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Scientific Article

Acute Toxicity of Total Body Irradiation Using Volumetric Arc Therapy With a Focus on the Effect of Lung Dose Rate

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Purpose: To report adverse effects of high dose total body irradiation (TBI) delivered using a volumetric arc therapy (VMAT) technique and to assess pulmonary toxicity at dose rates of 40 and 100 monitor units per minute (MU/min).

Methods and Materials: This retrospective study included patients >18 years old who received ≥8 Gy TBI using a VMAT technique. The TBI dose was prescribed to a planning target volume consisting of a 0.5 cm retraction of the body with the lungs subtracted. The objective function specified planning target volume coverage goals of D100% ≥ 90% and Dmax <130%. A lung dose control structure consisting of a 1 cm retraction of the lung volume was limited to Dmean <75%. Treatments were initially delivered with a dose rate of 40 MU/min for the thoracic isocenters and 100 MU/min for the other isocenters. Beginning in January 2021, a dose rate of 100 MU/min was used for all isocenters. All treatments were administered in 2 Gy fractions delivered twice daily. Acute toxicity was assessed for 30 days after TBI.

Results: A total of 29 patients were included in this analysis who received TBI between January 2019 and October 2021. Prescription dose ranged from 8 to 12 Gy. Mean lung dose was 7.9 Gy (SD, 1.4 Gy) for patients treated at 40 MU/min and for patients treated at 100 MU/min 7.1 Gy (SD, 1.3 Gy). Mucositis was the most common grade 3 toxicity and occurred in 10 (34%) patients. Only 1 instance of pneumonitis was observed and occurred in a patient who received a mean lung dose of 10.1 Gy delivered at 40 MU/min.

Conclusions: In this cohort of patients who received high dose TBI using a VMAT technique, the composite rate of acute toxicity was not unexpectedly high. We did not observe an increase in lung toxicity after increasing the dose rate of the thoracic isocenters from 40 MU/min to 100 MU/min.

Introduction

Total body irradiation (TBI) is an integral component of many conditioning regimens that are used for both benign and malignant hematologic diseases.[1] The purpose of TBI is to eradicate malignant cells, including those in sanctuary sites, which cannot be reached by chemotherapy, such as the brain and testes.[2] In conjunction with chemotherapy, TBI also functions to provide immunosuppression to prevent the rejection of the donor stem cells. Multiple studies have demonstrated improved outcomes in patients who receive conditioning regimens with TBI versus those without[3-6] associated toxicities.

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Although chemotherapy tends to distort the causation of toxicity, radiation pneumonitis is known to be associated with TBI, and often precedes chronic pulmonary fibrosis.[7] This complication is associated with significant morbidity, and its incidence has been shown to be minimized with the utilization of lung shielding.[8]

The historical delivery of TBI has been via extended source-to-surface distance patient positioning with large treatment vaults using standard linear accelerators. Many techniques require patients to maintain a standing position for long treatment times, which can be very burdensome for patients with cancer prone to movement, especially within the pediatric population. Additionally, extended-distance standing techniques are not able to be accurately modeled or calculated by commercial treatment planning systems, which decreases the ability to evaluate 3-dimensional dose distribution, common with standard radiation therapy practices. Recently, as improvements in radiation treatment delivery and dosimetry have continued to develop, TBI techniques have evolved. Modern TBI treatment planning uses advanced treatment planning systems and multileaf collimators to achieve superior dose homogeneity while providing maximal sparing of organs at risk.[9] Multiple groups have independently developed volumetric arc-therapy enabled TBI (VMAT-TBI) techniques; however, the clinical data regarding outcomes and toxicities are somewhat limited.[10-13] Historically, increased lung dose rate and lack of pulmonary shielding via conventional TBI methods have been associated with increased incidence of interstitial pneumonitis,[13,14] but this has not been properly evaluated with newer treatment modalities. The purpose of this study is to report our 3-year clinical experience with VMAT-TBI and to determine whether increasing the dose rate from 40 MU/min to 100 MU/min was associated with increased lung toxicity.

Methods and Materials

Inclusion criteria and statistical analyses

An Institutional Review Board-approved, retrospective review was performed for all patients treated with VMAT-TBI at our institution. All patients age ≥18 years of age who received high dose (≥8 Gy) VMAT-TBI were included in this analysis. Dosimetric statistics and patient toxicities were collected via review of the treatment planning systems and electronic medical record. Toxicities were graded by Common Terminology Criteria for Adverse Events, version 5 and reported regardless of perceived cause.

