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Guidelines

ESTRO ACROP and SIOPE recommendations for myeloablative Total Body Irradiation in children

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ABSTRACT

Background and purpose: Myeloablative Total Body Irradiation (TBI) is an important modality in conditioning for allogeneic hematopoietic stem cell transplantation (HSCT), especially in children with high-risk acute lymphoblastic leukemia (ALL). TBI practices are heterogeneous and institution-specific. Since TBI is associated with multiple late adverse effects, recommendations may help to standardize practices and improve the outcome versus toxicity ratio for children.

Material and methods: The European Society for Paediatric Oncology (SIOPE) Radiotherapy TBI Working Group together with ESTRO experts conducted a literature search and evaluation regarding myeloablative TBI techniques and toxicities in children. Findings were discussed in bimonthly virtual meetings and consensus recommendations were established.

Results: Myeloablative TBI in HSCT conditioning is mostly performed for high-risk ALL patients or patients with recurring hematologic malignancies. TBI is discouraged in children <3–4 years old because of increased toxicity risk. Publications regarding TBI are mostly retrospective studies with level III–IV evidence. Preferential TBI dose in children is 12–14.4 Gy in 1.6–2 Gy fractions b.i.d. Dose reduction should be considered for the lungs to <8 Gy, for the kidneys to $\leq$10 Gy, and for the lenses to <12 Gy, for dose rates $\geq$6 cGy/min. Highly conformal techniques i.e. TomoTherapy and VMAT TBI or Total Marrow (and/or Lymphoid) Irradiation as implemented in several centers, improve dose homogeneity and organ sparing, and should be evaluated in studies.

Abbreviations: AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; ALT, alanine aminotransferase; AP, Anterior-Posterior; AST, aspartate aminotransferase; AYA, adolescent and young adults; BED, biologically effective dose; CML, chronic myeloid leukemia; CNS, central nervous system; CRT, cranial radiotherapy; CSI, craniospinal irradiation; CVA, cerebrovascular incident; CVD, cardiovascular disease; DEXA, Dual-energy x-ray absorptiometry; EQD_2, dose delivered in 2-Gy fractions that is biologically equivalent to a total dose; fTBI, fractionated Total Body Irradiation; GVHD, graft versus host disease; HSCT, hematopoietic stem cell transplantation; IMRT, intensity modulated radiation therapy; IP, interstitial pneumonitis; MLC, multileaf collimator; MOSFET, metal–oxide–semiconductor field-effect transistor; MRD, minimal residual disease; NGS, next-generation sequencing; NRM, Non Relapse Mortality; PA, Posterior-Anterior; RT-qPCR, real-time quantitative polymerase chain reaction; SAD, source-axis distance; SSD, source to skin distance; TBI, Total Body Irradiation; TMI, Total Marrow Irradiation; TMLI, Total Marrow and Lymphoid Irradiation; TLD, thermoluminescent dosimeter; TLI, Total Lymphoid Irradiation; TPS, treatment planning system; sfTBI, single fraction Total Body Irradiation; SIOPE, European Society for Paediatric Oncology; SOS, sinusoidal obstruction syndrome.

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Conclusions: These ESTRO ACROP SIOPE recommendations provide expert consensus for conventional and highly conformal myeloablative TBI in children, as well as a supporting literature overview of TBI techniques and toxicities.

Myeloablative Total Body Irradiation (TBI) has long been a cornerstone of the conditioning for hematopoietic stem cell transplantation (HSCT) in children [1], but is associated with considerable late effects [2–6]. Currently, use of TBI is mainly indicated in allogeneic HSCT for high-risk hematologic malignancy [7–13]. Fractionated TBI (fTBI) is standard for pediatric radiotherapy centers, but practices vary [14,15]. While most centers perform conventional TBI, several institutions have introduced highly conformal TBI techniques or Total Marrow Irradiation (TMI), Total Lymphoid Irradiation (TLI), and Total Marrow and Lymphoid Irradiation (TMLI) [16–19]. After a survey regarding clinical practice of pediatric TBI in European Society for Paediatric Oncology (SIOPE) affiliated centers [14], the SIOPE Radiotherapy TBI Working Group together with selected ESTRO experts established recommendations for myeloablative TBI in pediatric patients, for whom optimization of TBI is particularly of importance.

Methods

Literature searches were conducted in PubMed regarding fractionated pediatric myeloablative TBI. Search terms were: "tbi"[All Fields] OR ("whole body irradiation"[MeSH Terms] OR ("whole body"[All Fields] AND "irradiation"[All Fields]) OR "whole body irradiation"[All Fields] OR ("total"[All Fields] AND "body"[All Fields] AND "irradiation"[All Fields]) OR "total body irradiation"[All Fields]) OR "TMI"[All Fields] OR ("total"[All Fields] AND "marrow*"[All Fields]) OR (("total"[All Fields] AND "lymphoid*"[All Fields]) OR "TMLI"[All Fields] OR "TLI"[All Fields]) AND "fraction*"[All Fields] AND ("pediatr*"[All Fields] OR "child*"[All Fields] OR "paediatr*"[All Fields]). Searches focused on conventional and highly conformal techniques of TBI; TMI; TMLI; TLI; technical and radiobiological considerations in publications since 1970. Systematic screening of search results on TBI toxicities in publications since 1980 was conducted using the AI screening tool ASReview LAB (Utrecht University, the Netherlands), and selected full-text analyzed publications were checked for further references. Inclusion criteria and search terms are given in Supplementary Tables 1–6. Members of the ESTRO-SIOPE writing committee held bimonthly virtual meetings to discuss the body of evidence and institutional experiences. Subgroups contributed specific sections and the entire manuscript was reviewed by all members. The Supplement Review provides an extended literature review as background to the recommendations. As exemplified in the Supplementary Tables regarding organ system-specific TBI-related toxicities, most recommendations and considerations are based on Level of Evidence III-IV publications. Considerations regarding boost radiotherapy should be graded as Level V, expert opinion, after evaluation of the literature and peer discussions. We attempted to compile and judge available data, knowing that high-level evidence is lacking for many open questions. All recommendations and considerations were accepted with majority approval.

Recommendation results

Indications for TBI-based myeloablative conditioning for HSCT in children

Myeloablative TBI combined with etoposide is indicated in children ≥4 years of age with high-risk acute lymphoblastic leukemia (ALL) in any remission, who have an indication for allogeneic HSCT, as established in the prospective ALL-SCT-BFM 2003 and the randomized multicenter FORUM trials [12,20]. TBI with cyclophosphamide is another traditionally used conditioning schedule. In study protocols, indications for HSCT and TBI are constantly evolving [21].

