Dosimetric evaluation of ovaries and pelvic bones associated with clinical outcomes in patients receiving total body irradiation with ovarian shielding

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ABSTRACT

Total body irradiation (TBI) with ovarian shielding is expected to preserve fertility among hematopoietic stem cell transplant (HSCT) patients with myeloablative TBI-based regimens. However, the radiation dose to the ovaries that preserves ovarian function in TBI remains poorly understood. Furthermore, it is uncertain whether the dose to the shielded organs is associated with relapse risk. Here, we retrospectively evaluated the relationship between fertility and the dose to the ovaries, and between relapse risk and the dose to the pelvic bones. A total of 20 patients (median age, 23 years) with standard-risk hematologic diseases were included. Median follow-up duration was 31.9 months. The TBI prescribed dose was 12 Gy in six fractions for three days. Patients’ ovaries were shielded with cylinder-type lead blocks. The dose–volume parameters ($D_{98\%}$ and $D_{\text{mean}}$) in the ovaries and the pelvic bones were extracted from the dose–volume histogram (DVH). The mean ovary $D_{\text{mean}}$ for all patients was 2.4 Gy, and 18 patients recovered menstruation (90%). The mean ovary $D_{\text{mean}}$ for patients with menstrual recovery and without recovery were 2.4 Gy and 2.4 Gy, respectively, with no significant difference ($P = 0.998$). Hematological relapse was observed in five patients. The mean pelvis $D_{\text{mean}}$ and pelvis $D_{98\%}$ for relapse and non-relapse patients were 11.6 Gy and 11.7 Gy and 5.6 Gy and 5.3 Gy, respectively. Both parameters showed no significant difference ($P = 0.827, 0.807$). In conclusion, TBI with ovarian shielding reduced the radiation dose to the ovaries to 2.4 Gy, and preserved fertility without increasing the risk of relapse.

Keywords: relapse; ovarian shielding; fertility; total body irradiation (TBI)

INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) is a well-established curative treatment widely used for various hematological diseases, including lymphoma, leukemia and multiple myeloma [1]. With the development of HSCT, these diseases have become more curable than previously. In combination with high-dose chemotherapy, total body irradiation (TBI) is an important part of the conditioning regimen for patients undergoing HSCT. TBI contributes to the eradication of malignant cells, and helps prevent graft rejection by the immune system among patients undergoing allogeneic HSCT. However, TBI and high-dose busulfan, which are often used for HSCT conditioning regimens, have been known as risk factors of ovarian failure [2–4]. Fertility preservation is a serious endeavor for patients who undergo HSCT because of the severe impact of infertility on the quality of...
life of long-term survivors. To preserve ovarian function in young women undergoing HSCT, there are two standard care of options: embryo cryopreservation and oocyte cryopreservation. Nevertheless, preserving ovarian function can be difficult when the treatment has to be started in an emergency during critical situations. Moreover, there is also a possibility of leukemia relapse after autologous transplantation of cryopreserved ovarian tissue from leukemic cell contamination in the graft [5–7].

Several studies have reported that the myeloablative TBI regimen with ovarian shielding could preserve fertility after HSCT [8–12]. According to these reports, after HSCT including myeloablative TBI regimen with ovarian shielding, the majority of patients have experienced menstrual recovery, with some becoming pregnant and delivering children. Based on the evidence, TBI with ovarian shielding is considered as an effective treatment in terms of preserving ovarian function. However, this approach has not been extensively studied, particularly in terms of whether or not the relapse risk increases due to the decreased radiation dose to the ovaries and the peripheral pelvic bones. Nakagawa et al. have shown that the average dose to the ovaries can be reduced from 12 Gy to 3.123 Gy (74% less), as measured using glass dosimeters with a humanoid phantom [11]. However, dosimetric evaluation using treatment plans has not yet been performed thus far. Hence, the aim of this study was to investigate the relationship between relapse risk and the radiation dose to the ovaries and the pelvic bones as well as between menstrual recovery and the dose to the ovaries for patients undergoing TBI with ovarian shielding.

