Late effects following HSCT childhood ALL: a national single center study using 3 different modalities of delivery of total body irradiation

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Abstract

Background: Total body irradiation (TBI) is a pivotal part of conditioning prior to hematopoietic stem cell transplantation (HSCT) for childhood acute lymphoblastic leukemia (ALL), yet evidence regarding the effect of TBI delivery techniques on acute and late toxicities is sparse. Design: In a national cohort of pediatric HSCT-recipients we compared 3 TBI schedules from different time-periods: (1) TBI 12 Gray (Gy) delivered in 3 fractions from 2008-2011 (n=12), (2) 6 fractions with 2-dimensional (2D) planning technology from 2012-2015 (n=16) and (3) 6 fractions with 3D-planning intensity-modulated radiotherapy (IMRT) from 2016-2020 (n=14). Results: The 5-year event-free survival was 75.0%, 81.3% and 81.3% in cohorts 1,2 and 3, respectively. Acute toxicity assessed as maximum ferritin and C-reactive protein during the first 3 months post-HSCT did not differ between cohorts, nor did the time to first hospital discharge (median 28, 32 and 31 days, p=0.25). The incidences of acute graft-versus-host disease (GvHD) (66%, 56%, 71%) and chronic GvHD (25%, 31% and 14%) were comparable. Pulmonary function assessed by spirometry did not differ significantly. More patients in cohort 1 developed cataract, with a 5-year cataract-free survival of 33.3%, 79% and 100% in cohorts 1,2 and 3, respectively. Acute toxicity assessed as maximum ferritin and C-reactive protein during the first 3 months post-HSCT did not differ between cohorts, nor did the time to first hospital discharge (median 28, 32 and 31 days, p=0.25). The incidences of acute graft-versus-host disease (GvHD) (66%, 56%, 71%) and chronic GvHD (25%, 31% and 14%) were comparable. Pulmonary function assessed by spirometry did not differ significantly. More patients in cohort 1 developed cataract, with a 5-year cataract-free survival of 33.3%, 79% and 100% in cohorts 1,2 and 3, respectively. There was a non-significant tendency towards more endocrinopathies in cohort 1 compared to cohorts 2 and 3. Conclusion: The change of modality did not result in more relapses. More fractionation improved outcome with a lower incidence of cataract and a tendency towards fewer endocrinopathies. The effect of 3D-planning-IMRT technology requires further evaluation in larger studies.

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**Abbreviations:**

<table>
<thead>
<tr>
<th>Abbreviation</th>
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<tr>
<td>HSCT</td>
<td>Hematopoietic Stem Cell Transplantation</td>
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<td>ALL</td>
<td>Acute lymphoblastic Leukemia</td>
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<td>FORUM</td>
<td>For Omitting Radiation Under Minority age</td>
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<td>TBI</td>
<td>Total Body Irradiation</td>
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<td>EBMT</td>
<td>European Society of Blood and Marrow Transplantation</td>
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<td>TRM</td>
<td>Treatment related mortality</td>
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<td>ESSD</td>
<td>Extended source-to-skin distance</td>
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<tr>
<td>2D, 3D</td>
<td>2-dimentional, 3-dimentional</td>
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<tr>
<td>IMRT</td>
<td>Intensity-modulated radiotherapy</td>
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<tr>
<td>VMAT</td>
<td>Volumetric modulated arc therapy</td>
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<td>CRP</td>
<td>C-reactive protein</td>
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<td>PF</td>
<td>Pulmonary function</td>
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<td>FEV1</td>
<td>Forced expiratory volume in 1. second</td>
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<td>FVC</td>
<td>Forced vital capacity</td>
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<td>LVEF</td>
<td>Left ventricular ejection fraction</td>
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<td>GHRT</td>
<td>Growth hormone replacement therapy</td>
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<td>SHRT</td>
<td>Sex hormone replacement therapy</td>
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<td>Gy</td>
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<td>OS</td>
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<td>Event free survival</td>
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<td>OAR</td>
<td>Organs at risk</td>
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The study was previously presented as an abstract at the 49th Annual Meeting of the European Society of Blood and Marrow Transplantation, P617 Total Body Irradiation for childhood ALL: Lower incidence of late effects with increased fractionation Bone Marrow Transplant vol 58, Supplement 1, 10. Of November 2023.