VMAT TBI treatment methodology

Simulation

Patients were simulated supine with the head in a neutral position and a full body length custom molded immobilization device, either Alpha Cradle (Smither's Medical Products) or Vac-Lok (CIVCO Radiation therapy), for reproducible setup and patient comfort. A head-first supine (HFS) scan from the top of the skull to mid-thigh was acquired with a 3 mm slice thickness and a maximum length of 120 cm. An additional feet-first supine (FFS) scan, using the same setup and parameters, was acquired with a minimum of 10 cm overlap in anatomy. Arms were placed close to the body to eliminate any possible air gaps. Because of field size limitations, special attention was paid to the maximum width of the patient. For patients wider than 40 cm, hands were placed on top of thighs parallel to both the hips and torso to reduce lateral distance, which became the standard setup for all patients in 2021. Additionally, a 5-point thermoplastic mask was used for the HFS simulation in some patients to reduce the risk of movement, and a 1 cm bolus on the anterior portion of the lower legs from the knee to the ankle was applied for the FFS simulation.

Treatment planning and delivery

To increase optimization capabilities, several organs at risk (Table 1) were contoured. Next, a step-by-step planning approach was used, which used VMAT arcs for the treatment of upper body isocenters and anterior-posterior (AP-PA) fields for lower body isocenters[16]:

Lower body AP-PA field planning:

1. Lower body isocenters were generated for the upper leg and lower leg. A mid leg isocenter was also added for larger patients. Standard isocenter utilization is depicted in Figure 1.
2. AP-PA fields were generated for the lower body isocenters using the 1 cm tissue equivalent bolus on the anterior aspect of the lower legs. Field sizes were chosen such that there was approximately a 3 cm overlap between isocenter groups in the AP fields.
3. Multi-leaf collimators (MLCs) were then used to create a field-in-field sequence, which allows for an optimally homogenous dose distribution. The fluence map generated in this step was used as the base dose for the upper body optimization.
4. The base dose was then propagated to the HFS by flipping the FFS scan and coregistering both scans to create the full body scan. The junction between upper body VMAT arcs and lower body AP-PA fields was at the midfemur.

Upper body VMAT planning:

1. Upper body isocenters were generated for the following: head, left chest, right chest, mid chest, abdomen, and pelvis. Up to 2 additional isocenters, left and right abdomen, were used for larger patients to allow for adequate coverage.

Table 1 VMAT TBI planning aims

Name of structure	DVH metric	Current objective
PTV^Upper PTV^Lower	D90	100% of Prescribed dose (ideal)≥ 95% of Prescribed dose (acceptable)
PTV^Upper	Dmax	<130% (ideal) <140% (acceptable)
PTV^Lower	Dmax	<140% (ideal) <150% (acceptable)
_LungEval	Dmean	Lower of the following: <60% of Rx Dose or <800 cGy (ideal) <75% of Rx Dose or <900 cGy (acceptable)
Spinal cord	Max dose [Gy]	1500 cGy at 0.125 cc
	Min dose	Between 90%-110% of Rx dose
Oral cavity	Dmax	1500 cGy at 0.125 cc
Heart	Dmax	1500 cGy at 0.125 cc
GI structures	Dmax	1500 cGy at 0.125 cc
Kidney (individual)	Mean	<1300 cGy
Whole brain	Dmax	1500 cGy at 0.125 cc

Abbreviations: GI = gastrointestinal; PTV = planning target volume; Rx = prescription; TBI = total body irradiation; VMAT = volumetric modulated arc therapy.

2. One to two 6 MV VMAT arcs were used for each upper body isocenter. By using 3 to 6 chest arcs with various collimator angles, the dose can be modulated to a greater extent at the lung interface while still applying adequate dose to nearby structures.
3. Three planning target volume (PTV) targets were created to facilitate planning, which encompassed the entire body PTV (PTV_BodyEval), as well as the PTVs derived from the HFS and FFS scans. PTV_BodyEval was a 5 mm retraction from the body contour minus the lung volume and represented the primary target, while the separate PTV_upper and PTV_lower, treated via VMAT and AP-PA fields, respectively, combine to equal PTV_bodyeval.

