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Technical recommendations for implementation of Volumetric Modulated Arc Therapy and Helical Tomotherapy Total Body Irradiation

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ABSTRACT

As a component of myeloablative conditioning before allogeneic hematopoietic stem cell transplantation (HSCT), Total Body Irradiation (TBI) is employed in radiotherapy centers all over the world. In recent and coming years, many centers are changing their technical setup from a conventional TBI technique to multi-isocenter conformal arc therapy techniques such as Volumetric Modulated Arc Therapy (VMAT) or Helical Tomotherapy (HT). These techniques allow better homogeneity and control of the target prescription dose, and provide more freedom for individualized organ-at-risk sparing. The technical design of multi-isocenter/multi-plan conformal TBI is complex and should be developed carefully. A group of early adopters with conformal TBI experience using different treatment machines and treatment planning systems came together to develop technical recommendations and share experiences, in order to assist departments wishing to implement conformal TBI, and to provide ideas for standardization of practices.

Abbreviations: AP, Anterior-Posterior; CBCT, Conebeam CT; dMLC, dynamic multileaf collimator; fTBI, fractionated Total Body Irradiation; FF, Feet First; FMEA, Failure Mode and Effect Analysis; FoV, Field of View; HF, Head First; HSCT, hematopoietic stem cell transplantation; HT, Helical Tomotherapy; ITV, Internal Target Volume; kVCT, kilovoltage CT; Linac, linear accelerator; MLC, multileaf collimator; MVCT, megavoltage CT; OAR, Organs-at-risk; PA, Posterior-Anterior; PO, Photon Optimizer; PPV, patient position verification; PRV, planning-organ at risk volume; QA, Quality Assurance; SGRT, Surface guided radiotherapy; TBI, Total Body Irradiation; TMLI, Total Marrow and Lymphoid Irradiation; TPS, treatment planning system; VMAT, Volumetric Modulated Arc Therapy.

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Introduction

Total Body Irradiation (TBI) is widely used in conditioning regimens for patients with high-risk hematological malignancies undergoing allogenic hematopoietic stem transplantation (HSCT) [1–8]. Fractionated TBI (fTBI) is a standard component of conditioning [9], especially for myeloablative regimens, but practices vary and conventional TBI is prone to dose inhomogeneity and dose distribution uncertainties [10,11]. To optimize treatment and incorporate CT-based calculated information on dose distribution and sparing of organs-at-risk (OAR), conformal TBI has been adopted in several centers in recent years, using different techniques: multi-isocenter Volumetric Modulated Arc Therapy (VMAT) and Helical Tomotherapy (HT) [12]. In an effort to homogenize practices, assist departments in the implementation of these conformal techniques, and to share gained experiences, an international group of early adopters assembled to form consensus regarding technical recommendations for the implementation of VMAT and HT TBI. Experts who conducted a literature review of conformal TBI practices joined the group of authors [12]. We describe recommendations for conformal TBI, from patient preparation to treatment.

Patient immobilization and positioning

Supine patient positioning needs to be stable and reproducible from the time of the planning CT through to the last TBI fraction (Table 1) [13–16]. The patient should be able to comfortably remain in the same position for 40—70 min. In order to minimize multileaf collimator (MLC) movement, improve the target dose homogeneity and maximize the body volume fitting within the field of view of MVCT or Conebeam CT (CBCT) (Fig. 1), the legs need to be placed close together, and the hands and arms against the body. The hands may hold on to a stable handlebar, or are positioned within a hollow in an extra-large vacuum bag. The head (and if needed, shoulders) can be positioned in an open-face mask. Individualized support can procure reproducible and comfortable knee-flexion and feet dorsiflexion to reduce patient length. The arms should lie below the body axillary midline, to enable marker placement on the lateral pelvis and thorax.

To ensure a robust treatment, partly in head-first (HF) and partly in feet-first (FF) orientation, a rotatable tabletop or body frame can facilitate stable patient rotation [17–20], while the patient remains immobilized in the treatment position. If it is critical to extend the prescription dose to the patient surface, bolus material can be placed over (subsections of) the body [22].

Planning CT

The total planning CT scan length should include the entire body from the vertex to the toes. Before acquiring the scans, patient positioning should be checked. For example, when the patient is immobilized in a whole-body vacuum bag and mask, ask if the patient feels comfortable in the actual position, if there are any pressure points, and if the mask is comfortably but tightly fitting. To avoid CT acquisition in deep expiration or inspiration, the patient should breathe calmly. Instruction to look straight forward during CT acquisition and treatment of the head section can ensure reproducible lens/optic disc position and allow for reduction of lens dose [23].

The image FOV should be wide enough to include the entire patient and immobilization devices. Depending on the maximum local CT scan length, total-body HF-only scans can be obtained for patients up to a certain length. For taller patients, 2 CT scans need to be acquired in HF and FF patient orientations. Longitudinal couch travel of the C-arm Linac or HT machine dictates the need to create separate HF and FF treatment plans, usually in accordance with the scanned HF and FF CT. In case of two separate HF and FF CT scans, an adequate overlap region (e.g. 20 cm in the longitudinal direction, typically around the pelvis/upper thigh region) must be included on both scans to ensure feasibility of image registration for treatment planning purposes (Supplementary Fig. 1).

A 5 mm CT slice thickness is advised for adults and larger children, while 3 mm can be appropriate for smaller children (see section "Pediatric patients"). Since the whole body of the patient is imaged, the imaging dose should be as low as possible without compromising image quality; for example, 120 kV and 131 mAs, which correspond to a CTDIvol = 7.7 mGy and DLP = 654 mGy*cm for an adult patient. CT scanners can automatically adjust technique parameters to achieve a desired level of image quality and/or reduction of dose. Dose modulation and reduction techniques vary by scanner manufacturer, model and software version. If the patient has an artificial hip, other prosthetic device or dental work, the use of metal artifact reduction methods is advised.

