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A comparative study between conventional VMAT-Total Body Irradiation (TBI) and VMAT Simultaneous Integrated Marrow Boost (SIB) TBI to determine dosimetric feasibility in pediatric patients

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Abstract

Introduction

Total body irradiation (TBI) plays a critical role in the myeloablative conditioning regimen for stem cell transplantations due to its ability to deliver dose to all tissues including sanctuary sites, giving an opportunity for cure in children suffering a relapse of leukemia. VMAT-TBI techniques have become the standard practice, but toxic doses to organs at risk (OARs) can lead to long-term complications, particularly in children who are living longer as cure rates improve. The purpose of this study is to demonstrate the feasibility of a simultaneous integrated boost (SIB) TBI technique to deliver a sufficient dose to the marrow, while reducing doses to sensitive OARs.

Methods

In this retrospective study, five pediatric patients who were previously treated with the institution's traditional VMAT-TBI technique were replanned using an SIB-TBI approach. The planning aims for the conventional TBI were designed to deliver 12 Gy in six fractions to a minimum of 90% of the total body. Planning aims for the SIB-TBI technique were to deliver 12 Gy to at least 90% of the marrow and 8 Gy to at least 90% of the total body while limiting the mean lung dose to less than 8 Gy.

Results

All five patients had significant reductions in mean dose to the lungs, heart, kidneys, and bowel, while achieving 12 Gy to at least 90% of the marrow and 8 Gy to at least 90% of the total body. Additionally, coverage of sanctuary sites in the central nervous system was maintained and maximum doses less than 16 Gy (130%) were achieved in the SIB-TBI plans.

Conclusion

This study supports the feasibility of SIB-TBI technique as an alternative to the institution's conventional VMAT-TBI regimen. SIB-TBI provided adequate doses to the marrow and sanctuary sites, while delivering reduced doses to the OARs. Future research should evaluate the radiobiological effects to OARs with the reduction in dose associated with the use of an SIB-TBI technique.

Introduction

Total body irradiation (TBI) and total marrow irradiation (TMI) play a critical role in the myeloablative conditioning regimen for hematopoietic cell transplantations (HCT). The rationale for using radiation in these conditioning regiments include its ability to deliver dose to all tissues including chemotherapy-resistant sanctuary sites in the central nervous system and, among males, the testes. HCT is the transplantation of healthy hematopoietic stem cells derived from bone marrow, umbilical cord blood or from peripheral blood in patients with bone marrow depleted from TBI or TMI treatments. Although chemotherapy cures most childhood blood and marrow malignancies, nearly 15% of all children suffering from acute leukemia have poor prognostic indicators, including high risk disease or relapse, and can potentially benefit from hematopoietic cell transplantations (HCT). (1) HCT gives a curative opportunity for children and adolescents who are at high risk of relapse or who are already suffering a relapse of leukemia. In preparation for hematopoietic cell transplantations (HCT), almost all children receive TBI or TMI, as compared to many adult patients who endure less intense regimens due to age and other pre-existing medical conditions. (2)

Total body irradiation (TBI) is a form of radiation therapy that depletes the bone marrow by delivering radiation to a patient's entire body, while sparing organs at risk (OARs) such as the lungs and kidneys. Another type of radiation therapy used to destroy the bone marrow, is total marrow irradiation (TMI), which focuses the dose on the skeletal system where bone marrow is produced. Bone marrow is the soft, spongy tissue within the bones that produces hematopoietic

stem cells. Either TBI or TMI can be used, in combination with chemotherapy, prior to hematopoietic cell transplantations (HCT) for three purposes: to eliminate residual malignant cells, destroy bone marrow to allow for the engraftment of new stem cells, and to suppress the immune system to decrease the possibility of rejection of donor cells. (3)

