Supplement: background literature review and expansion to the ESTRO ACROP and SIOPE recommendations for myeloablative Total Body Irradiation in children

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INTRODUCTION

Myeloablative Total Body Irradiation (TBI) since has long been a cornerstone of the conditioning for hematopoietic stem cell transplantation (HSCT) in children [1]. HSCT survivors suffer from multiple late effects, many of which associated with TBI [2-6]. Currently, chemotherapy-only conditioning schedules are standard for many indications, and use of TBI is mainly indicated for high-risk hematologic malignancy with allogeneic HSCT [7-11]. For high-risk Acute Lymphoblastic Leukemia (ALL) pediatric patients, studies consistently show superior survival outcomes after TBI-based conditioning schedules [12-15].

The aspiration to reduce acute and long-term effects has caused changes in HSCT and TBI protocols over time. Decreased toxicities with equal or improved survival can be reached with fractionated instead of single-fraction TBI [16-18], and this has become the standard. Still, institutions have varying site-specific setups and techniques for TBI, and do not treat many children per year [19-22]. Moreover, conventional TBI typically delivers heterogeneous doses to the patients. Several centers have introduced highly optimized techniques with improved dose homogeneity while affording more options to spare organs-at-risk (OAR), delivered at high dose rates [23-25]. Total Marrow Irradiation (TMI), Total Lymphoid Irradiation (TLI), and Total Marrow and Lymphoid Irradiation (TMLI) target the bone marrow and/or lymphoid volume while reducing doses in the remainder of the body, and clinical studies of these techniques are ongoing [26].

For growing children, several considerations regarding TBI setup, total dose, fractionation and organ shielding may be of even more interest than for adults. The lack of a specific pediatric guideline, and the low numbers of pediatric patients treated in each center makes international collaboration necessary to achieve homogenization of TBI practices. After a recent survey regarding clinical practice of pediatric TBI in European Society for Paediatric Oncology (SIOPE) affiliated centers [21], the SIOPE Radiotherapy TBI Working Group was formed to establish practical recommendations for myeloablative TBI in pediatric patients, together with selected ESTRO experts.

METHODS

Literature searches were conducted in PubMed regarding fractionated pediatric myeloablative TBI, between September 2020 and September 2021. 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 articles about conventional and highly conformal techniques of TBI; TMI; TMLI; TLI; and technical and radiobiological considerations regarding TBI in publications since 1970. Systematic abstract screening of search results on specific TBI toxicities in publications since 1980 were conducted using the AI screening tool ASReview LAB (Utrecht University, the Netherlands), and selected publications underwent full-text screening and were checked for further references. Search terms per toxicity and inclusion criteria are given in Supplementary Tables 1–6. Included publications were graded for Level of Evidence using the Elsevier journals levels of Evidence for clinical studies [27]. Members of the ESTRO-SIOPE writing committee held bimonthly virtual meetings to discuss and analyze the body of evidence and institutional experiences. Subgroups were formed that contributed specific sections of the recommendations based on the evaluated publications from the literature search and results from expert discussions, and the entire manuscript was reviewed by all members.

As can be seen in the Supplementary Tables, most recommendations 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. The recommendations and considerations in the recommendations and supplement were accepted with the majority approval from the writing committee.

RECOMMENDATIONS REVIEW RESULTS

Indications for TBI-based myeloablative conditioning for HSCT in children

Myeloablative doses of TBI with its potent anti-leukemic and immunosuppressive effects initially were the standard conditioning in the early days of HSCT, but their use has diminished over the decades due to concerns about long-term toxicity, particularly in children [28]. Currently, myeloablative TBI is indicated in children ≥4 years of age with high-risk ALL in any remission, who have an indication for allogeneic HSCT. The multi-center prospective ALL-SCT-BFM 2003 trial found excellent survival rates using a uniform 12 Gy TBI with etoposide conditioning in children above the age of two years with ALL, establishing this combination as the standard in Europe [29]. The randomization in the prospective FORUM trial was prematurely halted, because patients ≥4 years receiving TBI and etoposide conditioning had a significantly better survival and lower relapse risk and treatment-related mortality (TRM) than patients who received myeloablative chemotherapy [15].

In first HSCT for pediatric AML or advanced myelodysplastic syndrome, TBI is not the preferred conditioning choice because numerous studies have demonstrated either equivalent or superior survival as well as leukemia control with chemotherapy-based regimens [30-32]. A potential role of myeloablative TBI in subsequent HSCT for AML and juvenile myelomonocytic leukemia is unclear [33, 34].
Given the excellent survival rates with first-line chemotherapy in pediatric Non-Hodgkin lymphoma and anaplastic large cell lymphoma, no comparative studies in relapsed patients on HSCT with TBI are available. Nevertheless, myeloablative TBI is frequently used with encouraging success, depending on the histological subtype [35-37].

Myeloablative TBI-based conditioning is not indicated in children with non-malignant diseases such as i.e. inborn errors of immunity, metabolism, or bone marrow failure diseases [38-40]. Particularly in diseases with DNA repair defects (i.e. Fanconi anemia, Nijmegen breakage syndrome,...) irradiation should be avoided to prevent excessive long-term toxicity [41, 42].

Based on the correlation of cumulative dose and short- and long-term toxicities of TBI, lower non-myeloablative doses of TBI of 2–4 Gy in combination with chemotherapy are increasingly employed by some centers for their immunosuppressive effect. Too few comparative trials in specific indications (i.e. aplastic anemia) are currently available for these regimens to be discussed here [43, 44], and the focus is on myeloablative TBI.

**Patient evaluation before TBI**

Every patient must undergo a pre-transplant workup before HSCT. This evaluation should include complete physical examination, a comprehensive series of organ function tests (heart-, lung-, liver- and kidney-function; growth, thyroid and other hormones levels and baseline neurocognitive status) and consultations with members of the HSCT team to decide on the conditioning regimen [45]. Disease and treatment history needs to be documented completely and the most recent outcomes of bone marrow status and cerebrospinal fluid cytology should be known. Family history of malignancies should be documented. Evaluation of CNS-status (1-2-3) pre-transplant as well as minimal residual disease (MRD) is mandatory [46, 47]. Some groups base their decision to use a TBI- or non-TBI based regimen in ALL on MRD status as defined by means of next-generation sequencing, with conditioning regimens based on TBI reserved for patients that have not achieved MRD negativity prior to allogeneic HSCT [48], but this approach is yet to be evaluated in a prospective study. The randomized FORUM trial recently demonstrated superiority of TBI in known MRD negative patients as measured by flow cytometry as well, but these results will be further evaluated [15].

Age is a very important factor when deciding whether to include TBI in the conditioning. Children conditioned with TBI and transplanted at a very young age (<3–4 years) are more prone to develop serious side-effects over multiple organ systems, e.g. neurocognitive functioning, growth, vascular events, endocrine and metabolic dysfunctioning, and are more prone to develop treatment-related second malignancies [4, 49-54]. Therefore, chemotherapy-based regimens are generally first
choice for very young children and careful consideration of risks and benefits is needed before employing myeloablative TBI in specific cases.

For older children, cancer predisposition syndromes or other genetic aberrations are relative contraindications to the use of radiotherapy. In case of known encephalopathy or myelopathy one should consider potential additional damage of myeloablative TBI doses.

Previous radiotherapy has to be documented and potential conflicts with TBI evaluated. Previous cranial radiation (CRT) is not a contraindication for TBI, but the cumulative doses to the brain should be carefully considered, as outlined in the “boost section” of this review.

Because of the increased risk of oral complications associated with i.e. xerostomia after TBI, careful pre-transplant workup and care by a dentist is recommended to minimize the risk of serious morbidity [55]. Ophthalmologic examination and screening is indicated given the risk of ophthalmologic complications, among which cataract [56, 57]. It is also prudent to screen patients who will undergo HSCT for cardiovascular disease risk factors to minimize late morbidity and mortality [58, 59].

Last but not least, two very important aspects of pre-transplant evaluation include fertility given the high probability of sterility after TBI (options for gameate storage if necessary and possible should be addressed) [60-62], as well as social aspects such as psychosocial evaluation [63, 64].

TBI fractionation

After experience with single-fraction TBI (mainly 8–10 Gy) in the 1970s, efforts were undertaken to reduce early and late toxicities. Therapeutic ratio of toxicity versus immunosuppressive and anti-leukemic effects could be improved by decreasing the dose rate (which meant TBI lasting up to >10 hours) or by dose fractionation [65, 66]. Trials in mostly combined pediatric and adult patient cohorts showed equivalent disease outcome with toxicity reduction after fractionated TBI [17, 18, 67-73].

