Evolution of treatment planning and dose delivery methods during radiotherapy for patients undergoing bone marrow transplantation: a review

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Abstract. *Background and objectives*: This study describes the treatment planning and dose delivery methods of radiotherapy for patients undergoing bone marrow transplantation. The analysis was carried out in the context of the evolution of these methods over the last 60 years. *Materials and methods*: A systematic literature search was carried out using the PubMed search engine. Overall, 90 relevant studies were included: 24 general studies, 10 describing isotopes usage, 24 related to conventional and 32 to advanced methods. *Results*: The analysis of the evolution of radiotherapy methods shows how significantly the precision of dose planning methods and its delivery have changed. The atypical positioning caused by geometrical requirements for applications of isotopes or conventional techniques has been replaced by positioning on a therapeutic couch, which allows a more precise setup of the patient that is necessary for an exact delivery of the planned dose. The dose can be fully optimized and calculated on tomographic images by algorithms implemented in planning systems. Optimization process allows to reduce doses in organs at risk. The accuracy between planned and delivered doses can be checked by pretreatment verification methods, and the patient positioning can be checked by image guidance procedures. *Interpretation and conclusions*: Current radiotherapy solutions allow a precise delivery of doses to the planning target volume while reducing doses to organs at risk. Nevertheless, it should be kept in mind that establishing radiotherapy as an important element of the whole therapeutic regimen resulted from the follow-up of patients treated by conventional techniques. To confirm the clinical value of new advanced techniques, clinical trials are required.

Keywords: Total body irradiation • Total marrow irradiation • TBI/TMI planning • TBI/TMI dose delivery

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Introduction

The guidelines published by the International Lymphoma Radiation Oncology Group present total body irradiation (TBI) as one of the methods of conditioning regimen for patients with acute myeloid leukemia or acute lymphoid leukemia undergoing hematopoietic stem cell transplantation [1]. If TBI is to be combined with myeloablative conditioning regimens, the TBI can be delivered before or after chemotherapy, typically by cyclophosphamide [1, 2]. TBI procedure serves two main purposes. First, it eliminates the malignant cells that have escaped chemotherapy. Second, it is used to suppress the patient's immune system to prevent the rejection of donor bone marrow [3]. The irradiation schemes used vary depending on the dose, dose rate, fractionation and irradiation method. In general, TBI is carried out in an irradiation scheme of twice daily 2 Gy fractions given over 3 days, with a minimum interval of 4 h between fractions (total dose of 12 Gy) [1–5]. Other irradiation schedules are: twice daily 1.5 Gy fractions over 4–4.5 days (total dose 12–13.5 Gy);

three times daily 1.2 Gy fractions over 4 days (total dose 12–13.2 Gy) and once daily 3 Gy fractions for 4 days (total dose 12 Gy) [1, 2]. These schemes allow healthy tissues, such as the lung tissue, to repair damage caused by irradiation, increasing the likelihood that the abnormal cells, which grow rapidly and have a low ability to repair damage caused by radiation, will be killed.

It seems that regimens with TBI achieve better outcomes than those without it [6–12]. Even though TBI is an efficient part of a bone marrow transplantation conditioning treatment, it is responsible for many side effects associated with both acute toxicity (e.g. nausea, vomiting, diarrhea, stomatitis, temporary loss of taste, parotitis and rash) and late toxicity (e.g. interstitial pneumonitis, hepatic veno-occlusive disease, cataracts, infertility, hormone-related disorders, bone toxicity, growth retardation and secondary malignancies) [13–21]. To reduce side effects as much as possible, it is necessary to accurately select and compose complex therapeutic regimens. From the TBI perspective, improving the treatment planning methods of dose distribution, and, in consequence, methods of dose delivery to the patient could also reduce the side effects.

This study aims to review the literature about TBI techniques in a bone marrow transplantation with special emphasis on the methods of treatment planning and dose delivery.

Materials and methods

Information sources and search strategy

Systematic literature searches were carried out in December 2018 using the PubMed search engine that provides a free access to MEDLINE and links to full-text articles when possible. If open access to the articles was restricted, they were downloaded through our institutional access. Searching was limited to full--text articles including e-publications ahead of print; no date or language restrictions were applied. The keywords used were arranged according to the following scheme: [TBI and/or total marrow irradiation (TMI)] and (treatment planning and/or dose delivery and/or equipment) and (acute myeloid leukemia and/or acute lymphoid leukemia).

Eligibility criteria and review structure

Our review included studies describing conventional planning methods of TBI with limited visualization of dose distributions in treatment planning systems (TPSs) and advanced planning methods, fully realized by planners through TPS. Studies describing advanced planning methods include TBI as well as TMI for which therapeutic dose was limited to the bone marrow.

Overall, 90 relevant studies were included. While 24 of them were used for introduction, 10 concerned methods based on isotopes or nonconventional use of Co-60 source, 24 were related to conventional methods realized on Co-60 units or conventional (C-Arm) accelerators, and 32 described advanced methods applied on tomotherapy machine (12), dedicated cobalt units (2) and conventional accelerators (18).

The structure of our review includes three main parts describing and discussing the methods of treatment planning and dose delivery for TBI/TMI, namely: (i) era of isotopes, (ii) era of conventional treatment on cobalt units and linear accelerators and (iii) current solutions.