According to the Center for International Blood and Marrow Transplant Research, more than 100,000 hematopoietic cell transplantations (HCT) were performed in the United States between 2013 – 2017. (4) Approximately 13% of these hematopoietic cell transplantations (HCT) were performed on patients under the age of 20. (4) HCT including bone marrow transplant (BMT) and hematopoietic stem cell transplant (HSCT), are used to stimulate the growth of new, healthy bone marrow to restore the immune system in patients with cancers or non-malignant disorders of the blood or bone marrow, thereby reducing the risk of relapse. Blood and marrow diseases most commonly treated with HCT in pediatric patients include acute lymphoblastic leukemia (ALL) and acute myelogenous leukemia (AML), and aplastic anemia (AA). (4) Acute lymphoblastic leukemia (ALL), a type of blood cancer which produces immature lymphocytes, is the most common type of cancer in children. Acute myelogenous leukemia (AML) originates in the bone marrow, but quickly moves into the blood system. Aplastic anemia (AA) is a rare, non-cancerous condition in which the bone marrow stops producing enough new blood cells.

Total body irradiation, combined with chemotherapy agents such as cyclophosphamide, has been used routinely since 1969 to condition patients prior to transplant. (5) Originally, a single dose of 1000 cGy was given, but this produced significant toxicities, so a multiple-fraction approach is used. (5) The most common dose and fractionation for myeloablative TBI is 12 – 15

Gy given in 8-12 fractions, 2-3 treatments per day over 4 days. (3) The variations in patient thickness and difference in tissue densities throughout a body make it difficult to achieve a uniform dose. Traditionally, TBI has been delivered using numerous techniques including extended SSD anteroposterior (AP)/posteroanterior (PA) or bilateral (treating left and right sides of the body). Treatment rooms must be large enough to accommodate the significantly extended source to skin distances (SSDs). Specially designed chairs, rotating couches, compensators, and other set-up devices are often required to administer traditional TBI treatments. In the AP/PA technique, the patient is treated both supine and prone, having to be moved between treatments, leading to possible inconsistencies in set-up and treatment. In bilateral techniques, patients are rotated from one side to another while sitting in a reclining chair or laying on a stretcher. A beam spoiler of low atomic number material is placed close to the patient to avoid the skin-sparing effects of high energy photons. (5) Additionally, heavy shielding blocks are necessary to limit the dose to organs including the lungs, kidneys, and brain. Supplemental electron boost fields are often delivered to the areas of the chest wall that were shielded by the lung blocks and to the testes of male patients to ensure adequate dose to this chemotherapy-resistant sanctuary site. Traditional TBI methods have a long application time, inadequate sparing of individual organs at risk (OARs), as well as decreased homogeneity and non-conformality of beam-application with wide variations of dose distributions from patient to patient and even within the same patient. (5)

Despite its critical role in HCT, TBI can have severe acute complications including life-threatening pneumonitis, especially when combined with concurrent chemotherapy. Radiation pneumonitis, which can occur in up to 25% of patients receiving TBI and chemotherapy as part of conditioning regimen for HCT, is injury to the lungs which causes inflammation of the alveoli

(small air sacs) in the lungs. Because TBI delivers radiation to whole organs, patients are also at risk for long term complications such as cataract formation, temporary or permanent sterility, thyroid dysfunction and nodules, kidney dysfunction, decreased bone mineral density and secondary malignancies. (6) As pediatric patients experience remission and have longer life expectancies, they are increasingly at risk for long-term consequences of high dose total body irradiation. (7)

Peñagarícano et al. studied the clinical feasibility of delivering TBI with the use of helical tomotherapy (HT) in 2011. 12 Gy was prescribed in six equal fractions at two fractions per day, over 3 days, and with a minimum 6-h interfraction interval. This helical tomotherapy (HT) study demonstrated dosimetric superiority compared to traditional TBI. HT eliminated the need for blocks, compensators, extended SSDs, beam spoilers and uncomfortable set-ups. (8) In 2015, Chakraborty et al. conducted one of the first studies evaluating the use of volumetric modulated arc therapy (VMAT) using RapidArc for total body irradiation (TBI). A dose of 12 Gy in 10 fractions was prescribed to the target volume. The VMAT-TBI technique consisted of three isocenters and three overlapping arcs: the head and neck, the chest, and the pelvis. The plans were prescribed to ensure, at a minimum, 95% planning target volume dose coverage with the prescription dose. With results similar to TBI with HT, they concluded VMAT-TBI technique could be administered using a standard treatment couch, required shorter treatment times than traditional TBI techniques and the improved dose coverage would eliminate the need for electron boost fields. (9) Tas et al. further demonstrated the feasibility of TBI using VMAT. Patients were planned and treated with VMAT-based TBI, which consisted of three isocenters and three overlapping arcs. TBI dose was prescribed to 90% of the planning treatment volume (PTV)

