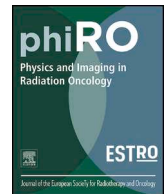




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## Review Article

# Total marrow irradiation for hematopoietic malignancies using volumetric modulated arc therapy: A review of treatment planning studies<sup>☆,☆☆</sup>

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## ABSTRACT

Total Marrow Irradiation (TMI) has been introduced in the management of hematopoietic malignancies with the aim of reducing toxicities induced by total body irradiation. TMI is one of the most challenging planning and delivery techniques of radiotherapy, as the whole skeleton should be irradiated, while sparing nearby organs at risk (OARs). Target volumes of 7–10 k cm<sup>3</sup> and healthy tissue volumes of 50–90 k cm<sup>3</sup> should be considered and inverse treatment planning is needed. This review focused on aspects of TMI delivery using volumetric modulated arc therapy (VMAT). In particular, multiple arcs from isocenters with different positions are required for VMAT-TMI as the cranial-caudal lengths of patients are much larger than the jaw aperture. Therefore, many field junctions between arcs with different isocenters should be managed. This review covered, in particular, feasibility studies for managing multiple isocenters, optimization of plan parameters, plan optimization of the lower extremities, robustness of field junctions and dosimetric plan verification of VMAT-TMI. This review demonstrated the possibility of VMAT in delivering TMI with multi-arcs and multi-isocenters. Care should be paid in the patient repositioning, with particular attention to the cranial-caudal direction.

## 1. Introduction

Total body irradiation (TBI) is used as part of the conditioning regimen for patients who are candidates for hematopoietic cell transplantation (typically leukemia, multiple myeloma, and some non-Hodgkin's lymphoma cases). TBI was proposed in 1956 by Nobel Prize laureate Thomas to treat patients with end-stage leukemia [1]. TBI helps in providing immunosuppression that facilitates the donor transplant acceptance. Randomized trials demonstrated that conditioning regimens to bone marrow transplantation including TBI have produced better outcomes (i.e. survival rates) than regimens with chemotherapy only [2–5]. By definition, TBI involves the whole body, including the target and the neighbor organs at risk (OAR). The widespread adoption of TBI in the nineties allowed the estimation of side effects related to this treatment [6]. In particular, TBI is mainly limited by normal tissue morbidities grade 2 and higher as reported for several prescription doses and for various hematologic diseases as shown in

Table 1 [7–10]. On the other hand, in a randomized study, Clift et al. demonstrated that higher dose (15.75 Gy) reduced relapse rates in comparison to 12 Gy in 6 fractions [11]. However, this did not lead to better survival rates.

Many groups have explored the possibility of sophisticated techniques for reducing the dose to healthy tissues while increasing the dose to the hematological target that includes the bone marrow, and, in case, the whole lymphatic system, liver, spleen and circulating blood. These newer approaches aim to generate Total Marrow Irradiation (TMI) (and/or total marrow lymph node irradiation – TMLI), sparing as much as possible non-skeletal and non-lymphoid structures. Fig. 1 shows hypothetical dose volume histograms (DVHs) for the target and the normal tissues using TMI instead of TBI.

The first TMI attempts were performed using helical tomotherapy (HT) [13–15]. Authors showed mean dose reductions compared to standard TBI in the OARs of 35–70% in the upper part of the body (from head to mid femurs – “Body plan”) [15]. TMI with large fields IMRT

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**Table 1**  
Reported toxicities larger than Grade 2 after TBI.

Organ	Toxicity	Dose	Reference
Lungs	G4 in 9/101 pts	3 × 3.33 Gy/fr; MLD > 9.5 Gy	Volpi [7]
Eyes	Cataracts G3 in 18% (495pts)	1 × 6.0–11.8 Gy	Van Kempen-Hartveldeye [8]
Heart	G3-G4: 0.9%	Not Reported	Murdoch [9]
Kidney	> G1 in 49%(71 pts)	Tot: 12–13.5 Gy	Mirabell [10]

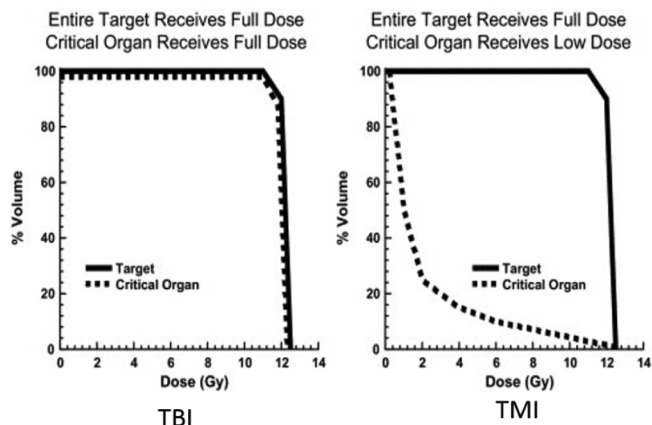


Fig. 1. Realistic DVH for TBI (left) and TMI (right) treatment (Modified from [12]).