In first HSCT for acute myeloid leukemia (AML) or advanced myelodysplastic syndrome, chemotherapy-only-based regimens are the rule, showing equivalent or superior survival as well as leukemia control compared with TBI-based regimens [22–24]. A potential role of myeloablative TBI in subsequent HSCT for AML and juvenile myelomonocytic leukemia is unclear [25,26]. No comparative studies on HSCT with TBI in pediatric patients with relapsed Non-Hodgkin (e.g. diffuse large B-cell, primary mediastinal large B-cell, Burkitt, lymphoblastic) lymphomas or anaplastic large cell lymphomas are available, but this treatment can be successful, depending on the histological subtype [27–29].

Myeloablative TBI-based conditioning is not indicated in children with non-malignant diseases such as inborn errors of immunity, metabolism, or bone marrow failure diseases [30–32]. Non-myeloablative doses of TBI of 2–4 Gy combined with chemotherapy can be employed for their immunosuppressive effect in reduced intensity conditioning [33,34]. These recommendations focus on myeloablative TBI.

Patient evaluation before TBI

Pre-HCST workup should include complete physical examination, a comprehensive series of organ function tests and consultations with members of the HSCT team (Table 1). Disease and complete treatment history, as well as recent outcomes of minimal residual disease (MRD) status and cerebrospinal fluid cytology are mandatory [35]. Age is a very important factor when deciding about TBI; young children (<3–4 years) are more prone to develop serious late complications [4,36–41].

Cancer predisposition syndromes may preclude radiotherapy. In case of known encephalopathy or myelopathy one should consider the potential additional damage of myeloablative TBI. Potential increased toxicity due to previous radiotherapy should be considered before deciding on TBI.

TBI fractionation

Fractionated TBI (fTBI) showed equality in disease outcome and reduced toxicity when compared with single-fraction TBI (sfTBI) [88–98]. Different fractionation schedules have been used [99] (Supplementary Tables 1–6). Extrapolating exclusive TBI-related effect differences from the literature is precluded by influences of conditioning-protocol variations, previous treatments and GVHD, in patient cohorts with various diseases and age groups. Fractionated TBI with doses of <9–10 Gy resulted in increased non-engraftment and disease-relapse in several reports [100,101]. Lung and/or liver adverse events were found to be the dose-limiting toxicity for fTBI 15.5–16 Gy [102–104]; non-relapse mortality (NRM) was increased for 15.75-Gy fTBI as compared with 12 Gy [95,96]; and secondary malignancy risk increased with conventionally performed fTBI ≥13–14.4 Gy in large retrospective cohorts [105,106]. To optimize the radiobiological therapeutic ratio, twice-daily frac-

Table 1
Patient evaluation before allogeneic HSCT conditioning with myeloablative TBI, and long-term follow-up recommendations after TBI.

Pre-TBI based HSCT conditioning evaluation		
Examination factor	**Test recommendation**	**References**
Age	<3 and preferably <4 years old; avoid myeloablative TBI because of increased risk of late effects. Consider potential toxicity effects of TBI at specific age and development stage of patients.	[4,36–41]
Medical history	Evaluate complete disease and treatment history and other relevant medical background details, including family history of malignancies.	
CNS status	Cerebrospinal fluid examination for CNS 1-2-3 status; preferably 1-2 before conditioning, otherwise consider CNS boost before TBI.	[42]
MRD status	RT-qPCR or NGS MRD negativity related with better prognosis. If positive, discuss potential further treatment to reach MRD negativity before HSCT.	[35,43,44]
Previous radiotherapy	Check cumulative dose and safety of additional TBI.	
Complete physical examination	i.e. lung, heart, abdomen, nodal, testes examination, growth.	[45]
Lung examination	Radiologic examination of lungs, previous pulmonary problems, respiratory function tests.	[45]
Cardiac examination and cardiovascular risk profile	Electrocardiogram, weight, blood pressure, cardiac ultrasonography or isotopic ventriculography (after previous cardiotoxic treatments e.g. exposure to anthracyclines, previous thoracic radiotherapy), glucose- lipid-, cholesterol- and triglycerides spectrum.	[45–47]
Kidney function	Blood pressure, renal function assessment (blood urea nitrogen and creatinine + clearance, urinary protein, and if necessary kidney ultrasonography).	
Liver function	Blood liver function test (bilirubin, AST, ALT), history of cirrhosis or hepatitis.	
Endocrine status	Check of growth, thyroid, gonadal hormone levels.	
Neurocognitive status	Baseline neurocognitive testing, cognitive development evaluation.	[48,49]
Fertility counseling	Fertility counseling by specialist, evaluate possibility of gamete storage pre-HSCT conditioning.	[50–53]
Ophthalmologic evaluation	Pre-conditioning inspection by ophthalmologist. Clinical symptoms, visual acuity, fundus exam, lens inspection.	[54,55]
Dental evaluation	Pre-conditioning inspection and preventive care by dental specialist.	[56]
Cancer predisposition syndromes	Avoid radiotherapy for these children if possible.	
Psychosocial and social evaluation	Psychological and social burden capacity of patient and caregivers.	[48,57,58]
Long-term follow-up after TBI-based HSCT conditioning		
Examination factor	**Test recommendation**	**References**
Chronic GVHD	Regular follow-up with evaluation of GVHD signs and symptoms (skin, mouth, gut, genitourinary system, liver, lungs). Treatment with steroids and other immunosuppressants if necessary.	[59–61]
Late respiratory complications	Pulmonary function testing and focused radiologic assessment at 1 and potentially 2 years after HSCT, and regularly thereafter for those with deficits. Regular routine clinical assessment. Discouragement of smoking.	[62–68]
Metabolic and cardiovascular function	Yearly check-ups, e.g. regular evaluation of weight, dyslipidemia, blood pressure and hyperglycemia.	[69]
Endocrine function	Yearly comprehensive blood screening for endocrine dysfunctions (growth, thyroid, gonadal, adrenocortical). Supplementation by endocrinologist when necessary.	[70–73]
Growth	Evaluation of growth curve and velocity with checks for influencing factors (hormone depletion, liver dysfunction, chronic GVHD). Supplementation by endocrinologist when necessary.	[74–76]
Fertility issues	Counseling and management of post-HSCT fertility issues. Pregnancies after TBI should be monitored by a gynecologist because of higher risk of miscarriages, preterm deliveries, and obstetrical complications.	[50,77]
Bone health	Monitoring of bone health i.e. signs of bone mineral density loss or osteoporosis through biochemical hormone assessments. DEXA scan evaluation at 1 year after HSCT and afterwards based on baseline findings (expert opinion). Counseling by a pediatric endocrinologist, weight-bearing exercise, and use of calcium and vitamin D supplements, hormone replacement in case of hypogonadism, or antiresorptive agents (bisphosphonates or calcitonin) if evidence of abnormalities.	[78–80]
Chronic renal dysfunction	Yearly screening of renal function (including blood pressure, renal function assessment (blood urea nitrogen and creatinine + clearance, urinary protein, and if necessary kidney ultrasonography).	[68,81]
Ocular complications	Yearly inspection by ophthalmologist. Clinical symptoms, visual acuity, fundus examination, lens inspection.	[55,68,82]
Dental evaluation	Examination by dentist 6–12 months post-HSCT and yearly thereafter; evaluation of caries and saliva production, dental hygiene, consideration fluoride application. After TBI, awareness of risk for oral malignancies.	[68]
Neurocognitive function	Neurocognitive testing in children is recommended before and 1 year after HSCT and then at the beginning of each new stage of education.	[49]
Secondary malignancies	Regular clinical assessment at outpatient clinic visits, advise patients and caregivers about the risks of secondary malignancies and encourage routine screening self-examinations, such as breast and skin examination. Consider dermatologic screening by a specialist every 1–2 years. Participation in national cancer screening protocols. Ultrasonography and MRI screening programs for thyroid cancer for all patients and breast cancer in young women $\geq$ 25 years can be considered. From age 50, annual fecal occult blood testing, or sigmoidoscopy every 5 years with occult blood testing every 3 years, or colonoscopy every 10 years can be considered. Discourage high-risk behaviors such as unprotected skin UV exposure and smoking.	[68,83–87]