receiving 12 Gy in six fractions, at two fractions per day. The authors noted an increase in treatment delivery efficiency, reduced set-up and beam-on time, an increase in both conformality and homogeneity in target-dose distribution and highly conformal sparing of OARs, improved patient comfort and improved patient positioning accuracy with the use of partial kvCBCT. (10)

Volumetric modulated arc therapy (VMAT) using RapidArc for total body irradiation (TBI) provides the opportunity to target the total body while reducing overall doses and toxicity to OARs including the lungs and kidneys, but it is difficult to escalate the dose to marrow and sanctuary sites (areas resistant to chemotherapy) due to associated normal organ toxicities. Wong et al. conducted a study to evaluate the potential advantages of targeted total marrow irradiation using helical tomotherapy (HT). Treatment plans for TMI to 20 Gy were evaluated and compared with TMI to 12 Gy and conventional TBI to 12 Gy. Treatment plans were also developed using total marrow and lymphoid irradiation (TMLI), with the TMI compartment escalated to 20 Gy while liver, spleen, and brain were treated to 12 Gy and all other organs were treated as avoidance structures. Their study confirmed the ability of TMI with HT to selectively deliver myeloablative doses to skeletal bone and bone marrow, and sanctuary sites, such as the central nervous system. They were also able to selectively minimize dose to areas that were previously irradiated. (11)

Han et al., compared the results of planning total marrow irradiation with helical tomotherapy and VMAT. In the study, 12 Gy in 8 fractions was prescribed to the target volumes which included skeletal bones from the skull to the mid-thigh level, major lymph nodes, and spleen using both HT and VMAT. Plans were generated with eight arc fields to cover the entire target volumes. They concluded, in terms of adequate dose coverage and normal organ sparing

that VMAT offered a feasible alternative to HT for TMI. (12) Unlike traditional TBI treatment methods, which often require a special table, chair, stretcher, spoilers, or extreme distances, VMAT-TBI or TMI uses conventional linac table. Although traditional TBI methods provide great dose uniformity, TBI using volumetric modulated arc therapy (VMAT) can achieve optimal dose distribution while reducing the dose to surrounding healthy tissue and critical organs such as the lungs and kidneys. TMI utilizing VMAT escalates the dose to the bone marrow while sparing the surrounding normal tissue and organs. One of the disadvantages of total marrow irradiation (TMI), however, is while targeting the bone and bone marrow, reduced doses are delivered to the rest of the body which may include malignant cells in circulation or in organs outside of the target area. (6)

To combine the advantages of both TBI and TBI while overcoming the disadvantages of these techniques, a simultaneous integrated boost (SIB) VMAT technique could be used. An SIB technique allows delivery of multiple dose levels to different targets within a single treatment fraction. Jaccard et al. conducted a study employing a VMAT/SIB technique with 5 adult patients. They concluded that adding 4 Gy to increase the TMI dose from 12 Gy to 16 Gy to be feasible without increasing the dose to OAR. (13)

The purpose of this study is to investigate the dosimetric feasibility of a novel approach using a multi-prescription VMAT technique to deliver a low dose of TBI while escalating dose to the marrow using a simultaneous integrated boost technique in pediatric patients as conditioning for HCT. The researcher hypothesizes that SIB-TBI technique is a feasible alternative to traditional VMAT-TBI.

