*Original Article*

# Total Marrow Irradiation by Volumetric Modulated Arc Therapy for Treatment of Hematologic Malignancy: A Dosimetric Feasibility Study

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***Objective***: The preclinical study was set to investigate the feasibility of volumetric modulated arc therapy (VMAT) technique for the total body irradiation (TBI) and total marrow irradiation (TMI).

***Materials and Methods***: Computed tomography (CT) simulation data sets for five patients were acquired to create plans for conventional-TBI (C-TBI), VMAT-TBI (V-TBI), and VMAT-TMI (V-TMI). Dose prescription was 12 Gray (Gy) in 2 Gy per fraction, which covered at least 90% of the planning target volume (PTV). Dosimetry of PTV and organs at risk (OARs) were analyzed. ArcCHECK and Radiochromic films were used for verification. Delivery parameters were also recorded.

***Results***: The average of $D_{90}$ of V-TBI and V-TMI were significantly higher than C-TBI (12.15 Gy versus 6.76 Gy, $p<0.001$). The improvement of homogeneity index (HI) in VMAT over C-TBI (1.15 versus 2.11, $p<0.001$) was also observed. However, VMAT planning technique could not decrease mean dose of critical organ beyond that by C-TBI technique. The OARs dose ranged from approximately 7.39 to 8.21 Gy for V-TBI and from 5.25 to 10.30 Gy for V-TMI. The average beam on time per fraction of both VMAT plannings were 11 minutes with the mean Gamma Index passing rate of 99.5%.

***Conclusion***: VMAT technique for TBI could improve dose conformity, homogeneity, and treatment delivery efficacy. The novel TMI could further decrease dose of the other OARs apart from lungs. The pre-treatment quality assurance (QA) confirmed reliability and accuracy. The present study results suggested that VMAT may be a feasible technique for TBI or TMI in the future.

***Keywords***: Total body irradiation (TBI), Total marrow irradiation (TMI), Volumetric modulated arc therapy (VMAT)

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Hematologic malignancies describe cancers that affect the blood and lymph system. It is one of the most common cancers worldwide. Based on Globocan 2012, the age-standardized incidence rate (ASR) of leukemia, lymphoma, and multiple myeloma is approximately 12/100,000 worldwide and 10/100,000 in Thailand. In 2015, more than 9,000 people were estimated as new cases in Thailand[1]. Hematopoietic cell transplantation is a potentially curative treatment for many types of hematologic malignancies such as: acute leukemia, myelodysplastic syndrome, chronic myeloid leukemia, and non-Hodgkin's lymphoma. Total body irradiation (TBI) is commonly used in conjunction with intensive chemotherapy prior to stem cell transplantation. TBI provides advantages for transplantation. For instance, TBI could be used to eradicate tumor cells, especially in the sanctuary sites, that could not easily be reached by chemotherapy drugs, killing the chemotherapy-resistant cell clones. In addition, TBI could suppress the patient's immune system, preventing the body from rejecting donor morrow. Previous retrospective and randomized trials[2-5] reported that the myeloablative regimens that included TBI in the allogeneic transplantation resulted in superior outcomes in comparison to when using only high-dose chemotherapy. Target volume

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of TBI is the entire body. Numerous techniques have been developed to achieve relative-dose homogeneity throughout the body with dose homogeneity within ±10% at the patient's midline[6]. Conventional TBI (C-TBI) treatment techniques can be classified into opposing anterior/posterior field (AP/PA) and parallel-opposed lateral (LAT) techniques. Even though both techniques could be employed before hematopoietic cell transplantation, the opposing anterior/posterior field (AP/PA) is generally employed in most healthcare institutes. The variation of body thickness and tissue densities over the entire treatment field could expand dose inhomogeneities when using C-TBI technique.

At Ramathibodi Hospital, C-TBI is performed by lateral opposing field in supine position with extended source-skin-distance (SSD) 350 centimeters technique. The six-megavoltage (MV) photon is used with dose rate of 9 centrigray/minute (cGy/min). A standard dose regimen is 2 Gray (Gy) twice daily for three consecutive days (total radiation dose of 12 Gy) prescribed at the midline of the body. The total treatment time is approximately an hour per fraction. Swangsilpa et al reported that TBI could exhibit dose homogeneity throughout the whole body in 53 patients within acceptable value[7]. Nevertheless, patients treated with TBI are at risk for radiation toxicities, which could have a negative impact on quality of life[8]. Particularly, the risk of interstitial pneumonitis is increased following TBI, leading to fatality[9]. In addition, due to the high dose irradiation to normal organs, the elevated risk of radiation-induced secondary cancer is concerning[10].