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CNS = central nervous system; DEXA = Dual-energy x-ray absorptiometry; GVHD = graft versus host disease; HSCT = hematopoietic stem cell transplantation; MRD = minimal residual disease; MRI = magnetic resonance imaging; NGS = next-generation sequencing; RT-qPCR = real-time quantitative polymerase chain reaction.

tionation of 1.6–2 Gy to total doses $\geq$12 Gy was advocated by several authors. Strongly hyperfractionated schedules with 3–4 fractions daily seem to have worse anti-leukemic/immunosuppressive effects, and are impractical in terms of delivery [89,107–109]. Giving 12 Gy fTBI in once-daily fractions of 3–4 Gy increases acute effects such as mucositis [110,111]. Considering radiobiological early and late effects for children, a maximum fraction dose of 2 Gy is advisable. Interplay between chemotherapy type/dose and TBI can be influential on outcome [112], but studies on the finesses are lacking. TBI as 12 Gy in 6 fractions b.i.d. combined with etoposide was employed in the recent randomized FORUM trial, and resulted in generally less NRM and acute toxicity than can be surmised from historical reports [12]. Other common schedules are 13.2 Gy or 14.4 Gy in 8 fractions over 4 days [14,15]. Currently, in conventional TBI, fTBI schedules of 12–14.4 Gy, in 1.6–2 Gy fractions b.i.d., are customary in pediatric radiation oncology centers [14,15]. Commonly used schedules are 6$\times$2 Gy, 8$\times$1.8 Gy or 8$\times$1.65 Gy b.i.d. Nonetheless, continuous re-

assessment is in order. For example, highly-conformal TBI or TM(L)I techniques, as described further-on, may be beneficial regarding reduction of organ-at-risk (OAR) toxicity and enabling of dose escalation for very high-risk patients [113].

TBI dose rate

The radiobiological effect of TBI depends on many interplaying factors, including radiation dose rate (see the supplement for more elaborate discussion). Preclinical studies have reported influence of TBI dose rate on normal tissues and malignant/hematopoietic cells. Changing the dose rate within the lower range of e.g. 0.5–30 cGy/min had more influence on biological acute and late radiation effects than changes between dose rates within the higher range of e.g. 100–1000 cGy/min [91,114–116]. Fractionation abrogated increased toxicity effects of high dose rates [91,114–116]. In the clinical situation, lowering dose rate decreases OAR toxicities in conventional sfTBI, but is less influential for 2-Gy fTBI, especially when OAR shielding is performed [97,104,117–120]. However, most clinical studies have been performed at reported patient midplane dose rates ≤15–20 cGy/min. Careful interpretation is needed, since dose rate evaluation and reporting differs between centers, and organ-dose is generally extrapolated from external measurements in 2D techniques. Therefore, unequivocal recommendations regarding dose rate in conventional fTBI cannot be given, other than to stress the importance of international consensus on dose rate reporting. Many pediatric centers report using dose rates of 6–15 cGy/min, with appropriate OAR shielding [15,118]. With the implementation of highly conformal TBI techniques, inherently high fluctuating instantaneous dose rates are applied. The first reports regarding toxicity and outcome with TomoTherapy and VMAT fTBI in 220 children show promising results [121].

Toxicities and organ-at-risk sparing

Acute toxicities that can be expected in the days and weeks after TBI include parotitis [122,123], nausea, vomiting, diarrhea, xerostomia, mucositis and esophagitis, skin erythema, headache, alopecia, loss of appetite, and fatigue [122].

TBI-based conditioning causes more late sequelae than chemotherapy-only conditioning, although many other factors should be taken into account [4,5,70,124]. Young children, especially <3–4 years of age, suffer more profound late effects than older children [4,36,41], e.g. negative effects on neurocognition [36,38,40,41,125–128], growth [39,53,129–131], and endocrine and metabolic functioning [4,36]. Myeloablative TBI in children <3 years, and preferably <4 years, should be avoided. However, individual disease risk and outcome considerations may outweigh potential concerns regarding negative sequelae.

Although many reports describe TBI-related late sequelae in mostly mixed cohorts of adults and children, the relationship between TBI total dose and fractionation and specific organ toxicities is described sparsely. We provide Supplementary Tables 1–6, summarizing the literature regarding pediatric fTBI-related toxicities of lungs, kidneys, eyes/lenses, liver, cardiovascular and endocrine systems.

The most evaluated TBI-related lung toxicity is interstitial pneumonitis (IP). IP usually occurs within 4 months post-HSCT. After fTBI in children, the incidence varies from 0–35%, with usually <20% fatal outcome (Supplementary Table 1) [22,66,67,118,132–139]. Risk can be decreased by reducing the biologically effective dose (BED), e.g. lowering total doses, use of low dose rates, fractionation and reduction of lung dose i.e. by shielding [94,104,117,140–143]. Publications describe shielding of the lungs to <40–85% of prescription dose for fractionated TBI doses of 10–16 Gy, or, less frequently, compensatory measures to limit lung dose to within 103–107% of prescription dose (Supplementary Table 1). Careful interpretation of lung dose in reports remains complicated, in view of the inherent inaccuracy of establishing lung doses in 2D conventional TBI techniques. Most pediatric radiotherapy centers perform lung shielding [14,15]. A multicenter analysis of 127 children with ALL who received allogeneic HSCT after fTBI 12 or 13.2 Gy in 6 or 8 fractions b.i.d. and midplane dose rates 6–15 cGy/min, found significantly worse OS with mean lung doses of ≥8 Gy (HR 1.85, p = 0.043), with lung doses analyzed as reported by participating centers (mean reported lung dose 8.18 Gy (±2.2 SD) for AP-PA field treatments and 11.39 Gy (±1.03 SD) for bilateral field treatments [118].

