

ORIGINAL ARTICLE

Does electron and proton therapy reduce the risk of radiation induced cancer after spinal irradiation for childhood medulloblastoma? A comparative treatment planning study

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Abstract

Aim. The aim of this treatment planning comparison study was to explore different spinal irradiation techniques with respect to the risk of late side-effects, particularly radiation-induced cancer. The radiotherapy techniques compared were conventional photon therapy, intensity modulated x-ray therapy (IMXT), conventional electron therapy, intensity/energy modulated electron therapy (IMET) and proton therapy (IMPT). **Material and methods.** CT images for radiotherapy use from five children, median age 8 and diagnosed with medulloblastoma, were selected for this study. Target volumes and organs at risk were defined in 3-D. Treatment plans using conventional photon therapy, IMXT, conventional electron therapy, IMET and IMPT were set up. The probability of normal tissue complication (NTCP) and the risk of cancer induction were calculated using models with parameters-sets taken from published data for the general population; dose data were taken from dose volume histograms (DVH). **Results.** Similar dose distributions in the targets were achieved with all techniques but the absorbed doses in the organs-at-risk varied significantly between the different techniques. The NTCP models based on available data predicted very low probabilities for side-effects in all cases. However, the effective mean doses outside the target volumes, and thus the predicted risk of cancer induction, varied significantly between the techniques. The highest lifetime risk of secondary cancers was estimated for IMXT (30%). The lowest risk was found with IMPT (4%). The risks associated with conventional photon therapy, electron therapy and IMET were 20%, 21% and 15%, respectively. **Conclusion.** This model study shows that spinal irradiation of young children with photon and electron techniques results in a substantial risk of radiation-induced secondary cancers. Multiple beam IMXT seems to be associated with a particularly high risk of secondary cancer induction. To minimise this risk, IMPT should be the treatment of choice. If proton therapy is not available, advanced electron therapy may provide a better alternative.

Primitive neuroectodermal tumour (PNET) of the central nervous system is the most common malignant brain tumour in children. The majority of these embryonal tumours are located in the posterior fossa and classified as medulloblastomas. The tumour is characterised by a high frequency of seeding or metastases; up to 40% have been reported [1]. The PNETs are usually sensitive to both chemo- and radiotherapy. Post-operative craniospinal radiother-

apy results in a 5-year survival between 55 and 70% for all stage groups [2]. The corresponding figure is 85% for standard-risk patients [3]. Accompanying the improvement in long-term survival, there is increasing concern about the late side-effects associated with radiotherapy, such as hormonal deficits, decreased bone growth, hearing loss, neuro-cognitive deficits, cardiac dysfunction, pneumonitis, stenosis of the oesophagus and secondary cancers.

Radiation-induced secondary cancer is a late side-effect of great concern in paediatric cancer treatment [4,5]. Several conformal techniques for treating the cranial part of the target volume have been described [6,7]. The classical conventional treatment of the spinal volume is a single posterior photon beam [8]. On the other hand, information about conformal treatment methods for the spine that minimise the dose to the cervical, thoracic and abdominal organs is quite scanty. This study focuses on radiation therapy of the spinal canal.

One approach to reducing the late side-effects associated with radiotherapy is to reduce the absorbed dose to the craniospinal axis. To date, when radio- and chemotherapy are combined, the total dose to the craniospinal axis has been successfully reduced from 35–36 Gy to 23.4 Gy, while maintaining a dose of 54 Gy to the posterior fossa, and this treatment protocol results in a lower risk of long-term side-effects [9]. Further dose reduction to 18 Gy led to an increased risk of recurrences and a similar risk of side-effects [10]. Thus, improving radiotherapy techniques is essential.

Another approach to reduce the risk of late side-effects is to decrease the dose to the organs outside the target volume while maintaining the dose to the tumour target. Some techniques could potentially be used for this aim, i.e. intensity modulated x-ray therapy (IMXT), conventional electron beam therapy or intensity and energy modulated electron (IMET) or intensity modulated proton therapy (IMPT). IMXT can improve the conformity of the dose distribution to the target, compared with three-dimensional conformal radiotherapy (3-D CRT), but it delivers a larger integral dose to the surrounding normal tissues [11]. This might be a critical risk factor for radiation-induced secondary cancer in long-term survivors [12].