The currently developed innovation in radiotherapy (RT) with advanced computerized planning system allows access to the distribution of radiation dose in the target volume and normal tissues in the irradiated area, providing an opportunity to perform complicated RT techniques to improve therapeutic ratio. Intensity-modulated radiation therapy (IMRT) is one of the advanced treatment planning techniques that can conform the high dose area to the target volume while minimizing the volume of normal tissue irradiation. Previous study demonstrated that TBI by helical tomotherapy (HT) system or volumetric modulated arc therapy (VMAT) could produce superior target dose homogeneity, coverage, and lung sparing when compared to extended-SSD C-TBI[11,12]. Recently, a more targeted form of TBI, namely total marrow irradiation (TMI) or total marrow lymphoid irradiation (TMLI), has been implemented. TMI can precisely focus the target volume on the major marrow sites where the cancer cells reside. Hui et al reported that TMI by HT (HT-TMI) allowed good target coverage while doses to the median organ at risk (OAR) were reduced to 35% to 70% of prescribed dose[13,14]. In clinical feasibility study, Wong et al showed that HT-TMI could lower median normal organ dose by 15% to 65% and reduce acute toxicities[15]. In addition, fixed-gantry intensity modulated total marrow irradiation (IM-TMI) technique also offered benefits. Excellent target coverage could be achieved with IM-TMI while the doses to organs at risk (OARs) was decreased by 29% to 65%[16-18]. However, IM-TMI technique also has several limitations. The major limitation concerns small field size and requires long treatment time. A beam-on time of 45 to 50 minutes, which could exceed to more than 1 hour with setup and verification times, is typically required for IM-TMI technique[17]. For the past few years, VMAT technique has been developed to exploit customized algorithms to deliver IMRT in a single or more than one arc rotation around the patient. In comparison to IM-TMI or HT-TMI techniques, TMI by VMAT (V-TMI) could provide similar target coverage with potentially improved dose sparing to the OARs in relatively shorter treatment time[19-21].

Here in, the authors aimed to investigate the feasibility of VMAT planning technique for TBI and TMI in Thai patients. The dosimetry of target and OARs in V-TBI and V-TMI were compared to C-TBI. RapidArc (Varian Medical System Inc., Palo Alto, CA) was employed as the representative VMAT technology in present study and conventional planning technique was simulated from the technique that was currently used in Ramathibodi Hospital.

## Materials and Methods

### *Patient selection*

Five planning computed tomography (CT) data sets were randomly selected from patients who had previously undergone craniospinal irradiation (CSI) at Ramathibodi Hospital. Each CT image was obtained from GE Optima 580 CT simulator with 512×512 pixels per slice. The scan extended from the vertex of the skull to the mid-thigh with 3 to 5 millimeters (mm) slice thickness in free-breathing mode.

### *Target volume and organ at risks definition*

In TBI treatment planning, the target volume (PTV) is the entire body trimmed to 3 mm below the skin[12], as illustrated in Figure 1A. The OARs including lung, kidneys, liver, bladder, brain, lens, oral cavity, heart, and bowels were contoured.