was subsequently proposed, using a standard linac in the typical isocentric setting with patient positioned on the ordinary couch [16,17]. It was demonstrated in an anthropomorphic phantom that IMRT could reduce the dose to OARs by 29–65% compared to conventional TBI [17]. Authors reported some limitations of this approach, including the relative small IMRT field size, the prolonged beam on time (BOT) required to deliver the dose to the whole target, the long treatment planning optimization time, and the occurrence of hotspots > 130% of the prescription dose [16,17].

Volumetric modulated arc therapy (VMAT) is an IMRT technique with inverse treatment planning optimization descending from the category of intensity modulated arc therapy [18,19]. Many groups demonstrated the superiority of VMAT vs. static field IMRT and 3D-Conformal RT for several tumor sites in terms of dose conformity, sparing of dose to OARs, and significant BOT reduction [20]. The rapid development of VMAT together with the possibilities of performing TMI using HT created interest in delivering TMI using VMAT. The aim of this study was to review treatment planning studies of TMI delivered using VMAT (VMAT-TMI).

**2. Search strategy**

A comprehensive search strategy through the indexed database “PubMed” was performed using the search path [(“TMI” or “Total marrow irradiation”) and (“VMAT” or “Volumetric modulated arc therapy” or “RapidArc”)]. Papers published in English between 2010 and 2018 were included. Twelve papers were identified [21–32] (Table 2). In particular, the papers covered feasibility planning studies [21–22,30,32], optimization of the plan parameters [24,28,30,31], plan optimization of the lower extremities [28], plan robustness [27,28,32], and dosimetric plan verification [21,22,25,26,29,32].

**3. Feasibility planning studies**

From a geometrical viewpoint, rotational techniques as VMAT could

**Table 2**  
Studies included in this review.

Ref	Authors	Patients	TPS	Dose	normaliz	# arcs	# iso	Aim
[21]	Fogliata 2011	5	Eclipse 10	2 Gy*6	V100% > 85%	8	4	To propose VMAT for TMI
[22]	Aydogan 2011	6	Eclipse 8.9	1.5 Gy*8	V100% > 95%	9 (3plans)	?	To propose VMAT for TMI
[23]	Han 2012	4	Eclipse 8.6 vs Tomotherapy	1.5 Gy*8	V100% > 85%	8	?	To compare VMAT to helical tomotherapy in TMI optimization
[24]	Mancosu 2012	5	Eclipse 10	2 Gy*6	V100% > 85%	8	4	To optimize the isocenters and jaws apertures to improve the dose distribution for VMAT-TMI
[25]	Suruca 2011	1 phant	Eclipse 8.9	1.5 Gy*8	V100% > 95%	9 (3plans)	?	To perform in vivo measurement on phantom by TLD and Mapcheck for VMAT-TMI phantom
[26]	Liang 2013	1 phant	Eclipse 8.9	2 Gy*6	V90% > 100	6/9 (3plans)	?	To perform pre treatment QA by 2D and 3D approaches for VMAT-TMI phantom
[27]	Mancosu 2013	4	Eclipse 11	2 Gy*6 (TMI)	V100% > 85% (TMI)	10	5/6	To study the VMAT-TMI isocenter robustness by isocenter shifts
[28]	Mancosu 2015	21	Eclipse 11	2 Gy*1 (TMLL)	V98% > 98% (TMLL)	10	5/6	To study the VMAT-TMI lower extremities with field junction robustness evaluation
[29]	Mancosu 2015	3	Eclipse 11	2 Gy*6 (TMI)	V100% > 85% (TMI)	10	5/6	To perform in vivo dosimetry of VMAT-TMI by GaChromics
[30]	Nalichowski 2016	1	Eclipse 8.9 vs VOLO (Tom)	2 Gy*1 (TMLL)	V98% > 98%	6/9 (3plans)	?	To compare VMAT to helical tomotherapy in TMI optimization
[31]	Cherpak 2018	10	Eclipse 11	2 Gy*6	V90% > 99%	10	5/6	To compare 6MV vs 10MV in VMAT-TMI plan optimization in fat patients (BMI > 30 kg/m²)
[32]	Symons 2018	5	Pinnacle 9.10	2 Gy*6	V100 > 90% and V95% > 95%	9 (3plans)	9	To propose VMAT for TMI using Pinnacle