The use of high energy electrons in spinal cord irradiation was recommended already in the early 1980s [13]. The expected benefit was related to the limited range of the electron beams and the accompanying dose reduction to the organs anterior to the vertebral column. However, due to dose calculation uncertainties inside the patient and poor delivery techniques, the use of electrons in medulloblastoma treatment has been limited. So far, only a few retrospective clinical reports using high energy electrons in craniospinal irradiation have been published [14–17]. It is likely that electron therapy results in a tumour control rate comparable to that of conventional photon therapy, with less acute side-effects and a similar rate of late side-effects. IMET techniques are under development [18–20]. High quality electron beams are available in racetrack microtrons (MM50, IBA, Belgium) [21] or can be

obtained by modification of the treatment head of general linear accelerators [22]. Therefore, we aim to re-investigate the use of electrons in medulloblastoma radiotherapy.

Proton beams have physical properties that might be especially beneficial in paediatric patients [23]. The usefulness of protons in medulloblastoma radiotherapy has been reported previously [7,16,24].

The aim of this treatment planning comparison study was to explore different techniques for spinal irradiation with respect to the risk of some late side-effects, particularly radiation-induced secondary cancer. The radiotherapy techniques compared were conventional photon therapy, IMXT, conventional electron therapy, IMET and IMPT.

Material and methods

CT images for radiotherapy use from five children diagnosed with ‘standard-risk’ medulloblastoma were selected for this study. Two subjects were girls and three were boys; the median age was 8 (6–11) years. The planning CT was obtained with the children in the prone position in a treatment immobilization device. The increment of the CT slices was 10 mm in the thorax and 5 mm in the rest of the volume. Clinical target volumes (CTV) comprising the entire subarachnoid theca and the intervertebral foramina were outlined in each transverse CT slice from C₅ to S₂. The S₂ was defined as the inferior border of the CTV for all patients [25]. The planning target volume (PTV) was obtained by expanding a margin of 3 mm in the ventral direction from the CTV, and of 5 mm in other directions in the transversal plane. To prevent the risk of uneven bone growth, the vertebral bodies were considered to be a secondary target. The thyroid gland, lungs, heart, oesophagus, kidneys, liver, pancreas, stomach, abdominal cavity (i.e. the remaining normal tissue in the abdominal cavity) and mammary glands in girls were determined to be organs-at-risk (OARs). The patient outline, excluding the already defined targets and OARs, was also considered to be an OAR and was included in the treatment plan evaluation.

The total prescribed dose was 23.4 Gy, administered in 13 daily fractions of 1.8 Gy to the PTV as stipulated in the recent Société Internationale d’Oncologie Pédiatrique (SIOP) PNET4 study [26]. The prescribed dose for IMPT treatment was converted to the biological equivalent dose (23.4 EGY) by applying a relative biological effectiveness (RBE) factor of 1.1 for proton therapy. All dose plans were normalised to the mean dose of the PTV for comparison, since the reference point defined in ICRU 50 [27] could not be applied to all plans.

The 6 MV photon beam generated from a linear accelerator was used for the conventional photon (Primus, Siemens AG, Erlangen Germany) and IMXT (Clinac 2100, Varian Medical Systems inc, Palo Alto USA) planning. High energy electrons generated from a MM50 racetrack microtron (MM50, IBA, Belgium) were used for conventional electron and IMET planning. The electron energy range was 7.5–50 MeV with 2.5 MeV energy steps. Theoretical data for a proton beam with spot-scanning was used for the IMPT technique. The beam spots were modeled as a product of a realistic depth dose curve and a lateral Gaussian distribution with a depth-dependent variance σ . The initial σ on the patient surface was assumed to be 3 mm which broadens with increasing depth, according to the principle of multiple Coulomb scattering. More details about the dose model can be found in [28].

