a HT and a 3DCRT patient are shown in the Supplementary Appendix.

There was a significant correlation between the nadir thrombocyte counts and the relative volume of red bone marrow exposed to low dose, for the patients included in this study. The correlation was significant ($p < 0.05$) in the dose interval between 2 and 6 Gy, with the strongest correlation for the volume that received 3 Gy or more ($r = -0.54$, $p = 0.01$), displayed in Figure 3a. There was no significant correlation between the relative volume of red bone marrow and the nadir leukocyte counts ($r = -0.23$) or haemoglobin values ($r = -0.14$). However, a significant correlation was found between the nadir leukocyte counts as well as the nadir haemoglobin values and the relative volume of the entire body exposed to low dose, for the HT patients. The correlation was significant for the volume that received 2 Gy or more ($r = -0.74$, $p=0.04$) for the leukocyte counts and in the dose interval between 3 and 4 Gy for

the haemoglobin values, with the strongest correlation for the volume that received 3 Gy or more ($r = -0.73$, $p = 0.04$), displayed in Figure 3b-c. These correlations were not significant for the 3DCRT patients.

Discussion

When a new treatment technique is introduced clinically, a thorough follow-up of the effects of the treatment is of great importance. This study describes the occurrence of acute haematological toxicity following the introduction of a new advanced treatment technique for CSI, *i.e.* HT. A low incidence of acute haematological toxicity for CSI treatment is desirable since it may have a positive impact on tumour control for the entire treatment, *i.e.* if severe thrombocytopenia which causes interruption of the chemotherapy treatment can be avoided, and also if the onset of anaemia can be avoided. It has been suggested that anaemia during treatment correlates with poorer prognosis, diminished survival, and a higher risk of treatment failure [15-17].

The nadir thrombocyte count and consequently the severity of thrombocytopenia for the patients in the study correlated significantly with the volume of red bone marrow that received a dose in the range 2 - 6 Gy, which we use to define the dose bath (emphasised in Figure 2). As a comparison, $TD_{50/5}$ for bone marrow has been estimated to 4.5 Gy [18]. The strongest correlation was seen for 3 Gy (Figure 3a). The results also showed significant correlation between the severity of leukopenia for the HT patients and the relative volume of body that received a dose of more than 2 Gy. No such correlation was found for the 3DCRT patients, which can be due to the large difference in the irradiated volumes between the techniques (bottom of Figure 1). Elsworthy and Plowman has previously reported that they found no significant difference in the severity of lymphopaenia for patients treated with HT compared to 3DCRT, for prostate cancer [10]. However, the volumes exposed to the dose bath are considerably smaller for prostate cancer treatment compared to CSI. We have not investigated any possible difference in behaviour of neutrophils or lymphocytes values during treatment. The results in this study also showed significant correlation between the severity of anaemia for the HT patients and the relative volume of body that received a dose in the range 3 - 4 Gy. The erythrocytes circulate in the blood for about 120 days before they are eliminated from the blood circulation. Hence, the true nadir value might not be reached until well after the radiotherapy treatment is finished , which makes the nadir values reached during treatment (used in this study) somewhat questionable as an evaluation parameter. However, it is the haemoglobin values during treatment that are of interest with regards to the effect of the radiotherapy treatment. Furthermore, two of the HT patients and five of the 3DCRT patients did not receive concomitant chemotherapy. On the other hand, its influence on the haemoglobin values is expected to be negligible.

The introduction of the revised HT planning protocol (Supplementary Appendix) resulted in reductions of absorbed dose in the CSI treatment plans for several OARs, *e.g.* pelvic bones, breast bone, and for the thyroid gland (see range versus median in Figure 1). There was also a considerable reduction of the volumes of the patients' red bone marrow that was exposed to a low absorbed dose (3 Gy). Though, the volume was still considerably larger for HT than 3DCRT. The issues addressed in this study should also be of concern for CSI treatment with other forms of rotational photon therapy, *e.g.* volumetric arc therapy (VMAT).

We believe that the increased severity of haematological toxicity following the shift of treatment technique was due to the increased dose bath. The severity of thrombocytopenia correlated significantly with how much (the fractional volume) of the red bone marrow that

was exposed to low dose. By delineating all bones (preferably with an auto-segmentation technique) and quantifying the red bone marrow content, the red bone marrow could be used in the treatment plan optimisation and consequently also be part of the plan evaluation process. This should diminish the incidence and severity of thrombocytopenia for HT treatment, at least to the same level as for 3DCRT treatment. Hence, more patients would be able to complete their chemotherapy treatment without interruptions, which should ensure a better treatment prognosis.