Results and discussion

While the first report of entire body irradiation was presented in 1932 by Heublein [22], radiotherapy in bone marrow transplantation conditioning regimens was officially introduced in the late 1950s by Nobel Prize winner E. D. Thomas [23]. The technical solution in radiotherapy in those years required large radiation fields for the TBI that guaranteed relatively homogeneous dose distribution (dose deposited in the irradiated region varied ±10%) and the possibility of dose reduction in healthy tissues/organs was susceptible to early radiation reactions (e.g. lungs) [24].

Era of isotopes

The first solution of TBI was based on multiple sources [25, 26]. On the basis of Webster recommendations for the design of facilities for the uniform TBI [25], Jacobs and Pape [26] built a TBI chamber where the sources of irradiations were four rods containing two Cs-137 sources in each of them. Rods were separated from each other by 2 m and were placed at each end of the treatment bed (Fig. 1a). The planning issues concerned the basic calculations of dose distribution in the therapeutic chamber, for which the times of irradiation from specified cesium rods were controlled by lead filters and a specific system that allowed to retract rods into the floor to turn the sources "off" or pulled rods from the floor to the therapeutic chamber to switch the sources "on". Although in the 1950s and 1960s, the solutions based on multiple sources were still developed [27, 28]; the conviction was growing that these solutions are too expensive for most medical facilities. In connection with the above, the researchers' interest was directed to the possibility of using cobalt units used in the conventional radiotherapy. In 1959, Sahler [29] developed a dual-source cobalt (Co-60) irradiator that consisted of a conventional rotating cobalt unit and an industrial large field cobalt irradiator. Using two Co-60 sources allows to arrange irradiation geometry to produce a parallel opposed field at about 3 m from the patient (Fig. 1b). However, the collimators of the conventional cobalt unit had to be removed for TBI to obtain a large field. The source characteristics and the distance between source and patient define this proposal as a low dose rate TBI (<10 cGy/min). Despite the limited possibilities of

dose calculation (the dose calculation based on 2D rules applicable in those years without dose visualization on computed tomography (CT) images), the dose measurements and verifications of the dose delivery confirmed the appeal of this method because of the reproducibility of the setup and relative dose uniformity [30–32]. To avoid irradiation from two Co-60 sources, the investigators from the Princess Margaret Hospital in Toronto designed and constructed a special single Co-60 source unit (Fig. 1c) [33]. This solution allowed to obtain relatively large fields of irradiation for the short (0.9 m) distance between the source and patient (source-to-skin distance, SSD). Taking into account the spatial dose distribution of gamma radiation emitted from Co-60 sources, the special flattening filter was used to compensate the dose variation across the beam. The short SSD and high activity of Co-60 (~10 000 Ci) allow to use high-dose treatment delivered in short times (~50 cGy/min). To allow TBI delivery in a low dose rate regime, a special lead attenuator has been designed and installed near the source. Cunningham and Wright [34] described a Co-60 unit mounted on a ceiling track, with a specially designed collimator. The source scanned the patient positioned at a therapeutic couch at about 120 cm SSD (Fig. 1d). While

for the solutions of two or one Co-60 sources dose was calculated manually using simplified formulas, the geometry of irradiation and methods of dose delivery guaranteed greater control over the doses, which was mainly performed during pretreatment and *in-vivo* measurements. Nevertheless, all the above-described solutions required the fundamental reorganization of the therapeutic bunker (insertion of additional Co-60 source and modification of the collimation) [29–32] or construction of a completely new machine dedicated only to TBI [33, 34]. There was a need to adapt the conventional cobalt unit without any additional sources in such a way that, in addition to TBI, the rest of conventional radiation therapy treatment could be delivered on this machine.

Era of conventional cobalt units and linear accelerators

The idea presented by Cunningham and Wright [34] was adapted for rotating Co-60 units by Quast (Fig. 1e) [35]. While in the Cunningham and Wright study [34], the source was moved along the long axis of the patient, Quast's solution allows the patient
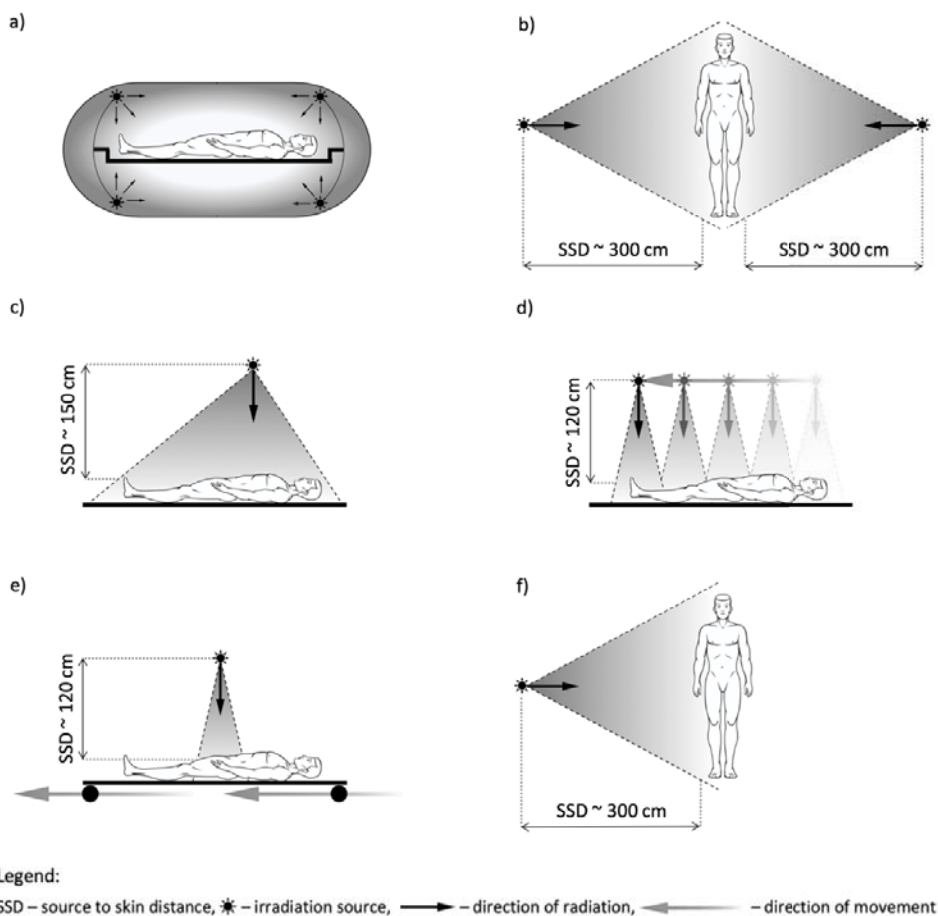

