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Two compound techniques for total body irradiation

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A R T I C L E I N F O

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A B S T R A C T

Introduction: Total body irradiation (TBI) is an important treatment modality that is used in combination with chemotherapy in many stem cell transplantation protocols. Therefore, the quality of the irradiation is important. Two techniques for planning and delivering TBI are presented and compared.
Methods and materials: The technique named ExIMRT is a combination of manually shaped conventional fields from an extended SSD and isocentric IMRT fields. The technique named ExVMAT is a combination of conventional and IMRT fields from an extended SSD and isocentric VMAT fields. Dosimetric data from 32 patients who were planned and treated according to one of the two techniques were compared.
Results: When comparing the two techniques, it is determined that the ExVMAT technique is able to significantly reduce the mean total volume overdosed by 120% from 408 to 12 cm^3. The dose covering 98% of the total lung volume is significantly increased by this technique from a mean of 9.7 Gy to 10.3 Gy. Additionally, the dose covering 2% of the total kidney volume is significantly decreased from a mean of 12.8 to 12.5 Gy. Furthermore, the population-based variance of the median dose to the total lung volume, the heart and the volume of the body prescribed to 12.5 Gy is significantly reduced. The results are obtained without compromising overall treatment quality as treatment time or dose rate to the lungs.
Conclusion: Using the ExVMAT technique, a superior dose distribution can be delivered both from a patient and a population perspective compared to the ExIMRT technique.

Introduction

High-dose total body irradiation (TBI) is a radiotherapy modality in which the whole body is irradiated. Typically, the body is irradiated to a mean of 12–15 Gray (Gy) in 8–12 fractions with one to three fractions a day over three to six days [1-6]. This modality is a part of the treatment of systemic hematologic malignancies [1-5,7]. Chemotherapy and bone marrow transplantation are an effective treatment regimen in combination with TBI [8,9]. However, side effects have to be considered [2,5,10-12]. Acute side effects typically seen are nausea, diarrhea, headache, fever and fatigue. A large collection of late effects has been observed, among others secondary malignancies, pneumonitis, nephritis, cataracts and infertility [2,4,10,12]. The treatment technique applied must be able to homogeneously treat all parts of the body to the prescribed dose. Underdosed regions may cause a recurrence, and overdosed regions may cause complications. Different techniques for planning and delivering TBI are used [6,13-15]. Treatment techniques that utilize extended source-to-skin distance (SSD) fields are among these [16-19]. Traditionally, the lungs are shielded with blocks, but this shielding causes unwanted dose inhomogeneities. An extended SSD treatment technique was adapted at our hospital. To improve the dose homogeneity, the technique was modified by applying a compensating IMRT boost given at four out of seven fractions under standard isocentric conditions (source-to-axis distance (SAD) of 100 cm) to the thorax. This technique is named extended SSD with IMRT boost (ExIMRT).

A new technique was devised that in addition to conventional extended SSD fields applies supplementary extended SSD intensity modulated radio therapy (IMRT) fields and a volumetric modulated arc therapy (VMAT) boost given at four out of seven fractions under standard isocentric conditions. The aim was to improve the dose homogeneity, to reduce the patient-to-patient variation and to automate the planning process without compromising other plan qualities as dose rate to the lungs and treatment time. This newly developed technique was named extended SSD with VMAT boost (ExVMAT) technique. The aim of this work is to describe the treatment planning procedure for both techniques and to compare them.

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Materials and methods

This study is based on data from 32 treated patients treated from 2016 to 2020. The patient material is not large but includes all patients available for study. Of these patients, 17 were treated with ExIMRT and 15 were treated with ExVMAT. All patients were adults with ages ranging from 18 to 66 years.

Prescription

The prescription for both techniques is a mean body dose of 12.5 Gy given over seven fractions with two fractions a day. For the lungs, the prescription is a mean dose of 11.0 Gy, and for the brain, heart and kidneys, the prescription is a mean dose between 11.25 and 12.5 Gy.

