Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Helical tomotherapy-based total body irradiation for hematopoietic stem cell transplantation: dosimetric, toxicity and survival outcomes in adults and children

Yassir Khattabi[1]
Institut de Cancérologie de Lorraine
Maria Jolnerovski[1]
Institut de Cancérologie de Lorraine
Aboubacar Diallo[2]
Institut de Cancérologie de Lorraine
Emilie Meknaci[3]
Institut de Cancérologie de Lorraine
Noé Grandgirard[3]
Institut de Cancérologie de Lorraine
Vincent Marchesi[3]
Institut de Cancérologie de Lorraine
Marie-Thérèse Rubio[4]
Centre Hospitalier Régional et Universitaire de Nancy
Cécile Pochon[5]
Centre Hospitalier Régional et Universitaire de Nancy
Arnaud Campidelli[5]
Centre Hospitalier Régional et Universitaire de Nancy
Maude D'Aveni-Piney[5]
Centre Hospitalier Régional et Universitaire de Nancy
William Gehin[1]
Institut de Cancérologie de Lorraine
Nicolas Martz[1]
Institut de Cancérologie de Lorraine
Marie Bruand[1]
Institut de Cancérologie de Lorraine
Anaïs Stefani[1]
Institut de Cancérologie de Lorraine
Claire Charra-Brunaud[1]
Institut de Cancérologie de Lorraine

Jean-Christophe Faivre[1]

jc.faivre@nancy.unicancer.fr

Institut de Cancérologie de Lorraine

Research Article

Keywords: Total body irradiation, Helical tomotherapy, Hematopoietic stem cell transplantation, Pediatrics, Organ-at-risk sparing, Toxicity

Posted Date: November 19th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11178198/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License. Read Full License

Additional Declarations: No competing interests reported.

Abstract

Background

Total body irradiation (TBI) remains a cornerstone of conditioning regimens before hematopoietic stem cell transplantation, particularly in lymphoid malignancies. Helical tomotherapy may improve dose homogeneity and organ-at-risk sparing compared with conventional techniques. We evaluated the dosimetric characteristics, toxicity profile and clinical outcomes of helical tomotherapy-based TBI in adults and children.

Methods

This retrospective single-centre study included all consecutive patients treated with helical tomotherapy-based TBI at the Institut de Cancérologie de Lorraine between March 2020 and July 2024. TBI consisted of 12 Gy in 6 fractions (n = 21) or 8 Gy in 4 fractions (n = 27), delivered twice daily, or 2 Gy in a single fraction (n = 20). Toxicities were graded using CTCAE v5.0. Dosimetric parameters were analysed by dose regimen and age group, and relapse incidence, progression-free survival (PFS) and overall survival (OS) were estimated.

Results

Sixty-eight patients were included (48 adults, 20 children); median follow-up was 18.5 months. Median PTV D90/D10 was 0.94 in both groups. In children treated with 12 Gy, median mean lung and kidney doses decreased from 8.5 and 12.1 Gy to 7.9 and 9.9 Gy after the introduction of paediatric-specific constraints in October 2022. The most frequent acute toxicities were fatigue (97%), anorexia (88%) and mucositis (78%), mostly grade 1–2. Grade ≥ 3 mucositis occurred in 10.4% of adults and 50% of children, and grade ≥ 3 anorexia in 58% of children receiving 12 Gy; no grade ≥ 3 radiation pneumonitis was observed. Late toxicities included chronic renal impairment (n = 2) and chronic pulmonary toxicity (n = 1) in adults, and hypothyroidism, growth impairment, chronic pericarditis, optic neuropathy and primary ovarian insufficiency (one each) in children. The 2-year cumulative incidence of relapse was 16.7% in adults and 20.0% in children; 2-year OS was 62.2% and 95.0%, and 2-year PFS 59.6% and 80.0%, respectively.

Conclusions

Helical tomotherapy-based TBI provided homogeneous target coverage and lung sparing with acceptable acute toxicity in adults and children, and paediatric-specific constraints improved kidney and lung sparing. Longer follow-up is required to assess late effects.

Background

Total body irradiation (TBI) is a key component of conditioning regimens before hematopoietic stem cell transplantation in patients with hematological malignancies, especially lymphoid. It ensures immunosuppression to prevent rejection and eliminates residual cancer cells (1–3). TBI has demonstrated favourable outcomes compared with chemotherapy-based regimens in pediatric patients with Acute Lymphoblastic Leukemia (ALL), with meta-analyses reporting improved event-free survival (RR 1.34) and reduced relapse risk (RR 0.69) for TBI-based conditioning (4, 5). Achieving a homogeneous and sufficient radiation dose is essential but challenging with conventional TBI (6, 7). Furthermore, many organs at risk (OARs) receive high radiation doses even with protective measures (1, 8, 9). Acute toxicities are frequent as parotitis, nausea, vomiting, mucositis, diarrhea, esophagitis, acute renal failure, radiation pneumonitis (10–12). Chronic toxicities are more concerning, as for example radiation pneumonitis (41), nephrotoxicity, secondary malignancies and endocrine disorders like thyroid diseases, infertility and growth retardation (13–19). Minimizing these late effects is vital, particularly in pediatric patients with long life expectancy (20).

Helical radiotherapy provides a more homogeneous dose distribution and a better sparing of OARs compared to 2D irradiation, reducing acute and chronic side effects (21–23). However, its use remains limited in many centers, mainly because of the complexity of planning and delivery, the machine and staff time required, and the small number of TBI patients treated in most centres, although VMAT now offers a widely available option for rotational TBI. With helical tomotherapy, the maximum treatment length of 135 cm means that taller patients require two treatment plans (head-first and feet-first) matched at a single junction region, which may introduce dose uncertainties at this junction (24). Another concern was the potential sensitivity of organs such as lungs, kidneys, and liver to higher dose rates which may contribute to toxicity. Preclinical TBI studies have shown that fractionation effectively mitigates these toxic effects (25). Clinical series have likewise shown that fractionation reduces TBI-related toxicity (10, 11), and fractionation largely offsets the influence of dose rate on normal-tissue toxicity (1, 25). Fractionation also enhances leukemic cell eradication, promotes successful allogeneic engraftment and significantly lowers the incidence of Grade II-IV Graft Versus Host Disease (GVHD) while maintaining equivalent disease-specific and survival outcomes (26, 27). As a consequence, the use of helical tomotherapy for TBI is increasing worldwide, and several dosimetric and clinical series have now been reported (22,38–40), although long-term clinical outcome data, particularly in cohorts combining adults and children, remain limited (28).

This study aimed to assess the acute and chronic toxicity of TBI delivered via helical tomotherapy at the Institut de Cancérologie de Lorraine (ICL), focusing on both adult and pediatric patients, while ensuring that no decrease in efficacy was observed with the use of helical tomotherapy in terms of oncologic effectiveness compared to published results of conventional techniques.

Methods

Design:

This retrospective single-center cohort study was conducted at the Institut de Cancérologie de Lorraine.

Population and inclusion criteria treatment:

We included all adults and pediatric patients who received TBI using helical tomotherapy in our center from March 2020 to July 2024. No patient treated during this period was excluded from the analysis. This period extends from the start of helical tomotherapy-based TBI in our department to the data cut-off. These patients were treated for all types of malignant and benign hematologic diseases.

Treatment

Imaging acquisition

Two planning CT scans were performed using a Siemens Go.Open Pro scanner with 5 mm slices and 120 kV, acquired by two radiotherapy technicians.

One scan was performed head-first supine (HFS) up to mid-thigh, and the other feet-first supine (FFS), due to the machine's length limitation, which restricts treatment to a maximum length of 135 cm per single helix. Patients measuring under 135 cm were treated using a single plan. All patients were positioned supine with a five-point thermoplastic mask to ensure reproducible immobilization. The arms were kept alongside close to the body using a pelvic strap. Two customized vacuum cushions were used for stabilization—one for the back and one for the legs. Additionally, knees were supported on a kneefix or foam cushion, and feet were secured in a vacuum mattress. Eight tattoo markers were applied during simulation to facilitate daily repositioning.

Volume delineation

Organs at risk (OARs) delineated included lungs, kidneys, lenses, heart, and liver. The clinical target volume (CTV) encompassed the entire body. Treatment planning was inspired from Sarradin et al. who conducted TBI using helical tomotherapy (29). Specific optimization volumes were defined to create a dose gradient at the junction between the two scans (29).