The clinical target volume (CTV) of TMI

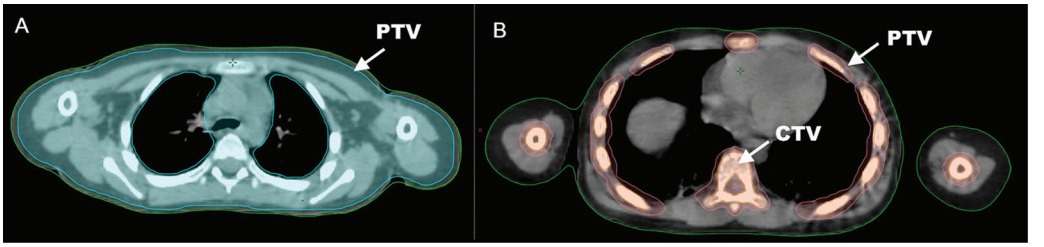


**Figure 1.** A) PTV of Conventional-TBI and VMAT-TBI, B) CTV and PTV of VMAT-TMI.

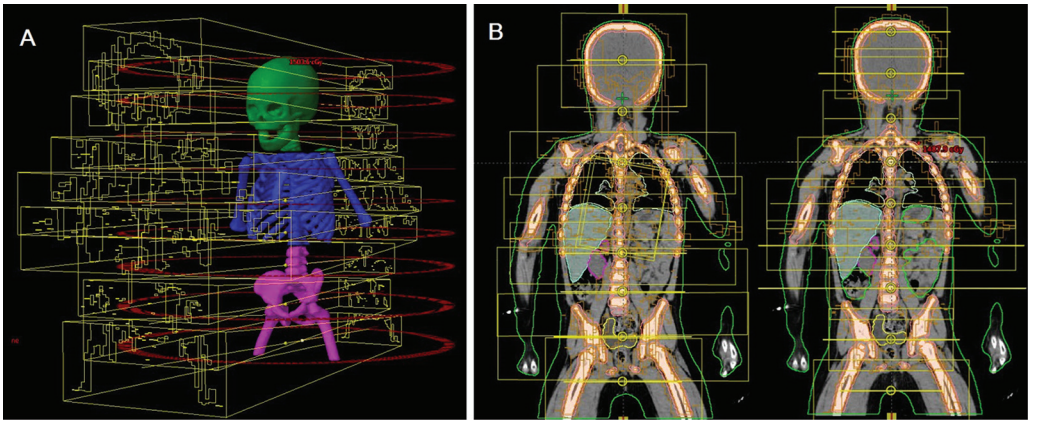


**Figure 2.** A) Three subvolumes in VMAT planning, B) VMAT-TBI and VMAT-TMI planning.

treatment planning was defined as all the bone in the body from head to the mid-femur[20]. The forearms and hands were excluded. The CTV was outlined by auto-contouring tools, which offer a more uniform method of contouring. A 3-mm margin was automatically added to CTV to obtain the PTV. However, the ribs were considered as an exceptional area due to the resulting uncertainties from respiration. A margin of 7 mm was added to provide the PTV in anterior-posterior (A-P) axis and a margin of 5 mm was added for the other axes. The CTV and PTV of TMI treatment planning were shown in Figure 1B. The OARs were contoured similarly to those in TBI plan.

### *Treatment planning techniques*

All of the treatment plannings were performed on the Eclipse version 13.0 platforms (Varian Medical Systems, Palo Alto, California, USA). A prescribed dose was 12 Gy in six fractions to cover the PTV.

*C-TBI technique*: The conventional TBI planning was simulated from currently used technique in Ramathibodi Hospital[7]. Irradiation with opposed lateral fields in supine position using 6-MV photon with extended SSD was performed. The collimator head was tilted into 45 degrees to achieve the maximum coverage diagonal field size from the head to thigh with gantry angle of 90 degrees. The prescribed point was placed at the patient's midline. Compensators were added to improve dose homogeneity. To prevent severe late complications after radiation therapy, the authors placed 1-HVL lead blocks beside the patient's body to reduce dose of lung, liver, kidneys, and urinary bladder. However, a beam spoiler, which was used to increase scattering electron beam for compensated surface under dosage of photon beam, was not included in the plan. The planning was calculated using the anisotropic analytical algorithm (AAA) provided by the Eclipse software.

*V-TBI and V-TMI technique*: The PTV was divided into three sub-volumes - head and neck (H&N), chest, and pelvis. The H&N and chest volumes were separated at C5 to C6 vertebral level. The junction point between chest and pelvic was located around L2 to L5. However, the adjustment of the location could be made based on the patient's height. The subvolumes for VMAT plan are illustrated in Figure 2A. Due to physical limits of MLC leaf extensions and jaw size, multiple fields were applied to complete treatment of all target volume. The 6-MV photon beams of 8 to 12 arc fields with multiple isocenters were used.

The range of gantry rotation angle was from 175 to 179 degrees to 185 to 189 degrees. Each arc field had the rotating gantry direction opposite to the adjacent arc fields. The second arc within each plan would be overlapped by a minimum of 1 cm with the adjacent arc. This overlap was applied in order to avoid hot and cold spots at the junction of the arcs. The collimator of all arcs was set to 90° with an exception in the chest subvolume planning. In the chest subvolume planning, a full arc with 10° or 350° collimator setting was added in order to increase dose modulation. Field width (Y direction) and length (X direction) were varied, depending on the size of subdivided target volume. The field was set to approximately 17 to 40 cm in width and 8 to 20 cm in length. The chest subvolume was selected as the first part for planning. Subsequently, it was used as the base plan for both H&N and pelvic subvolume plans to reduce hot and cold spots at the each plan junction. The planning is shown in Figure 2B.