HSCT- and TBI-related chronic renal disease (CRD) occurs in 0–30% of children, and publications inconsistently link CRD incidence to fTBI dose (Supplementary Table 2) [67,126,144–153]. fTBI ≥11–12 Gy induces more CRD [147,154–157]. Kal et al. advised to keep the BED below 16 Gy by shielding the kidneys, to keep CRD risk <3% [117,158]. This would mean using kidney shielding for fTBI 12–14.4 Gy at dose rates of ≥6 cGy/min, preferably to ≤10 Gy [157].

Lens cataract develops less frequently after fTBI of 1.8–2 Gy fractions than after higher doses per fraction, and is related to dose rate (Supplementary Table 3) [36,55,82,136,141,159–164]. After a median follow up of 10 years in 174 pediatric acute leukemia HSCT recipients, cataract incidence was 51.7% after mainly 12 Gy TBI in 6 fractions [70]. Using a meta-regression model, Hall et al. extrapolated 5-year risk of cataract after HSCT in children, which was related to TBI total dose and fractionation, and amounted to 60% after 12 Gy in 6 fractions [55]. Kal et al. extrapolated a BED of <40 Gy for which risk of severe cataract, needing surgery, will be <10% [158]. Since BED also depends on dose rate, 6 times 2 Gy with a dose rate >4 Gy would result in a BED > 40 Gy. In a single study, anterior-beam eye shielding to 55–58% of the total dose, reduced cataract incidence significantly while not distinctly increasing risk of CNS recurrence [165]. Highly conformal TBI techniques make lens sparing without compromising CNS dose attainable [166].

Recommendations:

For fTBI schedules of 12–14.4 Gy in 1.6–2 Gy fractions at dose rates ≥6 cGy/min during conditioning for allogeneic HSCT.

- Consider limiting the mean lung dose to <8 Gy.
- Consider limiting the mean kidney dose to ≤10 Gy.
- Consider reducing the lens dose to <12 Gy to decrease the risk of severe cataracts. For children with a high risk of CNS recurrence*, eye shielding should not be applied during conventional TBI.

*CNS3 (definite CNS involvement) or intra-ocular/optic leukemic involvement at any time-point, or after CNS recurrence.

For other toxicities, no recommendations can be made, other than to keep fTBI total dose <16 Gy. If previous irradiation has taken place, consider cumulative dose and related risks of additional fTBI. Further elaboration regarding specific fTBI-related toxicities is given in the Supplement.

Boost

A radiotherapy boost to sanctuary sites such as the testes, CNS, or extramedullary disease localizations can be considered. ALL with CNS3 involvement, either at diagnosis or at relapse, predicts a higher risk of post-transplant CNS relapse [167–170]. A CNS-directed radiotherapy boost can be considered for patients with overt CNS leukemia at diagnosis or those who develop CNS leukemia at disease relapse, especially when intrathecal/systemic therapy has failed [42,171].

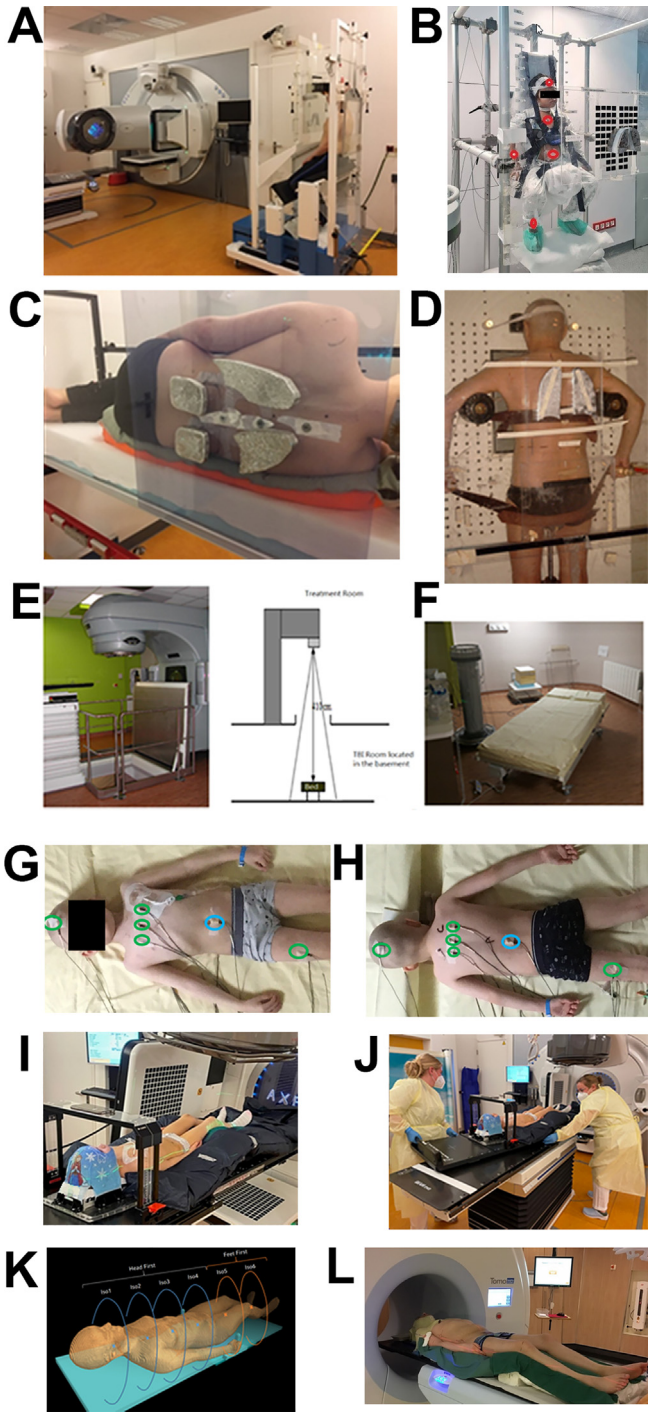

Fig. 1. Examples of setup for conventional TBI and highly conformal TBI. Setup with "chair" construction for AP-PA irradiation, with beam spoilers and blocks for lungs, kidneys and lenses in this setting (A). Setup with stool-sitting position for AP-PA irradiation, with beam spoilers and blocks for lungs, in vivo dosimetry diodes attached (red circles) (B). Setup with "bed" construction for AP-PA irradiation in lateral decubitus position, with beam spoilers and blocks for lungs and kidneys in this setting (C). Setup in "standing" position for AP-PA irradiation, with beam spoilers and blocks for lungs (D). Setup with "bed" construction for AP-PA irradiation, with patient in supine and prone position during treatment (E-F). Patient with diodes attached for in vivo dosimetry during irradiation; homogeneity check diodes circled green, dose verification check diode at prescription point circled blue (G + H). Patient in treatment position for VMAT TBI on rotatable tabletop (I + J). Patient is distracted with movie on smartphone. 3D CT reconstruction image of patient >150 cm with 6 isodose planes and Head First/Feet First planning area for VMAT TBI indicated (K). Patient in treatment position for TomoTherapy TBI (L).