Null hypothesis (H_0): Simultaneous integrated boost TBI technique is not a feasible alternative to traditional VMAT-TBI.

Alternative hypothesis (H_a): Simultaneous integrated boost TBI technique is a feasible alternative to VMAT-TBI.

Materials and Methods

Subjects

This is a retrospective dosimetric planning study involving five pediatric patients who previously received TBI treatment with a dose of 12 Gy in 6 fractions using the institution's conventional VMAT technique. The conventional VMAT-TBI technique, which will be used for comparison, has been in use at the institution for fewer than eight months at the time of this study, limiting the number of subjects. The subjects ranged in age from four to eight years and were included in the study if their planning CT/simulation images were acquired in a single, head-first scan. The conditions for which the subjects were treated with HCT included acute lymphoblastic leukemia (ALL) and acute myelogenous leukemia (AML), and aplastic anemia (AA).

IRB

A Human Subjects Protocol form, Waiver of Authorization and Informed Consent were submitted to the institution's Institutional Review Board (IRB) outlining the purpose and methods of the study, and safeguards taken to protect the personal health information (PHI) of subjects included in the study. After the population was selected, all participants were anonymized with de-identifying software and assigned a code by the investigators. This is a

minimal risk, retrospective study which does not involve diagnostic or therapeutic intervention or direct patient contact. No participant will be individually identifiable in the presentation of this material. Grand Valley State University (GVSU) Office of Research Compliance and Integrity (ORCI)/Institutional Review Board (IRB) agreed to rely on the external IRB approved by the institution.

Simulation

Computed tomography (CT) images with a 3mm slice thickness were obtained on each patient from a single planning scan using a Philips CT scanner. Patients were simulated in the head-first supine position with arms by side to reduce potential air gaps. A thermoplastic mask on the head and neck region and a full-body vacuum bag were used for immobilization, to ensure reproducibility and consistency of daily treatment positioning. When necessary, anesthesia was administered by the institution's anesthesia department for simulation, as well as treatment. Patients were scanned from the top of the skull to the bottom of the feet. The patients' age and size allowed CT/simulator personnel to accomplish this in a single scan.

Planning

For planning and optimization, the following organs were contoured: left, right and total lung, heart, left and right kidney, small bowel, whole brain, and spinal cord. Using techniques developed by Ouyang et al (14), conventional VMAT-TBI planning was performed using Varian Eclipse ™ treatment planning system Version 15.6. A total of 6 isocenters were placed along each patient's longitudinal axis starting with the superior portion of the skull. The isocenters: Head, Chest, Abdomen, Pelvis, and Legs, were placed ensuring a minimum of 5-centimeter

overlap in the anteroposterior-defined field size for each field. Leg fields were divided into Upper Leg and Lower Leg fields when necessitated by length, using a one-centimeter bolus on the anterior Lower Leg fields from the ankle through the knee joint, one to three 6 MV photon beam VMAT arcs were used for each of the four most superior isocenters (Head, Chest, Abdomen and Pelvis). One to two AP/PA fields were used for the most inferior isocenters (Legs or Upper leg and Lower Leg). Junctions and hotspots in the AP/PA fields were balanced using a "field in field" multi-leaf collimator (MLC) sequence technique prior to optimizing the arc fields. For planning purposes, three planning target volumes (PTV) were created (Table 1): PTV_BodyEval, PTV_Upper and PTV_Lower. The PTV_BodyEval, which served as the primary target, represented the Eclipse-defined body contour with a 5mm retraction from the skin, minus the entire lung volume and any optional OARs. The PTV_Upper target was defined as the portion of the PTV_BodyEval that encompassed the VMAT arc isocenters (Head, Chest, Abdomen and Pelvis). The PTV_Lower target was defined as the portion of the PTV_BodyEval that encompassed the field in field AP/PA beam isocenters (Legs or Upper Leg and Lower Leg). The PTV_BodyEval was the sum of the PTV_Upper + the PTV_Lower targets.