The planning target volume (PTV) was segmented into ten adjacent, non-overlapping sub-volumes along the cranio-caudal axis. No CTV-to-PTV expansion was applied: the PTV was defined as the external body contour contracted by 3 mm. Organs at risk were not subtracted from the PTV; instead, dedicated optimisation structures were used (lungs contracted by 1 cm and a 1-cm rib ring for 12-Gy prescriptions, a posterior patch to cover the vertebrae, and, in children, kidneys contracted by 3–5 mm), so that reported PTV statistics include these intentionally spared regions. On the head-first CT, the PTV

comprised PTV A (head), B (neck to thorax), C (thorax to 3 cm below the lungs), D1 (down to the pubis), four junction slabs D2–D5 (each four 5-mm slices, i.e., 2 cm) and D6 (remaining thigh); the feet-first CT comprised D1–D6 and PTV E (below D6). A radiopaque marker placed at mid-thigh at simulation had to lie within slab D3 on both CTs (D5 when the vertex-to-marker distance exceeded 104 cm). Complementary dose objectives were assigned to the two plans in slabs D2–D5 (for 12 Gy: 10.74, 7.56, 4.44 and 1.92 Gy on the head-first plan and 1.26, 4.44, 7.56 and 10.08 Gy on the feet-first plan), creating an 8-cm feathered gradient that sums to the prescribed dose and reduces sensitivity to longitudinal set-up errors (29). On the feet-first plan, an 8-mm virtual bolus (mass density 0.4) was used to secure superficial coverage of the lower limbs (Fig. 2).

Dose prescription and delivery:

The prescribed doses were as follows (2 Gy per fraction, 6 MV, minimum 6-h interval between fractions; field width 5.05 cm, pitch 0.38, reduced to 0.287 in case of marked thread effect), delivered twice daily on a TomoTherapy HD system (Accuray Incorporated, Madison, WI, USA) at a nominal dose rate of 850 cGy/min.: 12 Gy in 6 fractions for patients < 18 year-old without comorbidities; 8 Gy in 4 fractions for patients > 18 year-old and/or those with significant comorbidities; 2 Gy in 1 fraction for non-myeloablative conditioning. In patients with meningeal involvement, a meningeal boost was delivered before TBI (2 Gy per fraction, once daily); the CTV encompassed the brain (including the posterior third of the globes, the cribriform plate and the temporal fossae) and the spinal canal down to C2, with a 3-mm PTV margin; in one patient, the spinal canal was included down to the conus medullaris.

For OARs, lung protection was optimized to maintain a mean dose between 8 and 9 Gy over the lung minus 1 cm volume (lungs contracted by 1 cm from the pleural surface), ensuring adequate dosing of the ribs and vertebrae containing bone marrow. Lung-sparing optimisation was only used for 12-Gy prescriptions; in selected patients, the liver or kidneys could be spared to 8–9 Gy according to comorbidities. From October 2022 onwards, paediatric-specific objectives were added to the departmental protocol: mean whole-lung dose < 8 Gy and mean kidney dose < 10 Gy (using a kidney optimisation volume contracted by 3–5 mm); children treated before this date were planned with the adult objectives, without kidney sparing.

Treatment planning was performed on Accuray Precision TPS until February 2022 then on Raystation (Raysearch Lab., Stockholm, S). Both platforms were cross-validated on phantom measurements prior to clinical use; no clinically significant dosimetric discrepancies were identified between them. The optimization objective was 95% of the PTV must receive at least 95% of the prescribed dose on each of the head-first and feet-first plans, while regions receiving < 95% or > 110% of the prescribed dose were minimised on the summed plan. Dividing the PTV into ten parts allowed us to progressively degrade the delivered dose across the two treatment plans. The combined dose provided the intended coverage while minimizing the impact of any positioning errors. This approach helped avoid underdosed or overdosed regions, as previously described by Sarradin et al. (29).

A megavoltage CT (MVCT) scan was performed to verify patient positioning prior to each treatment delivery and for both treatment position (HFS and FFS).

Chemotherapy and GVHD prophylaxis:

Treatment protocols were determined by the Hematologist according to international guidelines or research protocols (ALL SCTped FORUM for children and GRAALL/GRAAPH 2003–2004 for adults) or other guideline depending on the pathology (5, 30). Chemotherapy regimens were adapted to patient's characteristics. Conditioning regimens are detailed in Table 2: all adults received fludarabine-based chemotherapy, whereas etoposide was used in 15 of the 20 children (75%). For GVHD prophylaxis, geno-identical transplants required cyclosporine alone for children and associated to MTX for adults, pheno-identical transplants required cyclosporine, MTX and ATG and haploidentical transplants received post-transplantation cyclophosphamide, cyclosporine and cellcept.

Table 2
Disease, transplant and treatment characteristics

Characteristic	Adults (N = 48) n (%)	Children (N = 20) n (%)
Disease		
Acute lymphoblastic leukaemia	22 (46)	20 (100)
BCR-ABL positive	6 (12)	1 (5)
Acute myeloid leukaemia	9 (19)	0 (0)
Chronic myeloid leukaemia	2 (4)	0 (0)
Lymphoma	11 (23)	0 (0)
Idiopathic myelofibrosis	1 (2)	0 (0)
Sézary syndrome	1 (2)	0 (0)
Idiopathic aplastic anaemia	2 (4)	0 (0)
Complex karyotype (any disease)	3 (6)	1 (5)
Indication		
Malignant disease, de novo	28 (58)	8 (40)
Malignant disease, relapse	18 (38)	12 (60)
Benign disease	2 (4)	0 (0)
Complete remission before transplantation	47 (98)	18 (90)
Conditioning chemotherapy		
Fludarabine	30 (62)	1 (5)
Fludarabine + cyclophosphamide	13 (27)	4 (20)
Fludarabine + treosulfan	5 (10)	0 (0)
Etoposide	0 (0)	12 (60)
ATG + etoposide	0 (0)	3 (15)
Post-transplant cyclophosphamide	31 (65)	6 (30)
Graft		

PBSC: peripheral blood stem cells; ATG: anti-thymocyte globulin; MMF: mycophenolate mofetil; MTX: methotrexate. BCR-ABL positivity is reported for ALL only. Meningeal boost: 16 Gy in two patients (extended to the conus medullaris in one) and 10 Gy in one, all before 8-Gy TBI.

Characteristic	Adults (N = 48) n (%)	Children (N = 20) n (%)
Disease		
Related (1st degree), PBSC	32 (67)	5 (25)
Related (1st degree), bone marrow	5 (10)	8 (40)
Unrelated, PBSC	10 (21)	4 (20)
Unrelated, bone marrow	0 (0)	2 (10)
Unrelated, cord blood	0 (0)	1 (5)
No transplant (death before graft)	1 (2)	0 (0)
HLA disparity		
None	36 (75)	16 (80)
1 mismatch	10 (21)	4 (20)
≥ 2 mismatches	1 (2)	0 (0)
GVHD prophylaxis		
MMF + ciclosporin	28 (58)	10 (50)
MTX + ciclosporin	17 (35)	6 (30)
Ciclosporin alone	1 (2)	4 (20)
MTX + tacrolimus	1 (2)	0 (0)
TBI regimen		
12 Gy in 6 fractions	2 (4)	19 (95)
8 Gy in 4 fractions	26 (54)	1 (5)
2 Gy in 1 fraction	20 (42)	0 (0)
Boost		
Meningeal, before TBI (10–16 Gy)	3 (6)	0 (0)
Testicular, during TBI (total testicular dose 18 Gy)	0 (0)	1 (5)

PBSC: peripheral blood stem cells; ATG: anti-thymocyte globulin; MMF: mycophenolate mofetil; MTX: methotrexate. BCR-ABL positivity is reported for ALL only. Meningeal boost: 16 Gy in two patients (extended to the conus medullaris in one) and 10 Gy in one, all before 8-Gy TBI.