The planning was aimed to decrease dose of critical OARs while keeping uniform dose to PTV in the acceptable criteria. The detailed planning criteria included 100% of the prescribed dose covered 90% of the PTV ($D_{90}$ ≥1,200 cGy) and 99% of PTV received dose at least 90% of prescribed dose ($D_{99}$ ≥1,080 cGy). In addition, the maximize dose of PTV should be less than 130% of prescribed dose ($D_{max}$ ≤1,560 cGy), and 1% of PTV should not receive dose more than 120% of prescribed dose ($D_1$ ≤1,440 cGy). In TBI planning, only three critical organs, which are the lung, liver, and kidneys, were selected to spare to the lowest dose. For the other OARs, the dose was reported as exactly received without sparing. While in TMI planning, all of OARs were spared to the lowest dose. AAA was used for final dose calculation.

### *Plan verification*

A plan quality assurance (QA) was performed using ArcCHECK (Sun Nuclear) with IC (0.13 cc) for verification of VMAT-TBI and TMI plan. The Radiochromic Film was used to verify the accuracy of doses in the junctional areas. Delivery parameters such as MU/Gy and the effective beam on time were recorded. The effective beam on time was defined as the pure beam-on time without any additional dead time caused by external conditions.

### *Statistics analysis*

The patient characteristics and details of target volume were explored by descriptive statistics. The categorical variables were shown in frequency (%), and the continuous variables were described in mean ± standard deviation (SD) or median (range). All Plans were quantitatively evaluated by dose-volume histograms (DVH). The median dose ($D_{50}$), mean dose ($D_{mean}$), maximal dose ($D_{max}$), the dose deliver to 1% of PTV ($D_1$), dose to 90% and 99% of PTV ($D_{90}$ and $D_{99}$) were recorded for PTV. The HI was calculated to assess the quality of the plan. HI was commonly defined as the ratio of maximum dose to the prescribed dose, ($D_{max}/D_{prescribed}$)[11]. However, in the present study, $D_1$ was used instead of $D_{max}$ due to the uncertainty of the maximum point dose. The calculation of maximum point dose was sensitive to the calculation parameters such as grid size, thereby, might be unreliable. $D_{prescribed}$ was also replaced with $D_{90}$. Thus, the authors' mathematical description of HI was $D_1/D_{90}$. The lower value of HI could indicate a more homogenous dose distribution within the PTV. The OARs were assessed by $D_{mean}$, $D_1$, and $D_{50}$ of each OAR volume. The statistical analysis was performed with SPSS statistic program version 17.0. Paired t-test and repeated measures ANOVA were used to compare average dosimetric parameters between different planning techniques. All statistical tests were performed two-sided and p-value lower than 0.05 was considered as statistical significance. Pre-treatment QA results were evaluated using γ analysis with the 3-mm distance to agreement and 3% dose agreement criteria.

## Results

### *Patient characteristics*

CT data sets of five randomly selected patients were used for pre-clinical C-TBI, V-TBI and V-TMI planning. The patient's clinical characteristics and treatment details are provided in Table 1. The height was measured from the maximum plane of PTV in craniocaudal direction while the width was from transverse direction. Note that, there were two teenagers (1 male and 1 female), whose body volume was bigger than others. The average of TMI target volume was approximately 4-fold less than TBI target volume.

### *Target parameters*

All of target parameters are shown in Table 2. The average of $D_{90}$ of C-TBI was 6.76±0.10 Gy, which accounted for approximately 2-fold less than $D_{90}$ of V-TBI. Meanwhile, the $D_{90}$ of V-TMI was comparable to that of V-TBI, (12.16±0.11 Gy for V-TMI and 12.15±0.10 Gy for V-TBI). The average of $D_1$ of C-TBI, V-TBI, and V-TMI were 14.25±0.66,

**Table 1.** Patient's characteristics and target volumes

| | P1 | P2 | P3 | P4 | P5 | Median | Range |
|---|---|---|---|---|---|---|---|
| Sex/age (year) | M/3 | F/15 | M/15 | M/11 | M/3 | 11 | 3 to 15 |
| Body volume ($cm^3$) | 11,882 | 39,907 | 38,009 | 14,148 | 12,839 | 14,148 | 11,882 to 39,907 |
| PTV-TBI | | | | | | | |
| Volume ($cm^3$) | 8,648 | 34,067 | 34,919 | 12,793 | 10,127 | 12,793 | 8,648 to 34,919 |
| Height (cm) | 64 | 92 | 106 | 66 | 62 | 66 | 62 to 106 |
| Width (cm) | 26 | 46 | 41 | 30 | 36 | 36 | 26 to 46 |
| PTV-TMI | | | | | | | |
| Volume ($cm^3$) | 2,478 | 4,803 | 8,231 | 3,469 | 2,426 | 3,469 | 2,426 to 8,231 |
| Height (cm) | 64 | 92 | 106 | 66 | 62 | 66 | 62 to 106 |
| Width (cm) | 18 | 39 | 40 | 29 | 32 | 32 | 18 to 39 |

