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Original Research Article

# Clinical implementation of low-dose total body irradiation using topotherapy technique

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ABSTRACT

*Background and Purpose:* The topotherapy technique was recently suggested as a robust alternative to helical radiation delivery for total body irradiation (TBI). It allows to deliver a discrete number of beams with fixed gantry. A Topotherapy-based low-dose TBI technique was optimized and clinically implemented.

*Materials and methods:* TBI delivery was split in two parts: the first treating from the head to half thigh and the second the remaining legs. An in-silico investigation aimed to optimize plan parameters was first carried out on four patients. For the upper plan, field width and pitch were fixed to 5 cm and 0.5: the combined impact of five modulation factor (MF) values and different field configurations (6/8/12 fields) was investigated. For the lower plan, two anterior/posterior beams (field width: 5 cm; pitch: 0.5; MF:1.5) were used. After assessing the optimal technique, set-up/quality assurance/image-guidance procedures were defined and the technique clinically implemented: 23 patients were treated up to now.

*Results:* The best compromise between treatment time and planning target volume (PTV) coverage/homogeneity was found for MF = 1.5 and 8 fields. All clinical plans were automatically optimized using an "ad-hoc" plan template: excellent PTV coverage (PTV95% > 98.5%) and homogeneity (median SD:4%) were found with a median beam-on time of 17/9 min for the upper/lower plan. All patients were successfully treated and transplanted.

*Conclusions:* TBI delivered with the topotherapy approach robustly guarantees adequate coverage and dose homogeneity. Semi-automatic clinical plans can be quickly generated and efficiently delivered.

## 1. Introduction

Total body irradiation (TBI) is widely used in conjunction with chemotherapy as a part of the conditioning regimen in hematopoietic stem cell transplantation for the treatment of malignant and non-malignant hematological diseases [1]. Conventional techniques with large fields (anterior/posterior or lateral beams), extended source-surface distances, beam spoiler and physical blocks/compensators were currently accepted and clinically used. In order to reduce the dose to critical organs at risk (OARs) (i.e. lungs, kidney, heart) and to improve dose distribution homogeneity, volumetric arc [2–4] and helical [5 –9] techniques were investigated and clinically implemented using the tomotherapy machine in recent years.

Few authors [10,11] recently suggested the use of the topotherapy approach (i.e.: delivering a discrete number of fan fields with fixed gantry positions) as a more robust alternative to helical delivery, thanks to the simpler handling of safety margins around the body, leading to an expected reduced impact of intra-fraction motion and of residual error. In addition, the topotherapy modality delivers TBI with a mean dose rate much lower than the one delivered with the helical mode. Although with a higher instantaneous dose rate, this approach allows to obtain mean dose rates nearer to the ones typically delivered with conventional techniques [10].

Salz et al [10] first reported the use of topotherapy in a high dose regimen delivering 12 Gy (2–3 Gy/fractions) to the body and reducing the lung dose to 8 Gy: twelve beams were suggested as an acceptable compromise in terms of planning performances and delivering time. The impact of modulation factor, pitch and field width was investigated

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in one patient. The impact of beams number was recently investigated by Kasai et al [11] in 13 patients for a range of doses (2–8 Gy): plans with 2–12 beams were optimized and compared against the helical modality, by keeping constant the modulation factor , the field width and the pitch values.

Recently, the possibility of implementing TBI using the tomotherapy machine was explored by our group. In particular, we focused on a low-dose (sub-myeloablative) regimens (2–4 Gy in one-two fractions) using the topotherapy technique, preferred over helical delivery for its expected robustness and the lower mean dose rate [10].

First, the effect of field number and modulation factor on planning optimization was investigated "in-silico", aiming to assess the best compromise between plan performances and delivery times. In addition, the definition of a semi –automatic planning optimization procedure was also explored and clinically implemented.