Legend:

SSD – source to skin distance, ✳ – irradiation source, ➝ – direction of radiation, ⟵ – direction of movement

Fig. 1. Historical and conventional methods of total body irradiation. The diagrams represent respectively: (a) cesium irradiation in therapeutic chamber (Jacobs and Pape [26]), (b) irradiation by two Co-60 sources (Sahler [29]), (c) irradiation on dedicated Co-60 unit (Princess Margaret Hospital, Toronto [33]), (d) irradiation by ceiling track mounted Co-60 source (Cunningham and Wright [34]), (e) irradiation by Co-60 with moving couch (Quast [35]), and (f) one of the lateral fields used for irradiation by conventional method realized on Co-60 unit or linear accelerator (Peters and Herer [37]).

to be moved (through a mobile couch) beneath a fixed Co-60 source [35]. Another adaptation of TBI to technical requirements of conventional Co-60 units was presented by Mulvey *et al.* [36], where isocentric treatment with automatic arcing facilities and a specially designed curved couch was presented. Finally, Peters and Herer [37] described a very simple procedure for removing the collimating system from a widely used Co-60 therapy unit. In less than 15 min, this unit could be modified to handle large field stationary treatment procedures.

These investigations allowed to adapt TBI to technical requirements of conventional Co-60 units. While a lot of methods adapt the conventional Co-60 unit to the TBI procedure [35, 36, 38, 39], the most prevalent method (referred to as "conventional" in this study) of delivering TBI is with the patient lying or standing at an extended SSD [31–33, 37, 40, 41]. The patient is usually treated for this purpose with a single radiation beam, with a large (~ from 3 m to 4 m) SSD and the largest possible field size. The collimator of the treatment field is rotated by 45° in order to use the diagonal dimension of the field. To achieve a uniform dose rate at the long axis of the patient's body, lead strips as compensating filters or boluses made of material imitating soft tissue in the area of the head and neck (H&N), lungs, abdomen, knees and ankles are used. To counteract the skin-sparing effect, a Plexiglas plate placed near the patient (between the source and the patient) is typically used. The accuracy of the patient positioning is checked by a light field simulating the irradiation field. Moreover, customized blocks are used to reduce the dose in the lungs. Anterior and posterior fields are used, often given in multiple treatment sessions with the dose prescribed to the mid-plane.

While the main purpose of TBI is to achieve a uniform dose distribution throughout the body, the aspects associated with the dose minimization in the lungs are just as important. The lungs are the main dose-limiting organ in this technique [3, 5]. Della Volpe *et al.* [19] reported about five times higher risk of the 6-month lethal pulmonary toxicity in patients with mean lung dose greater than 9.4 Gy. Usually, the median lung doses are kept to 8–10 Gy. The most significant pulmonary complication is radiation-induced pneumonia, which is the main cause of mortality after TBI. It should be noted that preference is given to blocks (typically made of lead or Wood's alloy) that correspond to a 50% reduction in radiation dose because overcompensation through the use of lung shields can increase the risk of leukemia recurrence. There have been reports of increased relapse rate in patients whose lung dose was limited to 6 Gy due to abnormal lung cover [42]. The solutions involving TBI delivery only at Co-60 units limited the possibility of simultaneous reduction of doses in the lungs and obtaining high (prescribed) doses in the chest wall. Therefore, a combined treatment was introduced taking into account the large irradiation fields on Co-60 units and the use of electron fields (on conventional linear accelerators) with energies from 6 MeV to 12 MeV (dependent on the

thickness of the chest wall) to boost the chest wall region [43]. This combined treatment provided the argument to move TBI entirely from Co-60 to linear accelerators. Although Barrett *et al.* [44] suggested potential problems with changing the low-dose rate schemes to high-dose rate schemes, the modification made by the manufacturers introducing the option to select a low-dose rate mode (dedicated for TBI) on conventional accelerators resolves this problem. The studies presented by Ozsahin *et al.* [45] and Gogna *et al.* [46] show no significance in induced radiation pneumonitis for patients treated on Co-60 and conventional accelerators. While energies that are typically used on conventional accelerators ranged from 6 MeV to 10 MeV [47, 48], there are studies showing the possibility of using higher energies (e.g. 15 MeV) [49–51]. Nevertheless, it should be noted that for certain types of TBI-treated diseases, like leukemia, it is preferred that the skin receive a full dose of radiation. Therefore, to defeat the skin-sparing effect (similarly as in Co-60 solution) of high-energy photons, a beam spoiler of low atomic number material, such as a plate of plastic is placed close to the patient [52, 53]. Figure 1f shows schematically the lateral field of irradiation as one of the fields used in the commonly applied technique of TBI on Co-60 units and conventional accelerators.