For VMAT planning, the use of one "reference point" isocenter for both HF and FF CT in the overlapping region is practical and, if used, should be included in both scans (Fig. 2). This reference point, essentially an anchor-point for both CTs/treatment positions, and for convenience set to 0.0 in the couch position for both patient orientations, assists in the co-registration of the two CT scans [20]. During treatment delivery it provides an extra assurance of correct HF and FF starting position, and serves as HF plan origin isocenter with accompanying fiducial markers and tattoos.

If multiple reference points are needed, e.g. for HT preparation, these are chosen typically in the mid-thorax or mid-abdomen and pelvic/upper thigh region in the HF and FF scan, respectively [24]. The reference position(s) is/are marked on the patient, though marking the vacuum bag (or table/immobilization devices) as well optimizes positioning and is useful for dry-runs during pre-treatment quality assurance (QA) of individual plans (Table 2, Fig. 1). Other fiducial markers and tattooed or drawn markings are placed at the potential location of the other isocenters in all anatomic regions; at the level of the head, the thorax/abdomen and centrally between the legs (Figs. 1 and 2).

3D CT imaging is required, but if desired, an additional 4D CT of the thorax region provides information about movement of the ribs and lymphatics as target regions and lungs/kidneys as OAR, for e.g. ITV formation and check of plan robustness [25].

Treatment planning prescriptions

Conformal TBI can achieve a homogeneous and optimal target dose

Table 1
Potential immobilization components.

Lock bars for secure positioning of vacuum bags and/or knee/feet supports, to minimize rotational positioning errors.
Vacuum bag enveloping the entire body from shoulders to feet (Fig. 1) [17–19].
Stable arm/hand support (within vacuum bag or with adjustable handlebar).
Firm feet and knee support (vacuum bag and/or adjustable knee/feet cushions) with comfortably bent knees and/or dorsiflexed feet, helping to minimize lumbar vertebrae curvature and decrease scanning and treatment length (Fig. 1) [20].
Individually molded head/neck support.
A 3-point open face mask or chin mask (the open face is preferable in case of sudden vomiting during treatment), provided that the shoulders can be positioned securely with a shoulder-encompassing vacuum bag (Fig. 1).
A 5-point open face mask over head, neck and shoulders combined with a vacuum bag. Allow for space for venous catheters below the mask [16].
An all-in-one base plate comprising 2–3 thermoplastic meshes to restrict regions of the head/neck (5-point (open face) mask), thorax/arms, and legs [21].

coverage with better OAR sparing than conventional TBI. We aim to describe clinical consensus recommendations for target volume delineation, target margins, dose prescription, dose / dose rate / fractionation specifications, OAR dose reduction, and treatment plan evaluation in a separate manuscript. Generally, the following target-volume prescription goals should be achievable: V90% > 98%; V95 > 90%; V110% < 5% and V120% < 1% [26]. In dose reporting, as a minimum, mean dose to OARs should be included together with the dose to 90/95% of the PTV. HT usually achieves better homogeneity than VMAT [27]. For plan optimization purposes, lungs and other OAR can be cropped from the PTV [28]. The PTV-OAR structure can be helpful during optimization and interpretation of coverage in the dose volume histogram. There are no large trial-derived OAR dose constraints for TBI, but practitioners need to be aware of OAR sensitivities in this fragile patient group, especially when higher dose rates may induce higher biologically effective doses than equally fractionated conventional TBI, and therefore a more critical need to reduce specific OAR dose [7,9,29,30]. If desired, Varian Linacs have the ability to decrease MU/min – and therefore average dose rate – in specific regions, such as the lungs [17,18,31,32]. For 1.5- to 2-Gy fractionated plans, the following constraints can be a guideline based on current knowledge: lungs mean dose <8 Gy [33–35], kidneys mean dose <8–10 Gy [36–39], lenses mean dose <6 Gy (with priority of preservation of optic nerve/CNS coverage [23]). For more hypofractionated myeloablative schedules such as 4x3 Gy, prescribing ±10 Gy to the liver may reduce sinusoidal obstructive syndrome risk [40–43]. Future studies will ideally provide an evidence base for more specific recommendations [7,9].

Treatment planning for conformal TBI

General aspects

The planning process generally takes 6–10 h, but differs with experience and between departments. In the case of two separate HF and FF CT scans, concatenation of these image sets is required for most treatment planning software (TPS) systems (Supplementary Fig. 1), but with e.g. HT TPS this is not an option. The dose calculation algorithm should be the same as the one used routinely for VMAT and HT plans, type b method considering volume scatter and changes in electron transport [44,45].

The presence of a (large) vacuum bag may induce dose build-up and hotspots (mainly within the mattress), therefore it is important to ensure that its volume is taken into account during plan optimization.

The PTV can be cropped 3–5 mm from the external body contour for planning. The rotational treatment, use of low energy beams (6MV), buildup of vacuum mattress dorsally, and tangent of the beams will reduce the skin-sparing effect. To ensure robust optimization to superficial parts of the target (e.g. skull, clavicle and shins), a virtual optimization bolus can be added [46]. This option depends on availability in a department's TPS and local dosimetry studies for this aspect. In Eclipse, a virtual bolus can be used in plan optimization, which can consecutively be removed during final dose calculation to ensure that the planned dose matches the actual dose in the patient setup. Some TPS's do not allow removal of virtual bolus in the final dose calculations (e.g. Monaco, TomoTherapy). For those systems, one needs to perform a dosimetric study to ensure that the calculated dose with the virtual bolus does not differ significantly from that without the bolus. An option is

Fig. 1. A) Customized large vacuum bag encompassing the shoulders and feet and enveloping the rotatable tabletop to avoid swerving of the vacuum bag on the tabletop; open face 3-point mask on short baseplate so that in case of necessity the patient can sit up without removing the mask; knee-support fixed on rotatable table top by lock bar. B) Markings on patient and vacuum bag in feet-first (FF) region. C) Pediatric patient positioning in vacuum bag and 5-point mask, under sedation. Positioning markings on patient and vacuum bag/mask.

using a bolus density of 0.6 g/cc (water) corresponding to −400HU; occurrence of high fluence in the tissue-air border is avoided with negligible (attenuating) impact on the dose distribution. Hence, recalculation without bolus is not necessary. Another option (e.g. in Monaco TPS version 5.11) is the so-called "autoflash" which may allow the user to set a margin from the skin surface to control MLC shaping and improve dose distribution robustness against possible setup errors and also compensate for potential intrafraction motion. To reduce the dose to OARs, while maintaining a steep dose gradient for target coverage, consider optimization by using planning structures 5–10 mm within the OAR to firmly steer the dose without compromising target coverage. Since kidney volume often increases during the TBI period because of continuous intravenous fluids, a 5-mm planning-organ at risk volume (PRV) could be included during planning, cropped against target organs such as the spleen.