Beam quality

Generally, low photon energy is preferable to high photon energy because of the better dose coverage of the skin. However, high beam energy is, appropriate for regions with large patient thickness. In our case, low energy means 6 MV, and high energy means 15 MV. The extended SSD fields are treated with a fixed rate of 200 MU/min, and the VMAT/IMRT fields are treated with a maximum rate of 300 MU/min.

Patient preparation CT scanning and delineation

The patients were fixated with the arms above the chest using vac-fix cushions in the same way for both techniques. A total of three cushions were used a large underlying and two minors under the knees and under the arms. The joining of the cushions was guided by tape markers. A one-centimetre thick Plexiglass spoiler was placed on both sides of the couch. The function of a spoilers during irradiation is to provide electrons that contribute to the dose in the outermost layer of the patient [18,20]. The CT scan comprised the whole body and was made with a slice thickness of 3 mm. Treatment planning was performed with the Eclipse planning system (Varian Medical Systems).

For both techniques the body, lungs, heart, kidneys and brain are delineated. A volume named "PTV" is derived from the body by adding a

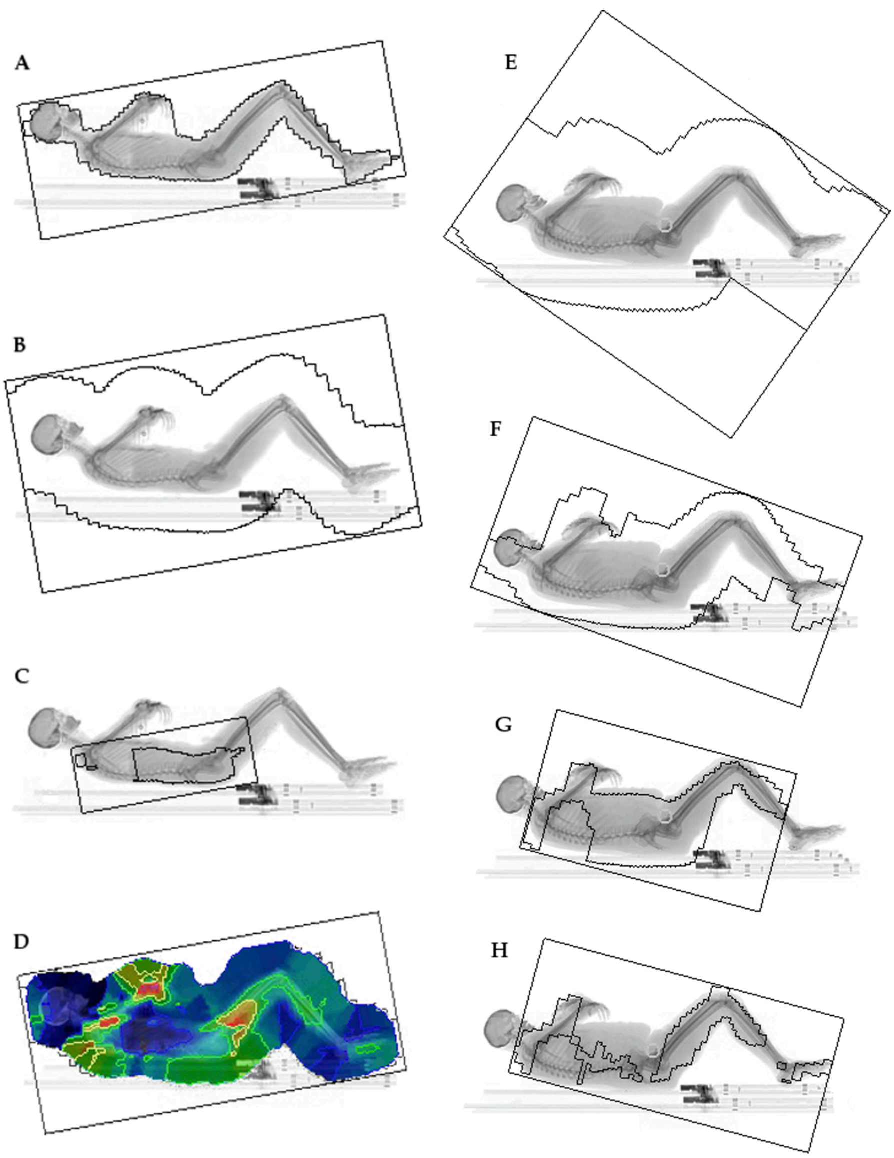

Fig. 1. A selection of fields used for the ExVMAT technique including a setup field (A), a field with low energy (B), a field with high energy (C) and an IMRT field (D). The fluence map is illustrated in colour. Additionally, an example of the main field (E) and three forward planned field segments (F-H) from the treatment using the ExIMRT technique.

negative margin of 5 mm. For the ExVMAT technique several additional structures are needed. The spoilers are not present during the CT scan and have to be manually introduced prior to the treatment planning. The spoilers have their Hounsfield unit set equal to water and added to the contour of the body.

Treatment set-up

Assuming unlimited space in the treatment room, the set-up for both techniques could be performed as follows. The lateral fields used for treatment have gantry angles of 85 and 275 degrees. The patient is placed on a free-standing and movable couch. The midline of this couch is placed 336.5 cm to the left and later symmetrically to the right side of the accelerator isocentre. Because of the gantry angulation the central axis of each field will decent 29.4 cm below the isocentre over the 336.5 cm. To accommodate this decent the surface of the couch is placed 50 cm below the isocentre of the accelerator. In this geometry the maximum field size at the couch midline is close to 175.1 × 175.1 cm, which is enough to circumscribe the crouching patient.