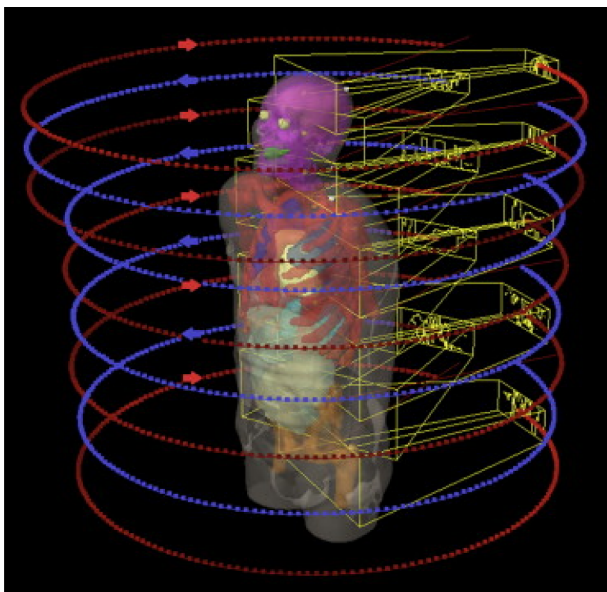


Fig. 2. Representation of arcs and isocenters positions for a TMI with VMAT (from Aydogan et al. [22]).

be satisfactory for TMI treatment, as both target and body have a nearly cylindrical symmetry. These techniques should, thus, simplify the request of dosimetric OARs sparing closed to the target region.

In 2011, the Humanitas Research Hospital [21] and the University of Chicago [22] published two independent feasibility studies of VMAT-TMI using similar approaches to optimize the “Body CT” series (defined as the region between skull and half of the femurs). In detail, Aydogan et al. reported the “Body plan” optimization of VMAT-TMI by nine overlapping arcs [22]. The optimizer used in the Aydogan paper (Eclipse 8.9, Varian Medical System) allowed the simultaneous optimization of “only” 1000° (i.e. 3 arcs of 333°), therefore three different plans were needed to fully include the whole body cranial-caudal (CC) length (excluding the lower extremities). Fogliata et al., using a more recent software version (Eclipse 10.0) that allowed the simultaneous optimization of 3600°, reported the optimization of a single plan with eight overlapping coplanar arcs of 360° [21]. Fig. 2 shows the arcs setting with multiple isocenters approach. In both studies, an overlapping field junction of 2 cm was considered between each couple of arcs. By definition, the field junction is the overlapping region covered by two (or more) fields/arcs with different treatment isocenters.

Plans objectives aimed to limit minimum and maximum doses to PTV. In both optimization approaches, the ALARA (as low as reliable achievable) method was followed for the OARs.

In both studies, a 120-leaf multi-leaf collimator (MLC) was used for beam modulation with 5–10 mm leaf thickness. The maximum dose rate was 600 monitor units (MU) per minute.

VMAT was shown to obtain satisfactory target coverage while sparing important OARs, with a “crude” BOT of 13–18 min. This compared favourably with the 45–50 min BOT reported for static field IMRT [17] and 20–50 min (depending on the HT version) [23,33,34].

Han et al. first directly compared standard HT to VMAT in optimizing TMI on four patients [23]. They found VMAT and HT plans to be comparable in terms of dose coverage to the target volumes, while they found a significant sparing of some OARs for VMAT (brain, right kidney, optic nerves, and thyroid) while the dose to the intestinal cavity was lower with HT. The mean BOT was  $628 \pm 32$  s with VMAT plans and  $1122 \pm 106$  s with HT.

More recently, Nalichowski et al. compared VMAT and HT (using a new optimization software for the latter) in terms of quality and efficiency of TMI plans [30]. The comparison was performed on a single phantom (Alderson Rando phantom by the Phantom Laboratory, Salem,

NY). They found that both planning systems can create high-quality plans for TMI, with HT resulting in superior OARs sparing, although no data from patients were reported.

Symons et al. recently reported a VMAT planning study (using the Pinnacle<sup>3</sup> planning system), showing high conformity to the hematological target and with reduced mean dose to both lungs, both kidneys and the liver (respectively, 66%, 75%, and 75% of the prescription dose) [32]. This paper focused on TBI with sparing of only five structures, without considering the other OARs.

#### 4. Optimization of the plan parameters

Since the introduction of inverse treatment planning systems, the selection of initial parameters is a fundamental step to ensure the best dose distribution. Therefore, the study and optimization of these parameters could help in obtaining adequate target coverage and organs at risk sparing. In VMAT-TMI plan optimization this is particular important due to the target length. Cherpak et al. investigated the effect of beam energy on target coverage and OAR sparing for VMAT-TMI of obese patients [31]. They considered ten patients with body mass index (BMI) > 30 kg/m<sup>2</sup> and two plans with 6 and 10 MV beams were optimized for each patient. Similar target coverage and MU were observed. Better CI (−11.0%,  $P < 0.01$ ), lower mean dose to OARs and normal tissue sparing for 10MV were observed for these obese patients.