The lower extremities can be treated either with AP-PA fields or with conformal planned fields. Compared with conformal fields, AP-PA fields may reduce overall treatment time (estimated reduction 2–6 min), but may decrease dose homogeneity and give lead to overdose in the HF-FF junction region.

Treatment planning for VMAT-TBI

Beam setup and plan optimization

The TPS Monaco (Elekta, Crawley, UK), Varian Eclipse (Varian Medical Systems, Palo Alto, California, USA) and Raystation (Raysearch Laboratories, Stockholm, Sweden) allow fusion of two CT scans, in HF and FF patient orientation. The best suggestion is to use rigid co-registration with HF orientation as primary dataset, *translations only,* since any rotations between the two CT scans cannot be corrected at the C-arm Linac.

Ideally, the vertical and lateral coordinates of the VMAT beam isocenters per HF/FF treatment direction should be identical, so that the couch height and lateralisation do not need to be adjusted when moving the couch from one isocenter to the next. The number of isocenters depends on: patient height in treatment position, maximum field size and MLC travel limits, position of non-irradiatable structures of the treatment couch (and rotatable tabletop), and department-specific choice for length of beam overlap areas in HF and FF position.

Frequently applicable numbers of isocenters per patient length are: 140 cm 4 isocenters; 160 cm 6 isocenters; 180 cm 7–8 isocenters; 200 cm 9 isocenters (Fig. 2), where in the HF plan isocenter spacing can be e.g. 25 cm and in the FF plan e.g. 35 cm. Some centers choose field arrangements where consecutive asymmetric fields share an isocenter; overlap for these fields may be narrow (e.g. 2 cm) while overlap with adjacent divergent fields from the next isocenter is wider (e.g. 4–6 cm) [47,48]. A wider beam overlap region can make a plan more robust against small longitudinal isocenter shifts, and this particularly applies to the HF and FF junction. For patients with BMI > 35, in whom underdosing of the lateral body may occur, potential solutions are to increase the beam overlap region between isocenters (by 1 or 2 cm each), to decrease the longitudinal space between isocenters in the HF part, and/or to use two lateralized coplanar isocenters.

Ideally, isocenter spacing is a fixed number per patient height. However, attention needs to be paid to isocenter and beam edge placement with regard to the position of treatment table structures that can influence dose delivery. Isocenters adjacent to the pivot point of a rotatable tabletop can be kept equidistant from this point to simplify shifts after patient rotation [49]. Table movement limitations of the Linac, the position of non-irradiatable hardware structures, and the position of the rotatable tabletop on the couch can potentially limit the options for isocenter positioning or maximum field length.

MLC leaf travel limits and maximum available Linac field width can lead to a need for additional isocenters. The HF plan is most affected by these technical limitations, as it encompasses most OAR and the widest part of the body.

MLC leaf travel limit (Varian and Elekta Linac): The MLC leaves move in the X-direction of the collimator and the maximum MLC leaf

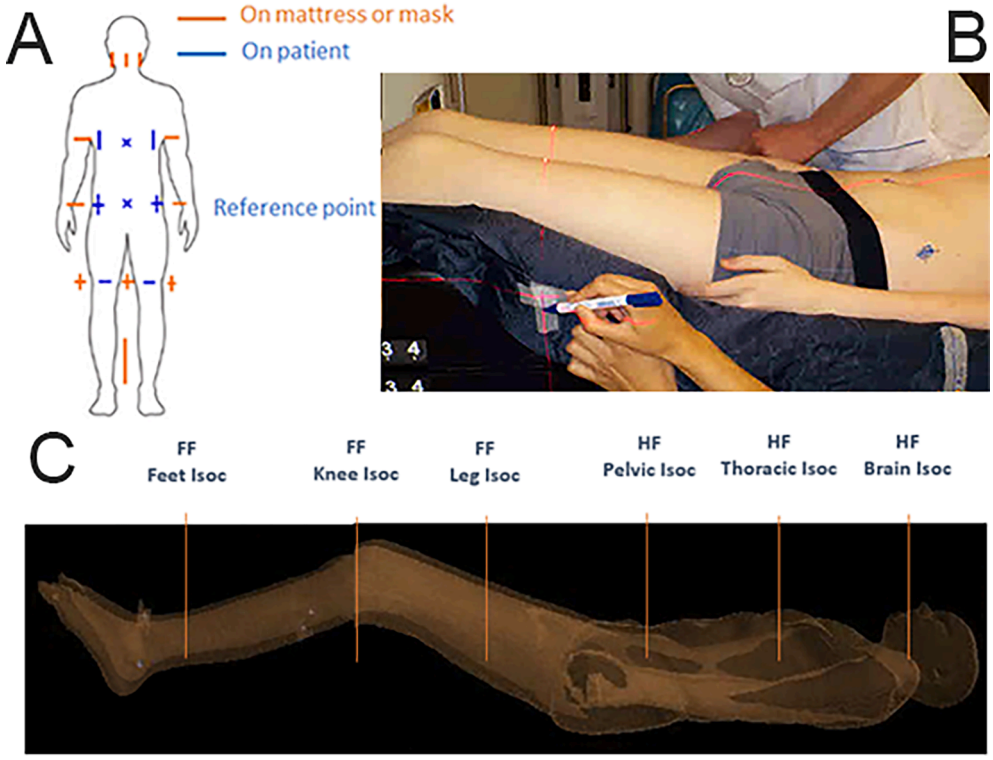

Fig. 2. CT scanning procedures. A) Marking locations (isocenters and longitudinal position verification markings) on patient and vacuum bag/immobilization devices. If 1 reference point is used (VMAT), this should be located in the overlapping region and included on both the HF and FF CT scans. B) Marking both patient and vacuum bag. C) Example of isocenter placement (VMAT) for a 164-cm tall patient.

overtravel is ±15 cm. In this case, the X-jaw setting should be no more than this limit to achieve adequate optimization results. However, if the collimator is rotated at 90°, the Y-jaw can be extended to the maximum size of 40 cm to ensure adequate coverage in the lateral direction especially over the thorax in the HF plan. In practice, the field size must be limited to 30x40cm (0° collimator) or 40x30cm (90° collimator). In the case of 90° collimator rotation, the field length is limited, leading to a smaller spread of isocenters (±23–26 cm). Positioning isocenters in the midline (both sagittal and coronal) of the patient limits leaf travel and therefore treatment time.