Because the space in the used treatment room is limited only extended SSD fields from one side were treatable. To treat fields from the other side, the patient was rotated from the head first to the feet first position, and the fields in question were modified by interchanging the gantry angle between 275 and 85 degrees and rotating the collimator 180 degrees.

The placement of the patient was assisted from each side by light from a setup field with an MLC (multileaf collimator) fitted to the outline of the patient (Fig. 1.A). At the first treatment session the position of the vac-fix cushions was marked on the movable couch with coloured tape to assist the placement on the following sessions. The light field from all field segment was prior to irradiation at the first treatment session manually checked with a maximum allowed deviation of 1 cm. After a satisfactory setup, the position of the legs of the movable couch was marked with coloured tape on the floor to assist patient setup at later sessions. The supplementary boost, that irradiated the volumes adjacent to the lungs was given under isocentric conditions on the standard treatment couch on four treatment sessions using the same fixation. The patient setup was guided by a cone beam CT.

The ExIMRT technique

The ExIMRT technique consists of conventional extended SSD fields encompassing the whole body with a wide margin (Fig. 1.E). These fields are supplemented with several manually forward planned field segments (Fig. 1.F-H). No special structures are needed for the planning of this technique. The planning aims at irradiating the whole PTV with 90% of the prescribed dose, and at the same time restrict the dose to the brain, heart, kidneys and especially the lungs. High-energy photons may be used but only for segments avoiding the lungs [10]. After optimization, the residual volume treated below 90% of the prescribed dose is identified. This volume is typically located in the upper thoracic region. The boost plan irradiates this volume typically with five to seven coplanar IMRT fields under standard isocentric conditions on the treatment couch of the accelerator. Noncoplanar field arrangements can be used. The combined doses obey the dose constraints presented in Table 1.

Table 1
Dose constraints that applies to the critical organs.