It is undetermined what the minimal dose, target volume (cranial radiotherapy (CRT) or craniospinal irradiation (CSI)) and the optimal timing of the boost alongside TBI should be, but in general a cumulative CNS-directed dose of 18–24 Gy is recommended, with the boost given in the days before TBI [42,172,173].

Considerations for radiotherapy boost:

- An interval of at least 2 weeks between CNS boost and intrathecal therapy is preferable.
- Boost fractions should be 1.5–2 Gy, with 1.5-Gy fractions specifically considered for patients <6 years old.
- Cumulative (EQD_2) dose of current CNS boost and TBI should not be >24 Gy.
- Total (EQD_2) cumulative CNS dose for TBI and previous CNS-directed radiotherapy should not be >30 Gy.
- If previous CRT ≥18 Gy (≥15 Gy for <3 year-old patients) has been given, CNS boost before TBI should be omitted.

A testicular boost is indicated for patients with a very high risk of testicular relapse, mainly in case of residual disease detected with ultrasound after chemotherapy and after testicular recurrence. This can be done with a cumulative dose of 18–24 Gy in 2-Gy fractions, or single 4-Gy fraction, in the days prior to TBI in case of subclinical or clinical involvement.

In the case of persistent disease in other extramedullary sites, a local boost to a cumulative dose of 24 Gy can be considered.

For highly conformal TBI techniques, simultaneous boost to the bone marrow or extramedullary sites is an option [19,113,121,174,175].

Long-term follow-up of patients after HSCT with TBI conditioning

Childhood HSCT survivors carry a great risk burden of subsequent morbidity, which calls for life-long monitoring of this population [2,5,70,176,177]. The Center for International Blood and Marrow Transplant Research (CIBMTR), European Group for Blood and Marrow Transplantation (EBMT), and American Society for Transplantation and Cellular Therapy (ASTCT) have developed recommendations for long-term screening and preventive practices for HSCT survivors [68]. General health maintenance is important, and active evaluation of psychosocial and quality of life factors should be part of follow-up programs [58]. Table 1 summarizes specific screening recommendations after myeloablative TBI.

Conventional TBI setup for children

TBI has historically been delivered using techniques with large fields at extended source-to-skin distance (SSD) [99], and most institutions still use these techniques in a locally designed setup dependent on the technical possibilities [15]. Fig. 1 displays several examples of extended SSD setups, with an example of lung shielding in Fig. 2. TBI at SSD requires the characterization of the beam at

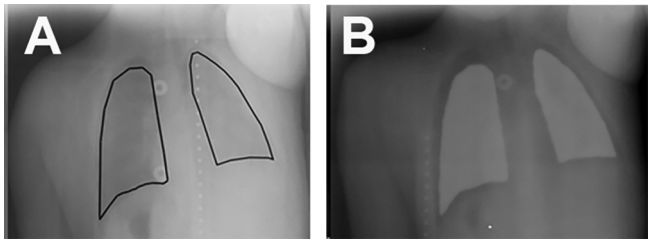

Fig. 2. Lung blocks. Block delineation on PA X-ray image in lateral decubitus position (A). Verification of block position with megavoltage X-ray image during treatment (B).

Table 2
Conventional TBI at extended SSD setup in children; considerations.

Conventional TBI at extended SSD; setup considerations	References
Beams	
Setup depends on local technical possibilities.	[15]
Patient should be placed in the flattened part of the radiation beam (usually over the diagonal of the beam).	[180]
AP-PA with horizontal beams.	
Lateral opposing with horizontal beams.	
Disadvantageous in children because of higher lung doses.	[118,181,182]
Dose calculations without lung density corrections are incorrect in the thorax by 16–24%, depending on beam energy.	[182]
Combination of AP-PA and bilateral beams.	[180]
Sweeping beam.	
Moving couch underneath a static beam.	
Dose homogeneity	
Effort should be made to maintain target volume dose homogeneity within 90–110% of prescription dose.	[178,179]
Field-in-field techniques can help to achieve a more homogeneous dose distribution; stable patient positioning is more vital.	
Regular quality assurance of the TBI technique should take place.	[183]
Patient positioning	
Markings on the patient should be used to ensure stable positioning on each fraction.	
Effort should be made to equalize patient diameter over body sections; compensators can be used for narrower parts of the body (head/neck, lower legs).	[183]
AP-PA Lateral decubitus position: patient in lateral decubitus, support with vacuum bag, stable tilted head position, drawn up knees, one arm extended along 1 side and the other encircling the head. Standing / leaning position: dedicated support, stable tilted head, bended legs. Supine and prone for sweeping beam technique. Use compensators.	
Lateral opposing Supine position: arms close to the side, stable head position. Use compensators. Sitting position on dedicated chair design: arms close to the side, stable head position. Use compensators.	
Sweeping beam and moving couch Supine and prone position: stable position, arms close to the side. Use compensators.	
Tissue compensators	
Compensators should be used to ensure homogeneous dose over narrow body parts depending on patient positioning (often head/neck, lower legs).	[139]
Compensation can be achieved by: increasing the thickness of the acrylic barrier that is placed in front of the patient in the beam attaching metal plates of appropriate thickness to the acrylic barrier that is placed in front of the patient in the beam positioning tissue-equivalent materials (bags or blocks) close to the body metal individual hemibody compensators made in styrodur moulds after calculating appropriate dimensions using a planning-CT	
Beam spoilers	
Beam spoilers counter skin- and subcutaneous tissue sparing effect of photon beams. Spoilers are typically made of 1–2 cm thick acrylic screens, to produce electrons that increase surface doses to at least 90% of prescription dose.	[184]
Beam energy	
AP-PA setup: 6–10 MV preferable for children no additional neutron production more homogeneity than lower energies	
Bilateral setup depth dose inhomogeneities of ±10% – ±30% including skin dose arise in the bilateral setup with 10 MV	[180]
Dose reference point	
International consensus advice: reference dose prescription point in the midplane at the level of the umbilicus lung dose reference point: mean dose at midpoint of both lungs	[180]
OAR shielding	
All shielding should be commissioned for transmission properties.	[183]
Placement of shielding needs to be verified before each beam delivery.	
Awareness of electron scatter behind the blocks. Compensation e.g. with bolus material or thickness of the block mount.	[185]
Partially transmitting individual lung shielding: shaped from metal alloy/cerrobend using X-ray images of the patient in treatment position manual positioning individually positioned MLC's	[186–189]
Partially transmitting individual kidney shielding: shaped from metal alloy / cerrobend using kidney outline in the skin made with ultrasonography performed in the TBI treatment position manual positioning	[157,190]
Partially transmitting eye (lens) shielding: standard thickness based on local TBI setup properties and measurements	[165]
Treatment planning system/planning CT	
No commercial treatment planning system for TBI available.	
Treatment planning systems can be commissioned for extended SSD use, but strict verification needs to take place and planning-CT in the treatment position should be used for calculations in individual patients.	[181,186]
In vivo dosimetry	
TBI setups need to be checked by using dosimetry under conditions that closely simulate the actual treatment situation.	[99]
The relation between entrance/exit/mid-plane dose should be established and verified in a phantom measurement.	[186]
Midplane dose can be converted from entrance/exit dose at prescription plane with a calibration curve.	[183]
It is advised to perform in vivo dosimetry for at least the first 10 patients as a quality check of the entire TBI procedure. Centers can also choose to ascertain in vivo doses during the first fraction in every patient, to recalibrate the prescribed dose for the remaining of the TBI fractions if necessary.	[183]
Dosimetry devices should be commissioned for TBI conditions. Sensitivity of the dosimeters can vary according to temperature, localization in the beam orientation, beam energy, radiation exposure and kind of readout.	[191,192]
Dosimetry devices: Diodes TLD optically stimulated luminescence dosimeters	