Maximum field size (Varian Halcyon or Ethos Linac): The MLC leaves can travel a longer distance to the maximum field width than for C-arm Linacs. However, the maximum jaw width is only 28x28cm. When treating a large (wide) patient on a Halcyon or Ethos Linac, bilaterally placed coplanar isocenters may be needed to ensure adequate coverage in the lateral aspects of the patient [22].

Junction between HF and FF

When two treatment plans use a co-registered CT image set, the user can set one treatment plan as the base plan for optimization of the other treatment plan, during which the dose of the base plan is automatically taken into account in the overlap region between the scans [20]. For planning systems that do not support base-dose planning, controlled dose gradients in several subdivided optimization structures may be constructed, with dose prescription increasing in the caudal plan while decreasing in each structure in the cranial plan to deliver a summed dose of 100% [50]; an overlap volume with e.g. five to six sub-regions of 2 cm each can be construed [24]. The planner should evaluate the actual dose gradient created by each field and test plan robustness by simulating dosimetric impact from setup errors (see QA section).

Monaco TPS

Beam setup and plan optimization

Monaco habitually produces broad transition between beams of different isocenters, if the junction areas are large enough (and collimator angles deviate from 0°). Isocenters need to be within the external body contour to be able to start optimization. An external contour should be extended to include any isocenter outside of the body contour, for example the one between the legs. In order to reduce calculation time, a dose grid of 5 mm, with statistical uncertainty of 1% per calculation, is generally accepted for VMAT TBI.

The use of fixed field sizes of 32–36 cm is preferable (as opposed to automatic or maximum field sizes), as it allows avoiding limitations during the optimization process associated with the physical characteristics of the collimators.

All devices outside of the external body contour (treatment table, tabletop, mask baseplate, etc.) need to be taken into account during plan optimization, as Monaco does not do so automatically. From version 5.5 and beyond, a fill of 0.01 g/cm^3 relative electron density should be used to ensure that devices outside of the external body are included during optimization (Fig. 3A).

A base doseplan is applied for the leg area on the FF scan (only mandatory for versions before 6.0, later versions allow HF base doseplan). This base plan is then used to create the HF plan.

Feet first treatment plan

The FF plan can be devised with either a dMLC AP-PA or a VMAT technique, per center preference.

dMLC

When the FF plan covers the legs but does not include the pelvic

Table 2
Conformal TBI process Quality Assurance checks.

	QA of	Name of test/ measurement	Description	Frequency
Implementation phase	Overall treatment workflow	Risk analysis	Risk analysis of the entire process.	1 time
		End-to-end test	End-to-end test of the overall workflow, with phantom.	1 time
	TPS/planning technique	TPS junction processing	Verify processing of the junctions of beams from different isocenters.	1 time
		TPS HF-FF base dose plan option	Verify correct processing of the base dose plan option if used for HF-FF junction.	1 time (if used)
		Robustness of the dose distribution	In-silico isocenter shifts in several directions, evaluate influence of shifts on the dose distribution.	For 3–5 cases
	Treatment plan	Dose gradient at the junction	Film dosimetry can be used to evaluate the dose distribution at the junctions. With commercial 2D/3D detector array systems, the dose gradient of a single field can be evaluated.	For 3–5 cases
		Single isocenter plan measurement	Measurements of all isocenters with a 2D/3D detector array system. Standard tolerances per institutional VMAT protocol. For HT, plan measurements with a 2D/3D detector array in one position per plan for HF and FF.	For 3–5 cases
	Treatment	Gantry-table position combinations	All safely executable gantry and table position combinations should be identified before clinical use. Potential collision at individual isocenter positions should be checked. Full rotation of a rotatable tabletop needs to be possible.	1 time
		Beam delivery	Potential beam delivery at the wrong isocenter should be investigated/ prevented.	1 time
Routine phase	Plan	Plan QA	Department-specific protocoled VMAT/HT QA checks.	For each patient
	Treatment	Dry-run	Pre-treatment dry-run without the patient (reference lines marked on the (rotatable) table top and/or vacuum bag): collision clearance ensure that no metal parts can be in treatment fields acquisition of absolute table positions of isocenters, to import into the Record and Verify software prior to treatment	For each patient
		Safety checks	– Is the treatment table column outlined at 0°? – Is the vacuum bag still vacuumed and in correct position? – Is the (rotatable) table top positioned correctly on treatment table? – Is the treatment team familiar with the treatment and backup procedures?	Before every fraction
		Updates hardware/ software	Check consequences for TBI planning and treatment chain	After every update

FF = Feet First; HF = Head First; HT = Helical Tomotherapy; TPS = Treatment Planning Software; VMAT = Volumetric Modulated Arc Therapy; QA = Quality Assurance.