The planning procedures for the conventional TBI method based on geometrical measurements and simplified calculations of doses are controlled by *in-vivo* measurements [41].

Before dose calculations, the characteristics of the therapeutic beams (e.g. percentage depth dose, profile function and standard dose) measured in TBI condition should be gathered. Geometrical measurements for planning purposes include the thickness, length of patient (form the feet to the top of the head and measured for a therapeutic position) and the distance from the central axis at the specific anatomic points, such as the head, neck, shoulders, chest wall, elbows, abdomen, pelvis, knees and ankles. If the boluses are used (instead of compensating filters), their geometrical dimensions are included during the measurements of the patient geometry. Depending on the patient's geometry, the differences in separate planes along the patient's length can result in dose heterogeneity. Dose heterogeneity should be reduced to below 10% of the prescribed dose by applying boluses (at the patient level) or compensators (at the accelerator gantry level). *In-vivo* dosimetry should be used to measure the calculated dose. Measurement points during *in-vivo* dosimetry should correspond to the planes of the patient's body where the doses were calculated. Figure 2 shows an example of the working sheet used for the reporting distances describing the patient's geometry related to the irradiation source and calculated and measured doses.

Most treatment regimens now require dose reduction in the lungs. In the above-described conventional method, this is possible through the use of a sequence of therapeutic fields consisting of lateral photon fields, anterior and posterior photon fields that include blocks for shielding the lung and
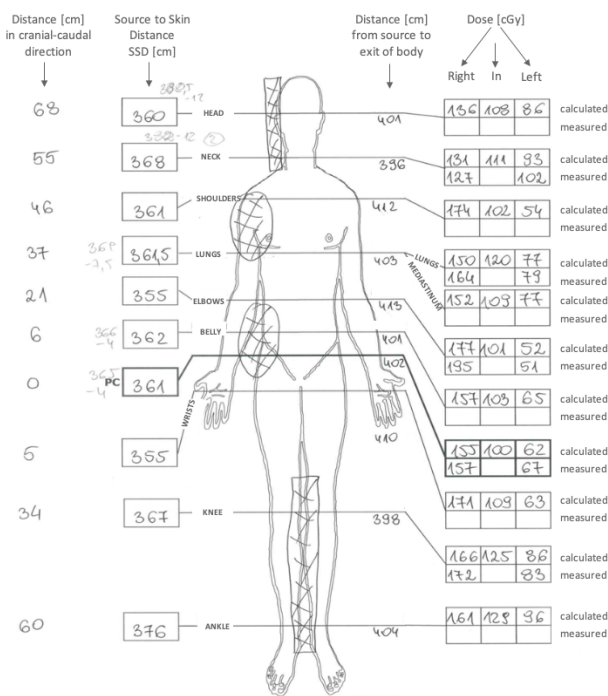
Distance [cm] in cranial-caudal direction	Source to Skin Distance SSD [cm]	Body part	Distance [cm] from source to exit of body	Dose [cGy] Right	In	Left	
68	360	HEAD	401	136	108	86	calculated / measured
55	368	NECK	336	131 / 127	111	93 / 102	calculated / measured
46	361	SHOULDERS	412	174	102	54	calculated / measured
37	3615	LUNGS	403	150 / 164	120	77 / 79	calculated / measured
		LUNGS-MEDIASTINUM		152	103	77	calculated / measured
21	355	ELBOWS	443				
6	362	BELLY	401 / 402	177 / 195	101	52 / 51	calculated / measured
0	PC 361	WRISTS		157	103	65	calculated / measured
5	355		410	153 / 157	100	62 / 67	calculated / measured
34	367	KNEE	398	171	109	63	calculated / measured
				166 / 172	125	86 / 83	calculated / measured
60	376	ANKLE	404	161	128	96	calculated / measured

Fig. 2. An example of the working sheet used for conventional methods of total body irradiation, for reporting distances describing the patient's geometry related to the irradiation source and calculated/measured doses. (Source: The authors).

electron fields used to deliver the dose to the chest wall region (shielded during anterior/posterior fields). The blocks used in the anterior/posterior fields cover the central portion of the lung, with approximately 1 or 2 cm between the edge of the lung shadow on the film and the edge of the block. To check the geometrical accuracy of the correctness of the block's position, radiographic films are used. Typically, blocks that transmit 50% of the primary beam are used rather than full-thickness lung blocks, which have a transmission factor of 3% [31, 42, 43]. At many centers, an additional 4 Gy single-fraction boost dose is delivered with electrons to the testes of male patients with acute lymphoid leukemia to reduce the risk of relapse in this sanctuary site [54].