Table 2 (*continued*)

Conventional TBI at extended SSD; setup considerations	References
MOSFETs	
film	
The ability to obtain a real-time measurement with a reusable dosimeter makes diodes particularly well suited to in vivo dosimetry for TBI.	
Sedation	
Sedation is found to be no obstacle during (twice-daily) fractionated TBI	[14]

A = anterior; MLC = multileaf collimator; MOSFET = metal–oxide–semiconductor field-effect transistor; OAR = organ at risk; P = posterior; SSD = source to skin distance; TBI = total body irradiation; TLD = thermoluminescent dosimeter.

extended SSD, careful planning, physics calculations and quality assurance [178,179]. Generally, doses are assessed using in vivo dosimetry. Table 2 gives considerations for conventional TBI setup in children. Differences in techniques preclude reliable comparison of TBI effectivity between centers and publications, and it is not clear if there is an optimal setup that can be recommended for all children, although AP-PA beam directions seem preferable [118]. To enable comparison of TBI data between centers, we need comprehensive standardized reporting of all relevant parameters. The reported information should include: beam setup, prescribed

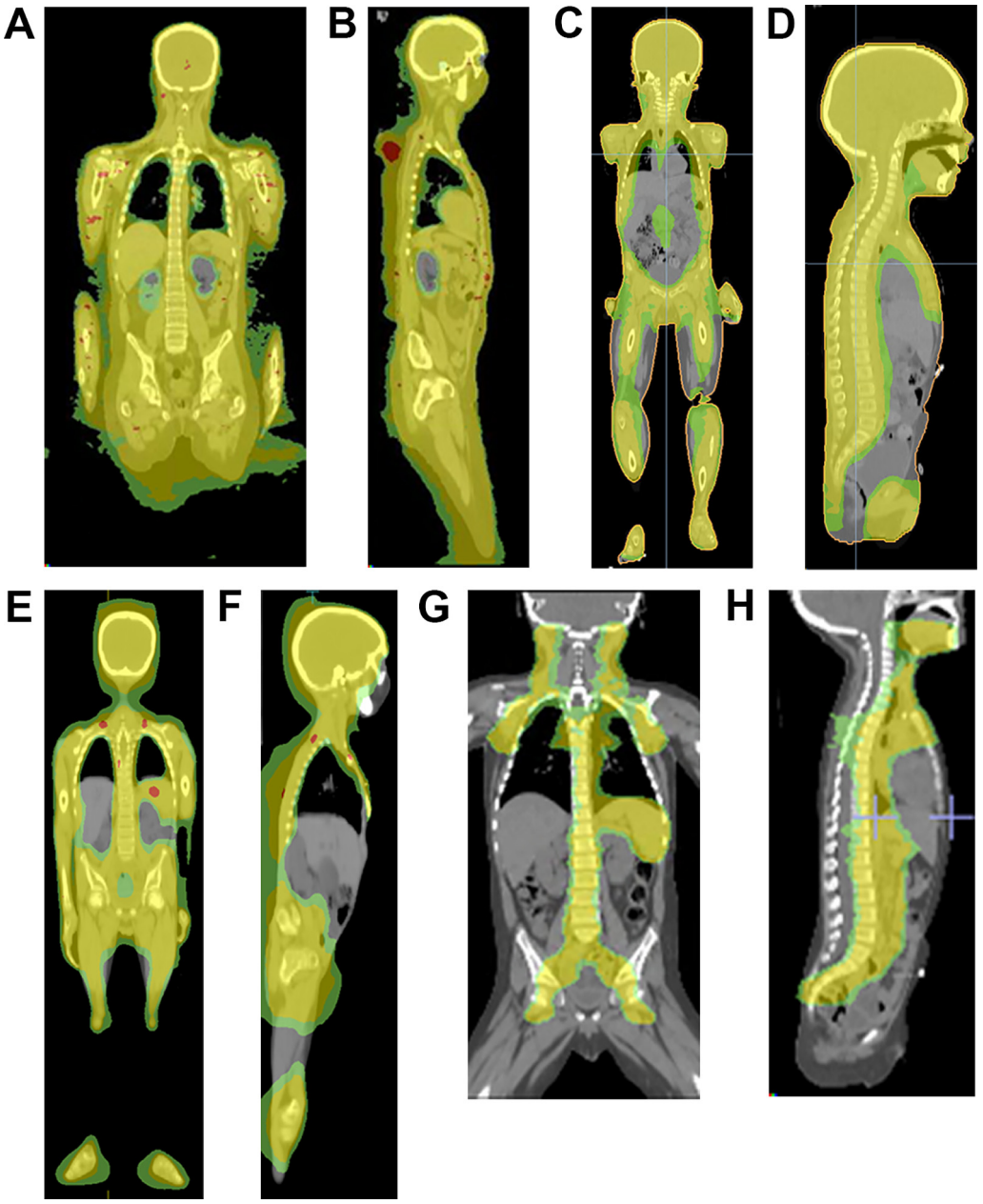

Fig. 3. CT-planned dose distribution for highly conformal optimized techniques. Coronal (A) and sagittal (B) isofill dose distribution of VMAT TBI with dose reduction to the lenses, kidneys and lungs. Coronal (C) and sagittal (D) isofill dose distribution of Total Myeloid Irradiation (with inclusion of CNS and testes). Coronal (E) and sagittal (F) isofill dose distribution of Total Marrow and Lymphoid Irradiation (with inclusion of CNS). Coronal (G) and sagittal (H) isofill dose distribution of Total Lymphoid Irradiation. Green = 75% isodose; yellow = 90% isodose; red = 110% isodose.