## 2. Material and methods

### 2.1. Implementation of the topotherapy approach for TBI

In the current study the topotherapy approach (TomoDirect®) available for Tomotherapy® machines (TomoHD™) [12] (Accuray, CA USA) was implemented for TBI. With this delivery technique, a discrete number of beams with fixed gantry can be selected *a priori*. For each beam an IMRT fluence is delivered, while the couch translates. In the TomoDirect® mode there is the possibility to expand the beam on both transversal edges by a maximum of five leaves each (3.125 cm at the isocenter), if the leaves on the edge of the MLC (multi-leaf collimator) are not used. This allows to ensure a sufficient margin for most of the beams and most of the body regions, even in case of "large" set-up errors at the body surface

Due the maximum couch travel length (160 cm), TBI treatment was split in two parts: an upper plan from the head to half leg with a head-first positon and a lower part, including the legs, with a feet-first set-up. The topotherapy approach was proposed and used for both plans.

### 2.2. Immobilization, CT acquisition, target definition

A thermoplastic head mask was used. Patients were in supine position with arms along the body. A kneeFix was used to position legs and foot. Two different scans were acquired with a 5 mm slice thickness: a head-first scan from the top of the skull to as far down possible towards the legs (upper scan) and a feet-first scan from the end of the feet to as far up as possible above the legs (lower scan). A line of radio-opaque markers were placed in the junction region, generally set in the middle of the thigh: the junction is generally placed to about 110–115 cm from the top of skull. This distance is generally precautionary with respect to the maximum target length that can be irradiated (around 135 cm).

The Planning Target Volumes PTVs (PTV_upper and PTV_lower) were defined as the whole body, cropped by 3 mm from the external body contour. Cropping was made necessary to avoid any potential skin overdosing during therapy due to the expected fluence peak to the skin due to the lack of electronic equilibrium [10]. The PTV_upper was defined from the top of the skull till the junction region. The PTV_lower, was defined starting from the slice 5 cm more caudal with respect to the most caudal slice where PTV_upper is defined up to the end of the feet. This choice was based on the quantification of the cranial-caudal dose gradients of the two plans in this region for the four patients considered in the in-silico investigation and, additionally confirmed considering the first six clinical plans; the results were highly reproducible for all patients. Specifically (Supplementary material, Fig. S1), based on the cranial-caudal dose gradients for the upper and lower plan, different distances (4, 5 and 6 cm) between the two PTVs were considered and simulated. For each distance, the dose summation in the junction region was estimated and the intermediate solution of 5 cm gap, was clinically implemented. With this approach, maximum overdosing up to 120% of the prescribed dose in the junction region is expected (considered to be not clinically relevant), with no risk of underdosing (due to possible intra-fraction motion).

### 2.3. Optimization planning process

Four patients, previously irradiated for Total Marrow Irradiation (TMI), were selected for an in-silico investigation to optimize the irradiation geometry and the optimal plan parameters, including the explicit aim of making the delivery and optimization phases fast and efficient. The patient set-up as well as CT scan parameters were consistent with the one subsequently followed for TBI. As representative, two male and two female were selected: in Table S1 (Supplementary data) selected anatomic characteristics of the four patients were reported.

Due to the low dose regimen, no critical structures were defined and used in planning optimization.

The impact of delivery geometry (beams number and angles) and the optimal plan parameters (modulation factor) were investigated in order to define the best compromise between target coverage, target homogeneity and treatment time. A field width equal to 5 cm (in the "fixed jaw mode") and a pitch equal to 0.5 were set for all simulations, aiming to keep the irradiation time reasonably low while expecting an acceptable dose distribution homogeneity. A dose of 4 Gy in two fractions was prescribed for all plans.

First, the impact of the modulation factor (MF) was investigated by considering five different values (MF = 1, 1.25, 1.5, 1.75, 2). For each MF value, three field configurations were considered, using 6 (angles: 0°, 60°, 120°, 180°, 240°, 300°) 8 (angles: 0°, 45°, 90°, 135°, 180°, 225°, 270°, 315°) and 12 (angles: 0°, 30°, 60°, 90°, 120°, 150°, 180°, 210°, 240°, 270°, 300°, 330°) fixed equidistant beams.

In order to reduce the impact of patient setup errors, the field width for each considered beam was expanded, on both edges, by the maximum value of five additional leaves with respect to the PTV contour (3.125 cm at the isocenter). This expansion is limited when leaves at the edges are already in use (i.e. the PTV width is near or larger to the maximum beam width of 40 cm). In all three considered beam configurations, only AP/PA beams reach the maximum width and no beam expansion was then applied for these fields.