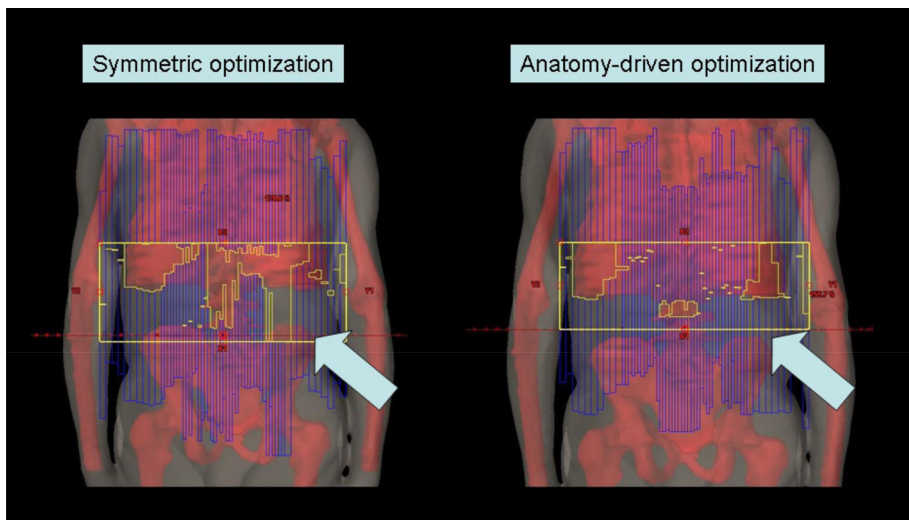
Nalichowski et al. tested several collimator rotation angles (0°, 45°, 90°). The jaw apertures were  $40 \times 16$  cm<sup>2</sup>, to use all coupled leaves along a space of 16 cm [30]. Using a collimator angle of 0° failed to provide “tangential” beamlets, which are decisive in getting dose to structures such as the ribs without overdosing the underlying lungs. By increasing the collimator to 45°, sufficient overlap region to provide smooth dose distribution between the sub-PTVs was obtained. However, acceptable, but not good, PTV coverage due to some parts of the PTV lacking the “tangential” beam was observed. Finally, by rotating the collimator to 90°, good lateral coverage was provided.

In the Fogliata study the gastrointestinal cavity (GIC) was the most critical organ in keeping median dose < 50% of the prescription dose [21]. Furthermore, Han et al. observed that HT resulted in significant better GIC sparing than VMAT (while in most other OARs, VMAT was better than HT) [23]. The possibility of dose distribution optimization by setting isocenter positions and jaw apertures according to patient’s anatomical features was performed for VMAT-TMI aiming, in particular, to reduce the dose to GIC [24]. Two models were investigated for geometrical settings of arcs: “Symmetric” and “Anatomy driven” approaches. In both cases, an overlapping field junction of 2 cm was considered between each couple of arcs. In the “Symmetric” model, isocenters were equal-spaced and field apertures were set equal for all arcs to cover uniformly the entire target length. In the “Anatomy driven” model, both field sizes and isocenter positions were optimized in order to minimize the target volume near the field edges (i.e., to maximize the freedom of motion of MLC leaves inside the field aperture). Fig. 3 shows a specific beam eye view (BEV) illustrating the differences between the two strategies.

Lower MU/fraction (mean reduction 7%; range −2% to 13%) was observed in the “Anatomy driven” model with respect to the “Symmetric” model. Target homogeneity, defined as ( $D_{2\%} - D_{98\%}$ ) was 18% better for the “Anatomy driven” model. Furthermore, significant reduction of mean dose to GIC was reported with the “Anatomy driven” approach.

#### 5. Plan optimization of the lower extremities

The maximum couch travel ability in the cranio-caudal (CC) direction of most linacs is around 130–150 cm; HT can reach 140 cm, (i.e. up to the knees). Therefore, in all adult patients, the skull and the lower extremities could not be treated using the same treatment position and the patient needs to be turned on to cover the entire body length.



**Fig. 3.** Specific BEV for the two-optimization strategies. In the “Symmetric” approach, two conflicting objectives could occur, as full dose to the two edges of the BEV and a sparing of the central part are required. As MLC moves along the CC direction, a suboptimal plan would occur. In the “Anatomy driven” optimization the conflict is resolved by closing the jaws in the caudal direction.