Follow-up

Patient follow-up, initially weekly or biweekly then every 2–4 weeks, focused on immune reconstitution and early detection of rejection, infection, toxicity, relapse, or GVHD. Monitoring included clinical exams, blood tests, imaging, viral Polymerase Chain Reaction (PCRs) (CMV, HHV6, toxoplasmosis, adenovirus in children), endocrine assessments, fusion transcript quantification when relevant, bone marrow aspiration, functional tests, and vaccination updates according to immune recovery.

Data collection

Data were collected from medical records, including demographics, treatments (induction, maintenance, GVHD prophylaxis), and toxicities assessed by hematologists using CTCAE v5.0. Dosimetric parameters were extracted from the treatment planning software: for PTV (Dmax, Dmin, Dmean, D2–98%), lungs and kidneys (V8–12, Dmean, Dmax, D5%, D95%), and for liver, heart, and lens (Dmean, Dmax). Dmax corresponds to the maximum point dose reported by the treatment planning system; in accordance with ICRU Report 83, D2% and D98% were used as near-maximum and near-minimum doses, respectively (42). Homogeneity indices were calculated for PTV and selected OARs using standard formulas (e.g., D5/D95, D90/D10, (D2–D98)/D50). The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Study endpoints

The primary objective was to assess acute and chronic toxicities according to CTCAE v5.0 for helical tomotherapy-based TBI. Acute toxicities were defined as those occurring within 90 days of the start of TBI; late toxicities were defined as those occurring beyond 90 days, in accordance with ESTRO ACROP/SIOPE recommendations (20). The secondary objectives were to describe oncological outcomes (OS, PFS, cumulative incidence of relapse) by evaluating dose distribution homogeneity, overall survival (OS), defined as the time from the first day of TBI to death from any cause, and progression-free survival (PFS), defined as the time from the start of TBI to documented disease progression, relapse, or death from any cause. We also analyzed cumulative incidence of relapse.

Statistics

Qualitative variables were described using frequencies and percentages, while quantitative variables were described using medians and interquartile ranges (IQR). Survival was estimated using the Kaplan–Meier method, with censoring at the date of last follow-up. OS was defined as the time from the first day of TBI to death, and PFS as the time from the first day to disease progression, relapse, or death. Overall survival (OS) and progression-free survival (PFS) were estimated using the Kaplan–Meier method and reported with 95% confidence intervals. Cumulative incidence of relapse was estimated using competing-risk methodology, considering death without relapse as a competing event. Descriptive analyses were conducted for the whole cohort and stratified by age group (adults vs. pediatric patients). Survival (OS and PFS) and cumulative incidence curves were generated accordingly. Statistical analyses were performed using R software version 4.3.3 (2024-02-29, ucrt).

Ethics:

In accordance with the French law, this retrospective study was conducted in compliance with the reference methodology MR-004 of the Commission Nationale de l'Informatique et des Libertés (CNIL), and ethics committee approval was not required. Patients were informed of the possible reuse of their data for research purposes and did not object. The study was registered under number 25484912.

Results

Population characteristics:

Inclusion was conducted from March 2020 to July 2024. Patients' characteristics are described in Table 1. Median Follow up was 18.5 months with a minimum of 6 days (early death) and a maximum of 4.5 years. Three adult patients had a history of prior radiotherapy. One patient had undergone a TBI of 8 Gy in 4 fractions 20 months earlier using 3D technique for a previous stem cell transplantation and received 2 Gy in the present series. The second patient had received 20 Gy/5 fraction for inguinal lymphoma 10 months earlier (current TBI: 2 Gy). The last one had undergone dual irradiation for nasal and oropharyngeal lymphoma, delivering respectively 40 Gy in 20 fractions 10 years earlier and 50 Gy in 25 fractions 3 years before present TBI (current TBI: 8 Gy). Additionally, three adults received a meningeal boost before 8-Gy TBI: 16 Gy in two patients (total dose 24 Gy; the boost volume extended to the conus medullaris in one) and 10 Gy in one (total dose 18 Gy). None of the pediatric patients had prior radiation exposure; however, one child received a testicular boost during TBI, bringing the total testicular dose to 18 Gy.

Table 1
Patient characteristics

Characteristics	Adults (N = 48)	Children (N = 20)
	n (%)	n (%)
Age	56 (43–65)	13 (11–16)
Median (Q1 - Q3)		
Age at diagnosis	53 (40–63)	10 (6–12)
Median (Q1 - Q3)		
Puberty		14 (70)
Prepuberty		
Sex	31 (65)	15 (75)
Male		
WHO performance status	34 (71)	18 (90)
0	13 (27)	2 (10)
1	1 (2.1)	0 (0)
2		
Body Mass Index (BMI)	24.8 (22.1–28.5)	17.6 (16.2–20.5)
M*edian (Q1 - Q3)*		
Alcohol consumption	42 (88)	20 (100)
No	2 (4.2)	0 (0)
Yes	4 (8.3)	0 (0)
Former		
Smoking	35 (73)	20 (100)
No	2 (4.2)	0 (0)
Yes	11 (23)	0 (0)
Former		

Treatment characteristics:

Tumor and treatment details are presented in Table 2. All patients were treated in two plans of treatment except one child who had undergone only one scan and one plan. Table 3 details the dosimetric data for the PTV and OARs. Because the PTV was not cropped from the lungs and, in children, the kidneys, PTV near-minimum doses (D98%) reflect the intentional under-dosage of these organs. In children receiving

12 Gy, median mean lung and kidney doses were 8.5 Gy and 12.1 Gy before October 2022 (n = 11), and 7.9 Gy and 9.9 Gy thereafter (n = 8); after this date, the mean lung dose was ≤ 8 Gy in 5 of 8 children and the mean kidney dose ≤ 10 Gy in 7 of 8. Following the conditioning regimen, transplantation was performed. All transplanted patients received an allogeneic graft; one adult died of acute respiratory distress syndrome after TBI and before transplantation. Donors were first-degree relatives in 37 of 47 adults (79%; peripheral blood stem cells in 32, bone marrow in 5) and 13 of 20 children (65%; bone marrow in 8, peripheral blood stem cells in 5); the other grafts came from unrelated donors (peripheral blood stem cells in 10 adults and 4 children, bone marrow in 2 children, cord blood in 1 child).

Table 3
Dosimetric data according to TBI dose and age group

Parameter	Adults 2 Gy n = 20	Adults 8 Gy n = 26	Adults 12 Gy† n = 2	Children 8 Gy† n = 1	Children 12 Gy, before Oct 2022 n = 11	Children 12 Gy, from Oct 2022 n = 8
PTV						
Dmean (Gy)	2.02 (2.02–2.03)	8.10 (8.09–8.11)	12.04 (12.03–12.04)	8.09	11.98 (11.94–12.01)	11.90 (11.89–11.92)
D2% (Gy)	2.13 (2.12–2.14)	8.56 (8.49–8.63)	13.07 (12.83–13.32)	8.60	12.73 (12.64–12.78)	12.75 (12.72–12.77)
D50% (Gy)	2.02 (2.02–2.02)	8.10 (8.08–8.11)	12.17 (12.15–12.19)	8.11	12.10 (12.09–12.11)	12.09 (12.08–12.11)
D95% (Gy)	1.96 (1.95–1.96)	7.82 (7.79–7.87)	11.51 (11.43–11.59)	7.69	11.40 (11.17–11.56)	10.46 (10.27–10.67)
D98% (Gy)	1.94 (1.92–1.95)	7.74 (7.47–7.80)	8.24 (7.91–8.57)	7.17	8.52 (7.79–9.42)	7.29 (7.21–7.45)
D90/D10	0.94 (0.94–0.95)	0.94 (0.94–0.95)	0.95 (0.94–0.96)	0.94	0.94 (0.94–0.95)	0.94 (0.93–0.95)
(D2–D98)/D50	0.10 (0.09–0.11)	0.11 (0.10–0.17)	0.40 (0.35–0.44)	0.18	0.34 (0.28–0.40)	0.45 (0.44–0.46)
Dmax/Dprescription	1.18 (1.15–1.18)	1.18 (1.16–1.20)	1.18 (1.16–1.20)	1.21	1.18 (1.15–1.20)	1.17 (1.17–1.18)
Lungs						
Dmean (Gy)	2.02 (2.01–2.02)	8.07 (8.06–8.09)	8.29 (8.21–8.38)	8.12	8.52 (8.44–8.81)	7.93 (7.82–8.05)

Values are median (interquartile range); † groups with fewer than five patients: median (minimum–maximum), or individual value when n = 1. The PTV was not cropped from the lungs and, in children, the kidneys; PTV near-minimum doses (D98%) and homogeneity indices therefore include these intentionally spared organs. Paediatric-specific objectives (mean lung dose < 8 Gy, mean kidney dose < 10 Gy) were introduced in October 2022.