For each simulation, an automatic optimization process with 300 iterations was used for the upper plan: following the formalism of the planning system (TomoHD, Version 2.1.3, Accuray Inc.), "PTV weight" was set equal to 10 and priority was set equal to 100 for minimum and maximum PTV_upper dose, equal to the prescribed dose (defined as the median dose). Dmin, Dmax, SD of the dose distribution, V90%, 95%, 105% and110% (the fraction of PTV_upper receiving more than 90%, 95%, 105%, 110% of the prescribed dose) were evaluated. For the lower plan, a unique solution with two anterior/posterior beams was proposed. A field width of 5 cm (fixed jaw), pitch of 0.5 and a MF equal to 1.5 were used. Similarly, a five leaves margin was set. This simple solution was considered sufficiently robust and efficient to create homogenous dose distribution while keeping short the beam-on time. An automatic optimization process with 100 iterations was used.

### 2.4. Dosimetric accuracy

The dosimetric accuracy of the defined optimal delivery technique was tested. Several patient Quality Assurance (QA) plans were created using the cylindrical phantom (known with the name of Cheese phantom; Med-Cal) usually used for QA. Several anatomical regions (head, thorax, abdomen/pelvis, leg) were considered for the patients considered in the in-silico investigation and for the clinical plans. The agreement between calculated and measured dose distribution was verified in terms of point absolute dose measurements by positioning an ionization chamber (Exradin A1SL, volume 0.053 cc) in several positions along the transversal plan.

### 2.5. Early clinical implementation

Twenty-three patients (15 male and 8 female) with a median age of 40 years (range: 19–62 years) were treated between May 2018 and August 2019. All patients signed a specific informed consent regarding the use of clinical, imaging and dosimetry data used for current study. Most patients were transplanted for hematological malignancies and received as conditioning regimen high dose chemotherapy followed by a low-dose TBI regimen: thirteen patients were treated with 4 Gy (2 Gy/day; 2 fractions) and ten patients with a single 2 Gy session. The optimal automatic solution assessed by the in-silico investigation was used. For the upper plan, a topotherapy technique with 8 beams was applied with a field width equal to 5 cm, a pitch equal to 0.5 and a modulation factor equal to 1.5. For the lower plan, an AP-PA topotherapy solution was applied with the same field width, pitch and modulation factor. A high resolution (grid: 2 mm) was used both for the optimization and the final dose calculation phases.

For both plans, the optimization's aim was to homogeneously cover the PTVs with the prescribed dose; for both PTVs V90% > 99%, V95% > 95%–98%; Dmax < 115%; V110% < 1% were considered as optimization's goals.

The patients were first treated head-first (PTV_upper plan) and then feet-first (PTV_lower plan) with the same immobilization system used for planning CT. The correct patient positioning and alignment was checked before each session using on board megavoltage CT (MVCT) scan. Two MVCT scans were performed for the alignment of the upper part: one including head-shoulder-thorax region, and the other one including abdomen-pelvic zone. The average shifts, estimated by the two scans, were definitely apply to correct patient position. One single MVCT scan was acquired for the lower plan including the whole legs and feet almost completely.

## 3. Results

### 3.1. In-silico investigation

For all configurations (Table 1) (6, 8 and 12 fields) MF equal to 1 resulted unacceptable in terms of PTV coverage (V95 around 80%) while an acceptable PTV coverage (PTV95 > 95% and PTV90 > 97%) was found for all the remaining MF values. The treatment time increase moving from MF = 1 to MF = 2 was slightly different, according to the beam geometry: around 9 min (approximately from 11 to 20 min) for 6 beams; around 8 min (approximately from 13 to 21 min) for 8 beams and around 3 min (approximately from 19 to 22 min) for 12 beams; similarly, PTV coverage increases (around 2–3%) if increasing the treatment time. A good compromise between treatment time, PTV coverage (PTV95 > 97%) and PTV homogeneity was considered the choice of MF = 1.5. More detailed results were reported in Table S2, S3 and S4 of Supplementary material.