Furthermore, the usual CT couch travel ability in CC direction is around 140 cm; consequently, two CTs are required: one head-first supine and a second feet-first supine. Hence, a particular field junction (“Body/Legs junction”) should be considered.

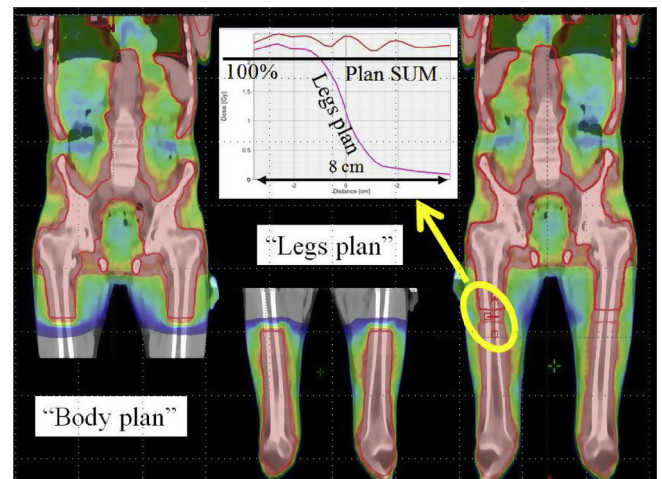
As stated by Fogliata et al., the lower parts of the legs were not included in the first papers [21]. Symons reported that the ideal method would be to treat the lower legs (“Legs plan”) with a series of VMAT arcs also to smooth doses in the junction regions. They noted that this has proved a challenge due to the difficulties in junctioning two VMAT arcs that have been planned on two CTs with different treatment orientations (i.e., head-first and feet-first supine orientation) [32].

A technique to produce a plan sum in the “Body/Legs junction” without creating under/over dosage on PTV and hotspots outside was elaborated [28]. Twenty-one patients treated with VMAT-TMI were considered. In the overlapping region (PTV<sub>J</sub>), two specular sigmoid dosimetric shapes were adopted for obtaining homogeneous integral dose. For this purpose, four PTVs of 1 cm thickness were defined: PTV<sub>100%</sub>, PTV<sub>75%</sub>, PTV<sub>50%</sub>, PTV<sub>25%</sub>. These PTVs were optimized, respectively, to the specific isodose percentage. The isodoses of 100%, 75%, 50%, and 25% from the “Body plan” were co-registered to the “Legs CT”. The “Legs plan” was specularly optimized by giving the residual dose to the co-registered isodoses. Authors obtained that 95% of the prescription dose covered > 99% of PTV<sub>J</sub> in all patients, with hotspots < 125%. Representative dose distribution along coronal view for the “Body/Legs” junction in a TMLI treatment is shown in Fig. 4.

## 6. Plan robustness

The treatment of TBI/TMI targets requires multiple isocenters. In this case, junctions are conventionally used to prevent over/underdosing which can be introduced by an imperfect alignment of neighbouring fields at the same location. Junction robustness could be studied by intentional shifting of the isocenters, creating a gap or overlap between the fields, and re-calculating the plan using the same MLC shape and MUs.

For the “Body plan”, a study by Mancosu et al considered four patients and three series of random shifts  $\pm 3/5$  mm were applied to each isocenter position [27]. Shifts were applied in the anterior-posterior (AP), left-right (LR), and CC directions, keeping the other two directions fixed. Concerning the single directions, similar values for LR and AP directions were observed, while, for the CC direction, the uncertainty was almost doubled. Maximum doses increased up to 15% for CC shifted plans. The fraction of the PTV covered by the 95% isodose decreased 2–8% revealing target underdosage with the highest values in CC direction. The influence was more pronounced in the overlapping



**Fig. 4.** Dose distributions of the “Body plan”, the “Legs plan”, and the resulting plan sum for a representative coronal view (from [28]). The dosimetric profile along the “Body/Legs” junction showed a sigmoid shape between 0% and 100% for the “Legs Plan” and an almost constant value for the sum of “Body plan” and “Legs plan”.

regions with underdosages of 3–11%. This study demonstrated correct isocenter repositioning of TMI-TMLI patients to be fundamental, in particular in CC direction, in order to avoid over- and under-dosage in particular in the overlap regions. Recently, Symons et al. confirmed the findings on a single patient plan: no major deviation for the target coverage was found for shifts  $\leq 5$  in LR and AP directions, while significant difference in CC direction was observed [32].