The institution's prescription for conventional TBI is 12 Gy in six fractions with the intent to deliver a uniform dose of 12 Gy to a minimum of 90% of the PTV_BodyEval target. (Table 2) For optimization, a base dose plan was created by planning and calculating the PTV_Lower fields first. The remaining arc fields used to treat the PTV_Upper target were optimized simultaneously for coverage and sparing of OARs. As previous studies by Oya et al. and Son et al. have demonstrated, (15, 16) a lower dose rate of 40 MU/minute was used for arcs directly irradiating the lungs to decrease pulmonary complications including interstitial

pneumonitis. To minimize treatment time, the dose rate for all other arcs was increased to 300 MU/minute, as indicated by Held at al. (17) All conventional TBI plans were generated for, and treatments delivered on a Varian TrueBeam™ STx.

To perform the retrospective SIB-TBI plans, the entire skeleton was contoured on each patient with the auto-segmentation function for bone, including necessary corrections and cleanup using Varian Eclipse ™ treatment planning system Version 16.1. Utilizing this new contour, two additional target volumes were created to facilitate SIB-TBI planning: PTV_Marrow target and PTV_TotalBody target. (Figure 1) The entire skeleton comprised the PTV_Marrow target and the PTV_TotalBody target was defined as the PTV_BodyEval target minus the PTV_Marrow target. (Table 1) To promote adequate planning comparisons between conventional VMAT-TBI and the simultaneous integrated marrow and body approach (SIB-TBI), the 6 isocenters (Head, Chest, Abdomen, Pelvis, Upper Leg and Lower Leg) were similarly placed and the same treatment fields were used (Figure 2): one to three 6 MV photon beam VMAT arcs for the four most superior isocenters (Head, Chest, Abdomen and Pelvis), one to two AP/PA fields for the most inferior isocenters (Legs or Upper Leg and Lower Leg) utilizing modulated “field in field” MLCs at the field junctions. Each patient was planned using the SIB-TBI treatment regimen, with the goal of delivering a uniform dose of 12 Gy to at least 90% of the PTV_Marrow target and 8 Gy to at least 90% of the PTV_TotalBody target while limiting the mean lung dose to less than 8 Gy. (Table 2) As in the conventional VMAT-TBI plans, for optimization, a base dose plan was created by planning and calculating the PTV_Lower target first. The remaining arc fields used to treat the PTV_Upper target were optimized to deliver 12 Gy to the PTV_Marrow target, while simultaneously limiting the

PTV_TotalBody target to 8 Gy and sparing the OARs. A lower dose rate of 40 MU/minute was used for arcs directly irradiating the lungs to decrease pulmonary complications. The dose rate for all other arcs was increased to 300 MU/minute to minimize treatment time. The SIB-TBI plans were optimized to keep 100% of the PTV_TotalBody target receiving as close to 90% of the dose as possible and normalized so 100% of the PTV_Marrow target received at least 90% of the dose. Plans were generated for a Varian TrueBeam™ STx.

Data Analysis

Comparisons of two different plans for each patient were conducted using dose-volume histogram (DVH) analysis. OAR doses were evaluated based on mean dose to the following organs: lung, heart, kidney, bowel, whole brain, and spinal cord. The same segmentation from the planning CT for the original conventional VMAT-TBI plan was used for all evaluated OARs. The same isocenter placements and field arrangements were used for both planning techniques. Dose coverage to PTV_Marrow and PTV_TotalBody targets and central nervous system sanctuary sites was also evaluated using coverage percentage. Maximum doses were also analyzed.

All data collected through DVH evaluation was entered into an Excel spreadsheet. Statistical analyses and testing were conducted with the assistance of the Statistical Consulting Center (SCC) at GVSU using Statistical Analysis Software (SAS) version 9.4. Because of the small sample sizes, proc means were used for basic statistical analysis which generated mean and median values and standard deviations for the dose distribution to OARs including the lungs, heart, kidneys, and bowel. It was determined that p-value statistics derived from the proc means had no true meaning and were not appropriate due to small sample sizes. The mean and median

PTV coverage percentages were analyzed and calculated for the total body and marrow targets, as well as central nervous system structures, and the mean and median body maximum dose values were calculated and evaluated. Proc means and boxplots generated by SCC from the provided sample data can be seen in Table 6 and Table 7.