Many different fractionation schedules have been used [74] (Supplementary Tables 1–6), and it is difficult to establish TBI-related differences in outcome and toxicity effects, because of multifactorial influences of treatments, conditioning-protocol variations, clinical characteristics and graft versus host disease (GVHD), in patient cohorts with various diseases and age groups. In the 1980s, fractionated doses <9–10 Gy showed increased non-engraftment and disease-relapse [75, 76]. In various reports, lung and/or liver was adverse events were found to be the dose-limiting toxicity for fractionated schedules of 15.5–16 Gy [77-79]; non-relapse mortality (NRM) was increased for 15.75-Gy fractionated TBI as compared with 12 Gy [70, 71]; and second malignancy risk was reported to be increased with fractionated TBI doses ≥13–14.4 Gy [80, 81]. In a phase I/II trial which compared 13.2 Gy with 14.4 Gy TBI at 1.2-Gy fractions given thrice daily, 14.4 Gy was better tolerated by children than adults in terms of toxicity [82]. To optimize the radiobiological therapeutic ratio, twice-daily
fractionation of 1.6–2 Gy doses to total doses ≥12 Gy was advocated by several authors, while strongly hyperfractionated schedules with 3-4 fractions daily seem to have worse anti-leukemic / immunosuppressive effects, and are impractical in terms of delivery within working hours while giving healthy tissues a 6-hour recovery period between fractions [66, 83-85]. Giving 12 Gy TBI in once-daily fractions of 3–4 Gy increases acute effects such as mucositis [86, 87].

For children, fractionated TBI is standard [21, 22], and 12 Gy in 6 fractions is most commonly used, typically delivering 2 fractions per day with at least a 6-hour inter-fraction interval. This schedule, combined with etoposide rather than cyclophosphamide, was employed in the recent randomized FORUM trial in children ≥4 years of age given HSCT for high-risk ALL, and resulted in less NRM and acute toxicity than can be surmised from historical reports [15]. Other common dose schedules are 13.2 Gy or 14.4 Gy in 8 fractions over 4 days [21, 22]. Considering radiobiological early and, in particular, late effects for children, a maximum fraction dose of 2 Gy is advisable.

It is not possible to give an unequivocal recommendation regarding dose and fractionation of TBI in children, given the inconsistent data from studies performed throughout decades, largely originating from non-randomized case-series and including patients of various ages with differing disease-, treatment- and HSCT conditioning characteristics. For the moment, in conventional TBI, fractionated schedules giving doses of 12–14.4 Gy, in 1.6–2 Gy fractions b.i.d., are customary in pediatric radiation oncology centers [21, 22]. As mentioned, commonly used schedules are 6x2 Gy, 8x1.8 Gy or 8x1.65 Gy b.i.d. Nonetheless, continuous re-assessment of these schedules is in order. Highly-conformal TBI or TM(L)I techniques may be beneficial in reducing OAR toxicity and might enable dose escalation for very high risk patients [88]. On the other hand, further identification of lower risk patient categories may allow individualized TBI dose de-escalation or elimination of TBI [44, 89, 90].

**TBI Dose Rate**

Study-to-study variability precludes giving an unequivocal recommendation regarding dose rate for pediatric TBI. First of all, the radiobiological effect of TBI on malignant and normal cells and tissues depends on many factors - inherent radiosensitivity and repair capacity, the micro-environment, total TBI dose and cumulative dose of other radiation treatments, fractionation, overall treatment time, dose rate, dose homogeneity, TBI setup, patient and disease characteristics, supportive care around HSCT, GVHD influence, and other therapies. Secondly, TBI setups in radiotherapy centers were typically developed locally and evolved according to local experience [8, 74, 91]. While international protocols through time gave guidance to uniform setup and dose prescriptions [92-96], current practices in pediatric TBI remain highly variable [21, 22]. Also, finding indisputably comparable information in published studies is challenging, since reported dose rate values can represent
measured or calculated data, obtained by different methods. Articles report dose rate in the air or in a specific point in the body; and then usually an extrapolated value at the midplane or at dose maximum inside the body of an average patient. In reality, dose rate in a patient will vary according to body type and tissue density. In older studies, TBI was often delivered with cobalt teletherapy, and source decay/changes gave rise to varying dose rates over time in the reported cohorts [76]. As far as we could establish, dose rates were compared in a prospective randomized trial in only 1 relatively small study, which included patients with varying ages, diseases, previous treatments and HSCT conditioning regimens [72, 97]. These shortcomings must kept in mind when interpreting the publications reported here.

The fact that TBI dose rate influenced HSCT success rates but also the incidence of toxicities, was already established in the 1970s, when single-fraction TBI doses of 8–10 Gy were delivered at low dose rates over several hours, to balance these two outcomes. In preclinical studies, Travis et al. studied the effect of low dose rate TBI, from 1 to 25 cGy/min, on mice lethality and late organ toxicity [98]. Non-hematopoietic deaths by acute gastrointestinal injury after TBI with stem cell transplantation were evaluated for graded doses at different dose rates. Late lethality syndromes were more dependent on dose rate than gut-related deaths, but both these endpoints were more dependent on dose rate than hematopoietic lethality, particularly at dose rates <5 cGy/min. Necropsies done at >60 days to 1 year after irradiation showed morphologic evidence of radiation injury in only 3 tissues: lung, kidney and liver, deeming these tissues as most critical for dose rate influences. In multiple preclinical studies combined, late tissue toxicities show a larger effect of dose rate changes between 1 and 10 cGy/min, than between e.g. 10 and 100 cGy/min, with flattening of the effect curve in the high dose rate range [99]. The same is true for hematopoietic cells but with a much more shallow dose-effect curve even in the lower dose rate range [99]. In dogs given autologous HSCT, TBI tolerance doses measured as 50% mortality at 7 days were comparable between single-fraction TBI and fractionated TBI (given as 2 Gy three times daily) at exposure rates of 2–10 cGy/min [100]. Fractionation benefit occurred at a dose rate of 20 cGy/min, with tolerance doses of 10.56 Gy (95% CI, 9.39–11.74) for single-fraction TBI versus 13.20 Gy (95% CI, 11.36–15.05) for fractionated TBI. Long term survival after ≥10 Gy was 1/18 after single-fraction TBI versus 19/22 after fractionated TBI. Regarding gastrointestinal tract toxicity; high dose rates of 75 cGy/min induced more damage in dogs after TBI, but this effect could be compensated for by fractionation [101]. In mice, low dose rates of 5 cGy/min as compared with 80 cGy/min, had a highly protective effect on late lethality in single-fraction TBI, but this effect diminished or disappeared when TBI was given in 1.2- or 2-Gy fractions [102]. Taken together, these observations are roughly in agreement with linear-quadratic fractionation biology. Lehnert et al. reported on experiments in mice, in which intermittent irradiation with 25 cGy/min to
an average dose rate of 6 cGy/min induced the same lung-toxicity-related mortality as continuous irradiation at 6 cGy/min, suggesting that average dose rate instead of instantaneous dose rate governs (lung) toxicity induction [103].

Bone marrow displays a marginally increased sensitivity for fractionation with 1.2- and 2-Gy fractions, and little effect of higher dose rates of 80 cGy/min when compared with 5 cGy/min in single-fraction TBI [102]. At dose rates >30 cGy/min, no extra dose rate effect for hematopoietic damage is expected [98, 99].

The difference between acute and late responding tissues versus the hematopoietic target cells makes fractionated high dose rate TBI with e.g. 2 Gy per fraction biologically superior to single-fraction low dose rate irradiation (with ranges of 2–5 cGy/min), and more practical in its execution - the single-fraction TBI procedure takes several hours, which causes logistic difficulties and is not comfortable for the patient [84, 99]. For leukemic cell-kill and allogeneic engraftment success, fractionated TBI with higher dose rate is preferable to low dose rate therapy [65, 84]. In preclinical studies, increased dose rates of 40, 100, 200 and 800 cGy/min during (fractionated) TBI improved leukemic cell kill or allogeneic engraftment [104-107]. In the 1980s, fractionated TBI was therefore introduced to improve the therapeutic ratio between normal tissues and the immunogenic and anti-leukemic effect, especially for children [65, 66].

In the clinical setting, several researchers evaluated the effect of dose rate on disease and toxicity outcomes. In cohort studies, dose rates of ≤4 cGy/min or ≤4.8 cGy/min showed significantly increased hematolymphoid disease relapses in patients given TBI doses of 8.4–12.5 Gy in 3 days or 10 Gy as single-fraction [76, 108]. Ozsahin et al. did not find different disease-free survival (DFS) between groups given TBI at dose rates of 6 cGy/min versus 15 cGy/min in 157 randomized patients with different hematolymphoid diseases undergoing autologous or allogeneic HSCT [72].