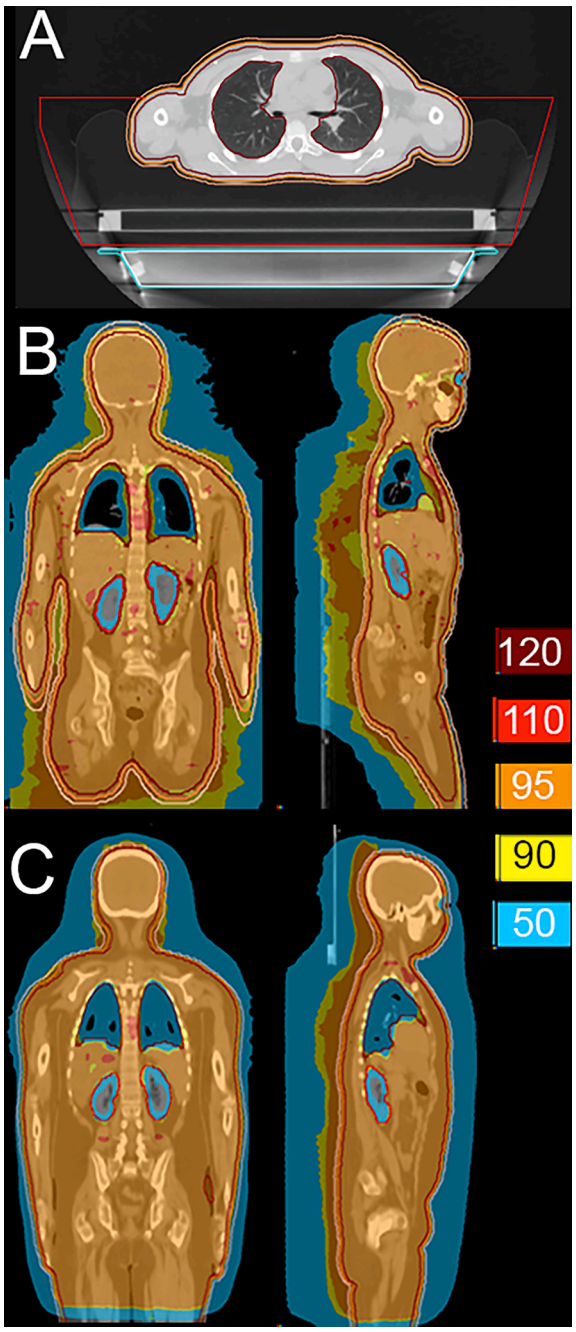

Fig. 3. Conformal TBI planning. A) Axial image of patient and external devices included in planning procedures. Red = included external devices with 0.01 g/cm^3 fill, Pink = body contour + 5 mm, Orange = body contour, Maroon = PTV cropped 5 mm within body, excluding lungs as OAR. B) Coronal and sagittal image of VMAT HF plan of a patient 137-cm tall with PTV cropped 5 mm inside body contour. Devices outside patient included in plan. Delineations: Pink = body + 5 mm; Orange = body contour; Maroon = PTV (excluding OAR lungs + kidneys + lenses); Red = kidneys. Planning isodoses alongside Figure in %PD. C) Coronal and sagittal image of Helical Tomotherapy HF plan of a patient 139-cm tall with PTV cropped 3 mm inside body contour. Devices outside patient included in plan. Lung OAR minimum dose set to 50% PD. Delineations: Pink = body + 5 mm; Orange = body contour; Maroon = PTV (excluding OAR lungs + kidneys + lenses); Red = kidneys. Planning isodoses alongside Figure in %PD. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

region (to avoid pelvic dose hotspots), an AP-PA technique for the FF plan can be combined with homogeneous beam transition regions using dMLC optimization (Supplementary Fig. 2). To obtain beams that are as large and simple as possible, a collimator angle of 90°/270° and a low number of allowed segments (6–10) are recommended. An extended PTV or body in between the legs extends the target area and forces the TPS to plan a wide field over this area (see purple area in Supplementary Fig. 2A). For wide(r) patients, collimator- and gantry angles can be adjusted to improve coverage in lateral body parts.

VMAT

A simple FF VMAT approach is feasible by maximizing the longitudinal distance between the isocenters (25–35 cm; depending on leg length, usually the number of isocenters can be ≤4), using a wide beam angle (180° minimum), reducing the number of increments (35–40 for upper thigh and 50 for lower legs) and *sequencing parameters* such as number of arcs (1), number of control points (80–110), increasing minimum segment width (>1.5–2 cm), and setting fluence smoothing to High.

Adding an extra beam in the most caudal HF isocenter position during optimization of the baseplan, creates smooth gradients in the HF-FF junction area. This extra HF beam is removed after optimization of the FF plan, eventually forming the final baseplan [20].

Head first treatment plan

As HF contains the widest part of the body and OAR in close proximity to critical target structures, a more complex beam set up and treatment plan optimization is needed. A longitudinal distance between isocenters of preferably <25 cm, two arcs per isocenter, 100–120 control points, minimum segment width >1.5–2 cm, High fluence smoothing, a wide beam angle for all isocenters (260° minimum, preferable 360°), and number of increments set to 30 are recommended. The HF bias plan is optimized by taking the FF plan as basedose plan. In Monaco versions 5.11 and beyond, starting with HF as baseplan and optimizing FF as Bias plan is also feasible.

Eclipse TPS

Beam setup and plan optimization

Arc fields are placed along the consecutive isocenters. For efficient treatment delivery, each arc can be given a gantry rotation direction opposite to the following arc, so that after each rotation, the gantry will be at the starting position of the next arc/field. Dose homogeneity, especially for larger patients, may be improved by using 2–4 arcs per isocenter [28]. Collimator rotation between 80° and 100° makes MLCs travel along the superior-inferior direction to ease field modulation [19,25]. For each VMAT arc, both dose rate and gantry rotation speed can be allowed to modulate for each control point (e.g. 177 for full arcs) during optimization. If desired, the dose rate for beams in the thorax region may be lowered to 100–200 MU/min or less to keep the average dose rate in the lungs <20 cGy/min [28,32]. In optimization settings, the Normal Tissue Objective (NTO) option may be turned off as most of the body volume is included in the PTV. A grid size of 2.5 mm is recommended. For TBI plans, difference in mean dose calculation results between the AAA algorithm (a pencil beam convolution/superposition algorithm) and the Acuros algorithm (a grid-based boltzman equation solver) will be very small in the soft tissues, but will be greater in bones and lungs [51]. If well commissioned, the Acuros algorithm is recommended.