Conflict of interest notification

To the authors knowledge no conflicts of interest exist.

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Table 1: The type and grade of acute haematological toxicity experienced by the patients during treatment.

Toxicity [n†† (%)]	Grade	HT* [n (%)]	3DCRT† [n (%)]
Anaemia [14 (70%)]	No toxicity	4 (50%)	2 (17%)
	1	1 (13%)	6 (50%)
	2	3 (37%)	3 (25%)
	3	-	1 (8%)
Leukopenia [20 (100%)]	No toxicity	-	-
	1	2 (25%)	6 (50%)
	2	5 (62%)	4 (33%)
	3	1 (13%)	2 (17%)
Thrombocytopenia [19 (95%)]	No toxicity	-	1 (8%)
	1	4 (50%)	10 (84%)
	2	4 (50%)	1 (8%)

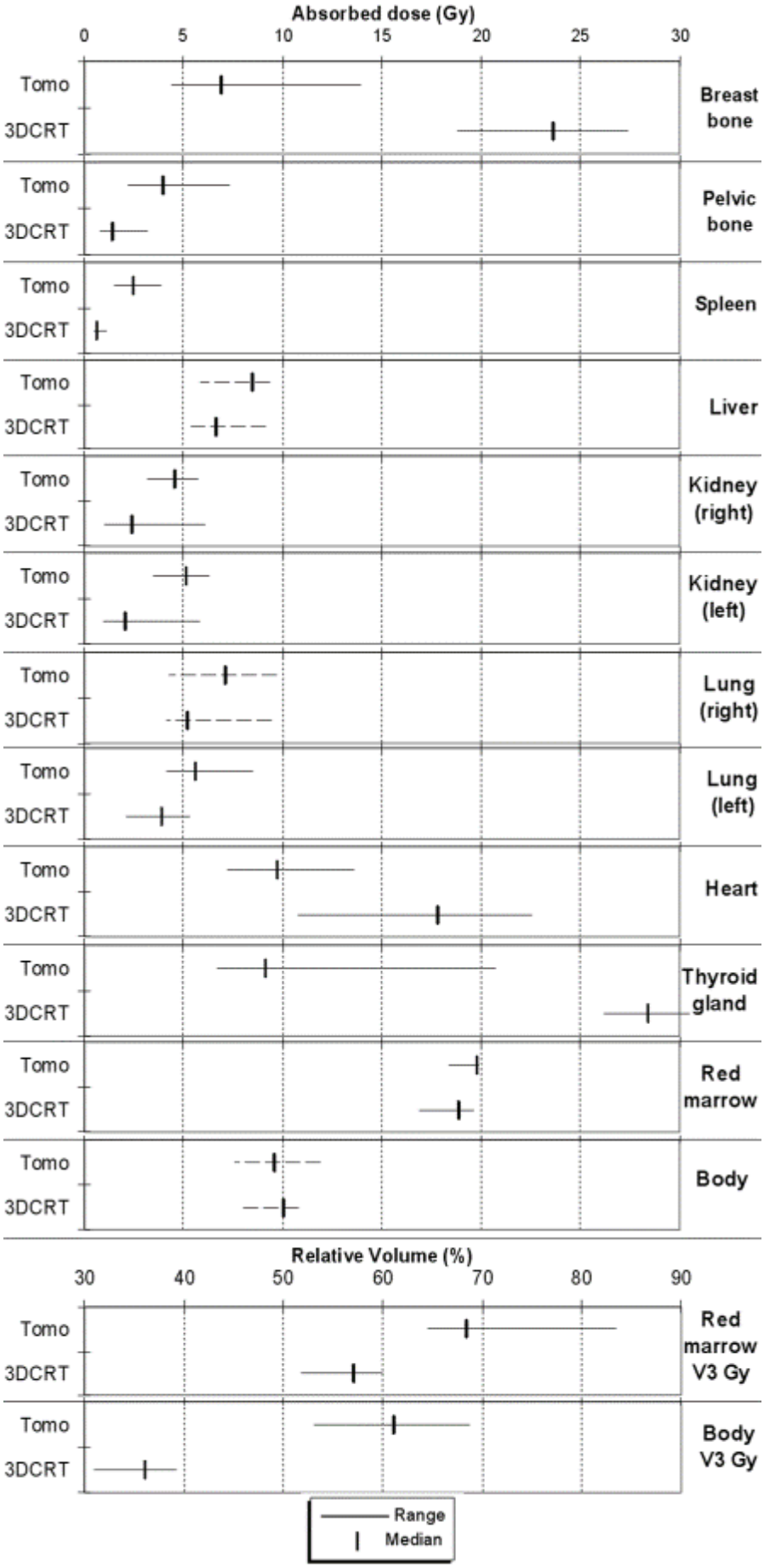
* Patients treated with helical tomotherapy
† Patients treated with three-dimensional conformal radiation therapy
†† Number of patients