Results

The aim of this retrospective study is to examine the feasibility of a novel approach using a multiple prescription VMAT technique to deliver a low dose of TBI while escalating dose to the bone marrow using a simultaneous integrated marrow boost technique in pediatric patients in preparation for HCT. Skeletal contours were added, and new planning target volumes were created from the scans of five pediatric patients who previously received TBI treatment with a dose of 12 Gy in 6 fractions using the institution's conventional VMAT-TBI technique. Each patient was planned using the SIB-TBI treatment regimen, with the goal of delivering a uniform dose of 12 Gy to at least 90% of the PTV_Marrow target and CNS sanctuary sites, and 8 Gy to at least 90% of the PTV_TotalBody target, while limiting the mean lung dose to less than 8 Gy. (Table 2)

All SIB-TBI treatment plans attained 12 Gy to at least 90% of the PTV_Marrow and CNS, and 8 Gy to the PTV_Totalbody, with mean lung doses of less than 8 Gy and maximum body doses of less than 16 Gy (130%). Coverage percentages for targets and sanctuary sites, mean doses for sensitive organs and overall maximum doses for both the conventional VMAT-TBI and the SIB-TBI plans were evaluated on DVHs for each subject. (Table 3) A comparison of the average mean dose values for the lung, heart, kidneys, and bowel between the traditional VMAT-TBI technique and SIB-TBI plans demonstrated a fundamental dose reduction to these

at-risk structures in the SIB-TBI plans. A comparison of the average mean dose values to the OARs between the conventional VMAT-TBI and the SIB-TBI plans, as well as the numerical and percentage differences between the two plans is seen in Table 4.

PTV_Marrow

The PTV_Marrow had a coverage of 100% in all conventional VMAT-TBI plans due to plan normalization. In the SIB-TBI plans, the coverage of the PTV_Marrow had a range of 90.8% to 93.6%, with a mean coverage of 91.92% and a median coverage of 91.8%. (Table 3) Although proc means data demonstrated an 8.08% reduction in mean PTV_Marrow dose in the SIB-TBI plans, compared to the conventional VMAT-TBI plans, the planning aim of >/= 90% was still met.

PTV_Totalbody

In all conventional VMAT-TBI plans, the PTV_TotalBody had a coverage of 12 Gy to 100% due to plan normalization. In the SIB-TBI plans, the PTV_TotalBody, prescribed to 8 Gy, had coverage in a range of 92.5% to 95.4%, with a mean coverage of 93.92% and a median coverage of 93.9%. (Table 3) This coverage met the VMAT-TBI planning aim for the PTV_TotalBody of V 8 Gy >/= 90%.

Body Maximum

The body maximum dose for the conventional VMAT-TBI plans had a range of 14.22 Gy to 15.32 Gy, with a mean of 14.72 Gy and a median of 14.79 Gy. The body maximum dose in the SIB-TBI plans had a range of 14.54 Gy to 15.66 Gy, with a mean of 14.95 Gy and a median of 14.92 Gy. (Table 5) Proc means analysis demonstrated a 1.56% increase in the body

maximum dose in the SIB-TBI plans, compared to the conventional VMAT-TBI plans, meeting the planning aim of < 16 Gy (130%).

Lung

The lung mean dose for the conventional VMAT-TBI plans had a range of 7.71 Gy to 10.30 Gy, with a mean of 9.25 Gy and a median of 9.54 Gy. The SIB-TBI plans had a range of 6.46 Gy to 8.64 Gy, with a mean of 7.8 Gy and a median of 7.88 Gy. Proc means analysis was performed demonstrating a 15.68% reduction in mean lung dose was observed in the SIB-TBI plans, compared to the conventional VMAT-TBI plans. The planning aim of limiting the mean lung dose to less than 8 Gy was met in three of the five patients with the SIB-TBI plans. The remaining two plans had lung mean doses of 8.11 Gy and 8.64 Gy.