Open-source scripts have been developed to automate the Eclipse optimization workflow [28,49,52].

Feet first treatment plan

If VMAT fields are to be used, a separate FF VMAT plan can be created, or the VMAT fields can be optimized together with the HF VMAT fields when the two image sets are co-registered and

concatenated. When fields are optimized together, enabling auto-feathering during optimization creates smooth gradients in the HF-FF junction area. One institution has developed computer code to convert VMAT fields from a HF treatment plan to fields for delivery with the patient in FF position [53]. In the case of an AP-PA FF plan, VMAT pelvis fields and AP-PA FF fields should be cleanly connected, by e.g. collimator rotation of 90° for the AP-PA fields [28].

Head first treatment plan

In recent versions (13.5 and later) of the Eclipse TPS, VMAT optimization is performed by the Photon Optimizer (PO) algorithm with iterative multi-resolution levels. During the optimization, the user can set the optimization process to "hold" at a specific level for a continued period to improve the dosimetry at a given level. It is recommended that adequate time is given at each level in VMAT TBI planning. It is recommended to turn on the "Convergence mode" of the PO algorithm so that the optimizer performs sufficient optimization at each level automatically. "Aperture shape controller" should be off.

Treatment planning for Helical Tomotherapy

General aspects

Due to HT constant couch movement, beam setup is relatively easy and the planner does not need to define multiple fields at multiple isocenters; the TomoDirect delivery mode, in which the gantry stays at a fixed angle while the couch moves at constant speed, allows efficient treatment of a large volume such as the lower extremities; and the MVCT or kVCT imaging system on HT enables the clinician to image a body section up to the maximum couch travel length for setup position verification of almost the entire target volume. It is strongly recommended to position the isocenter mid-plane (both sagittal and coronal) in the patient. A feature of HT is the heterogeneity of peripheral doses; the severity of this effect depends on the size of the PTV in the transverse direction and can vary depending on the degree of plan modulation [54]. For optimization, a 5-cm field width can be applied together with a pitch of e.g. 0.397 or 0.430 [54,55]. Centers may want to evaluate their optimal pitch for different size patients. For Helical HF and FF plans, planning modulation factors are in the range of 3.0–3.7 and 2.0–2.5, respectively.

TBI plan optimization is typically longer than usual due to the large target volume size and planning can take 3–4 days [24]. To obtain better dose homogeneity, it may be useful to divide the Total Body PTV in multiple regions (i.e. head&neck, thorax, abdomen, pelvis, lower extremities).

For the upper body, the reference point is located centrally in the mid-thorax or in the mid-abdomen, and for the lower body at the upper thigh level approximately 6 cm below the perineum. The lower body can be defined as right and left leg only.

Junction between HF and FF. When the HT TPS does not allow the use of a base plan-in-plan optimization, nor provides a mechanism to sum the dose of two plans based on different CT simulation images, junction dose optimization and evaluation is more difficult. There are two main approaches to reach a robust junction dose in the junction region of the two plans.

- First approach: create an overlap volume in the two plans with controlled dose gradients in several subdivided optimization structures with dose prescription ramping up from 10 to 90% and opposite decreasing from 90% to 10% in each leg, to deliver a summed dose of 100% [50]; e.g. in an overlap volume with five to six subregions of 2 cm each.
- The second approach implies that the PTV for the lower extremities is separated from the offset by about 4–6 cm from the upper body PTV when devising the FF field setup [27,56]. The optimal dimension of this offset depends on the field width, pitch, modulation factor, and CT slice thickness. It should be determined and dosimetrically validated by individual departments.

Dose data from the optimized HF and FF plans should be exported to another software system, where the dose can be summed and evaluated for junction dose homogeneity. If excessive cold or hot dose spots exist in the junction region, the lower extremity PTV can be extended or reduced by one or more slices in the junction region, after which the FF plan needs to be regenerated for subsequent junction dose evaluation.

Tomotherapy TPS

Beam setup and plan optimization. In creating a HT treatment plan with the helical delivery mode, the planner can choose between a few jaw widths. For adult patients, using a maximum field width of 5 cm provides acceptable dosimetry quality in HT TBI plans while the treatment time is significantly shorter compared to using smaller jaw widths [57]. Using a smaller field width increases delivery time by a factor of two or more and is usually not necessary. However, a field width of 2.5 cm with a pitch of 0.43 can be considered for small patients with a height less than 115 cm, as a smaller jaw width improves target dose conformity and dose homogeneity in the regions superior and inferior to the OAR (lungs, kidneys, and/or lenses) in the longitudinal direction [27]. Department-specific optimal settings for large and small patients should be evaluated.

Feet first treatment plan. The lower extremities can be treated with a HT or TomoDirect mode with gantry angles of 0° and 180°, the recommended field width is 5 cm and a pitch of 0.43–0.5 is commonly used.

Using a virtual bolus or similar techniques to flash MLC in air can be adopted, as described in [27,46,58–60], but should be dosimetrically validated to check the absence of excessive x-ray fluence.

Head first treatment plan. The HF PTV typically extends from the vertex to the mid-thigh level. The helical delivery mode is used for the HF TBI plan for optimal dosimetry quality. The pitch value of the HF plan should be selected to minimize the thread or ripple effect, especially for off-axis targets such as the arms, and to reach a compromise between dose homogeneity and gantry period. Takahashi et al. found adequate lateral arm dose homogeneity for a pitch of 0.397 in larger patients and 0.43 in smaller patients [55].

Raystation TPS

In Raystation, the modulation is not defined as an optimization input parameter, but rather the maximum allowed treatment time or maximum gantry rotation time is used. For treatment of the upper body, a maximum gantry period of 22 s is used, whereas for the lower body – which requires much less modulation – a gantry period of 15 s is used.

Quality assurance

A VMAT/HT TBI technique involves unique technical and dosimetric features, including a large number of junction fields, which need to be addressed in order to guarantee a safe and correct delivery of the planned dose distribution. In Table 2, an overview of the recommended QA checks is reported.