MATERIALS AND METHODS

Patients

Between July 2007 and March 2020, 21 patients with standard-risk hematologic diseases who underwent HSCT with myeloablative conditioning regimen including TBI with ovarian shielding at our hospital were included in this study. All patients desired to preserve ovarian function and gave informed consent to receive TBI with ovarian shielding. The patients’ data were collected from medical records. This study was approved by the Institutional Review Board of our hospital (S18–045). One patient was excluded because the field of view size of computed tomography (CT) was too small to calculate the radiation dose to the ovaries. Thus, 20 patients were included in this study and their characteristics are summarized in Table 1. Standard risk was defined as acute leukemia in first or second complete remission (CR), myelodysplastic syndrome (MDS) without leukemic transformation, or non-neoplastic disorder. All patients received TBI at 12 Gy over three consecutive days (two fractions of 2 Gy per day), and the irradiation interval was set to six hours or more. The median age at HSCT was 23 (range, 17–33 years), and the median follow-up period was 31.9 months (range, 3.9–144 months). The patients’ underlying disease included acute myeloid leukemia (AML) (n = 10), acute lymphoblastic leukemia (ALL) (n = 5), other types of acute leukemia including acute unclassified leukemia (AUL) (n = 1) and blastic plasmacytoid dendritic cell neoplasm (BPDCN) (n = 1), myelodysplastic syndrome (MDS) (n = 2) and primary aplastic anemia (AA) (n = 1). All patients except for 1 with MDS and AA received multiple courses of chemotherapy before HSCT. One patient with AA received HSCT from the syngeneic graft. Among acute leukemia patients, 10 and seven patients were each in first and second CR at HSCT, respectively. Eighteen patients received allogeneic grafts, whereas one patient each received autologous and syngeneic grafts, respectively. The conditioning regimen consisted of a combination of cyclophosphamide (60 mg/kg/day for two days) and TBI, except in one patient who experienced cardiac impaired function before HSCT and used cytarabine instead of cyclophosphamide. Antithymocyte globulin or alemtuzumab was combined with the conditioning regimen in two patients who received transplants from an HLA-mismatched donor.

Nineteen patients had regular menstruation before HSCT, and one patient was amenorrheic due to previous chemotherapy.

Total body irradiation with ovarian shielding

TBI with ovarian shielding was performed as previously described [12]. Briefly, CT images for treatment planning were acquired several days before TBI. Aquilion (Toshiba, Japan) was used for the acquisition of CT images, and a 2 mm slice thickness was implemented to contour the ovaries accurately. The ovaries were identified by a radiologist with reference to contrast-enhanced CT or magnetic resonance imaging (MRI). For ovarian shielding, a pair of cylinder-type blocks (diameter: 5 cm; thickness: 8 cm) were created using low-melting lead and fixed to the acrylic board of the treatment bed. The patients were irradiated in the lateral position using the long source-surface distance (SSD) method from anterior–posterior and posterior–anterior directions, and SSD was 400 cm. The linear accelerator was PRIMUS (Toshiba, Japan). The X-ray energy was 10 MV, and the dose rate was 10 cGy/min at the center of the patient. The reference point was set at the center of the pelvic region on CT images for treatment planning. A photograph representing the set-up position is shown in Fig. 1. A typical dose map and irradiation field are shown in Figs 2 and 3, respectively. Also, we measured radiation dose with a model GD-301 glass dosimeter (Asahi Techno Glass, Shizuoka, Japan) on each patient body. Effective atomic number and density were 12.039 and 2.61 g/cm³, respectively. The reading of a glass dosimeter has been converted to absorbed dose inside patient’s body with conversion factor, which was acquired by using an ionization chamber and solid water phantom. The dose–response was linear in the range of 0.5–10 Gy with correlation coefficient of 0.999. Since in this study we use only the absorbed dose simulated by radiation treatment planning system (RTPS) as an indicator, the values of this glass dosimeter are not mentioned.

Dose–volume histogram parameters

The dose–volume histogram (DVH) of the pelvic bones and the ovaries were calculated using the RTPS. Xio version 4.80 (Elekta AB, Stockholm, Sweden) was used for RTPS, and superposition with heterogeneous correction was used for the dose calculation algorithm. Dose–volume data regarding the mean dose (Dmean) to the ovaries and pelvic bones, and the dose delivered to 98% of the pelvic bones (D98%) were recorded. Virtual plans without ovarian shielding were also created using RTPS to compare the DVH parameters of the pelvic bones and the ovaries for plans with and without ovarian shielding.