Heart

The heart mean dose in the conventional VMAT-TBI plans ranged from 12.28 Gy to 13.09 Gy, with a mean of 12.63 Gy and a median of 12.73 Gy. The SIB-TBI plans ranged from 9.26 Gy to 9.71 Gy, with a mean of 9.46 Gy and a median of 9.47 Gy. Proc means analysis demonstrated a 25.61% decrease in dose to the heart was noted in the SIB-TBI plans, compared to the conventional VMAT-TBI plans.

Kidney

The kidney mean dose for the conventional VMAT-TBI plans had a range of 9.83 Gy to 12.49 Gy, with a mean of 11.30 Gy and a median of 11.76 Gy. The SIB-TBI plans had a range of 8.80 Gy to 10.39 Gy, with a mean of 9.73 Gy and a median of 9.78 Gy. Proc means analysis was

performed demonstrating a 13.98% reduction in mean kidney dose was observed in the SIB-TBI plans, compared to the conventional VMAT-TBI plans.

Bowel

The bowel mean dose in the conventional VMAT-TBI plans ranged from 12.54 Gy to 12.74 Gy, with a mean of 12.67 Gy and a median of 12.73 Gy. The SIB-TBI plans ranged from 9.90 Gy to 10.14 Gy, with a mean of 10.01 Gy and a median of 10.00 Gy. After performing proc means analysis a 20.99% decrease in dose to the bowel was noted in the SIB-TBI plans, compared to the conventional VMAT-TBI plans.

Brain & Spinal Cord

The brain and spinal cord which comprise the central nervous system, are chemotherapy-resistant sanctuary sites. The SIB-TBI plans were able to accomplish sufficient coverage to the central nervous system while still producing a significant decrease in doses to the OARs. Brain coverage had a range of 89.8% to 107.1%, with a mean coverage of 99.8%. Spinal cord coverage had a range of 92.8% to 105%, with a mean coverage of 97.7% as given by proc means.

Discussion

In this study, the investigators establish the SIB-TBI technique's ability to deliver similar coverage to the PTVs and sanctuary sites as the institution's conventional VMAT-TBI, while reducing dose to susceptible OARs and other normal body tissues. The SIB-TBI demonstrated the capability of reducing the dose to normal tissues in the body periphery and achieved

appreciable reductions in organ dose to the lungs, heart, kidneys, and small bowel, while escalating the dose to the marrow-producing skeletal components.

PTV_Marrow

In this study, the SIB-TBI plans for all subjects exceeded the planning aim of 90% coverage by achieving mean PTV_Marrow coverage of 91.92%. Optimizing this plan to reduce all radiation doses outside of the PTV_Marrow, did produce an 8.08% decrease in coverage to the PTV_Marrow in the SIB_TBI plans, however, achieving > 90% coverage of 12 Gy would produce sufficient myeloablative results.

PTV_Totalbody

Researchers decreased the prescribed dose to the PTV_TotalBody dose to 8 Gy in the SIB-TBI plans as opposed to 12 Gy in the original conventional VMAT-TBI plans, which had 100% coverage of 12 Gy in conventional VMAT-TBI due to plan normalization. In the SIB-TBI plans, the PTV_TotalBody was prescribed to 8 Gy to reduce dose to normal tissues in accordance with the ALARA principle to keep exposures “as low as is reasonably achievable.” The PTV_TotalBody had a mean coverage of 93.92% which was sufficient to meet the planning aim of >/= 90%, delivering an adequate dose to malignant cells in circulation or in organs outside of the target area.

Body Maximum

Utilizing a simultaneous integrated boost technique to escalate dose to the bone marrow, while minimizing the dose outside the PTV_Marrow in the SIB-TBI plans, produced a slight increase in the body maximum doses compared to the traditional VMAT-TBI plans. Although

the SIB-TBI body maximum dose of 14.95 Gy was 1.56% greater than the traditional VMAT-TBI dose of 14.72 Gy, it remained under 16 Gy (130%), satisfying the study's planning goals.