Volume	Constraint regarding the mean dose	Constraint regarding the max and min dose
PTV	12.502 Gy (±1%)	Max 100 cm^3 above 15.0 Gy
D98 PTV		Min 11.25 Gy
Total lung	11.00 (±2%)	Max 13.5
Heart	11.25 to 12.50 Gy	
Brain	11.25 to 12.50 Gy	
Total kidney	11.25 to 12.50 Gy	
PTV rest	12.502 to 12.75 Gy	

The ExVMAT technique

The idea behind the planning of this technique is to create a basic plan structure consisting of a plan with extended SSD conventional fields with low and high energy, extended SSD IMRT fields and an initial VMAT boost plan. On this basis the further optimization and adaptation of the plans is undertaken by the automatic optimization algorithm of the Eclipse treatment planning system and not manually as for the ExIMRT technique. The low-energy conventional fields encompass the whole body by a wide margin, and these fields deliver the majority of the total dose (Fig. 1.B). High-energy segments irradiate the regions with the highest patient thickness (Fig. 1.C). The purpose of the extended IMRT fields is to be a correction to all other fields by accurately adding dose where it is lacking (Fig. 1.D). The standard isocentric VMAT boost plan contains two arcs, both irradiating a full rotation. The isocentre is placed centrally in the thorax. A field design where both arcs have the same collimator rotation and both are longitudinal asymmetrical but in opposite directions is used. Incoming radiation from the VMAT fields through the chin is avoided. Special structures are used in Eclipse for optimization of the VMAT plan and the extended SSD IMRT fields.

The structure "PTV thorax" is the target of the boost plan (Fig. 2.A). This structure is supposed to represent the volume which needs irradiation by the boost plan in order to be treated properly. It is a region around the lungs, but it does not extend inside the lungs nor does it extend outside the PTV. The volume is obtained from the total lung volume by adding a margin of two cm in the cranial direction, four cm in the caudal direction and five cm in the transverse plane. Hereafter, the total lung volume is subtracted, and the parts extending outside the PTV removed. The structure "PTV H" is supposed to represent the deep-seated tissue which needs high energy photons in order to be treated sufficiently. This volume is created from the PTV by adding a negative margin of minus 10 cm in the left right direction and minus 4 cm in the ventral direction and zero otherwise. The parts of "PTV H" extending inside the brain, lungs, heart, kidneys or "PTV thorax" are removed (Fig. 2.B). Conventional fields with high energy are fitted to this volume (Fig. 1.C). The lungs are exempt from irradiation with these fields [10]. The structure "PTV rest" is PTV excluding the lungs, brain, kidneys, heart and "PTV thorax" (Fig. 2.C). The conventional part of the treatment is normalized to a mean dose of 10 Gy in PTV rest. The IMRT part is normalized to 2.5 Gy in PTV rest. The initial version of the boost plan is normalized to a mean dose of 2 Gy for PTV thorax.

Planning and optimization

The IMRT part and the VMAT plan are optimized by an iterative method (Fig. 3) and respecting the dose constraints presented in Table.1

Six steps constitute a single iteration. The first step is to optimize 'VMAT I, the initial version of the VMAT boost plan. The second step is the creation of the conventional part 'Conv'. The fields with low energy are fitted to PTV with a margin of 4 cm measured at an SSD of 1 m. The fields with high energy are fitted with a margin of 0 cm to "PTV H" and have as a starting point 2/5 the weight of a low energy field. The third step is to make the summation "VMAT I + Conv". The fourth step is the optimization of the plan "IMRT". That is performed with the plan sum "VMAT I + Conv" as a base plan. A skin flash tool is applied to the fluence and the plan delivered by step and shoot technique. The fifth step is the creation of the summed plan "IMRT + Conv". The sixth step is the optimization of a copy of the boost plan with the plan sum "IMRT + Conv" as the base plan. This plan is called "VMAT F", indicating that it aspires to be the final boost plan. This plan is not normalized. The final total plan proposal is the sum of the plans "Conv", "IMRT" and "VMAT F" that can be evaluated. Typically, a sufficiently good convergence is obtained after single iteration. If necessary, further iterations can be