The planning for conventional TBI is based on dose calculations in selected points and then dose verification methods. Some authors included in the treatment planning procedure the visualization of the dose distribution in a selected part of a patient's body (usually for the lungs region) [50]. Using point information about the dose distribution allows to confirm acceptable heterogeneity of the dose distribution. Nevertheless, it is rather obvious that point dose calculation is a big simplification of the full dose distribution in a patient's body, and real heterogeneity of the doses in the patient's body can be higher than that estimated from measuring points [55]. Most of the reports on the clinical efficacy of TBI are based on data gathered from patients treated by conventional TBI techniques [1, 2]. Full support of planning methods by advanced calculation algorithms that allow dose distribution optimization and visualization on computed tomographic images (not available for conventional methods) promises

to increase the accuracy of the dose distribution and reduce the toxicities of treatment in structures other than the lungs [56].

Current solutions

Owing to the complications accompanying the conventional TBI method, it is extremely important to develop and implement in the clinical practice irradiation techniques that allow to limit the dose in critical organs.

One of the new proposals is a refreshment of the solution assuming the irradiation of the patient placed on a mobile couch beneath a fixed Co-60 source (Fig. 1e) [35]. For this purpose, GammaBeam 500 (Best Theratronics Inc., Kanata, ON, Canada) was introduced to the clinic [57, 58]. This solution provides the adequate capability of delivering TBI in accordance with tolerances recommended by the AAPM Report #17 [24]. Nevertheless, it cannot be perceived as an innovative solution, but rather as a commercial product development based on Quast's prototype solutions [35].

At the beginning of this era, tomotherapeutic machines, previously called Tomotherapy™ and currently RadixAct™ (Accuray Inc., Sunnyvale, CA, USA), were introduced to clinical practice [59]. The method of dose delivery and image guidance procedures implemented on tomotherapeutic machines [60] revolutionized the concept of preparing and performing the TBI procedure. The possibility of preparing a treatment plan including the optimization of dose distribution on computed tomographic images for almost the whole body of the patient (from the scalp to the middle of the femur) and then irradiating at one beam-on procedure according to the treatment plan, and the possibility of advanced image guidance procedures allows to set the standards for TBI, such as for other radiotherapeutic procedures. Owing to the lack of organs at risk (OAR), the rest of a patient body (from the middle of femur to feet) is typically irradiated on conventional accelerators by using two opposite photon fields in anterior/posterior (AP/PA) direction. Nevertheless, Zeverino et al. [61] presented a more sophisticated planning technique that allows for matching the two helical dose distributions arising from the delivery of TMI with helical tomotherapy for the whole body of the patient, lower limbs included. To do it, they perform two distinct scans of computed tomography (CT) for treatment plans: the whole body CT and lower limb CT, reversed with respect to each other. The region of the junctions between the two CT was controlled during optimization by using special outlines placed on this region. After optimization, the plans were registered, and the accuracy of the doses in the junction's region was verified [61]. On the basis of the precise information on the dose distribution and the possibility of its optimization in selected anatomical parts, such as OAR, the general concept of TBI has been enriched by another treatment possibility called TMI – total marrow irradiation. The aim of TMI is to achieve a desired dose distribution in the

target volume, which in this case is the bone marrow, while limiting the dose in the surrounding healthy tissues, such as the eyes, lenses, brain, lungs, heart, esophagus, liver, kidneys, stomach, bladder, rectum and genitals [62, 63]. The application of TMI or TBI procedures on tomotherapeutic machines brings a number of benefits, such as simplifying the method by eliminating dose modifiers, increasing the patient's comfort during irradiation (patient lying on the back without bolus), limiting the doses in critical organs (not only the lungs) that provide less toxicity and in result, allow to increase dose rate (>>10 cGy/min) and dose escalation to targeted structures in the light of conventional solutions [61–67].

While tomotherapeutic procedures of the TMI or TBI were widely implemented in subsequent therapeutic centers, the relatively long time they took was pointed as a potential problem of stability of the patient's position during dose delivery [68]. These hypothetical problems were resolved by Takahashi and Hui [69] who showed in their study that the time needed to perform the TBI or TMI procedure on tomotherapeutic machine does not pose a risk of significant deviations from the original treatment plan regardless of the output variation.

Parallel to the development of TBI/TMI on tomotherapy, the implementation of intensity-modulated radiation therapy (IMRT) realized through large fields on conventional linear accelerators was discussed [70, 71]. Aydogan *et al.* [72] were the first who showed the possibility of TMI delivery by IMRT on conventional linear accelerators (IM-TMI; linac-based total marrow intensity-modulated radiotherapy). In their study [72], they implemented the technique that based on dosimetric data gathered on one patient. The presented methodology was repeated by Yeginer *et al.* [73] on a bigger group of patients. The authors of these publications considered several technical problems related to the use of large IMRT fields for TMI, such as field size limitations, planning with multiple isocenters and improving patient positioning and setup. To develop and verify the implementation of the IM-TMI treatment method on a conventional linear accelerator, they prepared a treatment plan using tomographic images of a TBI patient. The clinical target volume (CTV) was taken as all the skeletal bones including the cranium, mandible, sternum, ribs, complete vertebral body, os coxae, femoral head and upper half of femur. The area below the middle part of the femur was not included in the study. Similar to the TMI technique realized on tomotherapy machines, a simple AP/PA technique can be used for this region because there is no OAR. The OARs included in the study were the lenses, whole brain, lungs, liver, kidneys and heart. The CTV was divided into three subvolumes consisting of the H&N, chest and pelvic region. In a typical adult, linac-based IM-TMI, three plans with separate isocenters, were created. Each plan consisted of nine equispaced beams. To prevent hot spots at the field junctions, optimization using a base plan in Eclipse/Helios TPS (Varian Medical Systems, Palo Alto, CA, USA) was used. A dose reduction in median doses for OARs has been reported