Statistical analyses

The patients were divided into the relapse and non-relapse groups, and into the menstrual recovery and menstrual non-recovery groups. The mean differences in pelvis D98% and Dmean as well as ovary Dmean...
Table 1. Patient characteristics

| Characteristics | n   |
|-----------------|-----|
| Age (years)     |     |
| median          | 23  |
| range           | 17–33 |
| Follow-up period (months) |     |
| median          | 31.9 |
| range           | 3.9–144 |
| Disease         |     |
| AML             | 10  |
| ALL             | 5   |
| AUL             | 1   |
| BPDCN           | 1   |
| MDS             | 2   |
| Primary AA      | 1   |
| Disease status  |     |
| CR1             | 10  |
| CR2             | 7   |
| EB1             | 1   |
| EB2             | 1   |
| Moderate        | 1   |
| Stem cell source|     |
| related         | 10  |
| unrelated        | 8   |
| autologous       | 1   |
| syngeneic       | 1   |
| Conditioning regimen |     |
| CY (120 mg/kg) + TBI | 17  |
| CY (120 mg/kg) + TBI + ATG | 2   |
| CA (24 g/m²) + TBI | 1   |
| Acute GVHD      |     |
| Grade I         | 8   |
| Grade II        | 4   |
| Grade IV        | 1   |
| no              | 5   |
| Chronic GVHD    |     |
| extensive       | 3   |
| chronic         | 1   |
| no              | 11  |
| not evaluable   | 3   |
| Menstruation before HSCT |     |
| yes             | 19  |
| no              | 1   |

among the patient groups were assessed using the independent t-test. Differences were considered significant if the two-tailed p-value was <0.05. SPSS for Windows version 23 (IBM, Armonk, NY, USA) was used for statistical analyses.

RESULTS
Treatment outcomes
All but one patient achieved neutrophil engraftment at a median of 21 days (range, 11–38 days). The remaining patient experienced primary graft failure and achieved neutrophil engraftment at second HSCT. In this study, relapse was defined as hematological relapse and extramedullary relapse, excluding molecular relapse and five patients experienced hematological relapse at a median of 4.5 months (range, 3.4–36 months); however, one of them attained remission with additional treatment. No patient experienced extramedullary relapse and combined relapse. Two patients died because of treatment-related complications, which were extensive forms of severe bronchiolitis obliterans and post-transplant lymphoproliferative disorder. Thirteen patients developed acute graft-versus-host disease (GVHD): grade 1 in eight patients, grade 2 in four and grade 4 in one, while four patients developed chronic GVHD, including one with an extensive form of severe bronchiolitis obliterans.
Fertility after hematopoietic stem cell transplantation
One patient already had chemotherapy-induced amenorrhea before HSCT and received hormone replacement therapy five years after HSCT. Hormone replacement therapy was not performed in all but one patient. Eighteen out of 20 patients recovered menstruation one or more times after HSCT (90%). Among these 18 patients, two received a second HSCT due to relapse, and therefore eventually experienced premature menopause. By contrast, two patients achieved pregnancy. One patient delivered a normal-birth weight infant nine years after HSCT, and the other patient became pregnant at one year and 10 months after HSCT.

Dosimetric evaluation
A dose map of a representative case treated with TBI with ovarian shielding is shown in Fig. 2. In plans of TBI with ovarian shielding, ovary $D_{\text{mean}}$, pelvis $D_{\text{mean}}$, and pelvis $D_{98\%}$ were 2.4 Gy, 11.7 Gy and 5.4 Gy, respectively. On the other hand, in virtual plans of TBI without ovarian shielding, ovary $D_{\text{mean}}$, pelvis $D_{\text{mean}}$, and pelvis $D_{98\%}$ were 12.2 Gy, 12.2 Gy and 11.6 Gy, respectively. These results show that the ovarian shielding method of our institution could reduce ovary $D_{\text{mean}}$ by 80.3%, pelvis $D_{\text{mean}}$ by 4.7%, and pelvis $D_{98\%}$ by 53.2% (Fig. 4, 5).