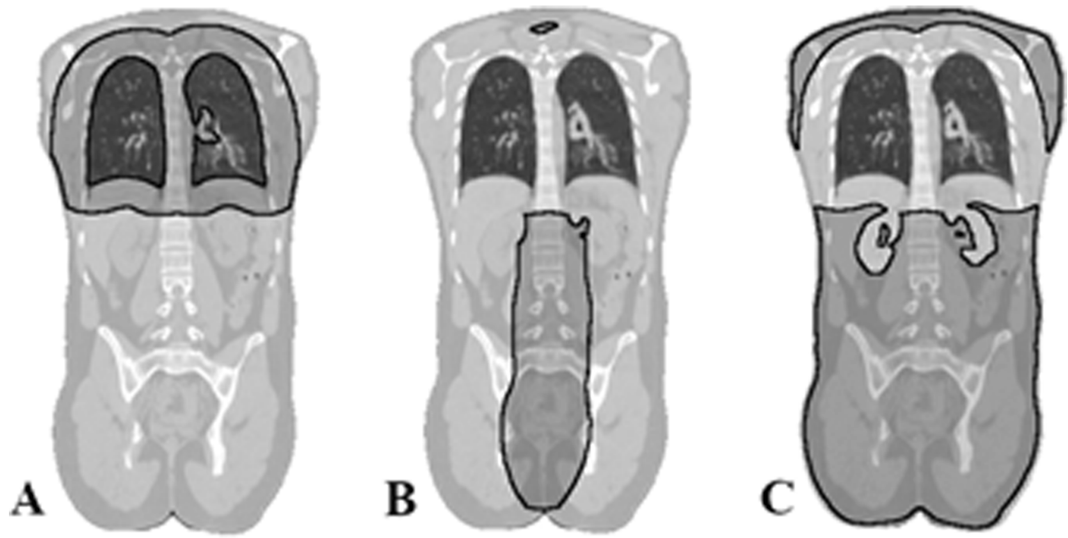

Fig. 2. Illustration of the special volumes needed for the ExVMAT optimization. PTV thorax (A), PTV H (B) and PTV rest (C).

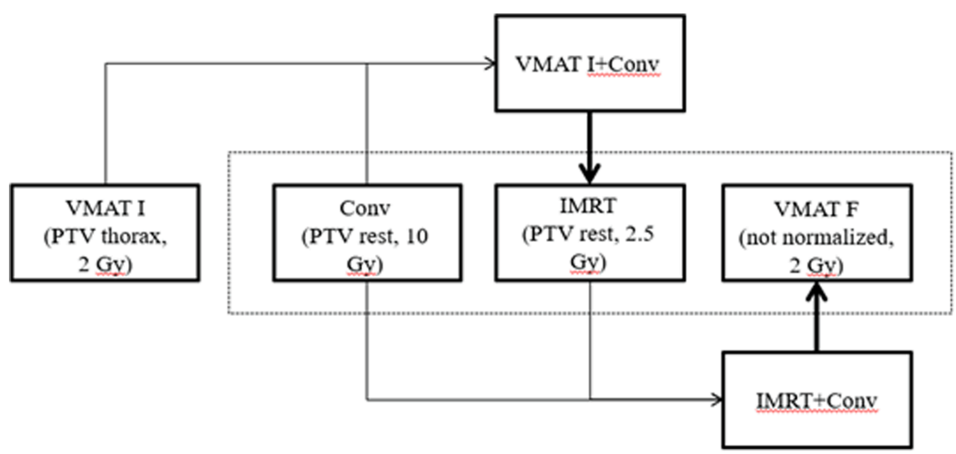

Fig. 3. An overview of the iterative optimization process. Thin lines indicate the summation of plans. Thick lines indicate that the resulting plan is optimized based on the preceding plan. Dotted lines circumscribe the planes that constitute the result.

performed where “VMAT I” is substituted with “VMAT F”. To minimize the calculation time, the AAA algorithm and a grid size of 5 mm are used for the dose calculation.

Dose constraints apply to ExVMAT in addition to those seen in Table. 1. The mean dose to “PTV rest” must be between 12.502 Gy and 12.75 Gy. The thoracic boost is not allowed to result in a fractional maximum dose in excess of 2.5 Gy.