by 1.3–4.5 times compared to a conventional TBI technique. The largest dose reduction was observed for the lenses, from 11.3 for the TBI to 2.5 for the IM-TMI. The median lung dose was reduced from 8.8 for TBI to 7.0 for IM-TMI. For other organs, the TMI and TBI median doses were, respectively: for the liver 6.5 Gy vs. 12.3 Gy, for the kidneys 6.8 Gy vs. 12.2 Gy, for the heart 7.1 Gy vs. 12.1 Gy, for the eyes 3 Gy vs. 11.3 Gy and for the brain 7.3 Gy vs. 12 Gy [72]. These data confirm the possibility of dose reduction to OARs for TMI in the light of conventional TBI. Nevertheless, these doses (except the doses to the eyes) were higher than those received during TMI on tomotherapeutic machines. The median doses for tomotherapy were, respectively: for the lenses 1.5 Gy, for the lungs 4.3 Gy, for the liver 6 Gy, for the kidneys 5.6 Gy, for the heart 6.2 Gy, for the eyes 6.6 Gy, and for the brain 4 Gy [64]. Moreover, the authors of the IM-TMI technique [72] also drew attention to the problem related to the accuracy of patient positioning during irradiation with their technique. It should be remembered that in contrast to the tomotherapeutic solution where one plan is prepared and implemented, IM-TMI technique is typically based on three isocenters (three multifield separate plans, for which separate setups are needed during the fraction dose delivery). Even a small patient rotation can have a very large impact on the dose delivered to the target and critical structures during IM-TMI. Therefore, the authors suggested that a whole-body frame may be useful in immobilizing the patient and to verify the patient's position daily cone-beam computed tomography (CBCT) may be used for each plan separately.

The introduction of volumetric modulated arc therapy (VMAT) technology in 2008 made it possible to reduce some of the problems associated with the implementation of TMI using IMRT on conventional linear accelerators [74]. Mancosu *et al.* [75] published a most recent review of the VMAT techniques used for the TMI. The VMAT is a technique that uses the full modulation of the intensity of dose rate while shaping the desired dose distribution in the target volume. The linear accelerator during the single arc rotation (360°) of the gantry around the patient's longitudinal axis irradiates the given volume with a cone beam shaped by dynamically moving leaves of multi-leaf collimator. To best match the dose distribution, the head rotation speed and radiation dose rate are modulated at the same time. The VMAT technique allows to achieve the desired dose distribution in the target volume while reducing the dose in critical organs. It also makes it possible to shorten the irradiation time for many cancer locations [76]. The application of VMAT to the implementation of TMI (VMAT-TMI) was first proposed by Fogliata *et al.* [77]. They prepared treatment plans using tomographic images of five patients. The gross tumour volume was taken as all the skeletal bones. The mandible and maxillary structures, the hands and the area below the middle part of the femur were not included in the study. The PTV was defined as all bones. Besides, neighboring small islands were connected into one contour

on each CT slice. The OARs included in the dose optimization process were the same as in previous solutions (TMI on tomotherapy and IM-TMI on conventional accelerators). The optimization aimed to reduce the dose in critical organs below 50–60% of the prescription dose (6–7 Gy). Plans prepared for each patient consisted of eight overlapping 360° arcs grouped into four isocenters. To cover the whole PTV length, asymmetric jaw settings were used. The collimator was set to 90°. The jaws were set to 40 cm in the craniocaudal direction, and from 15 cm to 16 cm in the in-plane directions. For PTV, the maximum $D_{1\%}$ was approximately 14.5 Gy (120% of the prescribed dose). For most OARs, a median dose below 7 Gy was obtained. The VMAT-TMI method was later investigated for a limited group of patients by Aydogan *et al.* [78], Han *et al.* [79] or examined on a humanlike phantom by Surucu *et al.* [80]. Although the segmentation strategies for these studies were similar to the strategy presented by Fogliata *et al.* [77], the optimization strategies including the number of plans and arcs contained in plans were different. Aydogan *et al.* [78] proposed the division of PTV into three parts including the area of the head of the neck, chest and pelvis. These parts were covered by three respective plans. Each of the plans consisted of three 330° arcs (from 165° to 195°). The base plan method was used. The chest plan was prepared first and served as the base plan for the remaining areas. The best dose distributions were obtained by setting the collimator at 90° position. The size of the irradiation fields was 40 cm in the craniocaudal direction and 10, 12 and 16 cm, respectively, in the in-plane directions for the H&N, chest and pelvis. The maximal accepted dose for OARs was 100%, when possible. For the OARs that were near PTV or overlapped with PTV, a 110% hot spot was accepted. For PTV, the maximum allowable dose was 130%. For most critical organs, the median doses below 6 Gy (50% of the set dose) were obtained. The median dose was about 7.2 Gy and 7.4 Gy for the lungs and brain, respectively. The methodology and results of the Aydogan group [78] were verified and confirmed by Surucu *et al.* [80] in the study performed on humanlike phantoms. In contrast to Aydogan *et al.* [78], Han *et al.* [79] proposed a division of PTV into four areas (the H&N, chest, abdomen and pelvis) for which four plans were proposed that consisted of eight arcs in total. The plan preparation was also based, as in the previous concept, on a base plan technique but was carried out differently. The plan for the H&N was first created and then set as a base plan for the chest area, and consequently, the plan for the chest was a basis for the abdomen plan and the abdomen plan was a basis for the pelvis plan. The collimator angle was set in the range from 80° to 100°. The size of the irradiation fields in the craniocaudal direction ranged from 15 cm to 20 cm for the H&N region, and from 27 cm to 32 cm for the chest, abdomen and pelvis. The size of the irradiation fields in the in-plane directions ranged from 12 cm to 14 cm for each region. Figure 3 shows schematically the geometry used for TMI delivered on a tomo-
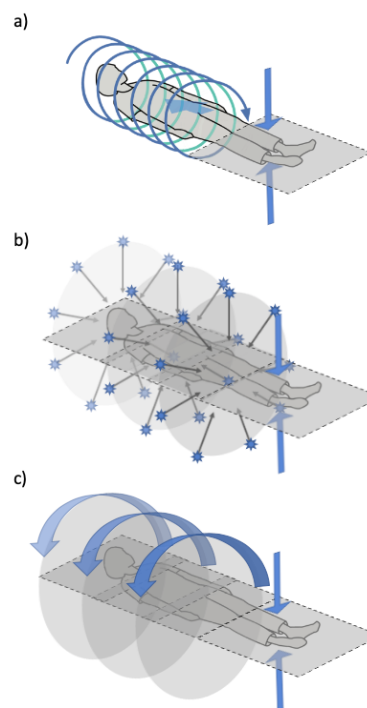