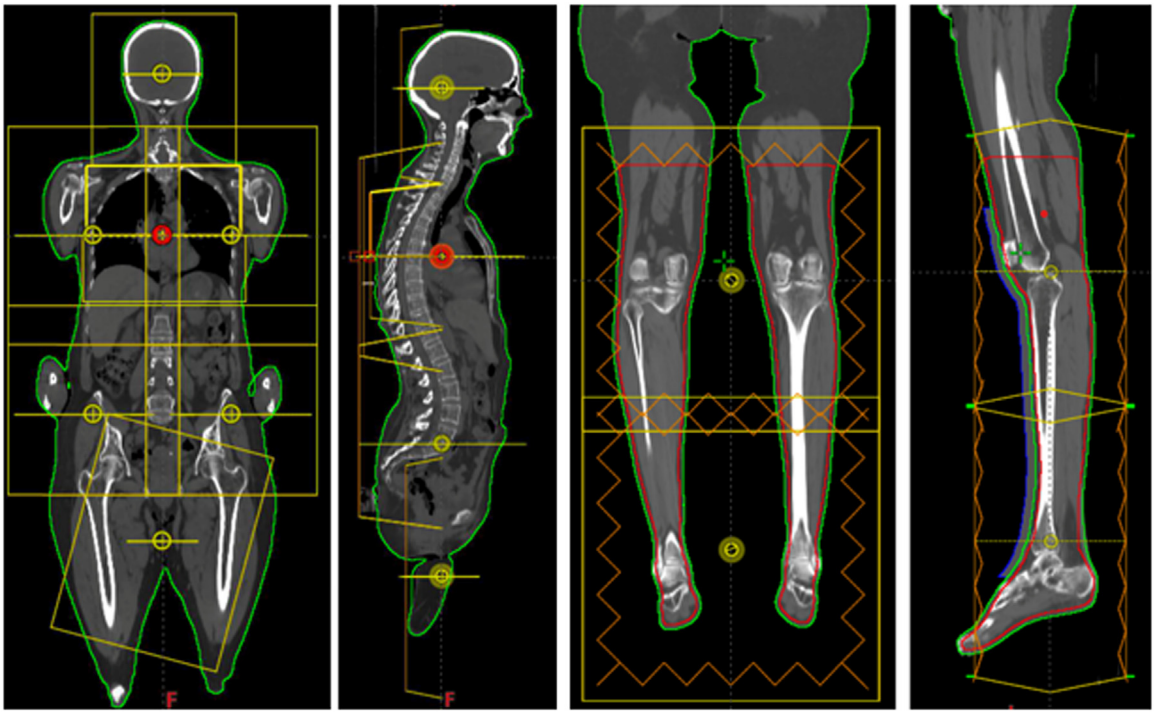

Figure 1 (Left) Coronal and sagittal views of head-first scan with standard isocenters plus lateral isocenters for chest and pelvis. (Right) Coronal and sagittal views of feet-first scan with standard 2 isocenters.

4. The remaining arc fields used to treat PTV_upper were then simultaneously optimized for coverage and organ sparing.
5. Because physician concern about lung toxicity which has previously been attributed to increased lung dose rate,[15,17-19] the dose rate for the arcs that directly irradiated the lungs was set to a decreased rate, while all other arcs were set to a rate of 600 MU/min.

Dose rate and prescription definition

Beginning in January 2021, the dose rate for the thoracic isocenters was increased from 40 to 100 MU/min to reduce the overall treatment time. Our prescription dose was based on the disease process and was determined by the treating radiation oncologist in collaboration with the bone marrow transplant (BMT) physician. The prescription ranged from 8 to 12 Gy delivered in twice-daily 2 Gy fractions with a planning aim of delivering a uniform prescription dose to at least 90% of the PTV_bodyeval. Another goal was to limit the mean dose to _lungeval, a 1 cm isotropic contraction of the lungs, to <60% of the prescription dose, although <75% was considered an acceptable deviation. All planning objectives can be found in Table 1.

Results

Between January 2019 to October 2021, a total of 29 patients were treated with VMAT TBI and met the inclusion criteria. The median age was 45 years (range, 20-69 years) and the underlying disease process was leukemia in 23 (79.3%) patients, myelodysplastic syndrome in 4 (13.8%) patients, and lymphoma in 2 (6.9%) patients. The treatment dose was 8 Gy for 21 (72.4%) patients and 12 Gy for 8 (27.6%) patients (Table 2). Thoracic isocenters were delivered at 40 MU/min for 19 (65.5%) patients and 100 MU/min for 10 (34.5%) patients. The mean lung dose was 7.9 Gy (SD, 1.4 Gy) for patients treated at 40 MU/min and 7.1 Gy (SD, 1.3 Gy) for patients treated at 100 MU/min. The modulation factor was 2.66 MU/Rx (SD, 0.5 MU/Rx) for the 40 MU/min group and 4.83 MU/Rx (SD, 1.1 MU/Rx) for the 100 MU/min group.