Treatment techniques

Conventional photon technique. The treatment planning system (TPS) was Helax-TMS version 6.1 (Nucletron B. V., The Netherlands). A single posterior 6 MV photon beam was used to cover the PTV. Dose variation within the primary target was aimed at $\pm 10\%$. In order to avoid irradiation of the thyroid, the cranial part of the PTV was treated with lateral opposed beams. A pencil beam algorithm was used for dose calculation and verified with a collapsed cone algorithm in Helax-TMS. The dose distributions were similar irrespective of the method used.

IMXT. The treatment plans were created with inverse planning technique using Helios software in the Eclipse treatment planning system (Varian Medical Systems, Finland OY, Finland). The intensity-modulated beams were delivered with a dynamic MLC technique. Five isocentric beams, at gantry angles of 300, 325, 0, 35 and 60 degrees, were used for best avoidance of the OARs. The same beam setting was used for both isocentres. The maximal obtained length of the optimised cranial-caudal dose distribution in the TPS was about 35 cm. Due to this limitation, two isocentres had to be selected in order to cover the PTV. The gap on the patients' skin was between 4 and 9 mm, and it was moved 20 mm downward or upward after half of the treatment. The gap was positioned below the heart level. The isocentres were placed close to the matching line in order to minimise dose divergence in the beam junction. The dose constraints for PTVs and OARs are shown in Table I.

Table I. The dose constraints for OARs in IMXT, IMPT and IMET.

	Volume (%)	Dose (Gy)
Targets		
PTV	<5%	Max. 23.6
	<5%	Min. 23.4
Vertebral body	<5%	Min. 18.7
	<5%	Max. 23.6
OARs		
Oesophagus	10%	10
	75%	5
	2.6%	1.75
Thyroid	25%	0.5
Heart	75%	0.5
Mammary glands	10%	1
	50%	0.5
No Constraints defined for other OARs		

Conventional electron technique. The TPS was Helax-TMS 6.1 (Nucletron B. V., The Netherlands) with the electron dose calculated by a pencil beam algorithm. A single posterior high energy electron beam was divided into 2–3 sub-fields. Either 20 MeV or 25 MeV were selected for each sub-field according to the depth of the PTV. The beam weight of each sub-field was adjusted to reach the dose constraints for the PTV and the vertebral bodies. The dose variation within the primary target was aimed at $\pm 10\%$. The dose distribution in the vertebral bodies was required to be similar to that of the conventional photon plans. No dose constraints were used for OARs. Maximum electron energy of 25 MeV was chosen because most clinical accelerators cannot produce energies above that level. In cases of insufficient dose to the distal part of the PTV, a 6 MV photon beam was added through the same beam portal as the electron beam [19]. In two of the five cases, mixed photon and electron beams were used to cover the lumbo-sacral spine.

IMET. The IMET plans were produced in a modified research version of the KonRad program (DKFZ-Heidelberg, Department of Medical Physics, Germany) with Monte Carlo pre-calculated pencil kernels and density corrections performed by density-range scaling. Primary energy selection for the single posterior beam was performed according to a previously described method [20]. The energy was modulated by adding two additional energy layers consisting of -2.5 MeV and $+2.5$ MeV, respectively. The applied dose constraints are shown in Table I. In order to compare the calculations of electron doses by the KonRad and TMS systems used in this study, the conventional electron

plans produced with the TMS system were recalculated in the KonRad system. The differences between the calculated mean doses in the various structures were typically less than 5%.

IMPT. The optimisation system used for IMET was also applied for proton optimisation. The system uses an intensity modulated proton pencil beam algorithm [28]. The dose constraints applied are shown in Table I. A single posterior beam was used. The maximum energy was 160 MeV and the beam energy was modulated with a range shifter. The spatial grid size for the lateral scanning of beam spots was chosen to be 3 mm projected on the isocentre plane. The same size, 3 mm, was also adopted for the scanning distance in depth.