Most clinical studies evaluating TBI dose rate effects on toxicity have focused on lung, kidney, or lens toxicity. At midplane dose rates ≤15 cGy/min, fractionation of total TBI dose has a greater sparing effect on late-responding tissues than dose rate reduction [17, 99]. From a biologically effective dose (BED) calculation of 16 clinical studies, Kal et al. concluded that different dose rates at ≤15 cGy/min for fractionated schedules (with fraction doses of 1.2 to 2.25 Gy) do not induce large BED differences for leukemic cells and organs at risk (OAR), in contrast to single-fraction schedules [109].

**Lung toxicity**

The main lung toxicity occurring after HSCT with a TBI-related conditioning regimen, is interstitial pneumonitis (IP), also termed idiopathic interstitial pneumonia syndrome (IPS), which can develop
within days to months post-HSCT and is potentially fatal. In a retrospective study of 202 acute leukemia patients, Gao et al. found that 8 x 1.65-Gy fractionated TBI dose rates of >15 cGy/min induced significantly more IP and produced worse 1-year overall survival (OS) than dose rates of ≤15 cGy/min (IP 29% versus 10%, p<0.01; 1-year OS 60% versus 76%, p=0.01) [110]. Although compensators at the level of the lungs were used in 30% of patients to achieve calculated lung doses equal to the dose at the midplane prescription point, it has to be noted that lungs were only shielded by the patient’s arms in a bilateral beam setup, introducing higher doses in the anterior lungs [111, 112]. In fractionated conventional TBI studies, the influence of dose rates up to 15 cGy/min becomes inconsequential for IP development, as long as the lung dose does not exceed 8–9 Gy [72, 113-115]. At dose rates of 15–21 cGy/min for fractionated TBI schedules of 10.5 to 14 Gy, IP risk increased in 2 retrospective studies, with lung doses given as prescribed dose or shielded to 10 Gy [116, 117]. In contradiction with these findings, dose rate was not a significant factor for IP in a meta-analysis including TBI lung dose rates of 3–41 cGy/min (with applied dose rates as deducted from the included publications), while total lung dose was; 12 Gy TBI in 6 daily fractions induced an estimated IP incidence of ±11% without lung shielding. Fifty percent shielding of the lungs lowered the estimated incidence to ±2.3% [79]. In a recent systematic review on pulmonary toxicity after TBI in adults and children, the authors state that dose rates ≤15 cGy/min to minimize risk of IP/IPS are supported by the literature, although they did raise the abovementioned concerns regarding interpretability of published data [118].

Renal toxicity

Late chronic renal toxicity after HSCT is influenced by many factors. Fractionated TBI is inconsistently reported as a risk factor in children, with TBI doses >10–12 Gy mentioned as specific risk factor in those publications that find a correlation between TBI and renal toxicity [119-124]. Ellis et al. calculated an OR of 2.56 for TBI doses >11 Gy from 7 combined cohorts in a meta-analysis [125]. Dose rate was hardly ever reported or investigated as separate risk factor in publications on fractionated TBI in children. For 192 children evaluated as a separate group, dose rates of <10 cGy/min versus ≥10 cGy/min were not found to be a significant risk factor in fractionated TBI, while it was an influential factor for 479 adults and all patients combined in a retrospective study [119]. High dose rate affects late renal damage inasmuch as it can increase BED to levels above tolerance doses, generating the need for kidney shielding to lower BED. From a meta-analysis of 11 studies combining adult and pediatric patients, Kal et al. advised to keep the BED below 16 Gy by shielding the kidneys if needed, to keep the risk of TBI-related chronic renal disease <3% [126].
**Lens toxicity**

A clear dose rate effect on the induction of cataract was established in prospective and retrospective TBI studies [73, 97], and fractionated TBI versus single-fraction TBI also profoundly decreases risk of cataract [17, 127]. For 2149 EBMT registry-patients, Belkacémi et al. reported 10-year estimated cataract incidences of 60% after single-fraction TBI, 43% after <6 fractions, and 7% after TBI given in >6 fractions (p<10^-4), as well as lower incidence with dose rate ≤4 cGy/min (30%) than with dose rate >4 cGy/min (59%, p<10^-4) [73]. BED of the lens, and therefore cataract risk, can be decreased by shielding, irrespective of dose rate [128].

 Recommending an optimal dose rate for TBI is not possible because of the many uncertainties regarding the numerous influential variables on immunogenic, disease and toxicity effects and inconsistent publications on the issue of TBI dose rate, and not to mention impossibility of normalizing dose rates between publications. Still, it appears that dose rates between ±4 and ±20 cGy/min are the most reported-on and clinically used for extended source-to-skin-distance (SSD) fractionated conventional TBI schedules in pediatric patients. Many pediatric centers report using dose rates of 6–15 cGy/min, with appropriate OAR shielding [22, 113]. For more definitive conclusions, we would need well-designed studies and comparisons between centers with detailed reporting of applied dose rates, and clear descriptions on how these were measured or calculated in centers.

 Modern highly conformal TBI techniques provide better target dose homogeneity and OAR sparing. Along with fractionation and accurate dose delivery it may allow favorable toxicity profiles, even with high instantaneous dose rates. First experiences with an image-guided intensity-modulated radiotherapy (IMRT)-technique at extended SSD derived 15% dose reduction to lungs/kidneys with SSD-related dose rates at midplane of 14—46 cGy/min and show encouraging results of treatment outcome and toxicity [129-131]. Highly conformal optimized TBI techniques with source to axis distance (SAD) setup assume intensity modulation combined with sequential body irradiation. In this case, rather high dose rates values are required to achieve an adequate dose delivery time. Helical TomoTherapy delivery using simultaneous translational movement of the couch and constant radiation source rotation have an instantaneous dose rate of about two orders of magnitude higher than conventional TBI [132]. Like Helical TomoTherapy, volumetric modulated arc therapy (VMAT) also uses high dose rates (up to 1000 cGy/min), but these can be adjusted during treatment if desired. Centers can decrease monitor unit output for selected beams while irradiating the OARs and achieve even <6 cGy/min, or increase the dose rate during irradiation of other body areas [133-135]. The first reports regarding experiences with TomoTherapy and VMAT TBI, with overall instantaneous dose rates of ±1300 cGy/min and ±31 cGy/min and instantaneous dose rates around the lung of ±840
cGy/min and ±11 cGy/min, respectively, described promising results in 220 children regarding outcome and toxicity profiles [136].

Fractionated TMI / TLI / TMLI provides substantial dose decrease outside of the target volumes, that may contribute a means to preserve immunosuppressive and leukemic effects while providing highly acceptable toxicity profiles even with high instantaneous dose rates [26, 137]. Future clinical data accumulation could confirm if highly conformal TBI or TMI/TLI/TMLI techniques offer equal disease outcomes while improving toxicity effects [26].

TBI toxicities and organ-at-risk sparing

Acute toxicities in the days and weeks after TBI can be parotitis [138, 139], nausea and vomiting or diarrhea, xerostomia, mucositis and esophagitis, skin erythema, headache, alopecia, loss of appetite, and fatigue [138]. Complaints are affected by other components of HSCT conditioning and are generally transient. Supporting measures such as dexamethasone and anti-emetics before TBI, pain medication and skincare can alleviate symptoms.

Morbidity and mortality rates of HSCT survivors are higher than those of the general population or other childhood cancer survivors [5, 6, 140, 141]. TBI-based conditioning tends to cause more late sequelae than chemotherapy-only conditioning, although many factors must be taken into account when comparing the two [4, 5, 142, 143]. This is especially true for very young children, who have a higher risk of severe late effects [4, 49, 54]. Among the concerns are negative effects on neurocognition [49, 51, 53, 54, 144-147], growth [52, 62, 148-150], and endocrine and metabolic functioning [4, 49]. Thus, myeloablative TBI in children below the age of 3 years, and preferably below 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, the relationship between dose and fractionation of TBI and specific organ toxicities is described sparsely, and mainly concern lung-, kidney-, and lens toxicity. These publications are mostly level of evidence grade III-IV. Most cohorts in these papers are a mix of adults and children with different disease entities, previous treatments, stem cell sources and conditioning regimens. This precludes clear and singular directions on TBI dose-reduction for specific organs, and we can only provide general considerations and recommendations here. We have summarized TBI-related information from publications, evaluated after a systematic literature search, in Supplementary Tables 1–6, concerning toxicities for lungs, kidneys, eyes/lenses, liver, cardiovascular and endocrine systems, respectively. Publications were included when it was reported or could be assumed that the cohort comprised at least 15 children who were treated with
fractionated TBI. Here, we give a short overview of late effects for which general recommendations on dose restrictions for fractionated myeloablative TBI can be extrapolated from the collected publications.