Quality assurance

Dose verification was performed for both techniques by an independent dose calculation system (Mobius3D, Varian Medical Systems). Additionally, manual control of the shape of the multileaf collimator (MLC) was performed at the first treatment session for all field segments. The VMAT or IMRT boost plan was verified by portal dose imaging. The patient setup regarding the boost plans was verified by CBCT (cone beam computed tomography). The dose to the patient at the first treatment session was verified with TLD (thermoluminescence dosimetry) measurements at seven points on the body. The points were the left and right side of the head, the left and right hip, the left and right knee and a point between the knees. Doses were measured with two TLD-crystals at each point. The TLDs were packed in plastic and fixed with surgical tape, and the combined thickness of this material was estimated to be one millimetre. The TLDs themselves were 1 mm thick.

Data acquisition and analysis

Dose volume histograms (DVHs) for all patients and for the relevant structures were exported from the Eclipse treatment planning system for analysis. Statistical analysis was performed regarding doses D98 and D2 by applying the two-sided Wilcoxon rank sum test. Additionally, the variance of the median dose (D50) was analysed by the two-sample F-test.

Treatment times for all patients and fractions were extracted from the treatment log of the verification system. The data extracted were the start of treatment of the first field and the time of treatment closure. Treatment times were compared between the two techniques by applying a *t*-test. An additional test was performed regarding the associated calculated dose rates for the lungs.

For each patient, a predicted value for the TLD- measurements was obtained by creating a volume containing all tissue with a lateral depth between 1 and 2 mm. The TLD-measurements are equivalent to the mean doses in this volume.

Results

Several significant differences between the dose distributions obtained from the two techniques were found. The findings are shown in Fig. 4. The associated statistical analysis is presented in Table 2.

The volume in the upper thoracic region of the PTV treated with a dose above 15 Gy was significantly lower by the ExVMAT technique than by the ExIMRT technique. A related finding is that the PTV mean dose and D2 of the structure PTV rest were significantly reduced by the ExVMAT technique relative to ExIMRT. D2 for the total kidney volume also underwent a significant reduction of 0.3 Gy. The D98 dose to the total lung volume was significantly increased by the ExVMAT technique without increasing the mean dose to this volume, meaning that the homogeneity was improved. A significant reduction in the variance of the D50 was found for the total lung volume, the heart and the structure “PTV rest” by ExVMAT. The ExVMAT technique is therefore better capable of providing uniform dose distributions viewed over a population.

The time study showed that the mean treatment times for sessions without boost were 53.3[39,72] min for the ExIMRT and 53.0[40,158] min for the ExVMAT technique. A statistical *t*-test for equality showed no statistical difference with a p-value of 0.94. Regarding treatment sessions with boost the mean treatment times were 81.2[57,125] min for the ExIMRT and 71.0[49,126] min for the ExVMAT technique. The difference of approximately 10 min was found to be significant with a p-value of 0.0001.

A value for the delivered dose rate to the lungs was for each patient obtained by dividing the planned mean lung dose by the summed treatment times for the seven treatment fractions given to the patient. Averaging over patients treated with the two techniques resulted in a mean lung dose rate of 2.29[1.87,2.69] cGy/min for the ExIMRT technique and 2.54[1.95,3.10] cGy/min for the ExVMAT technique. These values were found to be significantly different with a p-value of 0.018. Within the group of observed patients, no definite cases of severe lung toxicity were observed.

Table 2
Listed are the results of the performed analysis. The p-value is stated in bold if significant.