Table 3
Highly conformal optimized TBI at SAD setup in children; considerations.

Highly conformal optimized TBI at SAD setup considerations	References
Patient positioning	
Supine patient positioning has to be stable and reproducible.	[201–204]
The patient's hands and arms are placed close to the body, potentially holding a stable handle bar, and legs close together, in order to minimize the lateral distance and improve the target dose homogeneity in case of helical delivery (TomoTherapy) and to maximize the body volume within the FOV of MV-CT or CBCT.	
The patient has to be able to lay in the same position for 40–70 minutes.	
Immobilization components that can be useful:	[17,196–198]
lock bars for secure positioning of vacuum bags and/or knee supports	
vacuum bag covering the entire body from shoulders to feet	
stable arm/hand support (vacuum bag or adjustable handle bar)	
feet and knee support (vacuum bag or adjustable knee/feet cushions)	
3-point open face mask or chin mask	
all-in-one base plate comprising 2–3 thermoplastic meshes to restrict regions of the head/neck, thorax/arms, and legs	
The challenge is performing robust combination of HF and FF treatment.	[17,196–198,205]
A rotatable tabletop or body frame can facilitate stable patient rotation for separate HF and FF irradiation.	
If assurance of skin dose to prescription dose is vital, bolus material can be placed over the body.	[199]
Planning CT	
Patients should be checked for reproducible stable positioning.	
Fiducial markers need to be placed:	
"0" or origin position of the treatment couch, that needs to be included in all scan directions in the PTV cut plane *and is usually around the mid or upper thigh*, needs to be marked on the table bilaterally and on the vacuum bag or patient in the midline	
other fiducial markers are placed at the location of several isocenters, at least at the level of the head, the thorax/abdomen and the legsFiducial marker locations are marked on the patient with tattoos or felt pen markings.	
The total scan length should include the entire body from the vertex down to the toes.	
Patients <110 cm may be scanned and treated in HF position only	
Patients ≥110 cm are scanned in HF and FF position separately	
Ensure an adequate broad overlap region on both CT's.	
Ensure that all markers are visible on head-first and feet-first images for image registration.	
For CT scanning 5-mm sections are preferable.	
For small patients, 3-mm sections can be preferable to be able to distinguish the vertebral body (useful for patient position verification).	
Longitudinal laser lines may be marked along the entire body to facilitate reproducible patient setup.	
Delineation	
The PTV is adjusted 3–5 mm inside of the body contour	[17,18,198,200]
For planning ease, PRV of OAR can be excluded from the body PTV	
PRVs of 3–5 mm inside OAR (e.g. lungs, kidneys) may help to ensure adequate dose on surrounding lymphatic or medullary structures.	
For compensation of respiratory motion, lung PRV contraction of 5–10 mm can be applied or respiratory motion can be assessed with a 4D CT.	[16,206]
PRV around lenses at least 5 mm if lens sparing is desired	[166,207]
Ensure adequate coverage of optic nerve CSF extension and retina.	
The patient is asked to keep the eyes still during head irradiation.	
In the case of TPS failing because of large patient's size, the PTV may be subdivided into several subsections, to optimize one by one using a bias dose planning option. Additional structures to perform smooth dose gradients will be needed in this case.	
Treatment Planning	
6 MV or 10 MV	[17,196–198]
18 MV is not recommended due to increased build-up length and neutron contamination.	
Use of beam spoilers is not needed.	
Arcs	
HF: Dual arc is recommended	
o more efficient leaf travel for VMAT	
o potentially less dose in OAR and better homogeneity	
FF: 1 arc, or AP-PA arcs might be sufficient and a fast option	
Collimator rotation:	[208]
rotating the collimator to 90° provides better lateral coverage	
MLC travel along superior-inferior direction can relay easier field modulation	
The collimator jaws should be selected in accordance with the individual anatomy of the patient.	[209]
Effort should be made to maintain target dose homogeneity within 90–110% of prescription dose.	
Demands for TPS:	[210]
optimization of multiple isocenters needs to be possible providing homogeneity in junction areas, as in CSI	[211]
gradient optimization is possible by the optimization and segmentation algorithm	
sufficiently capable algorithm, such as Monte Carlo	
image fusion options, to merge HF and FF orientation CTs	
sufficient calculation in HF – FF settings	
Depending on patient length, 4–9 isocenters are applicable (VMAT):	[17,196–198]
2–5 in head-first position and 1–3 in feet-first position	
patients <110 cm 4 isocenters	
patients 110–150 cm 4–6 isocenters	
patients 150–180 cm 6–7 isocenters	
patients >180 cm 6–9 isocenters	
in wide patients: 2 lateral isocenters in chest and/or pelvis may help with dose homogeneity	
AP-PA treatment of legs can be acceptable if inhomogeneities from missing divergence compensation is allowed.	[196,197]
Specialized autoplanning scripts can reduce planning-time.	[212]
Devices such as vacuumbag (boluseffect), rotatable tabletop and baseplate should be taken into account during optimization.	
Calculation Gridsize should be kept within 5 mm.	

Table 3 (*continued*)