Regarding the lungs, the most evaluated TBI-related, and potentially fatal, toxicity is interstitial pneumonitis (IP). The term IP is interchangeably used to describe idiopathic interstitial pneumonia syndrome or infectious pneumonitis, and publications do not always make the distinction when listing incidences [118]. IP usually occurs within 4 months post-HSCT, with a peak incidence at 60–90 days. Overall, fractionated TBI incurs less IP than single-fraction TBI, and children experience less IP than adults; in pediatric series the incidence varies from 0–35%, with usually <20% fatal outcome (Supplementary Table 1) [30, 82, 113, 116, 123, 151-157]. Risk is correlated with lung radiation dose and can be decreased by factors that reduce the BED, such as lower total doses, low dose rates, fractionation and lung shielding [69, 79, 108, 109, 117, 158, 159]. 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). Most pediatric radiotherapy centers perform lung shielding [21, 22]. An analysis of 127 children with ALL who received allogeneic HSCT after TBI-conditioning with fractionated 12 or 13.2 Gy given as 6 or 8 twice-daily fractions in various centers, found that OS was significantly better after mean lung doses of <8 Gy (HR 1.85, p=0.043), while lung shielding did not cause increased disease relapses [113].

→ For fractionated TBI 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.

Radiotherapy-related chronic renal disease (CRD) develops in different stages and is caused by multiple pathomechanisms such as inflammation, fibrosis and vasculopathy [160]. HSCT-related CRD usually develops after months to years, more after allogeneic HSCT than autologous HSCT, occurs more frequently in adults than in children (children 0–30%), and publications inconsistently link incidence to fractionated TBI dose (Supplementary Table 2) [119-123, 125, 145, 161-165]. However, when TBI is associated with CRD in mostly single-center cohorts, fractionated TBI doses of ≥11–12 Gy induce more CRD than lower evaluated doses [125, 166-169]. From combined analysis of 11 reports, Kal et al. advised to keep the BED below 16 Gy by shielding the kidneys if needed, to keep the risk of TBI-related CRD <3% [109, 170]. This would mean using kidney shielding even for fractionated TBI doses 12–14.4 Gy at dose rates of ≥6 cGy/min. Lawton et al. performed 14 Gy TBI in 9 fractions of 1.56 Gy over 3 days at 8–20 cGy/min, and found decreasing rates of post-HSCT CRD with no shielding,
versus 15% or 30% shielding – the actuarial 2.5 year risks of CRD were 29±7%, 14±5%, and 0%, respectively [169].

- For fractionated TBI 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 kidney dose to ≤10 Gy.

Lens cataracts develop frequently after TBI; more frequently after single-fraction than fractionated TBI, less after TBI fractionated in 1.8–2 Gy doses than in higher fraction doses, and more with increasing dose rate (Supplementary Table 3) [49, 57, 97, 154, 158, 171-176]. After median 10 years follow up of 174 pediatric acute leukemia HSCT recipients, cataract incidence was 51.7% after mainly 12 Gy TBI in 6 fractions [142]. In a meta-regression model calculated from 1386 patients in 21 series, Hall et al. extrapolated a 5-year pediatric cataract risk after HSCT of 28% after 0 Gy TBI; 60% after 12 Gy in 6 fractions; 58% after 13.2 Gy in 8 fractions; and 87% after 8 Gy single-fraction [57]. From 17 published series, Kal et al. extrapolated a BED of <40 Gy for which risk of severe cataract, defined as needing surgery, will be <10% [170]. 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 study of 188 children given myeloablative TBI in 1 or 2 fractions, eye shielding to 55–58% of prescribed dose reduced cataract incidence from 90% without shielding to 31% with shielding, while CNS recurrence was observed in 0% and 1.4%, respectively [128]. One of the 2 children with CNS recurrence had CNS involvement at relapse before HSCT. Few pediatric radiotherapy centers apply eye shielding during TBI [21]. Highly optimized TBI techniques make lens sparing without compromising CNS dose better attainable [177].

- For fractionated TBI schedules of 12–14.4 Gy in 1.6–2 Gy fractions at dose rates ≥6 cGy/min during conditioning for allogeneic HSCT, it can be considered to reduce 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 setup TBI.

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

For other organs or toxicities, no recommendations can be made based on the literature, other than to perform (1.6–2-Gy) fractionated TBI as opposed to single-fraction TBI, and to keep the total dose <16 Gy. If previous irradiation has taken place, consider cumulative dose and related risks when contemplating myeloablative fractionated TBI. Supplementary tables 4, 5 and 6 summarize publications on (pediatric) fractionated TBI regarding liver toxicity, cardiovascular toxicity and endocrinopathies, respectively.
Sinusoidal obstructive syndrome (SOS) has a mean incidence of 14% after HSCT and severe SOS has a high mortality [178-181]. HSCT-conditioning with chemotherapy but also with TBI are associated risk factors (Supplementary table 4). Several investigations found no significant relation between single-fraction or fractionated TBI and SOS [72, 182], but Girinski et al. noticed more SOS after 10 Gy single-fraction TBI (n=73; 8-year incidence 14%) versus fractionated 14.85-Gy TBI (n=74; 8-year incidence 4%) in a randomized trial of adult hematologic malignancies patients (p=0.04) [114]. In fractionated TBI dose-escalation studies, SOS was the dose-limiting toxicity at 16 Gy in 2-Gy fractions twice per day, or 14–14.4 Gy in 1.2- to 1.6-Gy fractions three times per day [77, 82, 159]. In one study, a 10% dose-reduction over the liver during 14 Gy fractionated TBI decreased risk of fatal SOS from 3 in 20 patients without shielding to 5 in 98 patients with shielding [159].

HSCT survivors have a higher prevalence of metabolic syndrome and atherosclerosis, predisposing patients to cardiovascular adverse events such as myocardial infarction, stroke and peripheral vascular disease [183-190]. Neither TBI (as compared to chemotherapy-only conditioning) nor TBI dose or fractionation (less or more than 10 Gy; single-fraction versus multiple fractions) was associated with direct (cardio)vascular outcomes in several studies (Supplementary Table 5) [185, 190]. However, in studies that followed children for extensive periods after HSCT, TBI-conditioning and higher TBI dose were recognized as cardiovascular event risk factors such as metabolic syndrome, higher blood pressure, higher fasting insulin, adverse lipid profile, subclinical decreased systolic and diastolic heart function, and higher waist-to-hip ratio (Supplementary Table 5) [58, 185, 191-197]. Also, in a general study of 24,214 5-year childhood cancer survivors, increased incidence of cardiac diseases was found for children receiving 5–19.9 Gy to large cardiac volumes [198, 199], as is true for TBI. Therefore, TBI-treated patients should be chronically monitored to ameliorate risk factors for cardiovascular adverse events where possible.

HSCT with or without TBI is related to occurrence of endocrinopathies such as growth hormone deficiencies, uncompensated and compensated hypothyroidism, metabolic dysregulation and pre- or post-pubertal gonadal failure, with potential disturbances throughout hormonal axes; from pituitary to secreting organs [142, 200, 201]. Whether or not fractionated TBI-conditioning causes more endocrine issues than chemotherapy-only conditioning is unclear from published series (Supplementary Table 6), but all children should be monitored for disturbances in the endocrine and metabolic spectrum after HSCT, and therapies should be instigated where possible.

TBI is associated with growth impairment, through effects on growth hormone production, and a direct effect on bone growth which mainly occurs after total doses of more than the equivalent of 15 Gy in 2-Gy fractions (EQD₂) [202, 203]. The final height can be diminished by -1.0 to -2.5 standard
deviation scores compared to the average population or the expected final height calculated from parental heights [52, 62, 148]. Other factors are younger age at TBI and more influence of single-fraction TBI than fractionated TBI [52, 62, 67, 148, 150]. After fractionated TBI, >75% of patients reach a final height within the normal range of the general population [67].

Neurocognitive effects after single-fraction or fractionated TBI were reported in studies as statistically, but overall not clinically significant decrements in IQ or sensory-motor and cognitive functioning, with however extensive effects in children less than 3-4 years old at the time of TBI [49, 51, 53, 54, 144-147]. In contrast, there are studies of patients with various diseases that find no significant changes in children’s cognitive status after TBI-conditioned HSCT [63, 204-206]. The additive adverse effect of (intrathecal) methotrexate therapy may play a role in children with leukemia. The PENTEC investigation group recently modelled the interaction between cranial radiation and administered methotrexate [207]. The risk of an IQ <85 was 5% for children who had received a whole-brain dose of radiotherapy of 18.1 Gy, and methotrexate increased any risk of an IQ <85 in equivalence to a generalized uniform brain dose of 5.9 Gy. However, even at HSCT-conditioning with fractionated TBI with doses of 12 Gy, more changes in neuroanatomy on MRI and several neuropsychological outcomes may be found than in children not undergoing HSCT [208]. Cumulative doses to the brain and potential effect on neurocognitive function should always be considered when a child has an indication for TBI-conditioning before HSCT.