Relationship between relapse risk and radiation dose to the shielded organs, including the pelvic bones and ovaries
The mean pelvis $D_{\text{mean}}$ for relapse and non-relapse patients were 11.6 Gy and 11.7 Gy, respectively; however, it did not have a statistically significant difference ($P = 0.827$). The mean pelvis $D_{98\%}$ for relapse and non-relapse patients were 5.6 Gy and 5.3 Gy, respectively, and did not have a statistically significant difference ($P = 0.807$) (Table 2). The mean ovary $D_{\text{mean}}$ for relapse and non-relapse patients was 2.5 Gy and 2.4 Gy, respectively, which also did not have a statistically significant difference ($P = 0.583$).

DISCUSSION
In this study, 18 out of 20 patients who underwent the myeloablative TBI regimen with ovarian shielding recovered menstruation. In addition, pregnancy and childbirth were observed in two patients and one patient, respectively. TBI and busulfan have a significant impact on fertility [2], and several patients recover gonadal function following myeloablative TBI-based conditioning regimens. Socie et al. have reported that recovery of gonadal function occurred in only 10% to 14% of patients with myeloablative TBI-based conditioning regimens [3]. In contrast, it has been reported that TBI with ovarian shielding showed high gonadal function recovery. Nakagawa et al. have reported that among eight patients who underwent myeloablative TBI with ovarian shielding, six recovered ovarian function at a median of 15 months after HSCT [9]. Similarly, Kanda et al. have reported that among 16 patients who underwent myeloablative TBI with ovarian shielding, 10 of 11 patients who did not have relapse or non-relapse mortality after HSCT achieved ovarian recovery [8]. We have previously reported six-month and one-year cumulative rates of menstrual recovery at 42% and 78% among patients who received myeloablative TBI regimen with ovarian shielding, with five pregnancies resulting in one normal delivery, one selective cesarean operation, and one current pregnancy [12]. These studies indicate that TBI with ovarian shielding can preserve ovarian function better than conventional TBI, and the results of the present study on the high recovery of ovarian function are similar to those of previous studies.

Radiation damage to the ovaries is dose-dependent and the risk of inducing amenorrhea increases with age [13]. Radiation effects are dependent on the irradiated volume, total irradiation dose, fractionation schedule and patient age at the time of treatment [13]. Radiation exerts direct toxicity to oocytes and a dose of just 2 Gy to the ovaries results in a 50% loss of oocytes [14]. Wallace et al. calculated the radiation dose that would result in immediate ovarian failure in 97.5% of patients as follows: 20.3 Gy at birth, 18.4 Gy at 10-years-old, 16.5 Gy at 20-years-old and 14.3 Gy at 30-years-old [13]. TBI is often used in combination with chemotherapy; hence a lower dose may still influence ovarian function and cause ovarian failure. For patients with cervical cancer who need to receive adjuvant pelvic radiotherapy and maintain ovarian function, transposing the ovaries out of the pelvis is recommended to reduce the radiation dose to the ovaries to <3 Gy, in order to preserve ovarian function [15, 16]. In the present study, ovary $D_{\text{mean}}$ was reduced to 2.4 Gy by ovarian shielding, and this dose reduction is considered to have contributed to the preservation of ovarian function. Patients’ ovarian function could be affected by not only radiotherapy but also the previous chemotherapy. Further study to measure the serum hormone concentrations at each treatment is warranted to clarify which treatments damage the ovary. Additionally, one of the two patients who did not recover menstruation after HSCT had chemotherapy-induced amenorrhea before HSCT, and it is a subject of

Fig. 1. A patient’s position treated with TBI with ovarian shielding: the lung-shielding consisted of lead blocks is located on the cranial side and ovarian shielding is on the caudal side of a patient.
future study to select patients undergoing TBI with ovarian shielding from the point of view of ovarian function before TBI.