**Table 1**
Dose/Volume planning endpoints (V95%, PTVmax and sigma) and treatment time for the simulations with different modulation factor values and different field configurations (6, 8 and 12 fields).

| MF | V95 % | PTVmax (Gy) | Sigma | Time (min) |
|---|---|---|---|---|
| 6 Fields | | | | |
| 1 | 80.7 (75–83.2) | 4.4 (4.4–4.6) | 0.3 (0.2–0.3) | 11 (9.5–12.2) |
| 1.25 | 95.2 (93.9–99.7) | 4.4 (4.23–4.4) | 0.2 (0.05–0.18) | 12.9 (11.6–14.6) |
| 1.5 | 96.7 (96.4–99.9) | 4.5 (4.35–4.51) | 0.1 (0.04–0.12) | 15.2 (13.6–17,5) |
| 1.75 | 98.5 (97.6–99.9) | 4.5 (4.36–4.66) | 0.09 (0.04–0.1) | 17.5 (15.3–20.4) |
| 2 | 99 (98–99.9) | 4.5 (4.3–4.7) | 0.08 (0.04–0.1) | 20 (16.8–23.3) |
| 8 Fields | | | | |
| 1 | 82 (76.3–84.2) | 4.4 (4.3–4.5) | 0.3 (0.2–0.3) | 13.4 (11.5–18.7) |
| 1.25 | 96 (94.6–99.8) | 4.4 (4.2–4.5) | 0.1 (0.04–0.2) | 14.4 (12.1–18.7) |
| 1.5 | 97.8 (96.1–99.9) | 4.4 (4.25–4.58) | 0.08 (0.03–0.1) | 16.7 (14.3–18.7) |
| 1.75 | 98.6 (97.6–99.9) | 4.4 (4.4–4.7) | 0.07 (0.04–0.1) | 18.9 (15.3–20.4) |
| 2 | 99 (98–100) | 4.5 (4.4–4.6) | 0.06 (0.03–0.1) | 21 (17.7–23.7) |
| 12 Fields | | | | |
| 1 | 82.3 (77.6–84.9) | 4.3 (4.3–4.5) | 0.3 (0.2–0.3) | 18.5 (17.3–20.7) |
| 1.25 | 95.2 (94.1–99.8) | 4.4 (4.2–4.4) | 0.1 (0.03–0.2) | 18.6 (17.3–20.7) |
| 1.5 | 97.1 (96.3–99.9) | 4.5 (4.3–4.5) | 0.1 (0.03–0.12) | 18.9 (17.3–21.2) |
| 1.75 | 98.4 (97.4–100) | 4.5 (4.3–4.5) | 0.08 (0.03–0.1) | 19.6 (17.7–22.6) |
| 2 | 99 (98–100) | 4.5 (4.3–4.6) | 0.07 (0.03–0.09) | 21.8 (18.8–24.5) |

When fixing MF = 1.5, the beam geometry impact was summarized in Table 2. An average treatment time increase of approximately 5 min was found moving from 6 to 12 beams, without any relevant improvement of PTV coverage between 8 and 12 beams. Based on the results reported in Table 2, a good compromise for all simulated cases was suggested to be the 8 beam solution. More detailed resulted were reported in Table S5.

### 3.2. Dosimetric accuracy

Around ninety point dose measurements from 10 plans were considered. On average, an agreement within 1% was found between measured and calculated dose, both for simulated and for clinical plans: an average difference equal to −0.3% (range: −4.5–3.5%) was found. Differences were found to be independent of the considered anatomical level: average deviations equal to −1.6%(range: −4.5–0.3%), −0.1% (range: −2.6–3.1%), 0.3% (range: −1.3–1.9%) and −0.1% (range: −2–3.5%) were respectively found for head, thorax, abdomen/pelvis and legs level.

### 3.3. Clinical implementation: planning data and early outcome

A typical TBI plan obtained is shown in Fig. 1. As can be seen, a highly homogeneous dose distribution was obtained: only in the junction region an overdosing, typically around 110–120% was evident, due to the priority of avoiding any possible underdosing, due to possible intra-fraction motion.

In Table 3 some selected planning parameters were reported for the considered patients and for both plans. A median V95% > 98.5% with a median sigma of 0.05 and a median V95% > 99% with a median sigma value of 0.04 were respectively found for the upper and lower plan. D98% around 97% for both plans and D1% equal to 103.7% and 102.5% for the upper and lower plan were respectively found.

A MF = 1.5 was set in the optimization phase for both plans; an average actual MF equal to 1.7 (1.66–1.72) and to 1.6 (1.56–1.66) were estimated, respectively for the upper and lower plan. Of note, also if not specifically evaluated, organs at risk (i.e. lungs, liver and kidney) received a dose similar (well within ± 5%) to the prescribed one.