In two patients of the adult 8-Gy group, PTV Dmax and D2% include the dose of the meningeal boost planned together with TBI.

Parameter	Adults 2 Gy n = 20	Adults 8 Gy n = 26	Adults 12 Gy† n = 2	Children 8 Gy† n = 1	Children 12 Gy, before Oct 2022 n = 11	Children 12 Gy, from Oct 2022 n = 8
PTV						
V8 (%)	0 (0–0)	76 (70–85)	48 (47–50)	87	54 (51–59)	44 (42–46)
V10 (%)	0 (0–0)	0 (0–0)	18 (17–20)	0	24 (22–27)	17 (17–20)
V12 (%)	0 (0–0)	0 (0–0)	3 (3–4)	0	5 (4–5)	3 (3–4)
D5%/D95%	1.04 (1.03–1.05)	1.04 (1.03–1.04)	1.88 (1.87–1.88)	1.04	1.89 (1.86–1.92)	2.17 (2.08–2.25)
Kidneys						
Dmean (Gy)	2.01 (2.01–2.02)	8.06 (8.06–8.08)	12.07 (12.05–12.08)	8.10	12.06 (12.05–12.08)	9.88 (9.81–9.96)
V8 (%)	0 (0–0)	63 (59–67)	100 (100–100)	73	100 (100–100)	100 (97–100)
V10 (%)	0 (0–0)	0 (0–0)	100 (100–100)	0	100 (100–100)	46 (28–49)
V12 (%)	0 (0–0)	0 (0–0)	65 (65–65)	0	58 (55–61)	0 (0–0)
Liver						
Dmean (Gy)	2.01 (2.01–2.02)	8.06 (8.05–8.07)	12.09 (12.07–12.11)	8.10	12.07 (12.06–12.08)	12.03 (12.02–12.04)
Heart						

Values are median (interquartile range); † groups with fewer than five patients: median (minimum–maximum), or individual value when n = 1. The PTV was not cropped from the lungs and, in children, the kidneys; PTV near-minimum doses (D98%) and homogeneity indices therefore include these intentionally spared organs. Paediatric-specific objectives (mean lung dose < 8 Gy, mean kidney dose < 10 Gy) were introduced in October 2022.

In two patients of the adult 8-Gy group, PTV Dmax and D2% include the dose of the meningeal boost planned together with TBI.

Parameter	Adults 2 Gy n = 20	Adults 8 Gy n = 26	Adults 12 Gy† n = 2	Children 8 Gy† n = 1	Children 12 Gy, before Oct 2022 n = 11	Children 12 Gy, from Oct 2022 n = 8
PTV						
Dmean (Gy)	2.01 (2.01–2.02)	8.06 (8.05–8.07)	11.94 (11.93–11.96)	8.08	11.95 (11.89–12.02)	11.76 (11.71–11.81)
Lenses						
Dmean (Gy)	2.04 (2.03–2.06)	8.12 (8.03–8.22)	12.21 (12.20–12.22)	8.25	12.12 (12.01–12.28)	12.16 (11.89–12.29)
Dmax (Gy)	2.11 (2.09–2.14)	8.40 (8.26–8.57)	12.38 (12.37–12.40)	8.40	12.58 (12.40–12.72)	12.59 (12.40–12.70)
Delivery						
Total treatment time (min)	32.2 (31.4–34.6)	33.4 (31.8–34.7)	36.2 (32.6–39.7)	35.9	23.1 (21.5–29.2)	26.4 (24.7–27.5)
Values are median (interquartile range); † groups with fewer than five patients: median (minimum–maximum), or individual value when n = 1. The PTV was not cropped from the lungs and, in children, the kidneys; PTV near-minimum doses (D98%) and homogeneity indices therefore include these intentionally spared organs. Paediatric-specific objectives (mean lung dose < 8 Gy, mean kidney dose < 10 Gy) were introduced in October 2022.						
In two patients of the adult 8-Gy group, PTV Dmax and D2% include the dose of the meningeal boost planned together with TBI.						

Acute toxicities:

Toxicity data are summarized in Table 4. Grade ≥ 3 acute GVHD was infrequent: cutaneous in two adults (both in the 2-Gy group) and one child, and digestive in one adult (2-Gy group) and one child. Chronic GVHD was recorded in four adults (cutaneous in all, with digestive involvement in one; 2-Gy group, n = 2; 8 Gy, n = 1; 12 Gy, n = 1) and in no child. Additionally, 12% of adults experienced grade ≥ 3 acute pneumonia due to pulmonary infection (6/48: three in the 2-Gy and three in the 8-Gy group). No grade 3 or 4 radiation-induced pneumonitis was reported. Hepatic veno-occlusive disease was recorded in three adults (grade 2) and four children (grade 1–3). All other toxicities, including pulmonary complications, were grade 2 or lower in 95% of cases. Among the three patients with a history of prior irradiation, toxicity did not appear increased. Most adverse events were grade 0 or 1. Only the patient who had undergone two previous courses of irradiation (for nasal lymphoma and oropharyngeal) developed grade 3 anorexia. Of note, grade ≥ 3 anorexia was observed in 58% of children receiving 12 Gy (11 of 19

patients), representing the most severe acute toxicity in the paediatric subgroup and warranting dedicated nutritional and anti-emetic support protocols in myeloablative paediatric TBI.

Table 4
Acute toxicities and late events according to TBI dose and age group

Toxicity	Adults 2 Gy N = 20 n (%)	Adults 8 Gy N = 26 n (%)	Adults 12 Gy N = 2 n (%)	Children 8 Gy N = 1 n (%)	Children 12 Gy N = 19 n (%)
Acute toxicities (≤ 90 days)					
Acute cutaneous GVHD*					
Grade 0	13 (65)	19 (73)	1 (50)	1 (100)	13 (68)
Grade 1–2	5 (25)	7 (27)	1 (50)	0 (0)	5 (26)
Grade ≥ 3	2 (10)	0 (0)	0 (0)	0 (0)	1 (5)
Acute digestive GVHD*					
Grade 0	17 (85)	26 (100)	2 (100)	1 (100)	15 (79)
Grade 1–2	2 (10)	0 (0)	0 (0)	0 (0)	3 (16)
Grade ≥ 3	1 (5)	0 (0)	0 (0)	0 (0)	1 (5)
Fatigue					
Grade 0	2 (10)	0 (0)	0 (0)	0 (0)	0 (0)
Grade 1–2	16 (80)	24 (92)	2 (100)	1 (100)	19 (100)
Grade ≥ 3	2 (10)	2 (8)	0 (0)	0 (0)	0 (0)
Nausea					
Grade 0	8 (40)	6 (23)	1 (50)	0 (0)	3 (16)
Grade 1–2	12 (60)	18 (69)	1 (50)	1 (100)	14 (74)
Grade ≥ 3	0 (0)	2 (8)	0 (0)	0 (0)	2 (11)
Vomiting					
Grade 0	15 (75)	16 (62)	1 (50)	0 (0)	3 (16)
Grade 1–2	5 (25)	9 (35)	1 (50)	1 (100)	15 (79)
Grade ≥ 3	0 (0)	1 (4)	0 (0)	0 (0)	1 (5)
Anorexia					

Toxicities graded with CTCAE v5.0; * acute GVHD graded according to Glucksberg. † Events recorded in the free-text field of the database (to be confirmed from the medical records). Median follow-up: 18.5 months.