Dose plan evaluation

Since the conventional photon technique has a long history and has been used extensively, it was used as a baseline for comparisons. Dose volume histograms (DVH) for targets and OARs were obtained for dose planning evaluation. The average mean doses to the OARs for the five patients were calculated and are presented in Table II.

The normal tissue complication probability (NTCP) was estimated for a number of OARs and endpoints of interest. The NTCP models used in this study were the relative seriality model (RS model) [29] and the Lyman-Kutcher-Burman model

(LKB model) [30–32]. The calculation was performed with the BioPlan program [33]. The probabilities of acute side-effects, such as radiation pneumonitis [34] and radiation hepatitis [35], and late side-effects, such as radiation-induced ischemic heart disease [36], oesophagus stricture [37] and small and large bowel obstruction (the abdominal cavity volume was used for calculation) [32], respectively, were estimated. The DVHs were converted to 2 Gy/fraction regimes by application of the linear quadratic model [38], since the parameters of NTCP models were derived based on the assumption that the fraction dose is close to 2 Gy. The α/β values used for DVH conversion were taken from [39].

The risk of secondary lethal cancer (SLC) was estimated according to the model recommended in the ICRP recommendations [40]. The probability of SLC is the product of the effective dose (E) and the nominal probability coefficient of SLC, and E can be expressed by

$$E = \sum_T W_T \cdot \sum_R W_R \cdot D_{TR} \quad (1)$$

in which D_{TR} denotes the mean absorbed dose in a tissue or organ (T), due to incident radiation (R), and W_R and W_T are the radiation modality and tissue weighting factors, respectively.

The dose to red marrow and bone surfaces were not included in the calculation of the effective dose; thus, only the risk of lethal solid cancers was

Table II. Mean absorbed dose in the volumes of interest (average for the five cases).

	Photon Gy (s.d.)	IMXT Gy (s.d.)	Electron Gy (s.d.)	IMET Gy (s.d.)	IMPT Gy (s.d.)
Target					
PTV					
Minimum dose	20.4 (0.5)	19.8 (1.5)	19.5 (0.4)	18.1 (0.6)	19.0 (0.9)
Maximum dose	26.0 (0.2)	26.8 (1.3)	25.6 (0.5)	27.4 (0.8)	27.2 (1.5)
Mean dose	23.4 (0.0)	23.2 (0.2)	23.4 (0.0)	23.3 (0.0)	23.5 (0.4)
Vertebral bodies					
Minimum dose	17.6 (0.8)	15.1 (1.3)	12.9 (4.0)	12.7 (0.6)	11.7 (0.9)
Maximum dose	24.8 (0.5)	26.4 (1.6)	25.5 (0.5)	24.8 (0.3)	25.9 (0.1)
Mean dose	19.5 (1.4)	20.7 (0.6)	19.9 (1.1)	20.1 (0.4)	22.1 (0.1)
OARs (Mean doses)					
Thyroid	8.2 (6.3)	4.7 (0.5)	6.3 (3.1)	3.8 (0.3)	0.0 (0.0)
Mammary glands	0.3 (0.2)	0.9 (0.2)	0.2 (0.1)	0.3 (0.0)	0.0 (0.0)
Heart	11.9 (0.9)	4.8 (0.3)	6.1 (1.0)	2.2 (0.5)	0.0 (0.0)
Oesophagus	18.2 (0.6)	13.2 (0.7)	16.2 (1.1)	9.4 (0.7)	2.3 (0.4)
Lung	3.0 (0.6)	6.5 (0.5)	3.2 (0.6)	2.0 (0.5)	2.2 (0.1)
Liver	5.5 (0.4)	5.6 (0.2)	2.2 (0.3)	1.2 (0.3)	0.0 (0.0)
Pancreas	13.5 (2.7)	9.2 (1.6)	6.0 (1.6)	4.9 (1.7)	0.0 (0.0)
Spleen	0.6 (0.2)	3.8 (0.5)	0.4 (0.3)	0.2 (0.1)	0.0 (0.0)
Stomach	4.1 (1.4)	6.9 (0.8)	3.2 (1.4)	1.8 (0.6)	0.1 (0.1)
Kidney	2.7 (0.5)	8.9 (0.7)	3.3 (0.8)	1.7 (0.4)	1.3 (0.1)
Abdominal cavity	6.7 (0.9)	7.6 (0.9)	4.7 (1.0)	3.3 (0.7)	0.2 (0.1)
Patient outline	4.7 (0.6)	5.3 (0.2)	4.0 (0.8)	2.2 (0.3)	1.2 (0.1)

considered. The probability of solid SLC has been estimated to 0.045 based on ICRP (Table IV) for the entire population and has been further adjusted for children by multiplying with a factor of 2.5 [40].