Secondary malignancies are relatively frequently observed after childhood HSCT [80, 175, 209-213]. In children and adults, the risk of secondary malignancies associated with TBI was decreased after fractionated TBI compared with single-fraction TBI, but this benefit was lost when high total cumulative doses were administered, especially at doses above 14.4 Gy [81, 214]. In a cohort of 3,182 childhood acute leukemia HSCT survivors, cumulative risk of solid cancers increased to 11% at 15 years and multivariate analyses showed increased solid tumor risks associated with high-dose TBI of ≥10 Gy single-fraction or ≥13 Gy fractionated TBI, and younger age of especially <5 years at HSCT [80]. Younger age at HSCT stands out as a risk factor; children <10 years, but especially those <3 years, develop more secondary malignancies than older patients [50, 80, 214, 215]. All HSCT recipients and their caregivers should be advised about secondary malignancy risks and undergo appropriate screening [215, 216].

TBI and radiotherapy boost of sanctuary sites

Radiotherapy delivery to target sites is not dependent on blood supply; not influenced by variability in drug absorption, metabolism, bio-distribution, or clearance kinetics; and can reach sanctuary sites, such as the testes and the CNS. Systemic treatment has less penetration in these sites, leaving them
at higher risk of local recurrence after chemotherapy, especially in ALL patients. Based on this, additional radiotherapy boosts to sanctuary sites may be required at the time of TBI.

The routine use of CNS radiotherapy prophylaxis in standard risk ALL [217-222] has been abandoned after numerous studies showed equal prophylactic effect of intrathecal therapy [223-225]. A potential benefit of CNS radiotherapy may exist in patients with high-risk ALL, especially T-cell ALL, although different treatment allocations in non-randomized trials preclude definite recommendations for these patients [226, 227]. ALL with CNS3 involvement, either at diagnosis or at relapse, predicts a higher risk of post-transplant CNS relapse [228-230]. A meta-analysis of 47 trials by the Childhood Acute Lymphoblastic Leukemia Collaborative Group (CALLCG) concluded that in general, adequately given systemic and intrathecal therapy yielded similar survival outcomes as radiotherapy [231]. Another meta-analysis concluded that CNS radiotherapy may decrease CNS relapse risk for patients with CNS3 disease at diagnosis [232]. The 2018 International Lymphoma Radiation Oncology Group (ILROG) guideline for CNS radiotherapy advises consideration of CNS-directed radiotherapy for patients with overt CNS leukemia at diagnosis or those who develop CNS leukemia at disease relapse, especially when intrathecal / systemic therapy has failed [233].

With regard to patients who are scheduled for TBI-based HSCT, the CNS as sanctuary site should not be shielded from the prescribed, and perhaps adequately prophylactic, dose in leukemia patients. Whether the brain can be excluded from the target volume in other indications, remains unknown and may become clear when more TMI and TMLI studies specifically underdosing this structure become available. For patients with AML or ALL who have a history of CNS involvement, a CNS boost before TBI should be considered [233]. In a study by Gao et al., a 9-Gy cranial boost before 13.2 Gy fractionated TBI for ALL patients with previous CNS-involvement significantly reduced the 2-year rate of post-transplant CNS relapse (0% of 30 patients with boost vs 21% of 11 patients without boost; p=0.03) [234]. Despite the improvement of CNS disease control, there were no differences in overall survival.

It is still undetermined what the minimal dose, precise target volume (cranial or craniospinal radiotherapy) and the optimal timing of the boost should be to prevent CNS relapse. Authors suggested to give CNS directed radiotherapy in the days immediately prior to TBI in high-risk ALL patients, as 9 Gy in 5 fractions [234] or 6 Gy in 3 fractions [223, 235]. Pinnix et al. recommended a cumulative CNS-directed dose of 18 to 24 Gy [233]. Notably, in the retrospective study by Su et al. of 55 high-risk adult ALL patients undergoing HSCT with or without pre-TBI cranial boost, there were post-transplant CNS relapses in patients without prior CNS involvement who received no 6-Gy cranial
boost, therefore it remains difficult to exactly pinpoint which patients may require CNS treatment intensification [235].

The CNS target volume should at least include the entire cerebrum down to the second cervical vertebra including the cerebrospinal fluid extensions around the optical nerves and the skull base, with extra attention for coverage of the lamina cribrosa and the extending cranial nerves [236]. Craniospinal irradiation (CSI) should include these targets as well as the subarachnoid space along the spinal axis with CSF extensions into the nerve roots [237]. Currently, there is no clear evidence whether CSI versus cranial irradiation has a greater benefit in the control of CNS relapses and, therefore, there is no consensus on the specific CNS target volume. If the objective is to treat circulating malignant cells in the cerebrospinal fluid, CSI may be a logical choice. Some reports suggest that CSI may improve CNS disease control before HSCT to a greater extent than cranial radiotherapy [223, 238]. In 41 ALL patients with CNS involvement who received TBI and CNS boost, there was good neurocognitive tolerance and efficacy of treatment with a total cranial dose of 24 Gy and median 18 Gy total dose to the spine [238]. However, specific patient characteristics, toxicity risks and outcome expectations should be weighed for each individual child.

Several considerations for CNS boost alongside TBI can be given:

- 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 (EQD2) dose of current CNS boost and TBI should not be >24 Gy.
- Total (EQD2) 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.

Isolated testicular failures may occur in boys who undergo HSCT, especially for ALL. With current treatment strategies, testicular relapses are rare [239]. Testicular radiotherapy 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. The scrotal content including both testes (or contralateral testes after orchiectomy) is irradiated to a cumulative testes dose of 16–24 Gy [240]. This can be done with an additional 4-Gy fraction (photon or electron beams) given in the days either concurrently or immediately prior to TBI for patients after orchiectomy and no evidence of disease in the contralateral testicle [241], or as cumulative 18–24 Gy in 2-Gy fractions in the days prior
to TBI in case of clinical involvement of 1 or 2 testicles. Patients can be placed in supine with frog leg position, and the penis can be taped to the abdomen to keep it out of the radiation field.

Persistent extramedullary leukemia localizations in other sites before HSCT conditioning are very rare with current treatment strategies that pursue minimal residual disease (MRD) negativity before HSCT [242]. In lymphoma or even leukemia patients, a boost may be considered to localizations that remain viable or enlarged until shortly before start of conditioning, but no conclusive recommendations can be given for these patients. A total dose of 24 Gy (or even up to 36 Gy for lymphoma patients) can be given to these sites, with the boost given in the days before TBI.

In selected very high-risk cases, TMI can be explored as a “selective boost” modality to increase radiation dose to the marrow after the conventional 12 Gy TBI [243]. In cases where modern highly conformal techniques are used for TBI-planning, the option of a simultaneous boost to the bone marrow or extramedullary sites can be considered [88, 136, 244, 245]. Selective conformal boost doses to sanctuary sites with simultaneous TMI or conformal dose avoidance to areas previously irradiated may also be possible [26].

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

Childhood HSCT survivors carry a significantly greater risk burden of morbidity not only compared with non-cancer populations but also compared with conventionally treated cancer patients, underlining the importance for life-long monitoring of this high-risk population [2, 3, 5, 141, 142]. Not only during childhood, but also after transition to adult care should HSCT recipients be cared for by experienced healthcare providers, with focus on surveillance, prevention and education, and treatment where needed [246-249]. 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 [250]. General health maintenance is important, and active evaluation of psychosocial and quality of life factors should be part of follow-up programs.

Chronic GVHD remains the most common late complication of allogeneic HSCT, which affects up to 40–50% of patients surviving more than one year post-transplant irrespective of the conditioning regimen [251, 252]. The median time to presentation is 4 to 6 months after HSCT. The pathogenesis is still poorly understood; thymic atrophy, lymphocyte depletion and autoantibody formation have been described. Prevention and care have improved in the last years so that most of the centers recommend counseling patients on vigilant monitoring and early treatment [253]. The observation of
potentially less chronic GVHD developing in TMI patients after HSCT compared with TBI patients is intriguing and relevant for future clinical trials [254].

Late respiratory complications are a significant source of morbidity and mortality [255]. Development of restrictive or obstructive lung disease after HSCT is multifactorial, including the transplant regimen, diagnosis, donor major histocompatibility complex mismatch, chronic GVHD, and time after transplant. Fractionated TBI is mostly not reported as significant factor but, nonetheless, increased incidence can be found after fractionated TBI-based conditioning [123, 153, 256-258]. However, allogeneic HSCT recipients with signs of lung compromise, regardless of their conditioning regimen, have an indication for pulmonary function testing and focused radiologic assessment at 1 and potentially 2 years after HSCT, and regular thereafter for those with deficits [250]. Regular routine clinical assessment and discouragement of smoking is applicable to all recipients.