In addition, the robustness of the “Body/Legs” junction has been evaluated, using an analogous method for shifts up to 10 mm to account for the patient's repositioning inaccuracy between the two deliveries [28]. The lowest isocenter of the “Body plan” and the highest isocenter of the “Legs plan” were considered as principal contributors to the junction. Differences  $\ll 1\%$  to mean, minimum ( $D_{98\%}$ ), and maximum ( $D_{2\%}$ ) doses to PTV<sub>J</sub> and surrounding healthy tissue in the three directions were found for 3 mm shifts [28]. Mean doses to PTV<sub>J</sub> was 98.9% and 96.1% for shifts of, respectively, 5 and 10 mm in CC direction.

## 7. Dosimetric plan verification

The high dose gradients obtained in VMAT plans could induce serious deviations between planned and delivered dose distributions,

particularly in regions adjacent to organs at risk; Complex RT plans such as those obtained with TMI-VMAT require dosimetric verification before clinical delivery.

The first two feasibility papers reported planar dose distribution measurements using either a 2D diode array [22] or portal imager [21], obtaining, respectively, global Gamma Agreement Index  $GAI(3\text{ mm},3\%) = 98.1\%$  (the standard deviation was not reported in the paper) and  $GAI(3\text{ mm},3\%) = 94.3 \pm 5.1\%$ . In the two studies, the three dimensional dose distribution from VMAT-TMI in an inhomogeneous phantom including the dose distribution in the field junctions was not studied.

Symons et al. performed pre-treatment QA with a cylindrical diode array using  $GAI(3\text{ mm},3\%)$  [32]. The diode array was shifted longitudinal by  $\pm 6\text{ cm}$ , and laterally by  $\pm 8\text{ cm}$  to verify all segments and the fields edge. A mean  $GAI(3\text{ mm},3\%) = 99.2\%$  (range 95.7%–100%) was obtained.

Liang et al. developed a dosimetric verification procedure for VMAT-TMI based on both planar and volumetric approaches using, respectively, radiochromic films for gamma evaluation linked to absolute point dose with ion chamber, and a commercial dose reconstruction software to reconstruct the doses from electronic portal imaging devices (EPID) images [26]. Three patients were taken into account and three plans per each patient were considered. Particular attention to the junction between neighboring plans regarding hot/cold spots was paid. Plans were recalculated on an IMRT phantom. The mean film dosimetry  $GAI(5\%, 3\text{ mm})$  was 98.2% and absolute dose difference was 3.9%. The mean 3D  $GAI(5\%, 3\text{ mm})$  was 90.7% and absolute difference was 2.4%.

Surucu et al. investigated the dosimetric distribution accuracy of VMAT-TMI technique inside a humanlike Rando phantom [25]. The VMAT-TMI dose distribution was measured and compared to the calculated dose with particular attention to the field junctions and the inhomogeneous tissues. Thermo-Luminescent Detectors (TLDs) were placed at 39 positions throughout the phantom and planar dose for each arc was verified. Three experiments were performed and at least two TLDs were placed for each patient for more than 300 TLDs analyzed. TLD readings demonstrated accurate dose delivery, with a median dose difference of 0.5% (range: 4.3% and 6.6%) from the calculated dose. In particular, the median dose difference for the H&N/chest junction was 2.1% (range: 0.4%–3.9%), whereas it was 1.2% (range: 1.2–4.1%) for the chest/pelvis junction.  $GAI(3\text{ mm},3\%)$  was higher than 96.8% (mean:  $97.8 \pm 1.2\%$ ) These results suggested that VMAT technique with field junctions is dosimetrically accurate, safe, and efficient in delivering TMI.

The Surucu study was conducted in the “ideal” situation, as the phantom was stationary. However, patients can have involuntary motions. In detail, the door-to-door time, including patient pre-positioning, image guided radiotherapy (IGRT), and BOT was around 60–90 min. This could increase the dosimetric uncertainty due to patient movements.

In vivo dosimetry has been used to verify the accuracy of delivered doses in RT [35]. A pilot study on three patients treated with TMLI using radiochromic films for two-dimensional in vivo dosimetry was performed [29].  $GAI(5\%,5\text{ mm})$ , with dose referred to maximum dose, resulted greater than 95% in all cases, and  $GAI(3\text{ mm},5\%)$  was larger than 88.7%. Therefore, TMI-TMLI patient immobilization along the standard radiotherapy position (i.e. SSD distance of 80–90 cm, instead of the  $> 300\text{ cm}$  for the traditional TBI) guarantees good correspondence between the TPS and the actual dose delivered to the patient.

## 8. Discussion

The Guidelines from the International Lymphoma Radiation Oncology Group (ILROG; ed. 2018) reported that the use of TBI is declining [36]. The guidelines stated that RT could have a role only if it does not induce additional toxicity. TMI presents the potential ability of higher dose homogeneity, inferior organ doses, toxicity decrease, dose

escalation to target structures, and reduced relapse rates. Researchers working in radiation oncology studied in detail TMI protocols, optimizing the treatment parameters, and increasing the whole treatment safety [36]. The same ILROG guidelines stated that TMI should still be considered a field of research and that TMI patients should be included only in controlled trials.