The current study on TBI with ovarian shielding shows comparable relapse rates to that of standard-risk patients who received conventional conditioning regimens [17]. In our study, extramedullary relapse was not observed and all relapses were hematological. However, the extramedullary relapse risk in the ovaries that is associated with the reduced radiation dose to the ovaries should be taken into

![Fig. 2. A dose map at the axial cross section of a representative case: the right and left ovaries are shown in pink and orange.](image1)

![Fig. 3. a) A digitally reconstructed radiography: the yellow and pink masses in this digital reconstruction represent the ovaries. b) A portal image: the two circles are the columnar lead blocks placed at the position of the ovaries.](image2)

### Table 2. Dosimetric comparisons between patients in the relapse and non-relapse groups

|        | all       | relapse (n = 5) | non-relapse (n = 15) | P-value |
|--------|-----------|----------------|----------------------|---------|
| Pelvis $D_{95\%}$ [Gy] | Mean ± SD | Mean ± SD | Mean ± SD | 0.807 |
|        | 5.4 ± 2.4 | 5.6 ± 2.8 | 5.3 ± 2.4 |         |
| Pelvis $D_{mean}$ [Gy] | 11.7 ± 0.5 | 11.6 ± 0.8 | 11.7 ± 0.4 | 0.827 |
| Ovary $D_{mean}$ [Gy] | 2.4 ± 0.3 | 2.5 ± 0.4 | 2.4 ± 0.2 | 0.583 |

SD = standard deviation
consideration. Although there are some case reports about acute leukemia recurring as extramedullary tumors in the ovaries following allogeneic HSCT, the predictive factor for extramedullary relapse in ovaries and the prognostic are not fully understood [18–21]. Cunningham et al. have reported that the prognosis of extramedullary relapse in the ovaries is extremely poor, with a one-year overall survival of 56% [22]. Therefore, we must carefully select patients who are suitable for TBI with ovarian shielding, and exclude patients with active malignancies.

Moreover, there is concern regarding bone marrow relapse due to the dose reduction to bone marrow associated with the pelvic bones. In this study, the relationship between relapse rate and the decreased radiation dose to the pelvic bones was examined, and no significant difference in terms of pelvis \( D_{98\%} \) and pelvis \( D_{mean} \) was observed between the relapse and non-relapse groups. Scarpati et al. have reported that patients with AML and chronic myeloid leukemia who received TBI and total radiation doses higher than 9.9 Gy in three fractions experienced a significantly lower relapse rate [23]. Therefore, it has been suggested that the total radiation dose when undergoing TBI should be > 10 Gy. In the current study, the pelvis \( D_{mean} \) was 11.7 Gy, and this result indicates that a radiation dose of > 10 Gy to the bone marrow might not have an impact on the hematological relapse rate. Therefore, we keep minimizing the extent of shielded pelvic bones not to reduce the dose to the pelvic bones significantly.

When performing ovarian shielding during TBI, we need to consider the internal movement of the ovaries. However, to our knowledge, few studies evaluating the inter- and intra-fractional ovarian motion have been published. Peters et al. have demonstrated the movement of normal ovaries using CT and MRI [24], and their results showed that the safety volumes around the ovaries encompassing 95% and 99% of ovarian movement were 11 cm³ and 25 cm³ (95%) and 24 cm³ and 54 cm³ (99%), for the left and the right ovary, respectively. Soda et al. have reported that 95% reference interval of transposed ovarian movement in the corresponding directions were 1.2 ~ 2.0 cm, and a transposed ovary needed the same margin as a normal ovary (~ 2.0 cm) [25]. In our study, a pair of columnar lead blocks (8 cm in height and 5 cm in diameter) have been used to shield the ovaries for all patients. The same block size used in TBI with ovarian shielding may be inappropriate for all patients. However, there is concern that the overlapping region between pelvic bones and shield area by using larger blocks will lead to increase relapse risk due to the decreased radiation dose to pelvic bones. In the future, it is necessary to evaluate intrafractional ovarian motion using cine-MRI and to examine the appropriate size of lead blocks in each case. Furthermore, the location of the ovaries

**Table 3. Dosimetric comparisons between patients in the menstrual recovery and non-recovery groups**

|                      | all               | recovery (n = 18) | non-recovery (n = 2) | P-value |
|----------------------|-------------------|-------------------|----------------------|---------|
| Ovary \( D_{mean} \) [Gy] | Mean ± SD         | Mean ± SD         | Mean ± SD            | 0.998   |
|                      | 2.4 ± 0.3         | 2.4 ± 0.3         | 2.4 ± 0.1            |         |

SD = standard deviation
during radiotherapy have not been confirmed thus far, and image-guided radiotherapy including cone-beam CT and on-board MRI may be useful.