Based on patients’ individual predisposition and previous and ongoing risk factors, such as exposure to TBI, CIBMTR and EBMT published recommendations on screening and preventive practices for metabolic and cardiovascular dysfunction, that include e.g. regular evaluation of weight, dyslipidemia, blood pressure and hyperglycemia [259].

Comprehensive blood screening for endocrine dysfunctions over all hormonal axes is mandatory because of high incidence of hormonal dysfunction after HSCT conditioning with or without TBI [142, 200, 201, 260]. Growth, thyroid, adrenocortical, ovarian and testicular hormone depletion should be supplemented. Fertility issues need to be addressed and counselled for. If a pregnancy occurs in a female patient after childhood HSCT with TBI, close monitoring of the pregnancy is indicated since there is a higher risk of miscarriages, preterm deliveries, and obstetrical complications, particularly during the third trimester of pregnancy, as a consequence of suboptimal uterine development [261]. Growth disturbance may be caused by TBI through growth hormone disturbance and direct effect on growth plates [202, 203]; other factors, including chronic GVHD and liver dysfunction, may also contribute. Growth velocity should be monitored until the end of the pubertal growth spurt. Growth hormone treatment has a positive effect on growth rate and final height, but does not produce a “catch-up” effect [262-264].

Monitoring of bone health i.e. growth and signs of bone mineral density loss or osteoporosis, can be achieved with growth and biochemical hormone assessments [265]. Dual-energy x-ray absorptiometry (DEXA) scan evaluation at 1 year after HSCT and afterwards based on baseline findings are based on
expert opinion, although exact timing has not been systematically clarified and interpretation may be
difficult in children with short stature [266]. Use of prolonged corticosteroids and calcineurin
inhibitors, and e.g. renal dysfunction, play a major role in osteoporosis and bone mineral density loss,
and direct influence of fractionated TBI influence is debatable, although induced hypogonadism by
chemotherapy and TBI is a major contributing factor [266, 267]. 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) can
be given in patients with evidence of abnormalities.

Chronic renal dysfunction encompasses a wide spectrum of functional and structural kidney
abnormalities and is observed in up to 62% of patients after allogeneic HSCT. It may be associated
with a wide range of risk factors including high-dose chemotherapy and fractionated TBI, sinusoidal
obstruction syndrome, hepatorenal syndrome, sepsis and consecutive antibiotic and antifungal
treatment [268]. Yearly screening of renal function (including blood pressure, renal function
assessment (blood urea nitrogen and creatinine and clearance, urinary protein, and if necessary
kidney ultrasonography) is recommended in all pediatric HSCT recipients.

Given the frequency of cataracts occurring after TBI [57, 174], patients should be monitored yearly by
an ophthalmologist for this and other late effects of the eye after HSCT, such as keratoconjunctivitis
sicca or microvascular retinopathy [250].

Sicca syndrome related to GVHD, but also xerostomia after TBI can make patients vulnerable for
development of oral complications such as caries of the teeth. At least annual evaluation by a dental
professional should take place with individualized intervention and follow-up in case of problems
[250].

CIBMTR together with EBMT issued an expert review on neurocognitive functioning in both adults and
children, recommending neurocognitive testing in children before and 1 year after HSCT and then at
the beginning of each new stage of education [269].

After 12 Gy fractionated TBI, splenic dysfunction might occur [270], and functional asplenia protocols
can be followed alongside post-HSCT vaccination programs if deemed relevant by the HSCT treatment
team [271].
The risk of secondary malignancies after allogeneic HSCT involving TBI is well-known and incidence increases in cohorts with longer follow-up [80, 175, 209-213, 272].

No generalized screening protocols are now instated, but besides regular clinical assessment at outpatient clinic visits, all patients and caregivers should be advised of the risks of secondary malignancies and encouraged to perform routinely recommended screening self-examinations, such as breast and skin examination [215, 216, 273]. Consider dermatologic screening by a specialist every 1-2 years. Patients should participate in national cancer screening protocols. Ultrasonography and MRI screening programs for thyroid cancer for all patients and breast cancer in young women ≥25 years, respectively, can be considered after childhood TBI [250, 274, 275]. 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. High-risk behavior such as unprotected skin UV exposure and smoking should be actively discouraged.

**Conventional TBI setup for children**

TBI has historically been delivered using techniques with large fields at extended SSD [74], and most institutions still use these techniques in a locally designed setup dependent on the local technical possibilities [22]. While TBI at SSD is prone to dose inhomogeneities, every effort should be made to maintain dose inhomogeneity to within ±10% of prescribed dose, an intricate task that requires careful planning, physics calculations and quality assurance [92, 95]. Different options are available to position the patient at distance within the flattened part of the radiation field, manytimes over the diagonal. One technique for anterior (A) posterior (P) / PA TBI is to position patients in a lateral decubitus position requiring a dedicated separate treatment couch. Lateral positioning on the couch is commonly done using a vacuum bag, stable tilted head position, drawn up knees, one arm extended along a side and the other arm supporting or encircling the head. Other positioning methods used are the standing/leaning position within a dedicated support setup, or allowing the patient to sit on a specifically designed chair [91]. Special attention has to be paid to extremity positioning within the extensions of the field, for patient comfort and dose homogeneity. Other institutions choose supine positioning for bilateral beam setups. Tissue equivalent compensators can be used around the head, neck and legs, to decrease buildup of dose in these narrow body parts. TBI at shorter distance can be achieved by using a sweeping beam technique or by translating the patient at a controlled steady rate beneath the beam, in supine and prone position [93].

Beams are typically delivered as opposed AP-PA, bilaterally or as a combination of both techniques. Usually the treatment couch or the patient is rotated 180 degrees in between fields to perform 1 treatment fraction. In extended SSD TBI, beam spoilers in front of the patient are used to abrogate
the surface-sparing effect of photon beams [94]. The use of field-in-field techniques can achieve more homogeneous dose distribution if necessary, but makes precise patient positioning even more vital. TBI techniques may have remained unchanged within institutions for decades – and much used manual and spreadsheet calculation workflows do not allow the computation of dose volume histograms (DVHs) of the body or the OAR. There are no dedicated commercial treatment planning systems (TPS) for dose calculations for TBI treatments at extended distance. However, if possible with an institution’s TPS, it is preferable to perform a planning CT and calculate dose distribution with the local TBI delivery parameters uploaded into the TPS [111, 276]. If needed, sedation is found to be no obstacle during (twice-daily) fractionated TBI [21].

Regarding beam energy choice; for solely bilateral or AP-PA beam setup, an energy of 6 to 10 MV does not produce additional neutron dose to patient and staff, provides more homogeneity than lower energies in this setup, and is often preferred in pediatric TBI. Depth dose inhomogeneities of ±10% up to ±30% including skin dose arise in the bilateral setup with 10 MV [93].

However, the use of a solely bilateral technique in children is disadvantageous since it results in higher lung doses (up to 40% higher than prescribed, depending on patient anatomy) which may decrease survival chances [111-113]. Of note, the use of correct tissue density corrections for lungs is important in any TBI setup; dose calculations for bilateral TBI without tissue density correction are incorrect in the thorax by up to 16–24%, depending on beam energy [112].

In TBI treatments with large open fields without shielding, the lung dose will be greater than the dose to the rest of the body because of the lower density of the lungs. Partially transmitting shielding can be used to reduce the lung dose to the prescription dose [112], or below the prescription dose, and may be achieved using individually shaped metal alloy / cerrobend blocks of calculated individual thickness or multileaf collimators (MLCs), which should be commissioned for transmission characteristics [129, 276-278]. There should be awareness of electron contamination behind the blocks. This can be compensated with e.g. bolus material or increasing the thickness of the block mount. [279]. Shielding of kidneys and lenses can be performed to decrease risk of chronic renal disease or cataract [109, 128]. The shape of the lung blocks can be obtained using an X-ray image of the patient in the treatment position, kidney blocks can be individually moulded after an outline is drawn on the skin during ultrasonography in TBI position, and eye shielding can be positioned manually. The placement of shielding should be verified before each beam is delivered. An example of an X-ray image used for the preparation of lung blocks (A) and for the verification of their positioning (B) is shown in Figure 2 of the recommendations manuscript.
The transmission of radiation through the blocks and scattering should not be neglected when determining the fraction of time the block is to be in place during treatment.

Dose prescription at reference point

The most frequently used treatment dose specification point is at the patient midplane, either in a single point, or averaged over multiple midline points. To enable comparison and equality of data-collection between different centers, uniformity in dose specification is preferable, with international consensus advising a reference point in the midplane at the level of the umbilicus and lung dose definition as the mean of the dose at the midpoint of both lungs [93].