M=male; F=female; PTV=planning target volume; TBI=total body irradiation; TMI=total marrow irradiation

**Table 2.** Dose of planning target volume

| Dosimetric parameter (Gy) | Conventional TBI Mean±SD | VMAT-TBI | | VMAT-TMI | |
|---|---|---|---|---|---|
| | | Mean±SD | p-value | Mean±SD | p-value |
| Mean dose | 9.79±0.33 | 12.79±0.08 | <0.001 | 12.92±0.05 | <0.001 |
| $D_{50}$ | 9.12±1.58 | 12.84±0.08 | 0.02 | 12.97±0.06 | 0.02 |
| $D_{max}$ | 15.47±0.93 | 15.08±0.39 | 0.96 | 15.04±0.31 | 0.78 |
| $D_1$ | 14.25±0.66 | 13.93±0.20 | 0.69 | 14.13±0.09 | 1.00 |
| $D_{99}$ | 6.30±0.19 | 10.93±0.22 | <0.001 | 11.05±0.26 | <0.001 |
| $D_{90}$ | 6.76±0.10 | 12.15±0.10 | <0.001 | 12.16±0.11 | <0.001 |
| HI | 2.11±0.10 | 1.15±0.02 | <0.001 | 1.16±0.01 | <0.001 |

SD=standard deviation; VMAT=volumetric modulated arc therapy; TBI=total body irradiation; TMI=total marrow irradiation; HI=homogeneity index

13.93±0.20, and 14.13±0.09 Gy, respectively. These values were less than 14.4 Gy (120% of prescribed dose), thereby, considered as in an acceptable range of planning criteria. Similar to $D_{max}$ of VMAT planning, a criterion was considered achieved as the dose was kept below 15.6 Gy (130% of prescribed dose). The Figure 3 demonstrates dose distributions in the C-TBI, V-TBI, and V-TMI of one patient. The mean HI value of C-TBI, V-TBI, and V-TMI were 2.11±0.10, 1.15±0.02, and 1.16±0.01, respectively. When compared to conventional technique, the results suggested that the homogeneity in both VMAT planning was significantly improved ($p<0.001$). However, the authors did not observe the difference of HI between V-TBI and V-TMI in the present study.

### *OARs parameters*

The average mean dose of critical organs such as lungs, kidneys, and liver are shown in Table 3. For TBI planning, the mean dose of lungs, left and right kidneys in VMAT technique were 7.41±0.57, 8.19±0.17, and 7.39±0.91 Gy, respectively. In comparison to the C-TBI with 1HVL-block technique, V-TBI planning could not decrease the mean dose of critical organs any further. However, there was a statistically significant increase in the mean dose of liver in V-TBI (8.21±0.63 for V-TBI versus 6.76±0.06 Gy for C-TBI, $p=0.02$). Note that V-TMI, when compared to C-TBI, resulted in the decrease in mean dose of all critical organs. The mean dose of lungs, left kidney, right kidney, and liver in V-TMI were 6.96±0.44, 6.06±1.02, 5.74±1.14 and 6.79±0.97 Gy, respectively.

The $D_{50}$ and $D_1$ of other OARs are reported in Table 4. In V-TBI planning, $D_{50}$ of majority of OARs in V-TBI planning were slightly lower but not statistically different from that in C-TBI. Several OARs such as

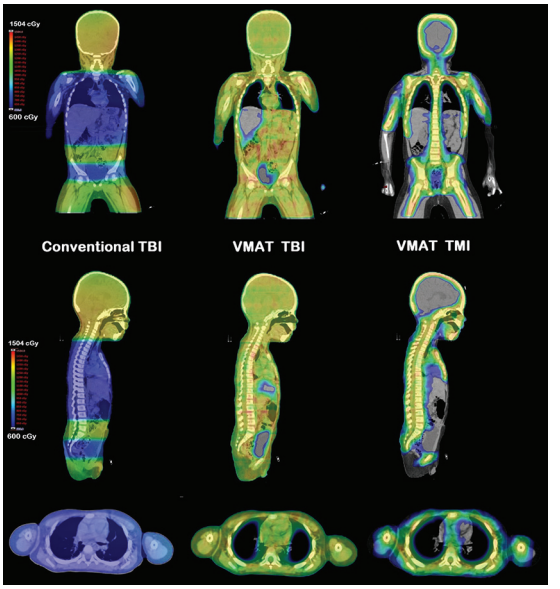


**Figure 3.** The color wash isodose distribution for conventional TBI, VMAT-TBI, and VMAT-TMI plans for one of randomly selected patients.

liver, heart, and bowel showed significantly higher $D_{50}$ in V-TBI planning. V-TMI planning, of which targets were limited to the bone, resulted in 3% to 40% reduction of $D_{50}$ of all OARs doses when compared to C-TBI, and 12% to 55% when compared to V-TBI.