Based on the assumption of a linear dose-response relationship up to 4 Gy and of a dose-independent relationship for doses exceeding 4 Gy [12], a corrected mean dose to each outlined structure was calculated from DVH data. This means that all doses of >4Gy in the DVH were given the value of 4 Gy. For use in models relating to radiation protection, a dose-rate effectiveness factor of 2 was included by ICRP [40]. This factor has been retained and considered as relevant for the present purpose as well [12]. A value of 1 for W_R was used for photon and electron beams, and 2 for proton beams [41]. The W_T factors recommended in the ICRP 60 [40] were used (Table III). The bone (red marrow and bone surface) and gonad factors were not included; thus, the sum of the weighting factors was equal to 0.67 (it would have been 1, had the entire body been considered). Therefore, the sum of the weighted effective doses in considered organs was renormalized (divided by 0.67). The interleaf leakage in IMXT was not included in the estimate.

Statistics

The two-sided Wilcoxon signed ranks test was used for statistical inference of paired samples.

Results

Table II shows some dose distribution parameters for the volumes of interest in this study. All five techniques produced a clinically acceptable dose distribution in the primary and secondary targets. The mean, maximum and minimum doses were similar for the PTV, as was the case for the vertebral bodies, but the minimum doses were slightly lower for all techniques, compared with conventional photons. However, the volume of the vertebral target receiving the low doses was small in all plans. CT sections and dose distributions are shown in Figure 1.

The absorbed doses in the OARs varied considerably with the treatment technique used (Table II). IMPT resulted in a significantly lower mean dose to the different OARs, except for the lungs, compared with all other techniques, and many of the OARs escaped irradiation. IMXT delivered significantly higher mean doses to the breast, lung, spleen, stomach and kidney than the conventional photon and electron techniques. As might be expected, conventional photon and electron techniques yielded the highest doses to the thyroid and oesophagus. Lower mean doses were observed to most OARs with IMET than with the IMXT, photon and electron beam techniques.

Applying the different NTCP models resulted in calculated probabilities for acute and late side-effects, for all techniques, that approached zero for all OARs.

Table III. Estimates of the risk of secondary lethal cancer (solid cancers).

	W_T	Photon		IMXT		Electron		IMET		IMPT	
		DTR (Gy)	$E_{TR} \times$ W_T (Sv)	DTR (Gy)	$E_{TR} \times$ W_T (Sv)	DTR (Gy)	$E_{TR} \times$ W_T	DTR (Gy) (Sv)	$E_{TR} \times$ W_T (Sv)	DTR (Gy)	$E_{TR} \times$ W_T^a (Sv)
Oesophagus	0.05	3.95	0.20	4.00	0.20	3.99	0.20	3.99	0.20	1.44	0.13
Thyroid	0.05	2.98	0.15	3.01	0.15	3.58	0.18	3.22	0.16	0.01	0.00
Lung	0.12	1.43	0.17	3.12	0.37	1.77	0.21	1.03	0.12	0.15	0.02
Mammary glands	0.05	1.05	0.05	2.35	0.12	0.68	0.03	0.05	0.00	0.01	0.00
Liver	0.05	2.15	0.11	3.05	0.15	1.73	0.09	0.92	0.05	0.02	0.00
Stomach	0.12	2.03	0.24	3.67	0.44	2.22	0.27	1.27	0.15	0.04	0.01
Abdominal cavity	0.20 ^b	1.17	0.23	1.69	0.34	1.23	0.24	0.96	0.19	0.06	0.02
Patient outline	0.03 ^c	0.82	0.02	1.11	0.03	1.33	0.02	0.38	0.01	0.15	0.01
Effective dose ^d			1.761		2.696		1.863		1.326		0.306
Total risk of SLC			0.198		0.303		0.210		0.149		0.034 ^e

D_{TR}: Average values for the five cases of mean absorbed dose in each organ after correction [12].