After haematopoietic stem cell transplatation (HSCT), patients were monitored daily by the BMT team while inpatient, and then on a biweekly or monthly basis after discharge with all toxicities documented. Acute toxicity was defined as any adverse effect occurring within 30 days of VMAT-TBI. A comprehensive description of acute toxicity is presented in Table 3. Only 1 grade 4 toxicity was observed and was due to acute kidney injury in a patient who received mean doses of 913 and 885 cGy to the left and right kidneys, respectively. This patient received a conditioning regimen of cyclophosphamide and palifermin as well as graft versus host disease prophylaxis with methotrexate and tacrolimus.

Mucositis was the most common grade 3 toxicity and occurred in 10 (34%) patients. Only 1 instance of pneumonitis was observed and occurred in a patient who received a mean lung dose of 10.1 Gy delivered at 40 MU/min with a modulation factor of 3.66.

Discussion

We performed this study to describe the clinical adverse effects among patients treated with high-dose VMAT TBI after 2 years of experience. VMAT is increasingly used for TBI delivery because of a combination of technical and clinical advantages compared with conventional TBI techniques; however, various aspects of VMAT planning and delivery are still evolving, and clinical outcomes data are lacking. Pneumonitis is a potentially devastating complication of TBI that has historically affected up to 35%[20] of patients, although more modern series have reported approximately 10%[15] of patients to be affected with the utilization of lung shielding and fractionation. In the context of conventional TBI, the rate at which dose to lung tissue is delivered has previously been shown to affect the risk of pneumonitis, [15,17-19] and our group has historically limited lung dose rate to 20 cGy/min with a standing extended field technique.

How radiation dose is delivered to lung tissue is fundamentally different between conventional TBI techniques and VMAT TBI. Conventional TBI delivers a dose to the entire lung tissue simultaneously with relatively homogeneous fluence and a consistent rate throughout the session. By contrast, modulated VMAT plans deliver doses through complex, nonuniform fluence patterns resulting in significant spatial and temporal variations in dose rate. Historically, the dose rate for conventional TBI techniques required the dose rate to the lungs to be ≤20 cGy/min to minimize the risk of radiation-induced pneumonitis.[21] However, this dose rate recommendation is no longer appropriate with intensity modulated TBI techniques as the instantaneous dose rate to small regions of an organ can be substantially greater than the mean dose rate to the entire organ. This ambiguity is likely one contributing factor in the variation in intensity modulated TBI techniques with respect to the selection of dose rate for beams treating the lungs.[19] As noted in Table 4 of the work by Kovalchuk and Simiele et al,[19] many groups elected to reduce the dose rate of the beams treating the lungs to the lowest possible dose rate or even commission special dose rates on their machines for this particular purpose. When our department transitioned to VMAT TBI, we conservatively chose to deliver the arcs that delivered the dose to the lungs at 40 MU/min but subsequently increased to 100 MU/min to reduce treatment time. Because of the

Table 2 Patient/disease characteristics and dosimetric quantities

Patient/disease characteristics		
Thoracic effective dose rate	**40 MU/min (%)**	**100 MU/min (%)**
Age, y		
Mean	43.2	44.0
Median	49.5	43.3
Range	48.6	30.7
Zubrod performance status		
0	12 (63)	1 (10)
1	7 (37)	9 (90)
Disease		
Leukemia	16 (84)	7 (70)
Myelodyplastic syndrome	1 (5)	3 (30)
Lymphoma	2 (11)	0
Dosimetric quantities		
Prescription dose		
800 cGy	13 (68)	8 (80)
1200 cGy	6 (32)	2 (20)
Mean lung dose (cGy)		
	788.1	707.8
No. lung isocenters		
4	8 (42)	0
5	11 (58)	0
6	0	10 (100)
Mean right kidney dose (cGy)		
	991.0	929.7
Mean left kidney dose (cGy)		
	995.0	933.0
Effective dose rate (MU/min)		
	39.48	96.30
MUs/Rx (modulation factor)		
	2.66	4.83

Abbreviations: MU = monitor units; Rx = prescription.

Table 3 Acute toxicity profiles for patients receiving VMAT TBI

	Grade 1 (%)	**Grade 2 (%)**	**Grade 3 (%)**	**Grade 4 (%)**	**Any grade (%)**
Fever	13 (45)	9 (21)	4 (14)	0	26 (90)
Mucositis	5 (17)	6 (21)	10 (34)	0	21 (72)
Vomiting	6 (21)	10 (34)	0	0	16 (55)
Xerostomia	2 (7)	0	0	0	2 (7)
Acute kidney injury	2 (7)	1 (3)	4 (14)	1 (3)	8 (28)
Proteinuria	3 (10)	7 (21)	0	0	10 (34)
Pneumonitis	0	1 (3)	0	0	1 (3)

Abbreviations: TBI = total body irradiation; VMAT = volumetric modulated arc therapy.

nonintuitive nature of intensity modulated dose delivery, much of the guidance regarding acceptable dose rates for VMAT TBI has been based on recent outcomes data.