### *Plan verification and delivery parameters*

The plan verification results were determined by using ArcCHECK (Sun Nuclear Corporation, USA) device and Radiochromic film. The overall Gamma Agreement Index pass rate, which scored with 3-mm and 3% thresholds, were 99.60±0.9% in V-TBI and 99.33±1.4% in TMI. With regards to delivery parameter, the average of total MU/Gy was 2,042±630.51 MU/Gy in V-TMI and 1,399±248.81 MU/Gy in V-TBI. The total MU of V-TMI tended to increase when compared to V-TBI (p=0.058). The average beam-on time of V-TBI and V-TMI was 11 minutes ± 6 seconds and 11 minutes 48 second ± 1 minute 44 seconds, respectively.

## Discussion

TBI is recognized as an important part of conditioning regimen for patients undergoing hematopoietic cell transplantation. The extended-SSD method is the most commonly used technique for TBI. However, the conventional technique with external shielding has limitation to achieving conformity and homogeneity. Moreover, dose escalation with traditional TBI techniques could be constrained by toxicity, especially radiation pneumonitis. Nowadays, IMRT is considered as one of the precise techniques that can maintain homogeneity and conformity dose to the target while limit dose to critical normal organs, thereby, reducing radiation complications. However, TBI by fixed-gantry IMRT and HT poses concern about long beam-on time. TBI with VMAT technique could achieve similar target conformity and homogeneity with shorter beam-on time.

In the present study, we investigated the feasibility of VMAT planning technique for TBI and TMI in Thai patients with hematologic malignancies. The results were compared to conventional technique that simulated from technique which currently used in Ramathibodi Hospital. The present data analyses suggested that V-TBI yielded statistically significant improvement in target coverage and homogeneity index while retaining the mean lung dose in comparable level to that by C-TBI. In addition, the present study mean lung doses were comparable to those previously reported from the other institutions[12,22]. With VMAT

**Table 3.** Critical OARs mean dose

| | Mean dose (Gy) | | | | |
|---|---|---|---|---|---|
| | Conventional TBI | VMAT-TBI | | VMAT-TMI | |
| | Mean±SD | Mean±SD | p-value | Mean±SD | p-value |
| Lungs | 7.01±0.09 | 7.41±0.57 | 0.54 | 6.96±0.44 | 1.00 |
| Kidney | | | | | |
| Left | 7.95±2.72 | 8.19±0.17 | 1.00 | 6.06±1.02 | 0.49 |
| Right | 7.98±2.73 | 7.39±0.91 | 1.00 | 5.74±1.14 | 0.37 |
| Liver | 6.76±0.06 | 8.21±0.63 | 0.02 | 6.79±0.97 | 1.00 |

OARs=organs at risk; SD=standard deviation; VMAT=volumetric modulated arc therapy; TBI=total body irradiation; TMI=total marrow irradiation