For all patients, the contouring and planning procedures were generally not longer than 1.5 h and the delivery comfortably fitted into the slot time of 1 h that was planned for each patient. A median beam-on time of 16.7 (range: 15.1–19.5 min) minutes was found for the upper plan and of 9 min (range: 7.0–10.7 min) for the lower plan. All patients completed their treatment without interruption. All patients underwent the transplant in the planned timeframe; no acute side effects were registered during treatment, due to TBI treatment. One patient experienced G1 and another patient experienced G2 itchy rash, respectively at three weeks and two months from the transplant. No aGvHD or cGvHD were actually registered.

## 4. Discussion

In this paper the implementation of a simple and semi-automatic planning optimization technique for TBI using the topotherapy approach was carried out and clinically activated. A major, practical reason was the unavailability of any back-up machine for the conventional lateral-opposed technique in use at our Institute since '80s [13] that forced us to use our Tomotherapy machines. As also reported by

**Table 2**
Dose/volume planning endpoints and treatment time for the different simulations for the three beam configurations (6, 8 and 12 fields) by fixing the MF = 1.5.

| | V95 % | PTVmax (Gy) | Sigma | Time (min) |
|---|---|---|---|---|
| 6 fields | 99.1 (98.3–99.9) | 4. 5 (4.3–4.7) | 0.06 (0.03–0.09) | 15.8 (13.8–18.3) |
| 8 fields | 99.5 (99.1–100) | 4.4 (4.3–4.7) | 0.05 (0.03–0.07) | 17.2 (14.3–19.3) |
| 12 fields | 99.4 (98.5–100) | 4.5 (4.3–4.6) | 0.05 (0.02–0.07) | 20.7 (17.3–22.4) |

few others [10,11], topotherapy was preferred for two main reasons: the possibility to have an average dose rate more similar to the one previously used with conventional Linac TBI; and the possibility to manage a beam margin of about 3 cm from the body surface able to robustly avoid any geographical miss even in case of "large" setup errors and patient motion during delivery. This allows to treat TBI patients avoiding sophisticated and specific positioning/immobilization system, making the treatment more comfortable to the patients and, at the same time, fast. The patient's treatment time slot was typically around 40–50 min, including image-guided set-up and treatment delivery.

In current study, a homogeneous dose distribution without OAR sparing in a low dose regimen was obtained for all considered beams configuration and planning parameters, by using MF > 1. The choice to use 8 equi-spaced fixed fields with a MF equal to 1.5 was found to be the best compromise between PTV coverage, PTV homogeneity and treatment time. Similar conclusions were found by Salz et al. [10], where a MF inferior to 2 was suggested. No differences in target