W_T: Tissue weighting factors. Gonads, red marrow and bone surface were excluded [40].

E_{TR}: Equivalent dose: effective dose to each organ.

^a: a beam quality factor of 2 was applied to proton technique [41].

^b: W_T includes the factors for colon, urinary bladder and remaining organs (adrenals, small intestine, kidneys, pancreas spleen and uterus).

^c: W_T includes the factors for skin and remaining organs (brain, muscle and thymus).

^d: Sum of weighted doses renormalized with the sum of considered weighting factors.

^e: the total risk of SLC for IMPT is 0.040 when the contribution of neutron is taken account.

SLC: secondary lethal cancer.

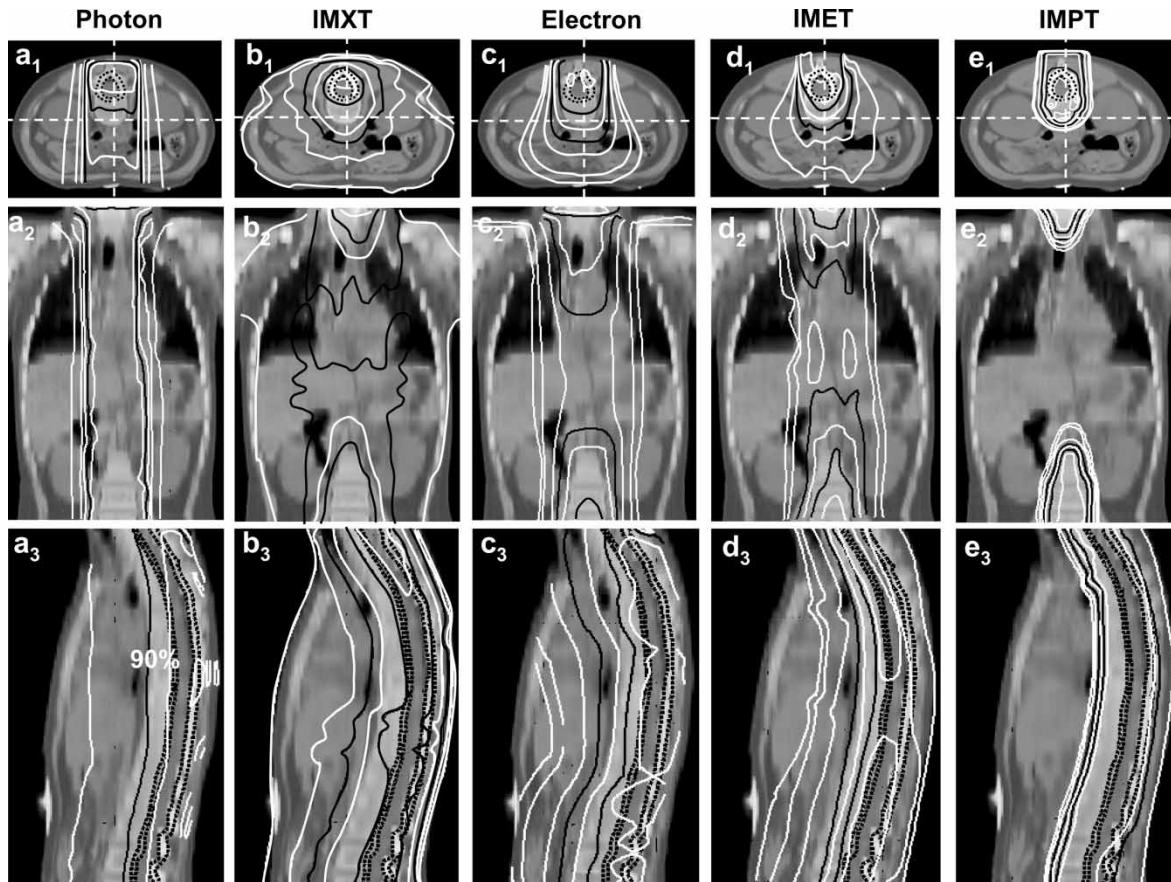


Figure 1. Dose distributions for Patient 2, showing the conventional photon (a₁–a₃), IMXT (b₁–b₃), conventional electron (c₁–c₃), IMET (d₁–d₃), IMPT (e₁–e₃) plan in a transverse (a₁–e₁), sagittal (a₂–e₂), and coronal (a₃–e₃) sections. The PTV and CTV are delineated with the dark dotted lines. Isodoses are, in percentage, 5%, 10%, 30%, 50%, 70%, 90%, and 100%. Isodose lines of 50% and 90% are in solid black lines, others are in white.

Table III shows the mean doses (D_{TR}) to OARs and the corresponding risks of SLC. There is a large variation in the estimated risk depending on the technique used. The highest estimated risk of SLC was equal to 30% after IMXT, while the lowest was 4%, after IMPT. In the case of the proton technique we also estimated the potential contributions from secondary neutrons by using measurements and Monte-Carlo simulations performed by Schneider et al. 2002 for the PSI treatment facility [42]. They observed an additional dose burden to OARs, due to secondary neutrons, ranging from 0.002 Sv to 0.004 Sv per treatment Gy. Based on these numbers, a conservative estimate of the effective neutron dose accumulated in all OARs leads to an additional dose burden of 0.002 Sv (i.e. the total effective dose was 0.047 Sv); the contribution of neutrons to the risk of SLC should thus be in the order of 1%. The effective dose from IMXT was significantly higher than that from the other techniques ($p=0.002$ in all patients). IMET resulted in a lower effective dose, compared with conventional photon beam, IMXT and conventional electron beam ($p=0.002$ in all patients).