Toxicity	Adults 2 Gy N = 20 n (%)	Adults 8 Gy N = 26 n (%)	Adults 12 Gy N = 2 n (%)	Children 8 Gy N = 1 n (%)	Children 12 Gy N = 19 n (%)
Acute toxicities (≤ 90 days)					
Acute cutaneous GVHD*					
Grade 0	6 (30)	2 (8)	0 (0)	0 (0)	0 (0)
Grade 1–2	12 (60)	20 (77)	2 (100)	1 (100)	8 (42)
Grade ≥ 3	2 (10)	4 (15)	0 (0)	0 (0)	11 (58)
Mucositis					
Grade 0	9 (45)	5 (19)	1 (50)	0 (0)	0 (0)
Grade 1–2	11 (55)	16 (62)	1 (50)	1 (100)	9 (47)
Grade ≥ 3	0 (0)	5 (19)	0 (0)	0 (0)	10 (53)
Xerostomia					
Grade 0	15 (75)	17 (65)	2 (100)	1 (100)	11 (58)
Grade 1–2	5 (25)	8 (31)	0 (0)	0 (0)	7 (37)
Grade ≥ 3	0 (0)	0 (0)	0 (0)	0 (0)	1 (5)
Diarrhoea					
Grade 0	7 (35)	8 (31)	1 (50)	0 (0)	0 (0)
Grade 1–2	13 (65)	17 (65)	1 (50)	1 (100)	17 (89)
Grade ≥ 3	0 (0)	1 (4)	0 (0)	0 (0)	2 (11)
Pneumonia (< 6 months)					
Grade 0	13 (65)	17 (65)	2 (100)	0 (0)	18 (95)
Grade 1–2	4 (20)	6 (23)	0 (0)	1 (100)	1 (5)
Grade ≥ 3	3 (15)	3 (12)	0 (0)	0 (0)	0 (0)
Skin erythema					
Grade 0	15 (75)	21 (81)	2 (100)	1 (100)	12 (63)

Toxicities graded with CTCAE v5.0; * acute GVHD graded according to Glucksberg. † Events recorded in the free-text field of the database (to be confirmed from the medical records). Median follow-up: 18.5 months.

Toxicity	Adults 2 Gy N = 20 n (%)	Adults 8 Gy N = 26 n (%)	Adults 12 Gy N = 2 n (%)	Children 8 Gy N = 1 n (%)	Children 12 Gy N = 19 n (%)
Acute toxicities (≤ 90 days)					
Acute cutaneous GVHD*					
Grade 1–2	5 (25)	5 (19)	0 (0)	0 (0)	7 (37)
Grade ≥ 3	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Acute kidney injury					
Grade 0	14 (70)	20 (77)	2 (100)	1 (100)	18 (95)
Grade 1–2	6 (30)	6 (23)	0 (0)	0 (0)	1 (5)
Grade ≥ 3	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Headache					
Grade 0	19 (95)	22 (85)	2 (100)	0 (0)	12 (63)
Grade 1–2	1 (5)	3 (12)	0 (0)	1 (100)	7 (37)
Grade ≥ 3	0 (0)	1 (4)	0 (0)	0 (0)	0 (0)
Conjunctivitis					
Grade 0	20 (100)	25 (96)	2 (100)	1 (100)	19 (100)
Grade 1–2	0 (0)	1 (4)	0 (0)	0 (0)	0 (0)
Grade ≥ 3	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Hepatic veno-occlusive disease (any grade)†	2 (10)	1 (4)	0 (0)	0 (0)	4 (21)
Late events (> 90 days)					
Chronic GVHD†	2 (10)	1 (4)	1 (50)	0 (0)	0 (0)
Chronic pulmonary toxicity	0 (0)	1 (4)	0 (0)	0 (0)	0 (0)
Chronic kidney disease	1 (5)	1 (4)	0 (0)	0 (0)	0 (0)
Hypothyroidism	0 (0)	0 (0)	0 (0)	0 (0)	1 (5)

Toxicities graded with CTCAE v5.0; * acute GVHD graded according to Glucksberg. † Events recorded in the free-text field of the database (to be confirmed from the medical records). Median follow-up: 18.5 months.

Toxicity	Adults 2 Gy	Adults 8 Gy	Adults 12 Gy	Children 8 Gy	Children 12 Gy
	N = 20	N = 26	N = 2	N = 1	N = 19
	n (%)	n (%)	n (%)	n (%)	n (%)
Acute toxicities (≤ 90 days)					
Acute cutaneous GVHD*					
Growth impairment	0 (0)	0 (0)	0 (0)	0 (0)	1 (5)
Chronic pericarditis†	0 (0)	0 (0)	0 (0)	0 (0)	1 (5)
Optic neuropathy†	0 (0)	0 (0)	0 (0)	0 (0)	1 (5)
Primary ovarian insufficiency†	0 (0)	0 (0)	0 (0)	0 (0)	1 (5)
Keratitis†	1 (5)	0 (0)	0 (0)	0 (0)	0 (0)
Decreased visual acuity†	0 (0)	2 (8)	0 (0)	0 (0)	0 (0)

Toxicities graded with CTCAE v5.0; * acute GVHD graded according to Glucksberg. † Events recorded in the free-text field of the database (to be confirmed from the medical records). Median follow-up: 18.5 months.

Chronic toxicities:

Regarding chronic toxicities, one pediatric patient developed hypothyroidism one year after irradiation, and another experienced growth impairment 14 months post- treatment. Among adults, two developed chronic kidney failure and one developed chronic lung disease, all occurring between 6 and 12 months after irradiation. Other late events included chronic pericarditis, optic neuropathy considered radiation-induced and primary ovarian insufficiency (one child each, all treated with 12 Gy), keratitis in one adult (2 Gy), and decreased visual acuity in two of the three adults who received a meningeal boost. No radiation-induced malignancy was reported to date (Table 4).

Relapse and Survivals:

At the end of follow-up, the median time from conditioning to last known status was 14 months (IQR 8–33) in adults and 28 months (IQR 16–46) in children. In the adult group, 31 patients (65%) were alive while 17 had died. Causes of death were relapse (n = 6), septic shock (n = 5), GVHD (n = 5) and respiratory failure (n = 1). In the pediatric group, only one patient (5%) died, due to early medullary relapse, while 95% remained alive at the end of follow-up.

Among patients transplanted for a hematological malignancy, relapses were exclusively medullary in children (4 cases), while in adults they were mostly extramedullary (7 of 8 cases). Median time to relapse was 4.9 months (IQR 2.7–6.3) in adults and 3.7 months (IQR 3.3–4.8) in children. The cumulative

incidence of relapse at 2 years was 16.7% for adults and 20% for children. Progression-free survival at 2 years was estimated at 59.6% (95% CI 47.0–75.6) in adults and 80% (95% CI 64.3–99.6) in children. Overall survival at 2 years was approximately 62.2% (95% CI 49.1–78.8) in adults and 95% (95% CI 85.9–100) in children. Importantly, no patient was lost to follow-up (Fig. 1). Adult relapses occurred in patients treated for ALL (n = 4), lymphoma (n = 2), AML (n = 1) and Sézary syndrome (n = 1), after 8-Gy (n = 6) or 2-Gy (n = 2) TBI. The predominance of extramedullary relapses in adults may partly reflect the low TBI doses (2 or 8 Gy) received by all of them, which are not expected to provide durable control of extramedullary disease.

Discussion

Our results support the feasibility and safety of helical tomotherapy for TBI delivery in both adults and pediatric patients. Homogeneity indices calculated for the PTV, lungs, kidneys and liver confirmed the quality of the planning, and lung dose objectives were achieved in most adults. In children, median mean lung (8.35 Gy) and kidney (12.0 Gy) doses exceeded the paediatric objectives over the whole period, because these objectives were only introduced in October 2022; thereafter, median mean lung and kidney doses fell to 7.9 Gy and 9.9 Gy, respectively. Given the importance of long-term preservation of organ function in children, further kidney and lens sparing remains desirable. These findings can be compared with those of Loginova et al., who treated 157 children with helical tomotherapy and 52 with VMAT using a PTV defined as the body contracted by 3 mm and excluding the lungs, kidneys and lenses, with objectives of lung V8 < 40% and mean kidney dose < 8 Gy. Their tomotherapy plans achieved a mean PTV D98% of 11.1 Gy, a homogeneity index (D2–D98)/D50 of 0.14, mean lung doses of 7.8–7.9 Gy (V8 36–38%), mean kidney doses of 7.6 Gy and mean lens doses of about 6 Gy; grade 2–3 nausea/vomiting occurred in 34% of patients, and no pneumonitis or late renal or pulmonary toxicity was observed at a median follow-up of 2.3 years. In our 12-Gy paediatric cohort, PTV statistics included the intentionally spared lungs and kidneys, which explains the lower D98% (median 7.8 Gy) and higher homogeneity index (0.42), whereas D95% remained 11.1 Gy. After October 2022, mean lung (7.9 Gy) and kidney (9.9 Gy) doses approached but did not reach their values, and the lenses were not spared (median mean dose 12.1 Gy). Grade ≥ 2 nausea/vomiting occurred in 30% of our children, comparable to their 34%, although toxicity scales differed (RTOG/EORTC versus CTCAE v5.0) (22).