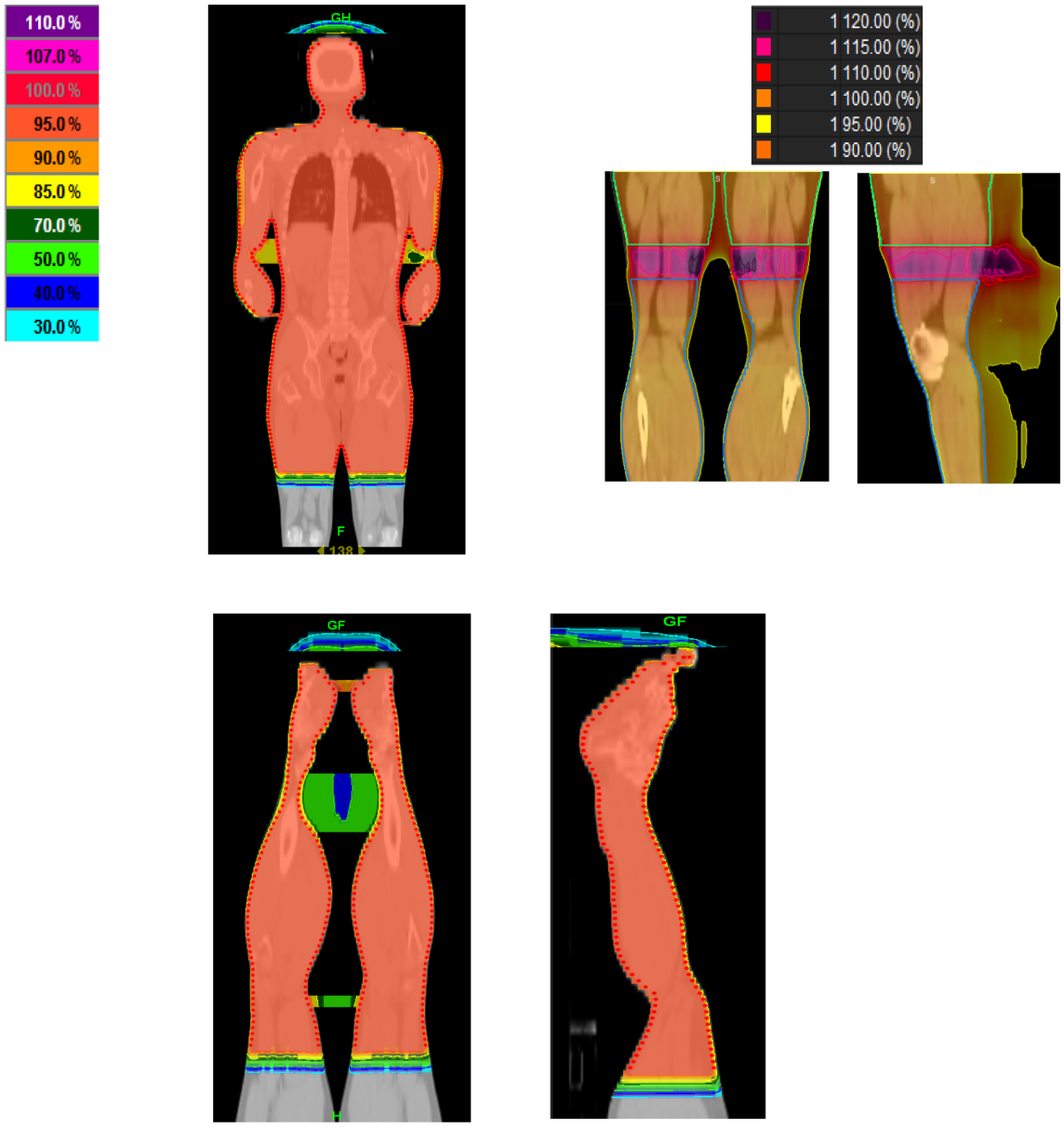


**Fig. 1.** Dose distributions for upper and lower plans (up) (100% = median dose to the body corresponding to the prescribed dose); laterally, the dose distribution obtained by summing the contributions of the upper and lower plans the dose distribution in the junction region resulted in an overdosing (typically around 110–120%): this choice was followed to avoid any risk of underdosing due to any residual intra-fraction error as this overdosing has no clinical relevance given the low-dose protocols applied.

**Table 3**
Dose/Volume planning endpoints for clinical plans.

| Plan Upper | | | | | |
|---|---|---|---|---|---|
| D_98% (%) | V_95% (%) | D_1% (%) | V_105%(%) | Sigma | Dmax % |
| 97.1 (94.5–98.7) | 98.9 (97.9–99.8) | 103.7 (102.3–106.1) | 0.3 (0.05–0.95) | 0.05 (0.02–0.09) | 111 (108.5–120.5) |
| Plan Lower | | | | | |
| D_98% (%) | V_95% | D_1% (%) | V_105% | Sigma | Dmax |
| 96.9 (95.1–97.8) | 99.1 (97.8–99.6) | 102.5 (100.2–103.5) | 0.1 (0–0.8) | 0.04 (0.02–0.06) | 107.8 (104–115) |

homogeneity was found between 2.5 and 5 cm field width against a treatment time doubling. A higher pitch value of 0.5 was used in this study compared to 0.25 used in Salz's experience [10], likely to be useful in better sparing the lungs in their high-dose regimen. The same pitch value of 0.5 was instead used in the Kasai paper [11] where a low dose homogeneous TBI treatment was implemented.