**ABSTRACT:**

Background: Total body irradiation (TBI) is a pivotal part of conditioning prior to hematopoietic stem cell transplantation (HSCT) for childhood acute lymphoblastic leukemia (ALL), yet evidence regarding the effect of TBI delivery techniques on acute and late toxicities is sparse.

Design: In a national cohort of pediatric HSCT-recipients we compared 3 TBI schedules from different time-periods: (1) TBI 12 Gray (Gy) delivered in 3 fractions from 2008-2011 (n=12), (2) 6 fractions with 2-dimensional (2D) planning technology from 2012-2015 (n=16) and (3) 6 fractions with 3D-planning intensity-modulated radiotherapy (IMRT) from 2016-2020 (n=14).

Results: The 5-year event-free survival was 75.0%, 81.3% and 81.3% in cohorts 1,2 and 3, respectively. Acute toxicity assessed as maximum ferritin and C-reactive protein during the first 3 months post-HSCT did not differ between cohorts, nor did the time to first hospital discharge (median 28, 32 and 31 days, p=0.25). The incidences of acute graft-versus-host disease (GvHD) (66%, 56%, 71%) and chronic GvHD (25%, 31% and 14%) were comparable. Pulmonary function assessed by spirometry did not differ significantly. More patients in cohort 1 developed cataract, with a 5-year cataract-free survival of 33.3%, 79% and 100% in cohorts 1,2 and 3, respectively. There was a non-significant tendency towards more endocrinopathies in cohort 1 compared to cohorts 2 and 3.

Conclusion: The change of modality did not result in more relapses. More fractionation improved outcome
with a lower incidence of cataract and a tendency towards fewer endocrinopathies. The effect of 3D-planning-IMRT technology requires further evaluation in larger studies.

**MAIN MANUSCRIPT**

The multinational, randomized trial For Omitting Radiation Under Minority age (FORUM) established Total Body Irradiation (TBI) as a pivotal part of conditioning prior to hematopoietic stem cell transplantation (HSCT) for acute lymphoblastic leukemia (ALL) in children (1). The trial reported significantly higher 2-year overall survival in patients above 4 years who received TBI and etoposide compared to myeloablative chemotherapy (91% vs. 75%, \( p < 0.0001 \)), and both the relapse incidence and treatment related mortality were lower in the group who received TBI (1). TBI is, however, associated with multiple toxicities and late effects (2-4), and the younger the patient, the higher the risk (5, 6). Efforts to reduce toxicity has led to a shift from single-fraction to fractionated TBI (7).

The current standard in pediatric oncology, applied in the majority of the FORUM participating centers, is to deliver a total of 12 Gray (Gy) TBI in 3 consecutive days, 2 fractions per day (7). A large retrospective study from the European Society of Blood and Marrow Transplantation (EBMT) database found no difference in disease control and survival in 2564 adult patients with AML or ALL following TBI 12 Gy delivered as 4 Gy in one versus 2 Gy in two daily fractions (8). However, a study of adult leukemia patients found mucositis to be less severe after TBI 12 Gy delivered in 6 versus 3 fractions (9). The FORUM study reported fewer acute toxicities and lower treatment related mortality (TRM) compared to historical reports (1), however no pediatric study has compared the level of toxicities in patients receiving TBI in 3 versus 6 fractions, and there are no comprehensive reports of differences in late-effects.

TBI delivery technique vary substantially between centers. The most common technique is to use a large open static field with extended source-to-skin distance (ESSD), that includes the entire body, while shielding certain organs at risk (OAS) (10, 11). Conventional 2-dimensional (2D) ESSD TBI is typically subject to dose gradients and inhomogeneities that diverge according to patient and technical factors. In efforts to improve dose uniformity and organ sparing, different techniques such as ESSD intensity-modulated radiotherapy (IMRT) and highly conformal isocentric TBI techniques e.g. TomoTherapy and volumetric modulated arc therapy (VMAT) have been implemented in various radiotherapy centers in recent years (7, 12-17). At the Danish national pediatric HSCT center, step-and-shoot IMRT, which requires the same equipment as delivery of other external beam radiation therapy, was introduced in 2016 (12). While still ensuring effective dose exposure to the bone marrow to achieve myeloablation, this method has been reported to reduce the radiation dose to the lungs and kidneys by around 15% compared to the prescribed dose, (12, 18), and thus reduce the risk of interstitial pneumonitis and chronic kidney failure (18).