Fig. 3. Current solutions of total body irradiation or TMI. The graphs represent respectively: (a) irradiation realized on tomotherapy machine (Hui *et al.* [62]), (b) irradiation realized through three plans, each plan containing nine equispaced intensity-modulated photon beams (Aydogan *et al.* [72]), and (c) irradiation realized through three plans, each plan containing three volumetric modulated photon arcs (Aydogan *et al.* [78]). In each method, two opposite photon beams are used for the irradiation of the area from the middle part of the femur to the toes.

therapeutic machine and on conventional linacs, and Fig. 4 shows the example of dose distribution for TMI delivered on a conventional accelerator.

While all the above-noted studies show the possibility of implementing TMI on Varian accelerators (Varian Medical Systems, Palo Alto, CA, USA),
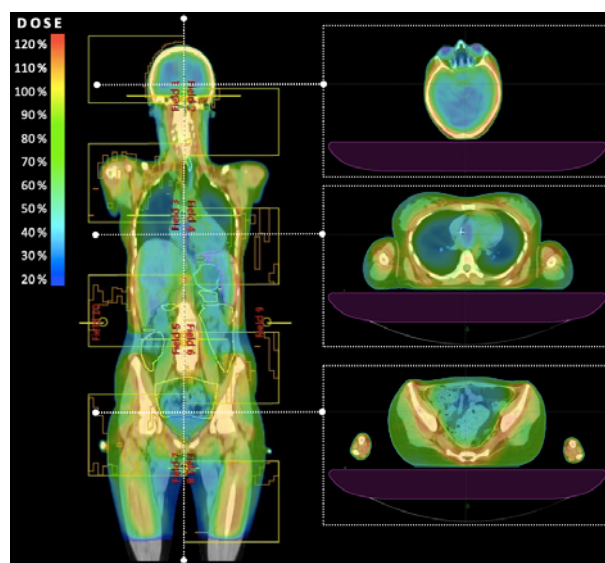

Fig. 4. The dose distribution for total marrow irradiation realized through volumetric modulated arc therapy proposed by Fogliata *et al.* [77]. (Source: The authors).

Symons *et al*. [81] showed a feasibility study using the Pinnacle³ TPS and Elekta Agility™ linac (Elekta Instruments AB, Stockholm, Sweden). Similar to Han *et al*. [79], the PTV was divided into four subsections (the H&N, chest, abdomen and pelvis). The head and chest beams were optimized together, followed by the abdomen and pelvis beams. The last stage of the planning process involved turning all beams on and performing a final optimization to achieve a clinically acceptable plan. Beam isocenters were shifted by 3 mm or 5 mm in each direction to simulate the effect of setup errors on the dose distribution. As a result, they showed that the VMAT--TMI technique was sensitive to patient setup errors, particularly in the craniocaudal direction. Nevertheless, the dose predicted by the planning system was consistent with measured doses. A similar study, but for Varian accelerators, was presented by Mancosu *et al*. [82]. The conclusions were almost the same as for the study presented by Symons *et al*. [81]. The authors recommend using a dedicated immobilization system when VMAT-TMI is delivered. In the other study, Mancosu *et al*. [83] presented a recipe to resolve another junctioning problem caused by different body orientations during the irradiation of the legs and main part of the body (from the skull to thighs). They show that potential under-/overdosage in the junction region can be eliminated by correct positioning between these two plans. Taking into account these observations, it should be underlined that the multi-isocenter scheme along with dedicated immobilization systems requires particular attention in the image-guided radiation therapy approach. In general, online cone beam CT should be performed for each isocenter before delivering the arcs to minimize the effect of wrong junction positioning matching [75].