Differently from other experiences [10,11], the PTV was cropped by 3 mm from the external body contour; this value was considered as a compromise to reduce possible underdosing close to the skin and to avoid unnecessary skin overdosing (that would occur in case of crop margin next to zero). Of note, as suggested by several papers [14,15], satisfactory accuracy is largely reported for dose calculation with Tomotherapy planning system also in the first few millimeters from the body contour.

The TBI delivery has to be divided by considering two separate segments. Two different approaches were reported in the literature to create a homogeneous dose distributions in the junction area: a simple and more precautionary approach where the dosimetric junction can be accomplished by looking to the distance of the PTVs from two separate plans [8] and a gradual dose gradient approach [9,10,16] more able to minimize the risk of over-or underdosing in the overlap region. Given our low dose scenario, we preferred to use the first approach: the PTV_lower was in fact defined from the slice 5 cm far from the most caudal slice where PTV_upper is present till the end of the feet. This solution, less homogeneous compared to a gradual penumbra technique, is highly safe against PTV coverage; on the other side, overdosing (up to about 120%) in a relatively small leg volume was considered to be acceptable, taking the low delivered doses into account.

The planning optimization technique for PTV_upper investigated in the in-silico study was found efficient, feasible and easy to implement in our clinical practice; all patient's treatment plans were automatically optimized without any subsequent user's manual optimization. Excellent target coverage and homogeneity was always reached for all plans.

Of note, compared to conventional techniques using opposed large beams, several OARs (such as lungs and kidney) may be expected to "incidentally" receive a lower dose with topotherapy, due to the highly homogeneous dose distribution; however, given our low-dose scenario, this issue is not clinically relevant in this specific situation.

Some additional considerations could be done for the upper delivery in case of very large patients and in case of higher dose regimen. To avoid beams that reach the maximum PTV contour and thus does not allow to use the beam expansion, a solution with 12 equispaced beams or a solution with 10 beams without the AP/PA fields could be considered in order to create a better PTV coverage also in correspondence of the large thickness (generally at shoulder/thorax level): in total, 7/23 patients were treated with these slightly modified field configuration. The shown clinical feasibility of our approach may allow to scan, plan and treat the patient in the same day.

TBI delivery with IMRT techniques generally requires a higher accuracy in patient positioning with respect to conventional Linac large fields technique; however, the image-guided set-up correction and the implementation of the topotherapy approach could be considered a robust approach against the impact of residual setup errors. Based on a previous multi-institutional study on residual patient set-up error and its dosimetry impact in a group of patients treated for Total Marrow Irradiation (TMI) involving our Institute [17], a maximum mean systematic global error of 8 mm was estimated, with maximum local shifts up to 20 mm. The possibility to enlarge the beam of about 3 cm with respect to PTV should allow to ensure a sufficient geometric coverage also in case of "large" setup errors. In addition, in [17] the impact of all possible setup errors on TMI dose delivery was assessed: overall, the delivered PTV mean dose was always found within 5% compared to the planned one. This result was found in a much more stressed situation, with high dose gradients between PTVs and critical structures. With more homogenous dose distribution, as in current study, we may expect a still lower difference between planned and delivered PTV dose. A head mask and the knee-fix device used to position the legs more comfortable is an adequate immobilization/positioning system to guarantee a sufficient accuracy. No other immobilization devices were required. Positioning and immobilization systems used were well tolerated and no patient repositioning was necessary, making set-up and delivery simple and fast.

Preliminary clinical results shows that TBI treatment with the topotherapy approach is feasible and safe: no treatment interruption due to machine breakdown or due to severe acute effects occurred. Two patients experiencing a G1 and G2 itchy rash, respectively at three weeks and two months from the transplant. All patients obtained a successful transplant.

This study has some limitations. First, we only investigated patients undergoing low-dose TBI, where OARs were not defined. The possibility and the efficacy to use topotherapy approach also for myeloablative schedules with specific OARs sparing was not investigated. Second, although we are confident on the dose delivery accuracy, more investigation to quantify plan delivery robustness may be suitable: for instance, dose verification tests could be performed in an anthropomorphic phantom, as a sort of "end-to-end" test, also incorporating the effect of set-up errors. This point will be considered for future investigations.

In conclusion, a fast, robust and efficient TBI technique with topotherapy was optimized and clinically implemented: due to our findings, including early clinical results, this approach appears as a valuable alternative to other, more time consuming and/or less robust, available techniques.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.phro.2019.11.009.

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