In children, TBI with helical tomotherapy was relatively well tolerated, with only isolated cases of grade 3 vomiting or diarrhea and 50% grade ≥ 3 mucositis, in line with prior reports of lower acute toxicity compared with VMAT or 2D techniques (22, 26). Despite median mean lung and kidney doses of 8.35 Gy and 12.0 Gy, respectively, no pediatric patient developed kidney toxicity or radiation pneumonitis, unlike cases reported with VMAT or 2D (26, 31, 32). Late toxicities observed to date were rare, with one case each of growth delay, hypothyroidism, chronic pericarditis, optic neuropathy and primary ovarian insufficiency, fewer than the rates reported in conventional TBI series (33). Growth impairment is, however, a multifactorial outcome in this population, potentially related to conditioning chemotherapy, GVHD, endocrine dysfunction, and radiation in combination; attributing it solely to TBI requires caution.These findings support the robustness and reproducibility of helical tomotherapy for pediatric

TBI, though longer follow-up is needed to assess late complications, notably growth delay and secondary malignancies, which more often emerge more than 10 years after irradiation (34). This cohort can be revisited in 5 to 10 years to address these questions.

In adults, TBI with helical tomotherapy was well tolerated. Acute toxicities were mostly grade 1–2, with few cases of grade ≥ 3 nausea, vomiting, or mucositis (13%), notably lower than rates reported in other series (≥ 30–44%) (35). No radiation-induced pneumonitis was observed, although six cases of infectious pneumonitis occurred, most likely related to post-transplant immunosuppression (conditioning chemotherapy, TBI and GVHD prophylaxis); they occurred in all dose groups, including three of the 20 adults who received 2 Gy. Nausea and vomiting were also less frequent than in large published cohorts, such as that of Pearlman et al. (35). Late toxicities were uncommon in adults: two developed chronic kidney disease and one chronic pulmonary symptoms, and two of the three patients who received a meningeal boost experienced decreased visual acuity. No cataracts were identified within the current follow-up period (median 18.5 months); however, given that lens doses reached up to 12.6 Gy in children, and that radiation-induced cataracts typically manifest 3–5 years post-irradiation, this observation should be interpreted with caution and re-evaluated at longer follow-up, whereas prior studies reported incidences up to 16% within 1–4 years after TBI (35).

Oncological outcomes were consistent with those reported in the literature for similar populations. The relapse rate of 17.6%, although not negligible, appears acceptable given the high proportion of patients treated for relapse (47%). The overall survival rate of 65% at end of follow-up in adults (31/48 alive) combined with 95% in children (19/20 alive), reflecting the distinct risk profiles of these two populations and is reassuring. In adults, the survival rate is lower than in children, which may be explained by more patients treated for relapse and also by the generally better physical condition of children, allowing them to tolerate more intensive treatments as shown in a large multicenter U.S. database study (36). Our paediatric survival outcomes compare favourably with the TBI arm of the FORUM trial, which reported 2-year OS of 91% and cumulative incidence of relapse of 12% with conventional fractionated 12 Gy TBI (5). Our 2-year OS of 95% and PFS of 80% are broadly consistent with these benchmarks, noting that direct comparison is limited by our retrospective single-centre design, smaller sample size, and heterogeneous case-mix. These findings nonetheless suggest that helical tomotherapy does not compromise disease control relative to conventional TBI and may offer a more favourable toxicity profile; prospective validation remains needed. Local control appeared better than the literature with a shorter treatment duration (3).

Our study presents several notable strengths. It includes both adult and pediatric patients, which remains uncommon in the TBI literature. To our knowledge, it represents one of the largest cohorts treated with helical tomotherapy, second only to the study by Loginova et al., thereby reinforcing the relevance of our findings. It also evaluates a modern technique that remains underused in clinical practice despite its known dosimetric advantages. We systematically collected and analyzed detailed dosimetric data and homogeneity indices, highlighting the precision and reproducibility of this approach.

Lastly, the use of a real-world cohort with consistent technique and follow-up enhances the clinical applicability of our results.

Several limitations should be acknowledged. First, this is a retrospective, single-center study, which may limit the generalizability of our findings due to potential biases, missing data, and uncontrolled confounders. Second, the heterogeneity of both conditioning regimens and patient characteristics reduced our ability to perform robust subgroup analyses. Third, although follow-up was sufficient to capture early and some late toxicities, it remains too short to fully assess long-term outcomes, particularly in pediatric patients. Prospective, multicenter studies with longer follow-up are needed to confirm these results and to better define optimal dose constraints, long-term efficacy, and the toxicity profile of helical tomotherapy-based TBI. In particular, the cohort includes three fundamentally distinct dose regimens (12 Gy myeloablative, 8 Gy myeloablative, and 2 Gy non-myeloablative), which differ in therapeutic intent, expected toxicity profile, and oncological objectives. Combining these subgroups in aggregate analyses limits clinical interpretability; future series should report these regimens separately. Moreover, children were treated almost exclusively with 12 Gy whereas most adults received 8 or 2 Gy, so that differences between age groups are confounded by dose, disease, conditioning regimen and transplant characteristics and should not be interpreted as age-related effects.

Conclusions

Our results support helical tomotherapy as a valuable alternative to conventional TBI techniques, offering homogeneous target coverage, acceptable acute toxicity, and a favorable early safety profile particularly in pediatric patients. Its ability to modulate the dose to organs at risk, particularly the lungs, makes it an attractive option in transplant conditioning, although renal sparing in children and long-term outcomes require further evaluation. However, its role is evolving, especially in light of long-term toxicity concerns and the growing use of chemotherapy-only regimens. Modern radiation techniques such as Total Marrow Irradiation (TMI), Total Marrow and Lymphoid Irradiation (TMLI), and individualized conformal TBI are under investigation and may offer improved efficacy-toxicity balance (37). Further prospective studies are needed to define the optimal use of TBI and clarify the place of more selective irradiation techniques in the future of transplant conditioning.

Abbreviations

ALL
acute lymphoblastic leukaemia
AML
acute myeloid leukaemia
ATG
anti-thymocyte globulin
CML
chronic myeloid leukaemia

CTCAE
Common Terminology Criteria for Adverse Events
CTV
clinical target volume
FFS
feet-first supine
GVHD
graft-versus-host disease
HFS
head-first supine
HSCT
hematopoietic stem cell transplantation
ICRU
International Commission on Radiation Units and Measurements
MMF
mycophenolate mofetil
MTX
methotrexate
MVCT
megavoltage computed tomography
OAR
organ at risk
OS
overall survival
PBSC
peripheral blood stem cells
PFS
progression-free survival
PTV
planning target volume
TBI
total body irradiation
TPS
treatment planning system
VMAT
volumetric modulated arc therapy.

Declarations

Ethics approval and consent to participate

This retrospective study was conducted in accordance with the Declaration of Helsinki; it was approved by the French Health Data Hub (approval number HDH301) and was declared to the French National Commission for Data Protection (CNIL, n° 25484912). All patients, or their parents or legal guardians for minors, gave informed consent to the use of their data for research purposes.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Funding

This research received no specific funding from any agency.

Author Contribution

YK, MJ and JCF conceived the study, performed the data analysis and wrote the manuscript. AD performed the statistical analysis. EM, NG, VM, MTR, CP, AC, MDP, WG, NM, MB, AS and CCB critically reviewed the manuscript for important intellectual content. All authors read and approved the final manuscript.

Acknowledgements

The authors would like to thank the medical physics, radiation therapist and radiation oncologist teams at the Institut de Cancérologie de Lorraine for their essential contributions to treatment planning and delivery. We also thank the hematology and pediatric hemato-oncology departments of CHRU de Nancy for their collaboration and patient care.