Highly conformal optimized TBI at SAD setup considerations	References
To avoid treatment of isocenters in the wrong patient orientation, the use of different table heights for isocenters in HF and FF orientation (>3 cm) is recommended.	
Robust planning:	
The treatment beams are positioned to cover the entire PTV with overlapping regions along the longitudinal axis to provide robust dose optimization.	
In junction areas the PTV can be divided into several subvolumes with gradual dose prescriptions.	[205,213]
Optimal field overlap length is TPS dependent and needs to be established in order to assure robust dose distribution versus setup errors (shift plans).	
Dose over transition areas between the CTs with 2 different orientations Bias dose addition in each plan orientation, or Help contours to create gradually increasing and decreasing doses	 [17,198] [199,205]
Field borders should extend from the patient surface for robust treatment (surface margins) Virtual bolus can be helpful. Auto flash margin of > 1.5 cm is recommended for robust surface dose planning.	[16,194,211,214,215]
Superficial dose: multiple arcs, oblique beam incidence and beam exit from all angles significantly reduces the intrinsic photon beam skin-sparing effect, therefore the skin dose is usually adequate. Take care that TPS does not compensate dose build-up with small highly weighted tangential fields.	[18] [216]
OAR dose reduction	
With VMAT, dose reduction in lungs is superior to reduction with blocking in conventional TBI.	[195,217]
Help structures with shrink margins within delineated OAR with low constraint values can help to steer dose optimization.	[199]
Dose reduction in lungs should not affect dose coverage of the ribs.	
Dose reduction in other OAR (e.g. kidneys, lenses) should not affect surrounding lymphoid, bone marrow or CNS target volumes.	
Dose rate	
High instantaneous dose rates are inherent to TomoTherapy and SAD linac based radiotherapy.	
If required, linac systems have the possibility to slow down the dose rate over specific OAR, which inherently increases beam-on time.	[196,197,212,218]
RTQA	
End-to-end test of overall workflow before clinical use of the technique has to be performed.	[197]
Recalculation of the plan in a second TPS system for independent dose verification.	[17]
Treatment dry-run with or without patient Verification of collision clearance, prepare workflow for specific patient. Pay special attention to metal parts at the posterior side of the table, through which divergent beams might go. Avoid beam mix-up, check the table positions. For smaller children a dry-run may give more confidence and familiarity at actual TBI.	[197]
A robustness check in the TPS should be performed by applying series of random isocenter shifts in several directions and analyzing the influence on the dose distribution. Simulate dose coverage under setup, geometric and intrafraction motion circumstances.	[205]
Position Establish tolerances according to plan complexity and robustness. Apply local corrections cautiously as they might influence inter-isocenter distances.	[17]
Dose Perform standard VMAT QA check per department protocol. Evaluate field junctions and large field dosimetry before clinical implementation.	
In vivo dosimetry can be performed if required: MOSFETS EBT-2 films to control junction and overlapping areas	[199] [203,219,220]
Conebeam CT or MV-CT for patient position verification at one or more isocenters.	
Treatment performance	
Be aware that with the lengthy PTV, small patient rotational errors can result in significant lateral shifts in body sections further away.	
In order to retain the planned inter-isocenter distance, set up corrections must never be made for single isocenter only but always for the entire beam set. Due to overlapping areas, setup needs to be correlated for all isocenters.	
A surface guidance system may be helpful to retain stable positioning during treatment.	[198,221]
Sedation is found to be no obstacle during (twice-daily) fractionated TBI.	[14]

CNS = central nervous system; CSI = craniospinal irradiation; HF = head first orientation; FF = feet first orientation; FOV = Field of View; linac = linear accelerator; MLC = multileaf collimator; MOSFET = Metal Oxide Semiconductor Field Effect Transistor; MV = megavolt; OAR = organ at risk; SAD = source to axis distance; TBI = total body irradiation; QA = quality assurance; RTQA = Radiation Therapy Quality Assurance; TPS = treatment planning system.

target volume dose in Gy and prescription point (e.g. midplane at the level of umbilicus), fraction dose, fractions per day and minimum interval between fractions, treatment time per fraction, instantaneous (and, if possible, also average) dose rate at midplane in the patient and in the lungs, shielding/dose reduction to specified organs.

Highly conformal optimized TBI techniques

As a conformal step-up from conventional TBI, step and shoot IMRT with extended SSD uses forward planned segments. A linear accelerator, treatment planning system (TPS) and bigbore CT provide the basics for implementation (see Supplement) [189].

Highly conformal optimized source-axis distance (SAD) TBI techniques use a fundamentally different approach compared to conventional extended SSD TBI. They can be introduced in any radiotherapy bunker because no extended SSD is needed. On the other hand, they require field junctioning, a longer planning and setup time and use fluctuating higher dose rates. Examples are TomoTherapy [16,193–195] and volumetric modulated arc therapy (VMAT) [17,196–199] (Figs. 1 and 3). Since the couch travel of linear accelerators is usually 120–150 cm, a patient rotation from head-first (HF) to feet-first (FF) position is required to be able to irradiate the whole body (Fig. 1). VMAT TBI requires a robust treatment plan calculated on two CT scans with FF and HF patient orientations that are co-registered on the overlapping anatomical region. Nonetheless, these techniques provide greater potential to regulate target dose homogeneity and to provide dose reduction to OAR while still adequately covering target volumes, thereby potentially producing a better balance between outcomes and risk

of toxicity for children. Several centers have implemented these techniques as standard TBI solution. The first reported clinical results are promising [121,196,200], but more reports and longer follow-up results need to establish its base for standard TBI setup. For implementation of optimized TBI, measures need to be taken to ensure robust planning, high reproducibility, safety, and stringent quality control. The intricate process advocates initial implementation in larger centers, where higher patient numbers yields familiarity with the technique and the potential to establish optimized protocols. Table 3 gives considerations for TBI with highly conformal planning techniques (VMAT and TomoTherapy).

Beyond TBI - highly conformal radiotherapy techniques; TMI/TMLI/TLI

Due to limitations in the use of TBI as well as concerns regarding toxicity and the increased risk of secondary malignancies, there has been a push for development of more targeted approaches [19]. In this regard TMI, TLI and TMLI represent highly conformal targeted forms of radiotherapy, with the potential to decrease toxicity to OARs outside the target volumes with 35–75%, compared to conventional TBI [18,222,223] (Fig. 3). Moreover, TM(L)I delivers the possibility for dose-escalation to the bone marrow for high-risk patients [224], while reducing the risk of radiation pneumonitis, renal toxicity, hypothyroidism, and cataract [225–227]. TLI, TMI and TMLI with VMAT or TomoTherapy have been successfully implemented in several centers [204,205,221,225,228,229]. In the first clinical studies in patients with several hematological malignancies in first or second complete remission, the risk of extramedullary relapses was not dose-dependent and comparable to reports of conventional TBI [230].

Adapting TLI/TMI/TMLI techniques in radiotherapy departments could be realized with the help of planning templates [221,231]. Whether TMI/TMLI techniques could be the future standard of care for children instead of TBI, has to be researched in robust clinical trials that evaluate safety and quality, clinical outcomes, acute and late toxicities, and feasibility of widespread implementation.

Final thoughts

Myeloablative TBI performance is heterogeneous and center-specific. Many radiotherapy centers do not perform TBI in children on a regular basis, while specific considerations regarding technique, dose, dose rate, fractionation and potential late effects induction are very relevant in this patient group. These ESTRO ACROP and SIOPE recommendations reflect such considerations for the clinical practice. Unfortunately, the limitation to providing strong recommendations for TBI practice is the lack of large studies providing high levels of evidence. Cooperation between centers can support new insights, valid research and implementation of new techniques, in order to improve outcome and reduce toxicity of myeloablative irradiation for HSCT in children.

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Conflicts of interest

There are no conflicts of interest to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2022.05.027.

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