TMI is one of the most challenging radiotherapy planning and delivery techniques as the whole skeleton (and, eventually, the lymph nodes and spleen in the TMLI treatment) should be irradiated, sparing nearby OARs. Target volume of 7–10  $\text{cm}^3$  and healthy tissues of 50–90  $\text{cm}^3$  should be considered in TMI. The mandible/maxillary structures and, eventually, heads were usually not part of the irradiated target aiming to reduce the unwanted side effects (as a reduced hemopoietic tissue in these regions is present). Furthermore, usually the whole chest wall was considered to include the ribs motion due to respiration. Target definition is complex and labor intensive in TMI and requires a dedicated team, including radiation oncologists, haematologists, and radiation physicists [21].

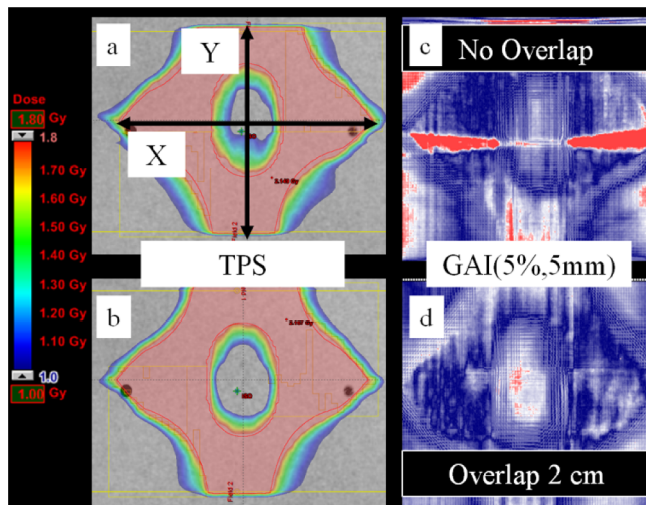
The body cylindrical symmetry could encourage the use of arc therapy approaches, as helical tomotherapy and VMAT, in TMI-TMLI treatments. These techniques simplify the demand for dosimetric sparing of OARs closed to the target region with respect to fixed gantry IMRT. In particular, the wide spread adoption of VMAT encourages the evaluation of TMI by VMAT. Twelve papers were discussed in the present review focusing on five major areas.

The first part focused on the initial feasibility papers as well as some later papers focused on the treatment planning concept and associated challenges. The treatment of a very large target requires multiple isocenters. In this case, junctions are conventionally used to prevent over/under-dosing which can be introduced by an imperfect alignment of neighbouring fields at the same location. The first studies on the management of doses from fields with different isocenters positions were performed for cranial spinal irradiation (CSI). Sohn et al. proposed a particular 3DCRT approach with independent and asymmetric collimator settings, and a penumbra modifier to administer uniformly radiation over the CSI axis [37]. They reported differences  $< 10\%$  through the craniospinal axis. Moving junction technique was also tested to reduce dose inhomogeneity through the head/spine junction in 3DCRT [38]. A two-isocenter IMRT technique for treating long targets was developed by Zeng et al. [39]. The technique utilized an extended dose gradient through a junction region for reducing the field match error and obtaining dose homogeneity along the junction. More recently also VMAT was shown to be feasible for CSI [40]. Regarding the VMAT-TMI multi-isocenter approach, adequate dose distribution using different TPSs (VMAT/RapidArc [21–23] and, more recently, VMAT/Pinnacle [32]) was shown. Some comparison between VMAT-TMI and other delivery technique reported comparable results.

It should be underlined that the multi-isocenter scheme require a particular attention in the IGRT approach. Usually, online cone beam CT (CBCT) should be performed for each isocenter before delivering the arcs in order to minimize the effect of wrong junction positioning matching. With the same aim, an ad hoc immobilization system should be considered to minimize the unwanted patient set-up motion due to the prolonged door-to-door time that could be  $> 1\text{ h}$ .

The second part of the review focused on studies to perform and to improve the VMAT-TMI plan quality by plan parameters optimization. In fact, since the introduction of inverse planning, the selection of initial parameters was a fundamental step to ensure the best dose distribution. In VMAT, the number of arcs, the total degree per arc, couch and collimator rotations, isocenter position, jaws apertures, are some of the parameters that could improve the dosimetric plan quality. This investigation confirmed the role of initial parameters as beam energy for obese patients [31], collimator angle position [30], isocenters and jaw apertures based on the specific anatomy of each patient [24] in improving the plan quality.