Recently, significant technical improvements such as intensity modulated radiation therapy (IMRT) have been achieved; moreover, helical tomotherapy, which is one of the IMRT techniques, is used for TBI in some institutions. Conventional linear accelerator-based TBI has an inability to individually spare organs at risk (OARs), hence its acute and late toxicity. Helical tomotherapy allows for steep dose gradients between target volumes and OARs and expected to reduce TBI has an inability to individually spare organs at risk (OARs), hence for TBI in some institutions. Conventional linear accelerator-based helical tomotherapy, which is one of the IMRT techniques, is used for IMRT has been achieved; moreover, this dose–volume parameter for the ovaries is considered to be a useful dose constraint to deliver TBI with IMRT techniques. Moreover, further studies are needed to prospectively evaluate whether this dose constraint is accurate in a larger number of patients.

Regarding the limitations of the present study, this is a single-institution retrospective study with a small sample size. In our study, the relapse rate was comparable to that with conventional TBI regimen without ovarian shielding, however, it remains unknown whether relapse rate increases or not in patients undergoing TBI with ovarian shielding. Therefore, the safety and efficacy of this study should be validated in a larger number of patients as a multi-institutional prospective study.

In conclusion, TBI with ovarian shielding reduced the radiation dose to the ovaries to approximately 2.4 Gy and preserved fertility compared to conventional TBI without ovarian shielding. Moreover, the radiation dose to the ovaries and pelvic bones were not associated with an apparent increase in relapse rates in standard-risk patients.

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CONFLICT OF INTEREST
The authors have no conflict of interest to disclose.