In the current study we analyze differences in acute and late toxicities in three different TBI schedule and technique combinations applied in a consecutive national cohort of pediatric HSCT recipients transplanted between 2008 and 2020. We hypothesized that the incidence of acute as well as late toxicities would be lower in the most recent cohorts who received TBI in more fractions and using modern 3D planning technique.

**Patients and methods:**

Children <18 years transplanted with any donor and who received TBI due to ALL between January 1st 2008 and December 31st 2020 at the national center at Rigshospitalet, Copenhagen, Denmark were included. Patient and transplant characteristics were retrieved from the institutional transplant database whereas parameters regarding toxicity and inflammation, duration of hospitalization, pulmonary and cardiac function, ocular and endocrinological late effects were retrieved from patients’ electronic files.

The level of acute inflammation was assessed as the maximum level of C-reactive protein (CRP) and ferritin during the first three months post-HSCT. The pulmonary function (PF) measured by forced expiratory volume in 1. second (FEV\(_1\)), forced vital capacity (FVC) and the FEV\(_1\)/FVC ratio were calculated as z-scores, based on age-matched reference values (19). PF at baseline within 3 months prior to HSCT was compared to PF at 1, 2 and 5 years post-HSCT. Routine echocardiography-reports, performed by trained
 pediatric cardiologists at 1 and 5 years post-HSCT were collected. A left ventricular ejection fraction (LVEF) below 50% was considered abnormal. Information on prescription of growth hormone replacement therapy (GHRT), sex hormone replacement therapy (SHRT) and/or thyroid hormonal substitution (THRT) after HSCT was retrieved from patient files. Information of emerging cataract following yearly eye examination by trained ophthalmologist were retrieved.

12 Gy TBI was delivered as 4 Gy fractions over 3 consecutive days in one large open static field until 2011, where the fractionation schedule was changed to 2 daily fractions of 2 Gy given over 3 consecutive days with the same large open field technique. In 2016, the 3D planned ESSD-IMRT was introduced. We thus compare the outcome and toxicity parameters of three historical cohorts: (1) Patients transplanted between 2008 and 2011 who received 12 Gy TBI in 3 fractions with the large open field technique (cohort 1), (2) Patients transplanted between 2012 and 2015 who received 12 Gy TBI in 6 fractions with the same large open field technique (cohort 2), and (3) Patients transplanted between 2016 and 2020 who received 12 Gy TBI in 6 fractions with 3D planned ESSD-IMRT technology (cohort 3).

Associations between categorical data were analyzed with Fisher’s exact test. Continuous data were compared with one-way ANOVA. Differences in the incidence of late effects in time from HSCT were analyzed with Kaplan-Meyer curves. Changes over time were analyzed with two-way repeated measures ANOVA. P-values < 0.05 were considered statistically significant. Statistical analyses were performed in IBM SPSS Statistics (version 28.0.1.0).

The study was approved by the regional ethics authorities (journal number R-21066075).

Results:
A total of 70 children with ALL were transplanted in the study period, of these, 42 received TBI during conditioning and were thus included in the analyses. Between 2008 and 2011, 12 patients received TBI in 3 fractions of 4 Gy (cohort 1), between 2012 and 2015 16 patients received TBI in 6 fractions of 2 Gy using 2D planning technology (cohort 2) and from 2016 to 2020 14 patients received TBI in 6 fractions of 2 Gy with 3D planning and ESSD-IMRT technique (cohort 3). In the same time periods, 5 (29%), 9 (36%) and 14 (47%) pediatric ALL patients, received pre-HSCT conditioning with chemotherapy only, mainly treosulfan, fludarabine and thiotepa. The lower incidence of TBI treated patients in cohort 3 was due to the FORUM-randomization.