The third part focused on the junction between the two CT series



**Fig. 5.** (a-b): Dose distribution (range 50%–90%) calculated by the TPS for the two phantom plans (a) without overlap and (b) with overlap of 2 cm. (c-d): GAI (5%,5mm) maps related to the two optimizations showing the necessity of an overlapping region of, at least, 2 cm between arcs with different isocenters.

**Table 3**

GAI(3/5 mm, 3/5%), obtained in the phantom study (partially included in [28]).

GAI	5 mm 5% [%]	3 mm 5% [%]	5 mm 3% [%]	3 mm 3% [%]
2 cm overlap	99.4	95.6	87.1	75.2
No overlap	86.4	82.1	75.0	66.7

[28]. A procedure to plan, match and add the doses from the upper and lower body plans (i.e. “Body plan” and “Legs plan”) was described by optimizing two specular gradients on the arcs bordering at the junction. On this point, Zeverino et al. reported similar experience using helical tomotherapy to treat TMI by splitting the treatment in two segments, with the lower limbs treated with feet first orientation [34].

The fourth part of this review focused on the evaluation of the plan robustness. In particular, junction robustness could be studied by intentional shifting of the isocenter in the three directions (AP, LR, CC). Seppälä et al. performed the first study on CSI treatment with shifts in the range of  $\pm 3$  mm [41]. They observed a limited influence on the dose distribution for IMRT, while an error of  $\pm 38\%$  was observed for 3DCRT. Sarkar et al. recently demonstrated that VMAT was insensitive to small longitudinal setup errors (1–3 mm) for CSI because of dose gradients at the junction [42]. They reported that 5 mm shift in CC direction of the most cranial isocenter generated a dosimetric gap of 5–10% between the two fields. However, CSI and TMI plans have different arc geometry and thus specific study is required for determining the TMI plan robustness. The correct isocenter repositioning of TMI/TMLI patients was demonstrated to be fundamental to minimize over- and under-dosages particularly in the CC direction. In particular, action levels of 5/5/3 mm should be considered for, respectively, AP, LR and CC directions for VMAT-TMI and collimator at  $90^\circ$  [27]. These results were obtained with a junction width of at least 2 cm between each arc. Authors strongly recommend to not use lower junction width. In an internal study, partially reported in [29], a CT of a phantom was performed and a complex target with a central hole was manually generated. Two plans composed of two 6 MV arcs with different isocenters positions were optimized with collimator rotation at  $90^\circ$ . The two plans had an overlapping region length in the central plane between the two arcs of, respectively, 0 cm and 2 cm. IGRT by CBCT with online couch adjustment using an action level of 1 mm for the two isocenters was performed. Automatic plus manual matching of CBCT series to the simulated CT was considered. Radiochromic films were placed inside a

cassette along the coronal plane.

Low differences in terms of target coverage and healthy tissue sparing were observed between the two plans (no overlap vs overlap of 2 cm) as shown in Fig. 5. The complete GAI analysis is reported in Table 3. Only the plan with the overlap could provide adequate results.

The final part of this review focused on TMI dose verification. A complete dosimetric study, mimicking as close as possible the clinical situation, is a standard in radiotherapy before a technique can be used to treat a patient. Without such a study, it would be difficult to make a reliable and safe clinical transition especially with a technique as complicated as VMAT-TMI. In particular, *in vivo* dosimetry is used to verify the accuracy of delivered doses in RT. In a “standard” TBI with patient at  $> 3$  m and jaws full opened doses, single point measurements could be enough for TBI verification.

However, the single points approach is not adequate for checking modulated plans when high dose gradients are present. Therefore, a two-dimensional approach was developed [29]. The TMI-TMLI possibility of immobilizing the patient along the standard radiotherapy position (i.e. SSD distance of 80–90 cm, instead of the  $> 300$  cm for standard TBI) guaranteed better correspondence between the TPS and the actual dose delivered to the patient. In fact,  $GAI(5\%,5mm) > 95\%$  was obtained in all cases.

In conclusion, this review presented the state of art of VMAT-TMI. Plan parameters optimization, plan optimization of the lower extremities, plan robustness evaluations, and dosimetric verification by pre-treatment quality assurance and *in vivo* measurements were evaluated. This review demonstrated the possibility of VMAT in delivering TMI with multi-arcs and multi-isocenters. Care should be paid in the patient repositioning, with particular attention for the cranial-caudal direction.

### Declaration of Competing Interest

Luca Cozzi acts as Scientific Advisor to Varian Medical Systems and is Clinical Research Scientist at Humanitas Cancer Center. All other co-authors declare that they have no competing interests.

### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.phro.2019.08.001>.

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