It is highly recommended to perform a prospective risk analysis and an end-to-end test of the overall TBI workflow before clinical introduction [18,61]. Additionally, if an external independent verification of TBI is available (e.g. an end-to-end dosimetry audit for clinical trials), it is strongly recommended to participate, to benchmark the local approach against others.

Implementation phase

TPS, treatment technique, treatment plan QA. Because of multiple isocenters in one plan and the HF-FF junction, TPS junction processing of arcs from different isocenters and correct processing of the HF-FF base-dose plan (if employed) needs evaluation. It is recommended to perform a robustness check of the dose distribution by applying a series of random in-silico isocenter shifts in several directions, i.e. 5/10 mm, and analyzing the influence of these shifts on dose distribution in at least the overlapping region (Supplementary Fig. 3) [21,26,62]. Based on the VMAT treatment plan robustness, tolerance values for the patient position verification (PPV) procedure can be established. These will vary between departments and depend on PPV workflow, junction dose distribution robustness, PTV and OAR dosimetry objectives. When multiple OAR are involved, permitted setup deviations may be restricted to 5/10 mm [26], but dose distribution robustness for patient position shifts of up to 20 mm is possible [20]. The majority of commercial phantom systems, e.g. Octavius, do not support measurement of multi-isocenter plans, but film dosimetry can be used for treatment plan QA of the summed dose of the field and HF-FF junctions. Alternatively, the dose gradient of a single field measured with the phantom system can be evaluated.

Treatment QA. Due to the extensive acquisition length, a minor longitudinal misalignment of the CT couch can induce a left–right (lateral) difference of several millimeters in the overlapping region between HF and FF scans. In addition to the processes reported in [63], scanning a phantom in HF and FF orientation with a similar longitudinal couch travel range used for TBI patients and overlaying these two scans can be useful in determining the magnitude of any misalignment and implications for the entire procedure.

For VMAT, using the complete range of longitudinal treatment couch movements increases the risk of couch-gantry or couch-wall collisions at the outermost positions. All safely deliverable gantry-table position combinations should be thoroughly identified before clinical use. Potential collision at individual isocenter positions and beam delivery at the wrong isocenter must be detected prior to clinical use. Absolute table positions of the isocenters can be imported in the Record and Verify software, to prevent treatment of an isocenter while the patient is positioned in another isocenter position. Collision clearance and verification that no metal parts will be in the treatment fields can be ensured by a pre-treatment dry-run without the patient. Full tabletop rotation needs to be possible. This dry-run is only possible without the patient when reference lines are marked on the (rotatable) table top and/or vacuum bag. If the dry-run is performed as soon as the treatment plan is ready, potential plan amendments can be applied before treatment. Strictly observing table positions can also help to keep the inter-isocenter distances in accordance with the planned values. Accuracy of couch movement between isocenters must be controlled as well.

Routine phase

For dose verification of separate isocenter and patient-specific plans department-specific protocoled VMAT/HT QA checks (independent MU check, plan QA, etc.) are advised.

For plan QA, the standard tolerances per institutional protocol as used for other VMAT plans are advised, e.g. 3%/2mm at 95% with 10% low dose threshold [64].

For HT, 2D/3D detector array measurements (e.g. Delta4 Phantom + detector or ArcCheck) are performed in one position per plan. Only representative parts of the entire TBI plan dose distribution can be verified due to the limited active volume of commercial phantom systems. For the upper body, the phantom is centered at the reference point in mid-thorax or mid-abdomen position to perform dose verification of this area including part of the lungs and kidneys. For the lower body plan, the dose at the HF-FF junction is verified, including the dose gradient over the upper thigh. Studies have explored the possibility of using data from the on-board detectors of the HT device for per-treatment dosimetry evaluation purposes [65,66] and verification of individual plans [67–71], including TBI/TMLI plans [72,73].

It is strongly recommended to continue dry-runs before treatment of *each* patient.

A few safety checks are recommended prior to every fraction:

- Is the treatment table plateau outlined at exactly 0° (C-arm Linac. Due to long longitudinal table movements, small misalignments can lead to clinically relevant differences in dose)?
- Is the vacuum bag (when employed) still vacuumed and in the correct position?
- Is the (rotatable) table top positioned correctly on the treatment table in longitudinal position, to prevent collisions or irradiation of metal parts?
- Is the treatment team familiar with the treatment and backup procedures (Table 3)?

Patient position verification

Before imaging, alignment between external lasers and the markings on patient and vacuum bag and/or table should be checked along the entire length.

C-arm Linac

Only if the robustness of the dose distribution against multiple isocenter shifts is guaranteed, online PPV and correction may be performed for all separate isocenters [48]. However, when dose distribution robustness for daily multi-isocenter shifts is not guaranteed, or when treatment time is an issue, PPV workflows for 1–2 isocenters are advisable with online correction only for the principal isocenter positions. Performing online PPV of the thorax area, containing the lungs and upper kidneys, is recommended (Fig. 4). Pelvic region imaging can be considered to evaluate potential detrimental deviations after online correction of the thoracic isocenter (Fig. 4). If translations or rotations exceed individual center-set tolerances, patient repositioning and repeated PPV procedure should be performed. After rotation of the patient to FF position, another image check may be acquired to verify and potentially correct the patient position. The acceptable translations between HF and FF depend on robustness of the plan [26].

Helical Tomotherapy

One of the advantages of HT is the ability to obtain a long scanning area; the limiting factor is the time spent on scanning. MVCT or kVCT imaging procedures are performed before each treatment session to verify patient position. The scan parameters are chosen to reduce scanning time as much as possible, while considering that it may be necessary to repeat the entire procedure. Coarse acquisition mode with 6-mm slice thickness may be a practical choice. The latest generation HT, Radixact® (Accuray, Sunnyvale, CA), allows kVCT image acquisition (ClearRT^{TM}) which can acquire 130 cm scan length in approximately 90 s with a FoV of 50 cm. Generally, a single acquisition covering the patient volume as much as possible is necessary for each plan.