Data Availability

The datasets generated and analysed during the current study are not publicly available because they contain individual patient health data protected by French regulations (study approved by the French Health Data Hub, approval number HDH301), but are available from the corresponding author on reasonable request, subject to approval by the Institut de Cancérologie de Lorraine and compliance with applicable data protection rules.

References

1. Wong JYC, Filippi AR, Dabaja BS, Yahalom J, Specht L. Total Body Irradiation: Guidelines from the International Lymphoma Radiation Oncology Group (ILROG). Int J Radiat Oncol Biol Phys 1 juill. 2018;101(3):521–9.
2. Paix A, Antoni D, Waissi W, Ledoux MP, Bilger K, Fornecker L, et al. Total body irradiation in allogeneic bone marrow transplantation conditioning regimens: A review. Crit Rev Oncol Hematol mars. 2018;123:138–48.
3. Hartman AR, Williams SF, Dillon JJ. Survival, disease-free survival and adverse effects of conditioning for allogeneic bone marrow transplantation with busulfan/cyclophosphamide vs total body irradiation: a meta-analysis. Bone Marrow Transpl sept. 1998;22(5):439–43.
4. Rehman MEU, Chattaraj A, Mahboob A, Ijaz Z, Franco D, Farhan M, et al. Total Body Irradiation Versus Chemotherapy Conditioning in Pediatric Acute Lymphoblastic Leukemia Patients Undergoing Hematopoietic Stem Cell Transplant: A Systematic Review and Meta-Analysis. Clin Lymphoma Myeloma Leuk avr. 2023;23(4):249–58.
5. Peters C, Dalle JH, Locatelli F, Poetschger U, Sedlacek P, Buechner J, et al. Total Body Irradiation or Chemotherapy Conditioning in Childhood ALL: A Multinational, Randomized, Noninferiority Phase III Study. JCO 1 févr. 2021;39(4):295–307.
6. Peters M, Taylor B, Turner E. An Evidence-Based Review of Total Body Irradiation. J Med Imaging Radiat Sci déc. 2015;46(4):442–9.
7. Hoseinnezhad Zarghani E, Geraily G, Hadisinia T. Comparison of different TBI techniques in terms of dose homogeneity - review study. Cancer Radiother juin. 2021;25(4):380–9.
8. Hill-Kayser CE, Plastaras JP, Tochner Z, Glatstein E. TBI during BM and SCT: review of the past, discussion of the present and consideration of future directions. Bone Marrow Transpl avr. 2011;46(4):475–84.
9. Belkacémi Y, Rio B, Touboul E. [Total body irradiation: techniques, dosimetry, and complications]. Cancer Radiother. 1999;3(2):162–73.
10. Deeg HJ, Sullivan KM, Buckner CD, Storb R, Appelbaum FR, Clift RA, et al. Marrow transplantation for acute nonlymphoblastic leukemia in first remission: toxicity and long-term follow-up of patients conditioned with single dose or fractionated total body irradiation. Bone Marrow Transpl déc. 1986;1(2):151–7.
11. Valls A, Grañena A, Carreras E, Ferrer E, Algara M. Total body irradiation in bone marrow transplantation: fractionated vs single dose. Acute toxicity and preliminary results. Bull Cancer. 1989;76(8):797–804.
12. Buchali A, Feyer P, Groll J, Massenkeil G, Arnold R, Budach V. Immediate toxicity during fractionated total body irradiation as conditioning for bone marrow transplantation. Radiother Oncol févr. 2000;54(2):157–62.

13. Keane TJ, Van Dyk J, Rider WD. Idiopathic interstitial pneumonia following bone marrow transplantation: the relationship with total body irradiation. Int J Radiat Oncol Biol Phys oct. 1981;7(10):1365–70.
14. Gerstein J, Meyer A, Sykora KW, Frühauf J, Karstens JH, Bremer M. Long-term renal toxicity in children following fractionated total-body irradiation (TBI) before allogeneic stem cell transplantation (SCT). Strahlenther Onkol nov. 2009;185(11):751–5.
15. Bouillet T, Ali AM, Thariat J. [Radiation-induced nephropathy]. Bull Cancer 1 mars. 2012;99(3):389–96.
16. Pommier P, Sunyach MP, Pasteuris C, Frappaz D, Carrie C. Second cancer after total-body irradiation (TBI) in childhood. Strahlenther Onkol août. 2009;185(Suppl 2):13–6.
17. Linsenmeier C, Thoennessen D, Negretti L, Bourquin JP, Streller T, Lütolf UM, et al. Pediatric-inspired therapy in adults with Philadelphia chromosome-negative acute lymphoblastic leukemia: the GRAALL-2003 study. Strahlenther Onkol nov. 2010;186(11):614–20.
18. Hoeben BAW, Wong JYC, Fog LS, Losert C, Filippi AR, Bentzen SM, et al. Total Body Irradiation in Haematopoietic Stem Cell Transplantation for Paediatric Acute Lymphoblastic Leukaemia: Review of the Literature and Future Directions. Front Pediatr. 2021;9:774348.
19. Bölling T, Kreuziger DC, Ernst I, Elsayed H, Willich N. Retrospective, monocentric analysis of late effects after Total Body Irradiation (TBI) in adults. Strahlenther Onkol mai. 2011;187(5):311–5.
20. Hoeben BAW, Pazos M, Seravalli E, Bosman ME, Losert C, Albert MH, et al. ESTRO ACROP and SIOPE recommendations for myeloablative Total Body Irradiation in children. Radiother Oncol août. 2022;173:119–33.
21. Zhuang AH, Liu A, Schultheiss TE, Wong JYC. Dosimetric study and verification of total body irradiation using helical tomotherapy and its comparison to extended SSD technique. Med Dosim. 2010;35(4):243–9.
22. Loginova AA, Tovmasian DA, Lisovskaya AO, Kobyzeva DA, Maschan MA, Chernyaev AP, et al. Optimized Conformal Total Body Irradiation methods with Helical TomoTherapy and Elekta VMAT: Implementation, Imaging, Planning and Dose Delivery for Pediatric Patients. Front Oncol. 2022;12:785917.
23. Wilhelm-Buchstab T, Leitzen C, Schmeel LC, Simon B, Koch D, Schmeel FC, et al. Total body irradiation: Significant dose sparing of lung tissue achievable by helical tomotherapy. Z Med Phys févr. 2020;30(1):17–23.
24. Sresty NVNM, Gudipudi D, Krishnam Raju A, Anil Kumar T, Lakshmi VRP, Srikanth G, et al. Total body irradiation of bone marrow transplant using helical TomoTherapy with a focus on the quality of dose contribution at junction target volumes. Strahlenther Onkol août. 2021;197(8):722–9.
25. Hoeben BAW, Saldi S, Aristei C, Engellau J, Ocanto A, Hiniker SM, et al. Rationale, implementation considerations, delineation and planning target objective recommendations for volumetric modulated arc therapy and helical tomotherapy total body irradiation, total marrow irradiation, total

marrow and lymphoid irradiation and total lymphoid irradiation. Radiotherapy Oncol mai. 2025;206:110822.