Property	ExIMRT technique	ExVMAT technique	P value
V15 PTV	407.5 cm^3	11.7 cm^3	**0.00002**
Mean PTV	12.7 Gy	12.5 Gy	**0.0004**
D98 PTV rest	11.5 Gy	11.5 Gy	0.3
D2 PTV rest	14.3 Gy	13.8 Gy	**0.0002**
D98 Total lung	9.7 Gy	10.3 Gy	**0.00001**
D2 Total lung	12.5 Gy	12.3 Gy	0.2
Mean Total lung	11.0 Gy	11.0 Gy	0.8
D98 Heart	11.2 Gy	11.4 Gy	0.06
D2 Heart	13.1 Gy	13.1 Gy	0.9
D98 Brain	11.8 Gy	11.7 Gy	0.054
D2 Brain	12.8 Gy	12.9 Gy	0.5
D98 Total kidney	11.9 Gy	11.8 Gy	0.2
D2 Total kidney	12.8 Gy	12.5 Gy	**0.0007**
Var(D50) PTV rest	0.021	0.003	**0.001**
Var(D50) Total lung	0.021	0.007	**0.03**
Var(D50) Heart	0.222	0.019	**0.00003**
Var(D50) Brain	0.070	0.041	0.3
Var(D50) Total kidney	0.042	0.025	0.3

Regarding the TLD results, the data from three patients treated with the ExIMRT technique and two treated with the ExVMAT technique were unfortunately not saved to a computer disc and therefore not recoverable. Based on the available data the mean patient doses measured with TLDs for the ExIMRT technique were 1.60 +/- 0.08 Gy, and the mean doses predicted by calculation were 1.55 +/- 0.08 Gy. The equivalent data for the ExVMAT technique were 1.62 +/- 0.05 Gy and 1.62 +/- 0.05. A statistical two-sided T-test were performed for equality between measured and predicted doses. This test confirmed the equality hypothesis with p-values of 0.93 and 0.10 respectively. Therefore, good agreement between the expected and measured doses was found.

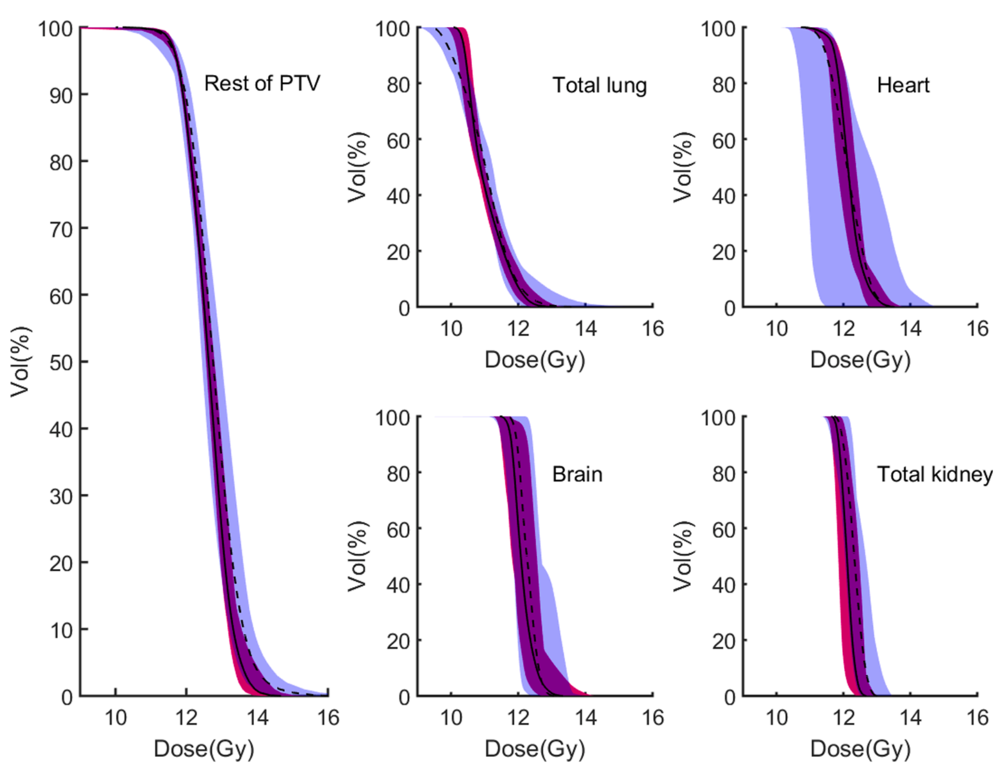

Fig. 4. Mean DVHs for the analysed structures. For a given volume fraction, the mean, maximum and minimum doses for both techniques are displayed. A solid line and red colour for ExVMAT and dotted line and blue colour for ExIMRT.