For the upper body, one long MVCT scan with coarse mode covering a large volume from the head to the pelvis is preferable to several separate scans, due to reduction in overall patient positioning error [14]. For the lower body, two separate scans may be adequate, e.g. at the level of the knees and feet, in order to control for possible rotation in this area. In this case, it is worthwhile using only the results of the first registration of the knees without averaging. If PPV image registration results are unsatisfactory, manual repositioning should be performed and scans repeated.

A typical PPV workflow involves an initial automatic image registration run followed by a visual quality check by a radiation oncologist with fine-tuning manual adjustments. HT has several automatic image

Table 3
Backup Procedures for specific TBI delivery problems.

Problem	Consequence	Potential fall-back scenarios
Vacuum bag is leaking or base/mask is not suitable (swollen face) or is missing	Patient preparation needs to be repeated	▪ Occurrence on day 1: on day 2 (and 3), 3 fractions are given with ≥6 h in between fractions. Alternatively 1 day postponement of 1 or more fractions may be possible, in consultation with the transplant team. ▪ Occurrence on day 2 or 3: the delivery is postponed to the afternoon and evening/if possible postponement of a last fraction to the morning 1 day later, in consultation with the transplant team. ▪ Dose per fraction could be changed in order to reduce the number of fractions/start once-daily fractionation.
(Parts of) Rotatable tabletop is broken	Treatment cannot be delivered	Use the backup rotatable tabletop when available, or a conventional TBI backup plan (prepared in advance for each patient).
C-arm Linac system failure (either in between fields or during treatment of a field)	Treatment needs to be resumed at another Linac	Patient positioning verification procedure is repeated when resuming the treatment on another Linac. Possible setup differences can be simulated in the treatment planning system to assess the influence of these on the dose distribution. HT specific: In case of failure between fields, the patient is moved to another HT unit and the treatment is resumed. If the breakdown occurs *during* treatment of a field, the elapsed time at the interruption is noted and the patient is then transferred to the twin machine. After positioning, imaging and registration, the treatment is resumed from the position of interruption. If there is only a single HT unit available, a conventional TBI back-up plan may be prepared in advance. In the case of HT failure, calculate the position of the beam interruption. The size and position of the conventional TBI treatment field is then adjusted to fit the junction of the last given HT field [24].
Patient is sick/cannot lie down for 1 fraction	Treatment cannot be delivered or needs to be interrupted	Start symptomatic treatment/medication. Delivery of the fraction later in the day or subsequent day. Maintain ≥6 h in between fractions.
Patient is postponed for HSCT for >2 weeks		Have the patient return for check of mattress + mask + setup, always re-scan and check plan/re-plan

registration settings that can be used. Bone and tissue automated registration mode at standard resolution is a common choice. If the couch can adjust only for translational and roll shifts, appropriate limits for jaw and pitch rotation values should be defined (e.g. <3°). During the registration quality check by the radiation oncologist, an assessment of the position of OAR and/or target volumes is performed. A residual discrepancy in the cranio-caudal and left–right direction of less than 5 mm can be accepted.

Surface guidance (C-arm Linac and Helical Tomotherapy)

Surface guided radiotherapy (SGRT) techniques can facilitate and accelerate patient positioning and help to monitor motion during treatment (Fig. 4) [24]. A fast initial SGRT positioning can be performed, and final adjustments can be made using 3D CT imaging. With appropriate margins applied, positioning of the lower body may be performed by SGRT only. Because of the long treatment time, motion monitoring may be especially beneficial for TBI.

Backup procedures

Given the strict timing between TBI delivery and HSCT, possible fallback scenarios should be developed for instances when (a) radiotherapy fraction(s) cannot be delivered. Risk analysis during the clinical implementation phase can identify potential hazards. Table 3 gives examples of backup procedures for several problems that can be encountered.

Pediatric patients

For pediatric patients, customized immobilization devices are crucial to match their size and anatomical features. Audiovisual aids during the treatment may help to relax and reduce anxiety [74]. When children cannot be compliant, sedation by an anesthesiology team is required, with constant monitoring of vital signs. Monitoring instruments should be placed outside of the irradiation field.

For VMAT, 3-mm CT slice thickness is advised for small children in order to be able to distinguish the vertebral bodies during the PPV procedure. Depending on the scanning travel and TPS/treatment options, small children (e.g. <116 cm) can be treated with a HF-only plan.

Conclusions

An increasing number of centers are implementing conformal-modulated (arc therapy) TBI techniques using CT data sets that provide better ability to homogenize dose distribution, with controlled reduction of dose to OAR and possibilities to individualize local dose decreases or increases where needed for specific patients. Consensus guidance is beneficial for the safe and optimal development of these complex techniques, and for standardization and collaboration between centers in order to improve, and possibly benchmark, treatment quality and clinical research options. Being familiar with the many intricacies of the planning and treatment process, a group of early adopters established these technical recommendations.

CRediT authorship contribution statement

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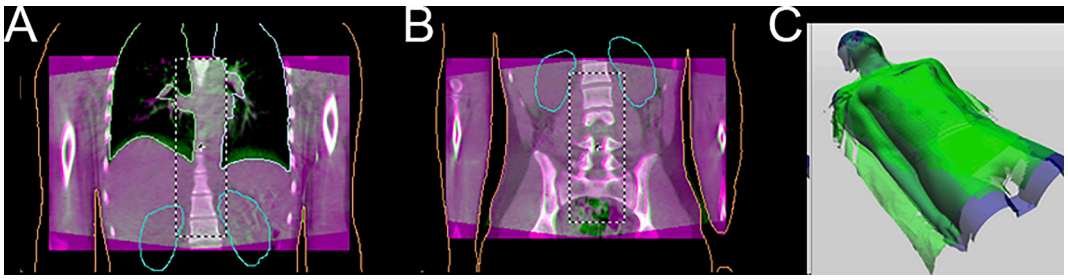

Fig. 4. Patient Position Verification (PPV) imaging examples. A) IGRT thorax PPV conebeam CT image (coronal view) with organs-at-risk and body contour delineations, for online positioning correction. B) IGRT abdomen/pelvis PPV conebeam CT image with organs-at-risk and body contour delineation, for position verification without further correction. B) Surface Guidance Radiotherapy image of upper body.

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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

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