IMPT resulted in the lowest effective dose in all comparisons ($p=0.002$ in all patients). Conventional photon and electron techniques resulted in similar effective doses.

Discussion

The NTCPs predicted by different biological models for the considered endpoints were very low for all five techniques, despite the considerable variation in absorbed dose to the surrounding OARs. This is probably due to the low total dose. However, the predictive ability of the NTCP models has actually not been fully tested as yet, especially in the case of late side-effects (e.g. cardiac mortality). Another noteworthy aspect when using NTCP models is that the dose distribution and clinical data on which the models are based reflect irradiation conditions in the specific patient groups. To our knowledge, no available NTCP parameters are based on data sets derived from a paediatric population. Furthermore, the relevant end-points in a paediatric population might not always be the same as in an adult

population. In paediatric populations more data for end-points such as, hormonal deficits, retardation of bone growth etc. are needed. Under these circumstances, minimization of the dose outside the target volumes is the appropriate general therapy principle. The largest reduction of absorbed dose outside the target volume was achieved by IMPT. IMXT also reduced the mean dose to heart and thyroid to 60% and 50% respectively, compared with conventional photon technique. The conventional electron technique also reduced the mean dose to heart and thyroid to 50% and 25%, respectively, and IMET reduced it further. This might be a clinical advantage of IMXT and electron techniques, i.e. improving the rates of radiation-induced hypothyroidism and cardiovascular disease [5], in the absence of available more advanced techniques.