**Table 4.** Mean $D_{50}$ and $D_1$ for OARs

| | $D_{50}$ (Gy) | | | | | | $D_1$ (Gy) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | C-TBI | V-TBI | | V-TMI | | V-TBI vs. V-TMI | C-TBI | V-TBI | | V-TMI | |
| | | Mean±SD | p-value | Mean±SD | p-value | p-value | | Mean±SD | p-value | Mean±SD | p-value |
| Lungs | 7.03±0.11 | 7.44±0.78 | 0.88 | 6.53±0.80 | 0.64 | 0.51 | 7.37±0.20 | 12.10±0.20 | <0.001 | 12.39±0.13 | <0.001 |
| Kidney | | | | | | | | | | | |
| Left | 7.94±2.73 | 8.34±0.18 | 1.00 | 5.32±1.23 | 0.25 | 0.015 | 7.11±0.34 | 12.06±0.66 | 0.001 | 11.91±0.12 | 0.003 |
| Right | 7.96±2.74 | 7.33±1.11 | 1.00 | 5.25±1.25 | 0.22 | 0.18 | 7.22±0.33 | 11.91±0.12 | <0.001 | 11.67±0.85 | 0.001 |
| Liver | 6.75±0.04 | 8.37±0.79 | 0.03 | 6.03±1.06 | 0.60 | 0.003 | 7.34±0.15 | 12.86±0.17 | <0.001 | 13.21±0.35 | <0.001 |
| Bladder | 7.90±1.04 | 8.30±1.11 | 1.00 | 5.62±1.63 | 0.27 | 0.03 | 11.30±2.66 | 12.12±0.28 | 1.00 | 12.07±0.18 | 1.00 |
| Brain | 12.96±0.32 | 12.71±0.10 | 0.34 | 8.08±1.86 | 0.01 | 0.005 | 13.54±0.21 | 13.26±0.25 | 0.12 | 13.32±0.31 | 0.28 |
| Lens | | | | | | | | | | | |
| Left | 11.77±2.85 | 9.31±1.50 | 0.61 | 7.38±1.80 | 0.15 | 0.74 | 13.04±0.35 | 9.99±1.33 | 0.03 | 8.56±1.93 | 0.01 |
| Right | 11.74±2.79 | 9.33±1.50 | 0.64 | 7.10±2.15 | 0.15 | 0.67 | 13.00±0.37 | 10.06±1.27 | 0.03 | 8.23±1.93 | 0.02 |
| Oral cavity | 13.13±0.16 | 12.54±0.50 | 0.17 | 10.30±1.14 | 0.02 | 0.03 | 13.54±0.13 | 12.51±0.82 | 0.16 | 12.59±0.48 | 0.07 |
| Heart | 7.18±0.19 | 12.52±0.15 | <0.001 | 6.99±1.00 | 1.00 | 0.001 | 7.46±0.26 | 13.63±0.08 | <0.001 | 12.25±0.61 | <0.001 |
| Bowel | 8.68±2.17 | 12.87±0.12 | 0.04 | 5.78±0.96 | 0.09 | <0.001 | 13.31±0.32 | 13.87±0.24 | 0.19 | 11.78±0.39 | 0.01 |

OARs=organs at risk; SD=standard deviation; C-TBI=conventional total body irradiation; V-TBI=total body irradiation by volumetric modulated arc therapy; V-TMI=total marrow irradiation by volumetric modulated arc therapy

technique, the mean lung dose could be spared to the level below 9.4 Gy. Based on previous study by Volpe et al, with the dose of lung was below 9.4 Gy, VMAT could significantly reduce the risk of radiation pneumonitis from 19% down to 4%[9]. Because the uniform dose to PTV must be kept in the acceptable criteria, it was difficult to reduce the mean dose of liver to the same level as by conventional technique with 1-HVL blockage. However, VMAT could decrease the mean dose of kidney and of liver to the level below 10 Gy, at which was the radiation threshold dose for renal damage[23] and veno-occlusive disease (VOD) of the liver[24]. Dose-volume histograms of the critical OARs doses were shown in Figure 4. VMAT technique could noticeably reduce volume of low dose in the critical organs even though the mean dose was not different when compared to the conventional technique. The authors envision that the reduction of volume of low dose could potentially be beneficial to the parallel type of critical normal organs.

In the present study, the TMI by VMAT technique yielded the median dose of OARs other than lung, liver, and both kidneys in the range of 5.25 to 10.30 Gy, which was calculated to be approximately 45% to 85% of prescribed dose. Previous clinical study by Wong et al[15] revealed that, in comparison to standard TBI planning, TMI could effectively reduce acute toxicities. Therefore, TMI by various planning techniques could potentially achieve dose escalation that are required for improved clinical outcome