In vivo dosimetry

TBI setups need to be checked by using dosimetry under conditions that closely simulate the actual treatment situation [74]. This procedure should therefore include beam spoilers. The relation between entrance/exit/mid-plane dose should be established and verified in a phantom measurement [276]. Midplane dose can be converted from entrance/exit dose at prescription plane with a calibration curve [96]. Possible measurement devices include diodes, thermoluminescent dosimeters (TLDs), optically stimulated luminescence (OSL) dosimeters, metal–oxide–semiconductor field-effect transistors (MOSFETs), ionization chambers and film [280]. These devices should be commissioned for TBI conditions (large SSD, field sizes, fraction dose, low dose rate, with spoiler screen). In case diodes are used, calibration should be done using a phantom. In vivo dosimetry allows documentation and verification of the actual treatment, and evaluation of potential treatment adaptations. The ability to obtain a real-time measurement with a reusable dosimeter makes diodes particularly well suited to in vivo dosimetry for TBI. In contrast, detectors such as OSLs or TLDs allow only post-fraction verification of the dose delivered to the patient. The sensitivity of the dosimeters can vary according to temperature, localization in the beam orientation, beam energy, radiation exposure and kind of readout [281].

It is advised to perform in vivo dosimetry for at least the first 10 patients as a quality check of the entire TBI procedure. Regular quality assurance of the TBI technique should take place. 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. Users should be aware that the in vivo dose measurement is an approximation of the dose in the patient.

To enable comparison of TBI data between centers, we need comprehensive standardized reporting of all relevant parameters. The minimally reported information should be: beam setup, prescribed target volume dose in Gy and prescription point (e.g. midplane at 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 (prescription point) and in the lungs, shielding / dose reduction to specified organs.

**Highly conformal optimized TBI techniques**

Highly conformal optimized SAD TBI techniques form a fundamentally different approach compared to conventional SSD TBI because they require use of a TPS, use a much higher dose rate and require field junctioning. Examples are TomoTherapy [23, 282-284] and VMAT [24, 133, 135, 285, 286]. Since the couch travel of linear accelerators is only 120–150 cm, VMAT TBI requires a challenging setup and planning, securing robust treatment with patient rotation from head-first to feet-first position. 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 [136, 285, 287], but more reports and longer follow-up results need to establish its base for standard TBI setup. For implementation of optimized TBI in a radiotherapy department, measures need to be taken to ensure robust planning, high reproducibility, safety, and stringent quality control.

**IMRT at extended source to skin distance**

TBI with IMRT combines the commonly used large fields at extended SSD of conventional techniques with several forward planned segments. From all novel techniques for TBI, IMRT at extended SSD technique is the smallest step-up from conventional TBI to implement clinically, since a common linear accelerator 6–18 MV, TPS and bigbore CT scan provide the basics for implementation [129, 131].

A vacuum bag is used to assure patient positioning. Both lateral decubitus positioning and supine positioning offer options for reduced dose to lungs and kidneys, while limiting hotspots in brain, lungs and kidneys [130]. Through a setup with bended knees, the full body length limitation of 160 cm for CT scan can be achieved in both patient positioning setups. Beam modeling by phantom measurements reduces deviations between TPS outcomes and in vivo dosimetry significantly and is recommended before clinical introduction of IMRT for TBI. A spoiler screen is added for surface dose buildup and can be taken into account during optimization of the treatment planning. With a beam setup of 273-275°, collimator rotation of 45° and a 40x40 cm collimation, a PTV length of 160 cm can be achieved at a Source to Midline Distance of ±350 cm.

With the use of a MLC setup field that follows the outer contour of the patient, patient positioning can be reproduced using the MLC light field. The use of IGRT with e.g. MV imaging is recommended.
Otherwise, in vivo dosimetry can be considered. Table 1_supplement gives technical considerations for SSD IMRT TBI.

Table 1_supplement. IMRT TBI at extended SSD setup in children; considerations.

<table>
<thead>
<tr>
<th>IMRT TBI at extended SSD setup considerations</th>
<th>References</th>
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<td><strong>Patient positioning</strong></td>
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<td>Markings on the patient must ensure reproducible positioning.</td>
<td>[129]</td>
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<td>Fullbody vacuumbag or two separate vacuumbags, bended knees (assure total PTV length &lt;160 cm).</td>
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<td>Supine or lateral decubitis positioning (latter preferable for lung dose reduction).</td>
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<td><strong>Supine Positioning</strong></td>
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<td>- hands attached to contralateral elbows, bended knees</td>
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<tr>
<td><strong>Lateral Decubitis Positioning</strong></td>
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<td>- stable tilted head position, ipsilateral arm encircling head, contralateral arm extended along the side, bended knees</td>
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<td><strong>Planning CT</strong></td>
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<td>Maximum FOV (include entire knees and arms).</td>
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<td>Total scan length should include the entire body from vertex to toes and adhere to a maximum of 160 cm.</td>
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<td>Slice thickness 5 mm.</td>
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<td>Markings (tattoos and / or ink markings) on skin and vacuum bag.</td>
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<td>Fiducial Marking at treatment reference point (ideally midrange 3D).</td>
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<td><strong>Delineation and DVH parameters</strong></td>
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</tr>
<tr>
<td>Kidneys</td>
<td>[131]</td>
</tr>
<tr>
<td>Dmin &gt;90%</td>
<td></td>
</tr>
<tr>
<td>Dmax &lt;5% of PD</td>
<td></td>
</tr>
<tr>
<td>Brain</td>
<td>[129, 131]</td>
</tr>
<tr>
<td>Dmin &gt;90%</td>
<td></td>
</tr>
<tr>
<td>Dmax &lt;110-120%</td>
<td></td>
</tr>
<tr>
<td><strong>Beam spoilers</strong></td>
<td></td>
</tr>
<tr>
<td>Beam spoilers counter skin- and subcutaneous tissue sparing effect of photon beams. Spoilers are typically made of 1-1.5 cm thick acrylic screens, to produce electrons that increase surface doses to at least 90% of prescription dose. Recommendation 1-1.5cm, depending on 6-18 MV use, Density Override 1.09-1.17 g/cm³.</td>
<td>[94, 129, 131]</td>
</tr>
<tr>
<td><strong>Beam and positioning setup</strong></td>
<td></td>
</tr>
<tr>
<td>6, 10 or 18 MV.</td>
<td>[129, 131]</td>
</tr>
<tr>
<td>SSD 350-355cm.</td>
<td></td>
</tr>
<tr>
<td>Gantry angle 273-275° and 85-87°</td>
<td></td>
</tr>
<tr>
<td>Hospital bed or similar, flat and firm underground.</td>
<td></td>
</tr>
<tr>
<td>40x40 cm collimator at 45°.</td>
<td></td>
</tr>
</tbody>
</table>
Dose rate 46 cGy/min (at 10 cm depth at source to midline distance 350-355 cm). Dose rate 100 Mu/min.
MLC setup-field outer contour (+5 cm) for patient setup. [131]
[129] [129, 131]

Dose reference point

Reference dose prescription point:
- 250 cm lateral to the linac isocenter (sagittal laser)
- 15 cm lowered from origin (positioning convenience and limitations of treatment height, horizontal laser)
- midline (350 or 355 cm, respectively, extra in-room laser) [129]

Treatment planning

Default beam modeling for extended SSD (dosimetry and quality assurance measurements needed).
Spoiler density overrides taken into account.
Manually added segments (4-6 per side).
Gantry angle 273-275° and 85-87° (mimic rotation of patient left to right side halfway), collimator 45 and 225 respectively.

In vivo dosimetry and setup verification

MOSFET Dosimeters or TLD
MLC setup-field outer contour (+5 cm) for patient setup
MV imaging (comparing lung DRR and MD image by a setup-field)
[129] [129, 131] [129]

Sedation

Sedation is found to be no obstacle during (twice-daily) fractionated TBI. [21]

A = anterior; ALARA = as low as reasonably achievable; Dmin = minimum dose relative to prescribed dose; Dmax = maximum dose relative to prescribed dose; DRR = digitally reconstructed radiographs; MLC = multileaf collimator; MLD = mean lung dose; MOSFET = Metal Oxide Semiconductor Field Effect Transistor; MV = megavoltage; OAR = organ at risk; P = posterior; PD = Prescribed Dose; SSD = source to skin distance; TBI = total body irradiation; TLD = thermoluminescent dosimeter

Patient positioning for highly conformal SAD TBI

Supine patient positioning has to be stable and reproducible from planning CT to the last fraction of TBI [254, 288-290]. The patient has to be able to lay in the same position for 40–70 minutes. The hands and arms are placed close to the body, the hands may hold on to a stable handle bar, and the legs need to be placed 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 conebeam CT (CBCT). Immobilization components that can be useful are 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), a 3-point open face mask or chin mask, and an all-in-one base plate comprising 2–3 thermoplastic meshes to restrict regions of the head/neck, thorax/arms, and legs [24, 133, 135, 285]. To perform a robust combination of head-first (HF) and feet-first (FF) treatment, a rotatable tabletop or body frame can facilitate stable patient
rotation [24, 133, 135, 285, 291]. If assurance of surface dose to the prescription dose is vital, bolus material can be placed over the body [286].