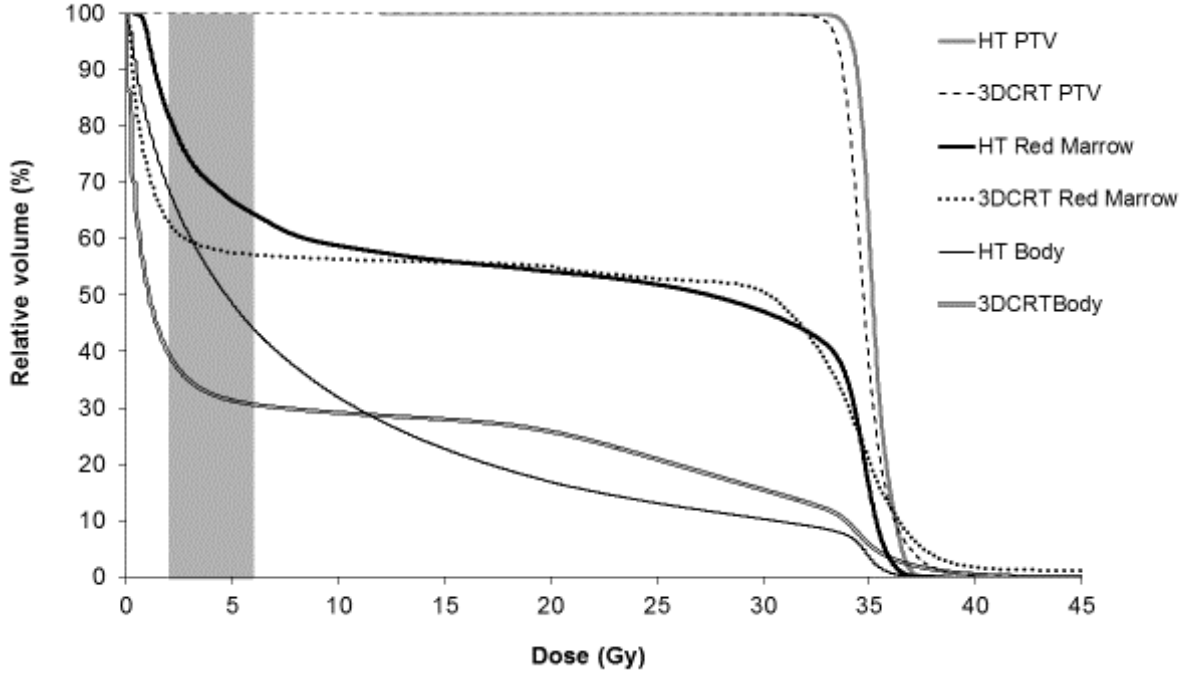
Figure Legends

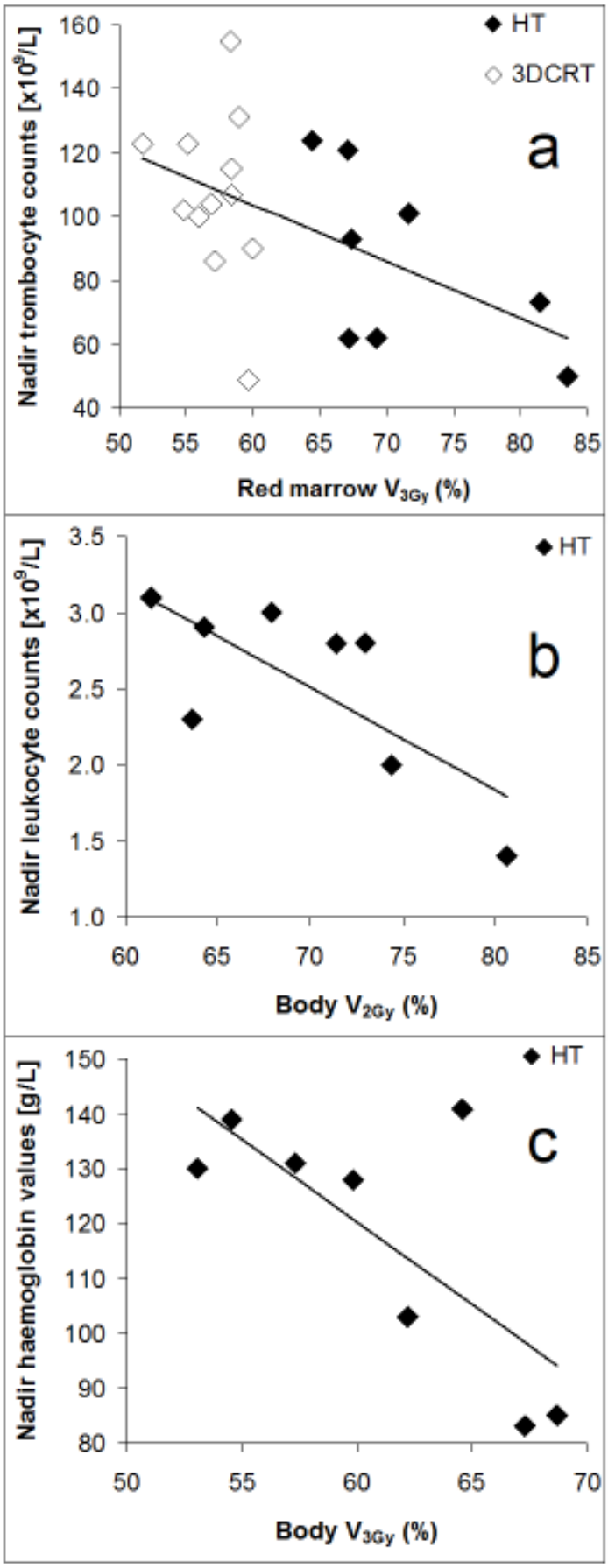
Figure 1: Mean absorbed doses for organs at risk, and relative volumes of red bone marrow and entire body that received ≥ 3 Gy, displayed on a population level for the treatment plans generated for craniospinal irradiation with helical tomotherapy (HT) or with three-dimensional conformal radiation therapy technique (3DCRT). Solid "Range" lines indicate that there is a significant difference between the treatment techniques, dashed lines means there is not.

Figure 2: A dose-volume histogram displaying the average dose-volume relationships of the planning target volume (PTV), body and red bone marrow, for patients treated with helical tomotherapy (HT) and patients treated with three-dimensional conformal radiation therapy (3DCRT) technique. The low-dose region between 2-6 Gy is emphasised.