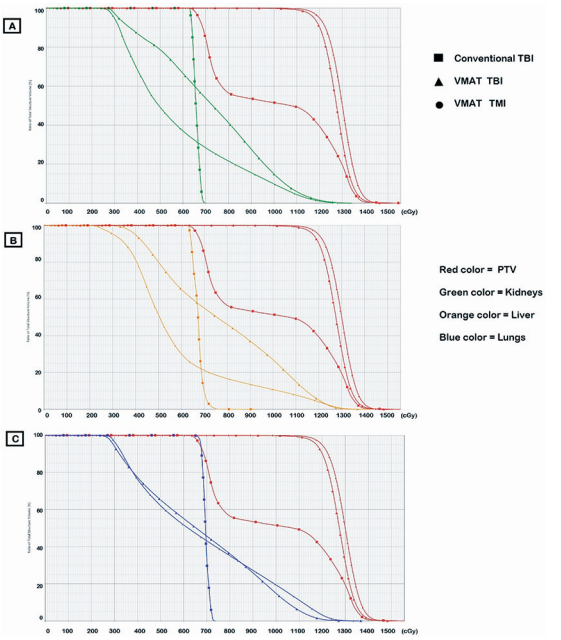


**Figure 4.** Dose volume histogram of A) kidneys; B) liver; C) lungs in Conventional-TBI, VMAT-TBI, and VMAT-TMI.

while reducing radiation toxicities during treatment. These highlight advantages gained by TMI raise consideration of using it as a new standard radiation technique in the future. However, there are several concerning points such as extramedullary (EM) relapse that should be addressed in the treatment of HCT patients. The investigation by Harris et al[25] indicated that, after HCT using TBI-containing regimens, the most common site of relapse was bone marrow (BM). The BM relapsed rate of 29% was 3-fold higher that of the EM site. EM relapsed rate could be around 9% at two years after transplantation. Other previously reported studies also observed comparable results of EM relapsed rate of 5% to 20% after TBI with HCT[26-29]. The techniques with improved targeted conformal radiation such as TMI or TMLI, when compared to standard TBI, did not significantly alter EM and bone marrow relapsed rates[30]. The results indicated the comparable incidence of EM relapse rate of 12.9%, at the sites receiving dose of less than 10 Gy or 10 Gy or more. Therefore, it was suggested that organ avoidance in TMLI was not associated with an increased risk of EM relapsed.

The VMAT technique provides the advantage of faster beam-on time. Currently, at the authors' institution, one fraction of conventional TBI consumes the treatment time of more than 1 hour (57 minutes 59 seconds ± 6 minutes 50 seconds). With VMAT technique, the treatment time could be decreased to 12 minutes per one fraction. The beam-on time of V-TBI or TMI is calculated to be approximately five times faster than that of C-TBI. However, TBI or TMI delivered using rotational techniques could bring up a potential problem of higher dose rate that may affect normal tissues, especially lung. To the best of the authors knowledge with currently available data, the effect of dose rate on fractionated TBI remains controversial. Several studies[31,32] showed that the higher dose rate was independent risk factor for interstitial pneumonitis. Nevertheless, the cut-points of dose rate that significantly increased risk of interstitial pneumonitis in these studies were various. In addition, several studies[33,34] also reported that there was no correlation between dose rate and risk of interstitial pneumonitis. Risk of interstitial pneumonitis was suggested to be dependent on the mean lung dose.

Regarding to the delivery parameters, the present study observed higher total MU/Gy in V-TMI than that of V-TBI plan, implicating that the planning technique in TMI is more complex. Therefore, to apply to real clinical situations, clinician must pay attention to the dose accuracy at each point prior to treatment. The pre-treatment QA was also assessed. The results, verified by overall Gamma Index pass rate, revealed that VMAT planning was reliable and accurate. The authors currently investigate dose verification with different tissue density in Rando phantom. The results and analyses shall be reported in due course. A proper immobilization and set-up strategy should be investigated prior to using VMAT planning technique for TBI or TMI in clinical practice.

## Conclusion

The present study with randomly selected Thai patients' data sets is in agreement with previously reported studies that VMAT planning technique for TBI and TMI could be used to improve target coverage and homogeneity while sparing critical normal organs dose in acceptable level. This new TMI technique could also further spare multiple OARs other than lung, liver, and kidneys. In comparison to the conventional TBI technique, the treatment time required for VMAT technique was significantly shorter. The pre-treatment QA confirmed reliability and accuracy of VMAT plan. These data highlighted the potential of VMAT as a feasible technique for TBI or TMI treatment of Thai patients in the future. To be applicable in clinical situation, further studies, for example on set-up strategy, are necessary to be investigated.

## What is already known on this topic?

TBI is commonly used in conjunction with intensive chemotherapy prior to stem cell transplantation for the treatment of hematologic malignancies.

Most institutions in Thailand currently use conventional TBI technique; however, the in-homogeneity of tissue dose throughout the whole body and high toxicity to critical surrounding normal organs raise concerns.

TBI or a more targeted form of TBI such as TMI and TMLI by modern techniques like IMRT, HT or VMAT can produce superior target dose homogeneity, coverage and minimize the volume of normal tissue irradiation.

## What this study adds?

This pre-clinical study investigated the feasibility of VMAT technique for TBI and TMI for hematopoietic cell transplantation in Thai patients.

The result based on randomly selected data from Thai patients at Ramathibodi Hospital supported that

VMAT planning technique for TBI and TMI could improve target coverage and homogeneity while sparing critical normal organs dose in acceptable level when compared to currently used conventional TBI technique. The pre-treatment quality assurance also confirmed reliability and accuracy.

These preclinical results highlighted the potential of VMAT as a feasible technique for TBI or TMI in clinical setting in the future.

## Conflicts of interest

The authors declare no conflict of interest.

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