REFERENCES
1. Copelan EA. Hematopoietic stem-cell transplantation. N Engl J Med 2006;354:1813–26.
2. Vatanen A, Wilhelmsson M, Borgström B et al. Ovarian function after allogeneic hematopoietic stem cell transplantation in childhood and adolescence. Eur J Endocrinol 2013;170:211–8.
3. Socié G, Salooja N, Cohen A et al. Nonmalignant late effects after allogeneic stem cell transplantation. Blood 2003;101:3373–85.
4. Sanders JE, Hawley J, Levy W et al. Pregnancies following high-dose cyclophosphamide with or without high-dose busulfan or total-body irradiation and bone marrow transplantation. Blood 1996;87:3045–52.
5. Loren AW. Fertility issues in patients with hematologic malignancies. Hematology Am Soc Hematol Educ Program 2015; 2015:138–45.
6. Courbiere B, Prebet T, Mozziconacci MJ et al. Tumor cell contamination in ovarian tissue cryopreserved before gonadotoxic treatment: should we systematically exclude ovarian autograft in a cancer survivor? Bone Marrow Transplant 2010;45:1247–8.
7. ISFP Practice Committee, Kim SS, Donnez J et al. Recommendations for fertility preservation in patients with lymphoma, leukemia, and breast cancer. J Assist Reprod Genet 2012;29:465–8.
8. Kanda Y, Wada H, Yamashita R et al. Protection of ovarian function by two distinct methods of ovarian shielding for young female patients who receive total body irradiation. Ann Hematol 2014;93:287–92.
9. Nakagawa K, Kanda Y, Yamashita H et al. Ovarian shielding allows ovarian recovery and normal birth in female hematopoietic SCT recipients undergoing TBI. Bone Marrow Transplant 2008;42:697–9.
10. Nakano H, Ashizawa M, Akahoshi Y et al. Assessment of the ovarian reserve with anti-Müllerian hormone in women who underwent allogeneic hematopoietic stem cell transplantation using reduced-intensity conditioning regimens or myeloablative regimens with ovarian shielding. Int J Hematol 2016;104:110–6.
11. Nakagawa K, Kanda Y, Yamashita H et al. Preservation of ovarian function by ovarian shielding when undergoing total body irradiation for hematopoietic stem cell transplantation: a report of two successful cases. Bone Marrow Transplant 2006;37:583–7.
12. Ashizawa M, Akahoshi Y, Nakano H et al. Updated clinical outcomes of hematopoietic stem cell transplantation using myeloablative total body irradiation with ovarian shielding to preserve fertility. Biol Blood Marrow Transplant 2019;25:2461–7.
13. Wallace WH, Thomson AB, Saran F et al. Predicting age of ovarian failure after radiation to a field that includes the ovaries. Int J Radiat Oncol Biol Phys 2005;62:738–44.
14. Wallace WH, Thomson AB, Kelsey TW. The radiosensitivity of the human oocyte. Hum Reprod 2003;18:117–21.
15. Van Eijkeren MA, Van Der Wijk I, El Sharouni SY et al. Benefits and side effects of lateral ovarian transposition (LOT) performed during radical hysterectomy and pelvic lymphadenectomy for early stage cervical cancer. Int J Gynecol Cancer 1999;9:396–400.
16. Chambers SK, Chambers JT, Holm C et al. Sequelae of lateral ovarian transposition in unirradiated cervical cancer patients. Gynecol Oncol 1990;39:155–9.
17. Machishima T, Kako S, Wada H et al. The safety and efficacy of acute graft-versus-host disease prophylaxis with a higher target blood concentration of cyclosporine around 500 ng/mL. Clin Transplant 2013;27:749–56.
18. George SM, Chandran N, Malik AK. Granulocytic sarcoma of ovary in a post allogeneic bone marrow transplant patient – a diagnostic challenge to the anatomic pathologist. Case report and review of literature. J Obstet Gynaecol 2016;36:567–70.
19. Nunes V, Della Starza I, Canichella M et al. A case of late isolated ovarian relapse of acute lymphoblastic leukemia after an allogeneic stem cell transplant. Leuk Lymphoma 2015;56:1517–20.
20. Sonoki T, Iwanaga E, Mitsuya H et al. Ovarian relapse seven years after bone marrow transplantation for B-cell acute lymphoblastic leukemia: an unusual Krukenberg tumor. Am J Hematol 2005;80:75–6.
21. Fadilah SA, Goh KY. Breast and ovarian recurrence of acute lymphoblastic leukaemia after allogeneic peripheral blood haematopoietic stem cell transplantation. *Singapore Med J* 2009;50:e407–9.

22. Cunningham I. The clinical behavior of 124 leukemic ovarian tumors: clues for improving the poor prognosis. *Leuk Lymphoma* 2013;54:1430–6.

23. Scarpati D, Frassoni F, Vitale V et al. Total body irradiation in acute myeloid leukemia and chronic myelogenous leukemia: influence of dose and dose-rate on leukemia relapse. *Int J Radiat Oncol Biol Phys* 1989;17:547–52.

24. Peters NH, Patterson AJ, Horan G et al. Assessment of ovarian movement on consecutive pelvic MRI examinations in patients with gynecological malignancies: what is the planning organ-at-risk volume for radiotherapy? *Br J Radiol* 2012;85:1407–14.

25. Soda I, Ishiyama H, Ono S et al. Assessment of transposed ovarian movement: how much of a safety margin should be added during pelvic radiotherapy? *J Radiat Res* 2015;56:354–9.

26. Jiang Z, Jia J, Yue C et al. Haploidentical hematopoietic SCT using helical tomotherapy for total-body irradiation and targeted dose boost in patients with high-risk/refractory acute lymphoblastic leukemia. *Bone Marrow Transplant* 2018;53:438–48.

27. Sarradin V, Simon L, Huynh A et al. Total body irradiation using Helical Tomotherapy: Treatment technique, dosimetric results and initial clinical experience. *Cancer Radiother Actions* 2018;22:17–24.

28. Wong JY, Forman S, Somlo G et al. Dose escalation of total marrow irradiation with concurrent chemotherapy in patients with advanced acute leukemia undergoing allogeneic hematopoietic cell transplantation. *Int J Radiat Oncol Biol Phys* 2013;85:148–56.