**CT scanning and delineation for highly conformal SAD TBI**

Before the planning CT takes place, reproducible stable positioning should be checked. Fiducial markers need to be placed:

- The “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 legs

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, while patients ≥110 cm are scanned in HF and FF position separately. An adequately broad overlap region has to be scanned on both CT’s to ensure robust planning. All markers in the overlap regions should be visible on the HF and FF images for reliable images registration. Five-millimeter sections are preferable, and for small patients 3-mm sections may be better for later patient position verification using the vertebrae. Longitudinal laser lines may be marked along the entire body to facilitate reproducible patient setup.

Depending on system and dose buildup characteristics of a radiotherapy center, the PTV is adjusted 3–5 mm inside of the outer body contour. For planning ease, the PRV of OAR can be excluded from the body PTV [24, 25, 135, 287]. Shrink margin PRVs of 3–5 mm inside OAR (e.g. lungs, kidneys) may help to ensure adequate dose on surrounding lymphatic or medullary structures. A lung PRV contraction of 5–10 mm to compensate for respiratory motion, or this can be assessed using a 4D CT [23, 292]. If lens sparing is pursued, the PRV around the lenses should be at least 5 mm [177], but adequate coverage of optic nerve cerebrospinal fluid extension and the retina needs to be preserved [237].

**Planning considerations for highly conformal SAD TBI**

Treatment plans for standard linear accelerator TBI can be created with the use of a multi-isocenter technique [133, 135, 286, 293, 294], with 6–10 MV beams overlapping along the longitudinal axis to provide robust dose optimization. Depending on patient length, e.g. 4–9 isocenters are applicable for VMAT planning [24, 133, 135, 285]. Optimal field overlap length is TPS dependent and needs to be established in order to assure robust dose distribution versus setup errors. The treatment beam positions should differ from each other only in the longitudinal direction. Movement between
isocenters should exclusively be performed by moving the treatment couch according to planned isocenter positions. For the planning of the upper body section, the use of dual arcs could provide more efficient leaf travel, potential better OAR sparing and improved homogeneity. Collimator rotation to 90° leads to a better lateral dose coverage [295]. For planning of the lower body section one arc or an AP-PA beam setup may be a sufficient and fast option, if one accepts inhomogeneities from missing divergence compensation for the latter option [133]. Field borders in longitudinal direction should be set up according to treatment linear accelerator-specific maximum MLC travel, to relay easier field modulation. The beam positions and collimator jaws should be selected in accordance with the individual anatomy of the patient [295]. Multiple arcs, oblique beam incidence and beam exit from all angles significantly reduces the intrinsic photon beam skin-sparing effect, provide adequate superficial skin dose and exempts from the need to use beam spoilers [25]. For compensation of respiratory motion a lung PRV contraction of 5–10 mm can be applied, or respiratory motion can be assessed with a 4D CT. To achieve robust planning an extension of the dose outside the patient skin may be performed using TPS specific options [296] or a virtual bolus [297]. In the case of a TPS failure caused by large calculation volume, the PTV may be divided 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. Fixation devices such as a vacuum bag, rotatable tabletop and baseplate should be taken into account during dose calculation. Junction areas between the CTs with head-first and feet-first orientation may be provided by the bias dose addition in each patient orientation, or help contours to create increasing and decreasing doses [291, 298]. EBT-2 films may be helpful to control dose in junction and overlapping areas. Specialized auto planning scripts can reduce planning-time [299]. 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 [291].

RTQA and treatment considerations

As with every radiotherapy procedure, quality assurance has to ensure
(a) safety,
(b) position and
(c) dose
of the treatment. However, the character of VMAT TBI involves some particular features that have to be addressed.

Treatment is delivered with multiple isocenters, and it has to be absolutely avoided that
- possible couch-gantry collisions at individual isocenters are not detected before the beginning of
the treatment and beams are delivered at the wrong isocenter

The widespread set of isocenters often utilizes the complete range of longitudinal couch movements. This implies the risk of couch-gantry collisions at the outermost positions. Collision clearance can be ensured by a patient dry-run [133] that might also help smaller children to develop more confidence and familiarity at the time of the actual TBI. In addition or as an alternative all safely deliverable gantry-table position combinations should be thoroughly identified before clinical use of the technique [291].

Mix-up of isocenters can be avoided by setting the tolerance of table positions in the R+V system to a value significantly smaller than the possible isocenter distances. Strictly observing table positions can also help to keep the inter-isocenter distances in accordance to the planned values. The required accuracy of this accordance largely depends on robustness and anatomical location of the field junction areas. Whereas beam distances should strictly be met in the upper body, positional corrections might be considered necessary and tolerable in a broad HF-FF treatment transition, which is preferably located in the thigh region.

Likewise, treatment imaging has to deal with TBI particularities that arise from PTV size and the combined HF-FF treatment. Be aware that with the lengthy PTV, small patient rotational errors can result in significant lateral shifts in body sections further away. Accuracy requirements should match plan robustness and intended OAR dose sparing. The head, for example, can be largely considered a sphere. Without lens sparing small rotational errors can be accepted and a chin mask or open-face mask is adequate for positioning. However, if lenses are spared, a significantly enhanced accuracy of head positioning and its verification is required and the patient should be asked to keep the eyes still and in the same position as during the planning-CT during radiation of the head. Generally speaking CBCT or MV-CT for patient position verification at one or more isocenters can be performed for best accuracy. Depending on plan complexity, a surface guidance system can be considered adequate as well and may furthermore be helpful to retain stable positioning during treatment [135, 300].

Dependence of dose distribution on positional errors should thus be thoroughly checked in advance (see planning section above) and tolerance values should be adapted accordingly.

Regarding dosimetry, VMAT TBI can be considered primarily as an intensity modulated technique, which requires the same QA procedures as other VMAT treatments in the clinic. However, most other treatments employ significantly smaller field sizes and the use of multiple isocenters is limited to specific cases like craniospinal irradiation. Those particularities should therefore be established before clinical implementation.
Beyond TBI - highly conformal radiotherapy techniques; TMI / TMLI / TLI

HSCT-conditioning programs have evolved throughout the years and the role of TBI gradually changed from a basic necessity to an addition for those indications in which enhanced cyto-reduction and immunosuppression is required. 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 [26]. In this regard TMI or TMLI represent targeted forms of radiotherapy, because of the potential to decrease toxicity to OARs approximately 35–75%, compared to the conventional TBI approach [25, 301, 302]. Moreover, the possibility to escalate the dose to the bone marrow for high-risk patients [303], while reducing the incidence of radiation pneumonitis, renal toxicity, hypothyroidism, and cataract make TMI and TMLI an attractive potential approach for pediatric patients [137, 304, 305]. Helical TomoTherapy offers a high degree of conformity, homogeneity of target coverage dose and significant sparing of OAR with optimal treatment efficiency, without the need for multiple junctions [290]. Total Lymphoid Irradiation (TLI), TMI and TMLI with VMAT have also been successfully implemented in several centers [254, 291, 304, 306, 307]. Concerns have been postulated regarding increased risk of extramedullary relapses with the dose reduction to the overall body volume. Kim et al. evaluated 101 patients undergoing allogeneic HSCT with TMLI during conditioning, and found extramedullary relapse rates comparable with those of published results with regimens including TBI [308]. Randomized data comparing TMLI with TBI are lacking.

Various strategies for functional and structural imaging of bone marrow are being investigated, aimed at revealing leukemic cell distribution in different bone marrow compartments [309-312]. Such imaging can serve the purpose of an even more targeted approach to radiotherapy within HSCT conditioning regimens; boosting of, or irradiation of only those volumes of the bone marrow that are in need of treatment intensification [311, 312].

Adapting conventional TBI techniques to new TLI/TMI/TMLI techniques could be realized in radiotherapy departments with the help of planning templates as published by multiple groups [300, 313]. Performance of these techniques is currently limited to a few centers. Whether modern TMI/TMLI techniques can be the future standard of care in place of TBI for children, has to be researched in robust clinical trials that evaluate safety and quality, clinical outcomes, acute and late toxicities, and feasibility of widespread homogeneous 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 many considerations regarding technique, dose,
fractionation and according late effects induction are relevant in this patient group. This ESTRO ACROP and SIOPE recommendations reflect such considerations for the clinical practice. Cooperation between centers can support new insights, valid research and implementation of new techniques, in order to further improve outcome and reduce toxicity of myeloablative irradiation for HSCT in children.
REFERENCES