Several reports have been published concerning secondary cancer in long-term survivors of childhood cancer [4,5,43]. Radiation therapy is the most important risk factor for secondary cancer; the risk is further increased when chemotherapy is added [44]. Low age at the time of treatment, high radiation dose and longer follow-up are factors that increase the risk of secondary cancers. The interval between primary cancer treatment and secondary cancer diagnosis is usually 5–15 years, but the risk keeps rising at 20–30 years follow-up [43]. The estimated risk of SLC was about 20% for conventional photon therapy and similar for conventional electrons. The corresponding risk was about 30% for IMXT, without including the extra absorbed dose due to interleaf leakage etc. The main reason for this is the large number of beams used for achieving a highly conformed, high radiation dose to the target, whilst a low radiation dose is delivered to a large volume of normal tissue. IMET treatment was predicted to yield a lifetime risk of 15%. The difference between conventional electrons and this technique is probably due to the use of a larger number of segments, allowing better dose distribution conformity. Another important factor might be that higher electron energies (maximum 40 MeV), which make the use of additional photon beams for target coverage, are obsolete. However, the vast majority of clinical accelerators do not currently have the capacity to deliver these high electron energies. In this context, the IMET technique was used to explore the potential of advanced electron therapy. IMPT resulted in the lowest risk estimates, 4%. The physical properties of protons seem almost optimal for this patient group. However, the production of neutrons may be a problem in the treatment rooms; even low physical doses of neutrons might increase the risk substantially. In the case of spot-scanned proton beams, the neutron contribution can be very low [42].

Although the ICRP model for cancer induction was not originally intended for radiotherapy [40], it is one of the few models available today that can be applied in this situation. In radiation protection, lower doses than those relevant for radiotherapy are usually considered. However, in [12], the dose range in which the risk of cancer increases linearly with dose is discussed. Their conclusion is that the risk of cancer induction levels out at doses above about 4 Gy. This hypothesis was taken as an assumption in this study, which might make the estimates of risk slightly conservative. On the other hand, any effects of cell kill and a consequent decrease in cancer risk at high doses were not taken into consideration due to the lack of available data on which to base such a correction. The absolute risks in this study should probably be regarded with caution due to uncertainties in the estimates. However, the relative differences between the treatments are probably only slightly influenced by these uncertainties.

In this model study, the estimated lifetime risk of SLC after conventional photon or electron radiotherapy is 20%. In a study of 1 262 medulloblastoma patients, 20 second cancers were diagnosed as compared with the expected 3.7 [48]. The average follow up was less than 5 years. For children exposed to radiation, the peak incidence of SLC is expected to occur between the sixth and the eighth decades of their lives [40]. Thus, an observation time longer than 50 years would be necessary for confirming the incidence of SLC in this population. In a later study on 446 patients that had undergone radiotherapy in childhood and survived for a minimum of 5 years, 26 developed second cancers whereas 5 would be expected [4]. The same authors estimate the cumulative risk for developing a second cancer to 13% after 30 years, and still the cumulative risk curve does not reach the plateau. It is not possible to verify the estimates of the risk for SLC in this model study by comparisons with published clinical data since the observation times are still too short. However, it can be concluded that radiotherapy in childhood leads to a significant risk for second cancers.

Bone deformity after electron radiotherapy is rarely reported in the literature [14]. The dose gradient to the vertebral bodies has usually been considered to be a cause of bone deformity. In this study, the vertebral bodies were considered as a secondary target, and a sufficient dose was delivered for avoiding uneven bone growth. It was reported that a dose of 20 Gy was considered as a critical dose to arrest bone growth [45,46]. In addition, the mean absorbed dose in the vertebral bodies was about 20 Gy with conventional photon treatment. Therefore, a mean dose of 20 Gy was used as a goal for the other treatments in this study. The low minimum

dose to the secondary target might cause concerns about uneven bone growth; however, the volume of vertebral bodies receiving the low dose might be too small for any effects to be noticeable. Furthermore, when kilovoltage X-ray was used for spinal canal radiotherapy, the minimum dose to the vertebral bodies was down to 9–11 Gy. No bone deformity was found in the long-term survivors [47].

In conclusion, this model study shows that spinal irradiation of young children results in a substantial risk of radiation-induced secondary cancers after treatment with photon and electron techniques. Multiple beam IMXT seems to be associated with a particularly high risk of secondary lethal cancer induction. To minimise this risk, IMPT should be the treatment of choice. If proton therapy is not available, advanced electron therapy may provide a better alternative to conventional photon therapy, provided that the algorithms for dose calculations are valid.

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