The three cohorts were comparable in age, immune phenotype, and basic transplant data (Table 1). Two patients died of relapse (cohort 2 and cohort 3), one of secondary malignancy (cohort 2), and one of respiratory and circulatory collapse due to pulmonary GvHD (cohort 2), which rendered a 5-year OS of 100%, 87.5% and 92.9% and EFS of 75.0%, 81.3% and 81.3%, respectively, with no significant difference between cohorts (Supplemental Figure 1A and 1B).

Time from HSCT to first hospital discharge were comparable between cohorts; median (range) 28 (24-48), 32 (22-144) and 31 (19-135) days, respectively (p=0.25). There were no significant differences in peak CRP during the first 3 months post-HSCT (Figure 1A). All patients had increased ferritin before HSCT, however, the level of ferritin increased significantly following HSCT in all three cohorts, and there was no difference in the change over time. (Figure 1B). There was no difference in the incidence of acute or chronic Graft-versus-Host Disease (GvHD) (Table 1).

Mean values of FEV$_1$ and FVC were lower pre-HSCT in cohort 3 compared to cohort 1 and 2 with mean z-scores of -1.6 vs. -0.1 and -0.4, respectively (Table 2 and Figure 2). Following HSCT, both absolute levels and changes over time in pulmonary function were comparable across all three cohorts, and differences in change over time did not reach statistical significance.

Two patients from cohorts 1 and 3 had abnormal LVEF prior to HSCT (40.5% and 40.0%, respectively), which later normalized. All surviving patients had normal LVEF at 1-year follow-up (mean 61.0%, range 53.7-71.0%). Among patients with available echocardiography at 5 years follow-up, abnormal values were
reported in 2 of 9 patients in cohort 1 (LVEF 48.4% and 45.0%) and 1 of 4 patients in cohort 3 (LVEF 40%). The numbers were too small for statistical analyses.

The number of patients with cataract was significantly higher in cohort 1 (n=8), compared to cohorts 2 (n=4) and 3 (n=0), with a 5-year cataract-free survival of 33.3%, 79% and 100%, respectively (Figure 3).

The development of endocrinopathies in the three cohorts are presented in Figure 4, and show a trend, though not statistically significant, towards more endocrinopathies in patients who received TBI in 3 fractions compared to 6. At last available follow-up at median 12.5, 8.8 and 3.7 years, respectively, hypothyroidism had been treated in 66.7% (8/12) of patients in cohort 1, 43.8% (7/16) of cohort 2 and 21.4% (3/14) of cohort 3. SHRT had been administered to 58.3% (7/12), 18.8% (3/16) and 28.6% (4/14) and GHRT to 41.7% (5/12), 12.5% (2/16) and 14.3% (2/14), respectively. Gonadal insufficiency was significantly more common in females across all cohorts; at last available follow-up 25.7% of boys (9/35) and 71.4% (5/7) of girls (p=0.031) had received SHRT.

Only one patient from cohort 2 suffered a secondary malignancy in the form of an intraspinal sarcoma.

Discussion:

The superiority of including TBI in the conditioning regimen prior to HSCT for pediatric ALL was reinforced by the results of the FORUM study (1), and due to high risk of relapse in ALL patients below 4 years (20), future protocols are expected to include TBI also to the very young patients between 2 and 4 years. The risk of acute and late toxicities is a serious concern.

We identified a significantly higher incidence of cataract among patients who received 12 Gy in 3 compared to 6 fractions. None of the patients from the most recent cohort who received TBI 12 Gy in 6 fractions with 3D planning technology developed cataract within the follow-up of 2.1-6.9 years. Since cataract is a relatively early toxicity these findings may be persistent, yet longer follow up is warranted. Our findings are in line with previous studies; in the early eighties, studies reported a higher incidence of cataract when TBI was given in 1 dose of 10 Gy (80%) compared to fractions of 2-2.5 Gy over 6-7 days (18%) (21) and several studies have since then found an effect of dose rate and fractionation on cataract incidence (22-24), which in the literature varies between 24 and 72% (25-28).