To date, only 1 patient (3%) treated at our institution with VMAT TBI has experienced symptoms of pneumonitis, which were mild and met the Common Terminology Criteria for Adverse Events, version 5 criteria for grade 1 toxicity. Similar findings were reported by other groups with a low incidence of radiation-induced pneumonitis.[19,22,23] The planning objective used at our institution requires the mean lung dose to be <900 cGy, which is consistent with other groups' planning objects for the lungs (Dmean <1000 cGy).[19] Prior studies of conventional TBI have observed that the risk of pneumonitis increases with the dose rate for mean lung doses ≥800 cGy.[24] Although our planning objective exceeds the dose threshold observed by Barrett et al,[24] the nonuniform delivery using VMAT results in significant dose heterogeneity to the lung compared with dose homogeneity offered by conventional TBI. Additional work is needed to better classify lung dose characteristics in intensity modulated TBI to provide clear guidance on appropriate dose rates for this modern treatment technique.

Pneumonitis rates should be viewed in the context of both lung dose rate and mean lung dose. Patients in this cohort received an average mean lung dose of 6.8 Gy. Although data about the risk of pneumonitis after VMAT TBI are sparse, Zhang-Velten et al[9] have observed a low risk of pneumonitis when delivering lung containing arcs at 20 to 40 MU/min. Their series included patients treated with low-dose TBI (2-4 Gy in one fraction) and standard-dose TBI (12-13.2 Gy in 6-8 bid fractions), with mean lung doses of ∼8.3 Gy and ∼1.5 Gy in the standard and low-dose cohorts, respectively, which were gradually decreased as the objective goal was lowered from 75% to 50% of the prescription dose. Kovalchuck[19] found low rates of pneumonitis in patients with mean lung doses of 7.2 Gy, although their dose rate was slightly more aggressive ranging from 100 to 200 MU/min and their prescription doses were slightly higher at 12 Gy in 6 fractions (n = 10) or 13.2 Gy in 8 fractions (n = 3).

The overall most common toxicity observed in this cohort was mucositis, which was grade 3 in 10 (34%) patients and grade 2 in 6 (21%) patients. Prior studies show the incidence of grade 3+ mucositis after TBI to be as high as 71%.[9] Given the setting of concurrent chemoconditioning followed by BMT in all cases, this toxicity has been deemed multifactorial and is not felt to be directly related to radiation therapy.

Severe (grade 3 or 4) kidney injury occurred in 5 (17% of patients). This is consistent with reported allogenic transplant kidney injury incidences in the literature and is likely multifactorial in nature including the type of transplant, comorbidities, chemotherapy, medications, and radiation therapy.[25] Medications protecting the kidneys have mixed results[26] and other groups have considered the use of kidney shielding[27] as the kidney is not considered a sanctuary site.

This was a retrospective and hypothesis generating study and the limitations should be recognized. Bias is always an important consideration, and to minimize bias we used broad inclusion criteria and highlight that patients were all treated in accordance with a prespecified clinical protocol. Even though patients were followed closely, assigning toxicity scores from clinical documentation may underestimate the true rates of toxicity and do not consider patients' perspectives. Although only one documented toxicity of grade 1 pneumonitis was observed, capturing grade 1 toxicities presents a significant challenge as they are typically based on clinical examination or radiographic findings in an asymptomatic patient. The small sample size limits statistical power, and the confidence intervals of the frequency events that were observed are wide as a result. This study was performed at a single institution by a team of physicians and physicists who are experienced delivering TBI, thus the observations of these study require external validation. Despite these limitations, this is among the first studies to investigate the effect of dose rate on pneumonitis risk in the setting of VMAT TBI. The observation that pneumonitis rates were not elevated compared with what is expected with conventional TBI delivery techniques is important because it suggests that treatment may be delivered quicker to improve patient comfort and reduce the uncertainties that are associated with prolonged treatment times. Although the total number of isocenters increased from an average of 9 to 10 with the increased thoracic dose rate, the average treatment time decreased from 67 to 59 minutes (12%). Future research should confirm these findings and explore what factors are most associated with pneumonitis risk in the setting of VMAT TBI.

Conclusion

Utilization of the described VMAT TBI technique appears to be safe and feasible, with significant improvements in treatment time and dose homogeneity compared with conventional TBI methodology. Thoracic dose rate escalation to 100 MU/min in the setting of VMAT TBI did not result in increased pulmonary toxicity in our small cohort of patients.

Disclosures

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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