26. Hui C, Simiele E, Lozko Y, Romero I, Skinner L, Binkley MS, et al. Volumetric modulated arc therapy total body irradiation improves toxicity outcomes compared to 2D total body irradiation. Front Oncol 16 sept. 2024;14:1459287.
27. Ladbury C, Hao C, Yang D, Hui S, Han C, Liu A, et al. Long-term follow up of patients with hematological malignancies treated with total body irradiation using intensity modulated radiation therapy. Front Oncol. 2022;12:1044539.
28. Sun R, Cuenca X, Itti R, Nguyen Quoc S, Vernant JP, Mazeron JJ, et al. First French experiences of total body irradiations using helical TomoTherapy ®. Cancer/Radiothérapie août. 2017;21(5):365–72.
29. Sarradin V, Simon L, Huynh A, Gilhodes J, Filleron T, Izar F. Total body irradiation using Helical Tomotherapy®: Treatment technique, dosimetric results and initial clinical experience. Cancer Radiother févr. 2018;22(1):17–24.
30. Huguet F, Leguay T, Raffoux E, Thomas X, Beldjord K, Delabesse E et al. Pediatric-Inspired Therapy in Adults With Philadelphia Chromosome–Negative Acute Lymphoblastic Leukemia: The GRAALL-2003 Study. JCO. 20 févr. 2009;27(6):911–8.
31. Esiashvili N, Chiang KY, Hasselle MD, Bryant C, Riffenburgh RH, Paulino AC. Renal toxicity in children undergoing total body irradiation for bone marrow transplant. Radiotherapy Oncol févr. 2009;90(2):242–6.
32. Esiashvili N, Lu X, Ulin K, Laurie F, Kessel S, Kalapurakal JA, et al. Higher Reported Lung Dose Received During Total Body Irradiation for Allogeneic Hematopoietic Stem Cell Transplantation in Children With Acute Lymphoblastic Leukemia Is Associated With Inferior Survival: A Report from the Children's Oncology Group. Int J Radiation Oncology*Biology*Physics juill. 2019;104(3):513–21.
33. Gruen A, Exner S, Kühl JS, Von Stackelberg A, Budach V, Stromberger C, et al. Total body irradiation as part of conditioning regimens in childhood leukemia—long-term outcome, toxicity, and secondary malignancies. Strahlenther Onkol janv. 2022;198(1):33–8.
34. Eichinger A, Poetschger U, Glogova E, Bader P, Basu O, Beier R, et al. Incidence of subsequent malignancies after total body irradiation-based allogeneic HSCT in children with ALL – long-term follow-up from the prospective ALL-SCT 2003 trial. Leuk nov. 2022;36(11):2567–76.
35. Pearlman R, Hanna R, Burmeister J, Abrams J, Dominello M. Adverse Effects of Total Body Irradiation: A Two-Decade, Single Institution Analysis. Adv Radiat Oncol. 2021;6(4):100723.
36. Gupta A, Damania RC, Talati R, O'Riordan MA, Matloub YH, Ahuja SP. Increased Toxicity Among Adolescents and Young Adults Compared with Children Hospitalized with Acute Lymphoblastic Leukemia at Children's Hospitals in the United States. J Adolesc Young Adult Oncol 1 déc. 2021;10(6):645–53.
37. Bao Z, Zhao H, Wang D, Gong J, Zhong Y, Xiong Y et al. Feasibility of a novel dose fractionation strategy in TMI/TMLI. Radiat Oncol. 17 déc. 2018;13(1):248.

Figures

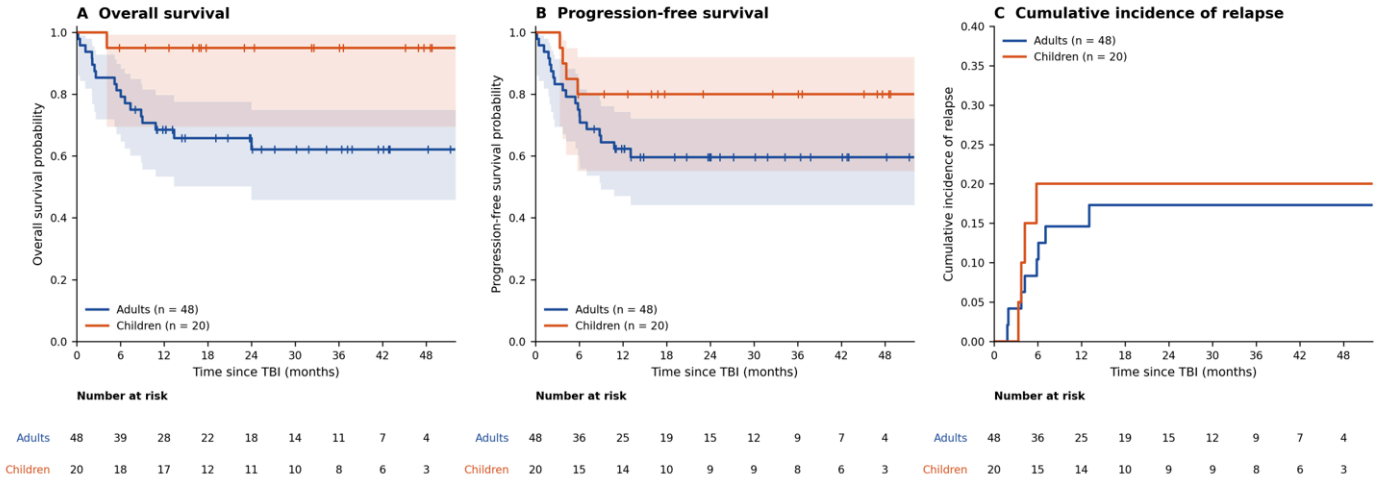


Figure 1

Relapse and survival outcomes in adults and children. (A) Overall survival and (B) progression-free survival (Kaplan–Meier estimates with 95% confidence intervals; tick marks indicate censored observations). (C) Cumulative incidence of relapse, with death without relapse as a competing event. Time is measured from the first day of TBI. Numbers at risk are shown below each panel.

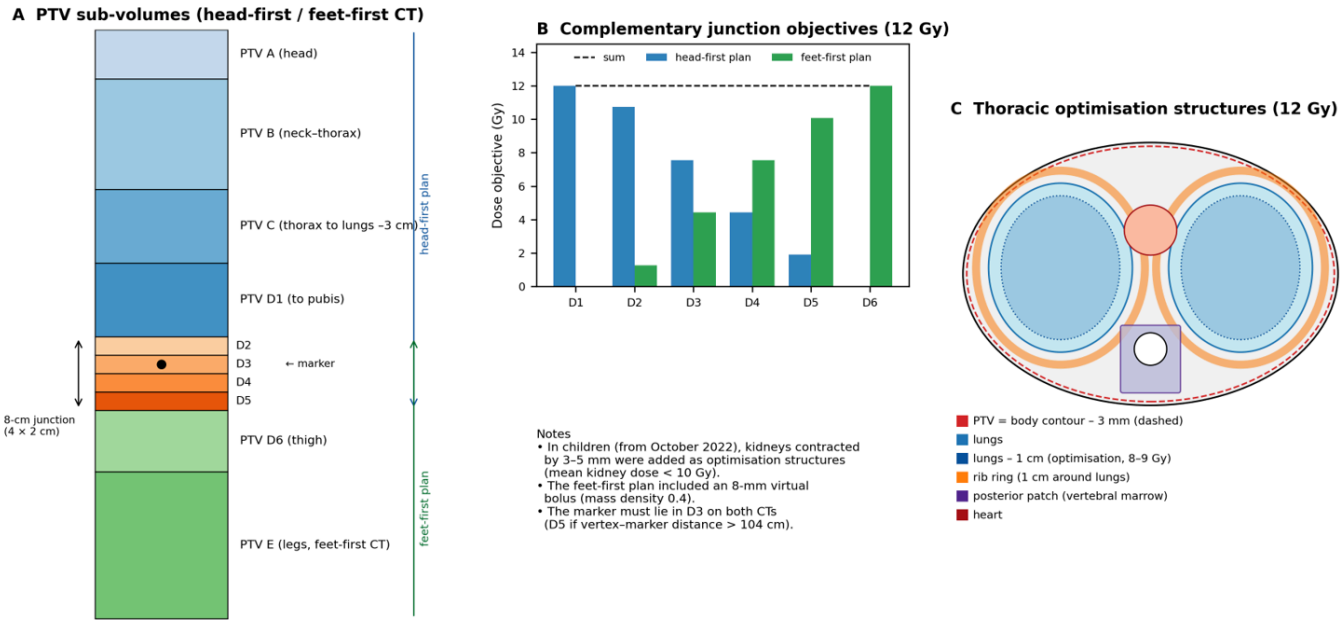


Figure 2

Planning structures for helical tomotherapy-based TBI. (A) Cranio-caudal segmentation of the PTV (body contour contracted by 3 mm) into sub-volumes on the head-first and feet-first planning CTs, with four 2-cm junction slabs (D2–D5); the radiopaque junction marker placed at mid-thigh lies in D3. (B) Complementary dose objectives assigned to the head-first and feet-first plans in the junction slabs for a 12-Gy prescription, summing to the prescribed dose. (C) Axial schematic of the thoracic optimisation structures used for 12-Gy prescriptions: lungs contracted by 1 cm (mean dose objective 8–9 Gy in adults), 1-cm rib ring and posterior patch ensuring coverage of the costal and vertebral marrow.