Our study is the first to assess the effect of TBI modality on the hormonal axes. We found a trend, yet not significant towards more endocrinopathies among patients who received TBI in 3 (cohort 1) compared to 6 fractions (cohorts 2 and 3). The incidence in our cohorts 2 and 3 fairly corresponds to a previous study on 109 patients aged 2-19 with malignant diseases who received TBI 12Gy/6 fractions between 1996 and 2015, of whom 12% developed GH deficiency and 12.5% hypothyroidism at median 8 (range 0.2-19) years follow-up (29). Another long-term follow-up including 152 HSCT recipients with both malignant and non-malignant diagnoses of whom 16% received TBI, reported a prevalence of both hypothyroidism and GH deficiency of 23% at median 9.9 years (30), where TBI was an independent risk factor for hypothyroidism, whereas craniospinal radiotherapy, but not TBI was associated with GH deficiency in the multivariate analysis (30).

Disturbingly, in a cohort of patients younger than 3 years who received pre-HSCT conditioning with TBI 12Gy/6 fractions, 91.7% (11/12) developed GH deficiency and 35.7% (5/14) hypothyroidism by 1.8-13 years of follow-up (6). In general, the level of endocrinopathies, may be underdiagnosed in clinical practice; when measuring GH deficiency by an insulin tolerance test, Davis et al found 82% (18/22) of survivors of hematological cancers to be GH deficient at (range) 1.4-19.2 years post TBI and HSCT (31).

Hypogonadism post-HSCT has been associated to female sex, age above 10 years at transplantation (26, 30, 32) as well as extensive cGvHD (32). In a study by Weinard et al. (32) including patients with malignant and non-malignant diseases transplanted between 1981 and 2017, 82.1% (23/28) of girls and 23.9% (11/46) of boys were administered SHRT following myeloablative conditioning with busulfan (46%) or 12 Gy/6 fractions TBI (56%). In line with this, Figueiredo et al.(30) reported primary hypogonadism in 46.3% of females and 12.9% of males at median 9 years of follow-up from HSCT for malignant and non-malignant diseases. Overall, these reports are in line with our results, however, longer follow-up is required to evaluate
whether the lower incidence in our most recent cohorts will be balanced with time from HSCT. Interestingly, a lower incidence of ovarian insufficiency of 36% (5/14) was described following a protocol of 8 Gy TBI to 14 female patients with hematological malignancies (33). This is of potential importance to the up-coming FORUM 2 study, in which patients are likely to be randomized to conditioning with 8 versus 12 Gy TBI in combination with etoposide.

Acute toxicity and inflammation assessed by the maximum levels of CRP and ferritin during HSCT and the number of days until first hospital discharge, did not differ significantly between patients conditioned by the three different TBI modalities in our study. Previously, a higher level of mucositis and hemorrhagic cystitis have been reported in adult patients following TBI delivered in 3 rather than 6 fractions (8, 9). Due to its retrospective nature, these parameters could not be accurately and uniformly assessed in our cohort. We did not encounter any difference in the incidence of acute or chronic GvHD. Though not fully comparable, this is in line with a large registry-based study comparing TBI delivery in 4 versus 6 fractions to AML patients older than 16 years, who found no difference in the cumulative incidence of Grade II-IV aGvHD, interstitial pneumonitis or extensive eGvHD (34). Correspondingly, Belkacemi et al. (8) did not detect a difference in eGvHD incidence when comparing TBI 12 Gy delivery to adult ALL patients in 3 versus 6 fractions, however, the incidence of eGvHD was higher when TBI was delivered in 2 compared to 6 fractions (HR 1.7, CI 1.03-2.8).

Organ toxicity did not differ significantly between our three cohorts. Pulmonary function was assessed as the level of FEV₁ and FVC from before and until 5 years post HSCT. Unfortunately, diffusion capacity which in adult patients seems to be the most sensitive pulmonary toxicity outcome affected by improvements in fractionation and technique (35), was not measured. Previous studies on the relation between dose fractionation and interstitial pneumonia have not encountered any difference between TBI 10-12 Gy delivery in 4 versus 6 fractions in autologous transplantations (36), nor 12 Gy delivery in 2, 4 or 6 fractions in allogeneic transplantations (8), which is in line with our results.