However, image-guided procedures do not provide information about the accuracy of the dose distribution during its delivery. While the dose delivery by modern solutions is preceded by the pre-treatment dose verification performed in dedicated dosimetric systems, the *in-vivo* dosimetry is still the only method that allows us to evaluate the impact of involuntary motions of the patient on the dose that is delivered during irradiation. Mancosu *et al*. [84] showed an interesting method of *in-vivo* dosimetry based on measurements by gafchromic films placed directly on the therapeutic couch and under the immobilization plates used for patient fixation. The analysis of these results allows to confirm the accuracy of the dose delivery targeted at multiple isocentric fields with special emphasis on the regions of arc junctions. Other interesting solutions are currently implemented on tomotherapy machines where an automated visualization of the dose distribution delivered during fraction on megavoltage computed tomography (MVCT) images gathered directly before the fraction is possible. Owing to a relatively new implementation, there is no scientific report on this topic yet. Only information in commercial brochures is available [85].

Conclusions

For tomotherapeutic machines, a potential problem is associated with the time of dose delivery and should be resolved during the optimization of the treatment plan, whereas for conventional linacs, a potential problem can lie in multi-isocentric treatment forcing multiple positioning (for each plan separately) resulting in uncertainty of junctioning of fields/arcs coming from plans that cover neighboring anatomical regions (e.g. the chest area and H&N area). These problems should be considered and resolved before TMI implementation on tomotherapeutic machines or on conventional linacs. Comparing these solutions with the application based on isotopes or conventional TBI techniques shows
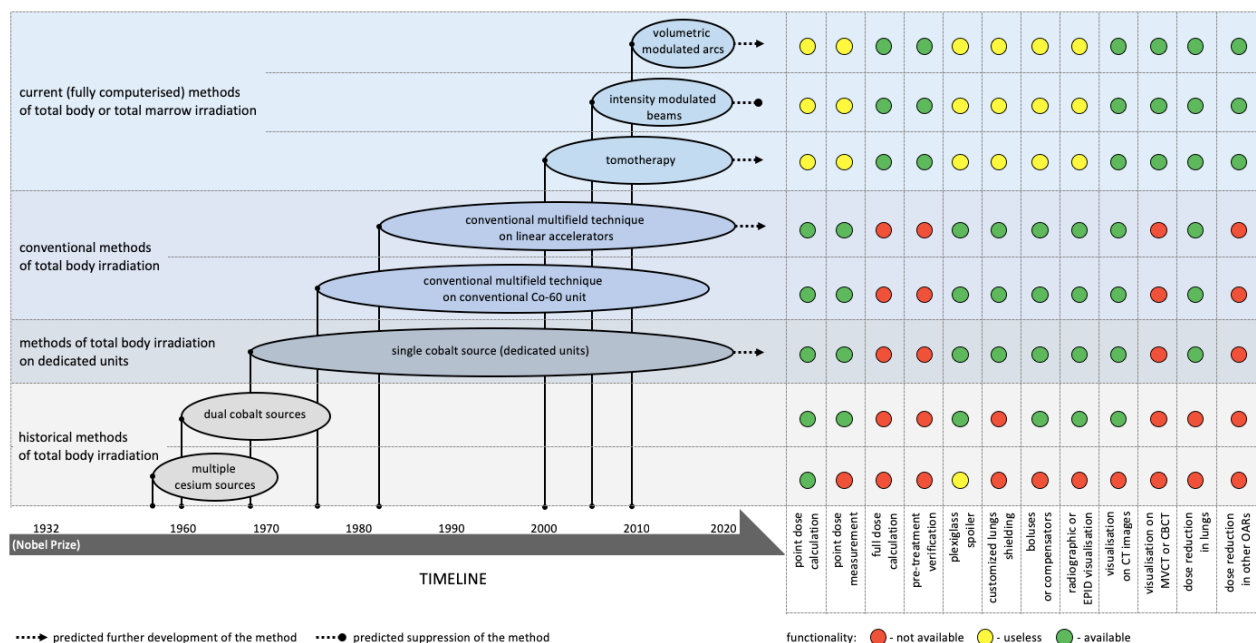

Fig. 5. Schematic timeline of milestone technical changes in total body irradiation.

how significantly the precision of dose planning methods and its delivery has improved. Figure 5 shows the timeline of milestone changes in radiotherapy methods used for patients undergoing the bone marrow transplantation. The nontypical positioning caused by geometrical requirements for the conventional TBI techniques was replaced by positioning on therapeutic couch as for other patients undergoing radiotherapy. That allows a more precise setup of the patient that is necessary for the exact delivery of the planned dose. The dose can be fully optimized and calculated on tomographic images by advanced algorithms implemented in TPSs. Advanced optimization process allows to reduce doses in OAR. The accuracy of the planned dose and its ability to be delivered can be checked by pretreatment verification made by well-established procedures used in radiotherapy [81, 86]. The accuracy of the patient positioning can be checked by advanced image guidance procedures through the use of MVCT on tomotherapeutic machines or CBCT on conventional linacs. Despite all these advantages, it should be kept in mind that establishing TBI as an important element of preparing patients undergoing hematopoietic stem cell transplantation resulted from the follow-up of patients treated by the conventional TBI techniques [1, 2]. To confirm the clinical value of new TBI/TMI techniques, clinical trials including conventional and novel dose fractionation strategies are required [87].

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