Discussion

The results of the comparison show that by using the ExVMAT technique it is possible to automate the planning process and to obtain a superior dose distribution with less patient to patient variation without prolonging the treatment procedure. Possible furtherer advantages could be less inter-planner variation and a reduced planning time. Treatment techniques based on extended SSD techniques have been studied by several investigators [1,2,6,17-19]. A study by Fog et al. [18] describes an extended SSD technique where large all-encompassing fields were supplemented by several forward planned field segments. The study shows that this method is useful for performing TBI. The treatment technique presented by Fog et al. is comparable to the ExIMRT technique, although it does not include a boost. Fog et al observed good agreement between doses calculated with the Eclipse treatment planning system and measured patient doses at an extended SSD. This agrees with the findings of this study.

While the extended SSD techniques are usable, the often-applied shielding of the lungs with blocks causes underdosage [1,17,18]. Extended SSD techniques lack the versatility that characterizes dynamical techniques such as VMAT or IMRT given at standard SSD [15,21,22]. A study by Springer et al [15] demonstrated that it is possible to deliver good TBI treatment by using only the VMAT technique. Springer et al. used several isocentres along the body where the fields from one isocentre were conjoint with the fields from the neighbouring isocentres. Using this technique, there is no need for lung shielding by blocks. The isocentre from the thoracic region is in many aspects comparable to the VMAT part of the ExVMAT technique. Although the VMAT part of ExVMAT only delivers a small part of the total dose. ExVMAT is an attempt to apply the best properties of the extended SSD technique and the VMAT technique by merging the two into one. The drawback is that the ExVMAT technique is cumbersome to plan and that the patient needs to be setup twice at four treatment sessions. However, in clinical practice, the use of two treatment setups has not been an issue. Because approximately 80% of the dose is given by large conventional fields, a lower limit exists for doses achievable to the critical organs. This is a drawback of both presented techniques that other techniques such as tomotherapy or full-body VMAT are without [4,14,21-24]. The issue of undertreatment of malignant cells circulating in the bloodstream has been raised regarding tomoterapy and VMAT-based techniques but has not been found to be important [25]. If this issue existed, it would likely be counteracted by the large conventional fields of the ExVMAT and ExIMRT techniques.

The ability of the Eclipse treatment planning system to predict doses at an extended distance has been studied, with an absolute accuracy of 0–5.5% but local deviations up to 10% have been found [17,20,26]. Our TLD measurements show good agreement between the predicted and measured doses for both techniques within 4%. The ExVMAT and ExIMRT techniques are estimated to be robust with regard to setup uncertainties. First, the majority of the dose is given by large all-encompassing conventional fields. Second, large SSD causes the photon penumbra to be expanded [26], which adds to the robustness of the plan. Finally, the treatment of the boost plans is guided by CBCT, which ensures high treatment precision.

The iterative planning approach presented can possibly be used in other contexts using planning systems capable of optimizing plans based on an existing treatment plan.

Dose rate

Previous studies have shown that radiation-induced lung injury (RILI) significantly correlates with poor survival [11,12]. The correlation between the dose rate in the lungs and the risk of RILI has been examined. Several studies find a correlation [11,19,27,28], while others do not [12,24,29]. During a tomotherapy-based treatment, the dose rate in the lungs is more than 100 cGy/min, which is not found to cause a high incidence of lung complications [4,14,23]. According to the studies that has found a correlation, a dose rate below 4–9 cGy/min is safe. Dose rates of 2.29 cGy/min and 2.54 cGy/min for the ExIMRT and ExVMAT techniques respectively indicates that both are safe with regard to RILI.

Conclusion

Two versions of the extended SSD technique for TBI have been compared. Analysis demonstrates that the ExVMAT technique is capable of providing dose distributions that are more homogenous and compliant with the dose prescription and with less variation from patient to patient than the ExIMRT technique.

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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