No previous studies have assessed the influence of TBI modality on cardiac dysfunction. In our study, 3 of 23 patients (13%) had an abnormal LVEF at 5 years follow-up, however we find the numbers too small to draw any conclusions on the effect of different TBI applications on LVEF. Cardiac dysfunction is highly related to pre-HSCT exposure to anthracyclines (37-39), but an effect of TBI exposure has also been suggested (40). However, in a follow-up of 95 children and young adults transplanted for bone marrow failure or malignant diseases, of whom 22% received TBI, no significant difference in LVEF or other echocardiographic markers were seen in patients receiving TBI versus non-TBI containing conditioning, and only 2/93 patients had abnormal LVEF at last follow up at (range) 1-5.6 years post HSCT (41). The risks of dyslipidemia and metabolic syndrome, as well as neurocognitive deficits, for which TBI has been described as an independent risk factor (30, 43), was not addressed by the current study.

In our three cohorts, only 1/42 patients (2.3%) developed a second malignancy following conditioning with 12 Gy in 6 fractions with 2D radiation planning (cohort 2). This is in line with the incidence in previous reports on similarly conditioned patients (8, 28, 29, 42).

This is the first study to comprehensively review the differences in acute toxicities and late effects following 12 Gy TBI in 3 versus 6 fractions, and 2D versus 3D radiation planning. Event free survival of the cohorts was excellent and the compliance to the follow up program was high allowing extensive studies of late effect parameters, which together with the population-based design is the major strength of this study. However, the study has serious limitations according to its design. The retrospective nature hampers comparison of acute toxicities, which is limited to an assessment of paraclinical measures. Changes in supportive care and pre-HSCT chemotherapy regimens over time from 2008 to 2020 may influence both the level of acute and long-term toxicities. The follow-up of cohort 3 is still too short to fully assess the level of long-term morbidity, and overall, the patient cohort is too small to draw any definite conclusions. To enable direct comparison of different TBI techniques comprehensive standardized reporting of all relevant radiotherapy data is required. No direct reporting of dose to OAR have been conducted in this study. As 2D conventional technique versus 3D IMRT are very different procedures with different dose homogeneity, the differences
reported between cohort 1 and 2 vs. 3 in this study could be due to the use of different TBI techniques and thus different doses to OAR. On the other hand, all patients were treated at the same center with the same setup for patients in cohort 1 and 2, which allows for a more direct comparison.

Conclusion:

Event free survival was excellent in all three cohorts. The change from 12 Gy TBI in 3 to 6 fractions significantly reduced the incidence of cataract and we found a tendency towards fewer endocrinopathies. Contrary to our hypothesis, we found no difference in paraclinical measures of acute toxicities. Future protocols should require TBI delivered as normo-fractionated to reduce the risk of long-term sequela. The 3D planning technology did not induce a detectable reduction in toxicity and sequelae in our small cohort, however, future prospective and preferably multi-center studies are needed to define the effect of 3D planning ESSD-IMRT or iso-centric technology and other organ sparing techniques on acute and chronic toxicities.

Conflict of interest statements:

LS is an advisory board member and speaker’s honoray at Kyowa Kirin, advisory board member at Takeda, and have received research funding from Varian and ViewRay. The other authors declare no conflict of interests relevant to the content of the current study.

REFERENCES:


**Figure legends:**

FIGURE 1A: Maximal C-reactive protein within 3 months post-HSCT, 1B: Maximal ferritin level within 1 month before and 3 months post-HSCT

FIGURE 2: Changes in pulmonary function in time from HSCT

FIGURE 3: Cataract development in time from HSCT

FIGURE 4: Proportion of patients in need of hormonal substitution therapy in time from HSCT

**Supplemental figures, legends:**

S1: Overall survival in time from HSCT S2: Event free survival in time from HSCT
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Table 1.docx available at https://authorea.com/users/787823/articles/1005060-late-effects-following-hsct-childhood-all-a-national-single-center-study-using-3-different-modalities-of-delivery-of-total-body-irradiation

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Table 2.docx available at https://authorea.com/users/787823/articles/1005060-late-effects-following-hsct-childhood-all-a-national-single-center-study-using-3-different-modalities-of-delivery-of-total-body-irradiation