Figure 3: Nadir thrombocyte counts (a), leukocyte counts (b), haemoglobin values (c) during radiotherapy treatment, and their correlation with the relative volume of red bone marrow that received a dose of ≥ 3 Gy, body that received a dose of ≥ 2 Gy, or body that received a dose of ≥ 3 Gy.


Absorbed dose (Gy)
0
5
10
15
20
25
30
Tomo
3DCRT
Breast bone
Pelvic bone
Spleen
Liver
Kidney (right)
Kidney (left)
Lung (right)
Lung (left)
Heart
Thyroid gland
Red marrow
Body
Relative Volume (%)
30
40
50
60
70
80
90
Red marrow V3 Gy
Body V3 Gy
Range
Median


Relative volume (%)
100
90
80
70
60
50
40
30
20
10
0
0
5
10
15
20
25
30
35
40
45
Dose (Gy)
HT PTV
3DCRT PTV
HT Red Marrow
3DCRT Red Marrow
HT Body
3DCRTBody


HT
3DCRT
a
Nadir trombocyte counts [x10⁹/L]
160
140
120
100
80
60
40
50
55
60
65
70
75
80
85
Red marrow V3Gy (%)
HT
b
Nadir leukocyte counts [x10⁹/L]
3.5
3.0
2.5
2.0
1.5
1.0
60
65
70
75
80
85
Body V2Gy (%)
HT
c
Nadir haemoglobin values [g/L]
150
140
130
120
110
100
90
80
50
55
60
65
70
Body V3Gy (%)

Supplementary Appendix Table 1: Patient and radiotherapy data for the cases involved in the study.

Patient	Age at diagnosis	Diagnosis	CSI* treatment dose(Gy)/# of fractions	Boost treatment dose(Gy)/# of fractions	RT† treatment period (days)	Concomitant chemotherapy
HT 1	25	PNET	35/20	20/10	45	yes
HT 2	20	Pineoblastoma, WHO grade IV	35/20 +9/5	12/6	45	yes
HT 3	31	PNET/Ewing sarcoma††, WHO grade IV	35/20	20/10	43	yes
HT 4	28	Neurocytoma WHO grad II	35/20	20/10	49	no
HT 5	23	Anaplastic ependymoma, WHO grade III	35/20	20/10	43	no
HT 6	29	Medulloblastoma	36/20	18/9	44	yes
HT 7	43	PNET	31.5/18 (discontinued)	-	31 (discontinued)	yes
HT 8	21	Medulloblastoma	35/20	20/10	44	yes
3DCRT 1	27	PNET	35/20	20/10	51	yes
3DCRT 2	28	PNET	35/20	20/10	43	yes
3DCRT 3	27	Medulloblastoma	35/20	20/10	61	yes
3DCRT 4	23	Pineoblastoma, WHO grade IV	35/20	20/10	53	yes
3DCRT 5	51	PNET	35/20	20/10	42	yes
3DCRT 6	32	Medulloblastoma	35/20	20/10	42	no
3DCRT 7	35	Medulloblastoma	35/20	20/10	39	no
3DCRT 8	34	PNET	35/20	20/10	41	no
3DCRT 9	40	Medulloblastoma	35/20	20/10	48	no
3DCRT 10	49	PNET	35.2/22	20/10	50	no
3DCRT 11	25	Medulloblastoma	35/20	20/10	42	yes
3DCRT 12	21	Pineoblastoma	35.2/22	19.2/12	49	yes

* Craniospinal irradiation
† Radiotherapy
†† LSI EWSR1 (22q12) rearrangement

Supplementary Appendix Table 2: Treatment planning protocol used for craniospinal irradiation (CSI) with helical tomotherapy (HT).

Priority	Structure	Constraints and objectives CSI (35 Gy)/ +Boost (55 Gy)
1	Clinical target volume (CTV)	*$D_{99\%}$† ≥33.5 Gy/52.5 Gy
2	Optic Chiasm / Optic nerve / Cochlea	*$D_{2\%}$† ≤ 35 Gy/45 Gy
3	Planning target volume (PTV)	$D_{99\%}$ ≥33.25 Gy/52.25 Gy
4	Pelvic bone	D_{mean}†† ≤ 3 Gy/3 Gy
5	Spleen	D_{mean} ≤ 3 Gy/3 Gy
6	Heart	D_{mean} ≤ 10 Gy/10 Gy
7	Thyroid gland	D_{mean} ≤ 10 Gy/10 Gy
8	Kidney	D_{mean} ≤ 5 Gy/5 Gy
9	Lung	D_{mean} ≤ 7 Gy/7 Gy
10	Breast (women)	D_{mean} ≤ 5 Gy/5 Gy
11	Liver	D_{mean} ≤ 8 Gy/8 Gy
12	Breast bone	D_{mean} ≤ 8 Gy/8 Gy
13	Retina	$D_{2\%}$ ≤ 30 Gy/45 Gy
14	Lens	$D_{2\%}$ ≤ 5 Gy/6 Gy
15	Lacrimal gland	D_{mean} ≤ 25 Gy/35 Gy
16	Eye	D_{mean} ≤ 15 Gy/25 Gy
17	Pituitary gland	D_{mean} ≤ 35 Gy/55 Gy
18	Parotid gland / Oral cavity	D_{mean} ≤ 15 Gy/26 Gy
19	Facial Skeleton	D_{mean} ≤ 15 Gy/25 Gy
20	Body	D_{max}†† ≤ 38 Gy/60 Gy
		$D_{45\%}$† ≤ 5 Gy/-

* Constraints
† The absorbed dose that covers 2 %, 45 %, or 99 % of the planning target volume.
†† The mean or maximum absorbed dose.

Supplementary Appendix Figure: The dose distributions in a transversal and in a sagittal slice for a craniospinal irradiation treatment with helical tomotherapy, shown above the dose distribution for a treatment with three-dimensional conformal radiation therapy technique.