Lung

In this study, a 15.68% reduction in mean lung dose was observed in the SIB-TBI plans, compared to the conventional VMAT-TBI plans. In three of the five SIB-TBI plans, the planning aim, limiting the mean lung dose to less than 8 Gy was met. A reduction in radiation dose to the lungs could decrease the incidence of late effects including pulmonary fibrosis, scarring and pneumonitis, although according to QUANTEC, even a mean dose of 7 Gy has a 5% risk of symptomatic pneumonitis. (18)

Heart

The researchers found a marked decrease of 25.61% in mean heart dose from 12.73 Gy in the conventional VMAT-TBI plans to 9.46 Gy in the SIB-TBI plans This reduction in dose can potentially reduce the likelihood of future complications associated with radiation-induced cardiotoxicity.

Kidney

The SIB-TBI plans in the study produced a 13.98% smaller mean kidney dose than the traditional VMAT-TBI plans, reducing the mean kidney dose from 11.3 Gy to 9.73 Gy. Decreasing the dose of radiation to the kidneys may reduce the risk of severe complications including chronic radiation nephropathy which can cause renal insufficiency and potential renal failure.

Bowel

The researchers found a 20.99% decrease in mean bowel dose from the traditional VMAT-TBI plans compared to the SIB-TBI plans, which had mean bowel doses of 12.67 Gy and 10.01 Gy, respectively. The risk of chronic radiation enteritis including symptoms of pain, nausea, bloating and diarrhea, could be significantly decreased with a reduction in the amount of radiation delivered to the small bowel.

Brain & spinal cord

Because of the difficulty of chemotherapy drugs to adequately penetrate the brain and spinal cord, it is crucial to deliver sufficient doses of radiation to these areas. Although researchers noted a decrease in the average maximum doses to the brain of 4.68% and spinal cord of 2.07%, necessary doses were received by these central nervous system sanctuary sites with the SIB-TBI plans.

Limitations and future research

The main limitation of this study was the number of patients available for investigation. The conventional VMAT-TBI technique had only been in use at the institution for a short time when the study was implemented. In addition, the study presumes a reduction in dose to sensitive OARs will produce an improvement in radiobiological effects to these organs, without a specific focus in this area. During the study, investigators noted the time involved in precisely contouring the entire skeleton to create the PTV_Marrow is a potential significant drawback to the SIB-TBI technique, as it produced a substantial increase in planning time. Future research could include a larger sample group of pediatric patients, could extend to adult patients and the utilization of

auto-contouring and auto-planning software could be employed to increase the speed and standardization of cases. A structured, long-term clinical trial, utilizing the SIB-TBI technique could be conducted to evaluate the specific radiobiological effects of reduced doses to the lungs, heart, kidneys, and small bowel.

Conclusion

With higher cure rates and longer life expectancies of HCT recipients, it is crucial to reduce radiation toxicity and injury to sensitive OARs. Because TBI delivers radiation to the whole body, pediatric patients are at increased risk for significant long-term complications including cardiac dysfunction, renal insufficiency, temporary or permanent sterility and secondary malignancies. (6) SIB-TBI technique has demonstrated the ability to deliver prescribed PTV coverage while significantly reducing radiation doses to critical organs, including the lungs, heart, kidneys, and bowel. (Figure 3)

The mean dose reduction to numerous OARs achieved with the SIB-TBI technique compared to the traditional VMAT-TBI is evident in Table 4. The dose delivered to all radiosensitive OARs in the SIB-TBI technique was less than the prescribed dose. Lung doses were reduced on average 15.68%, heart dose was reduced on average 25.61%, kidney doses were reduced on average 13.98%, and bowel dose was reduced on average 20.99%, in comparing traditional VMAT-TBI treatments to the SIB-TBI approach. In addition, the SIB-TBI technique provided adequate coverage to CNS sanctuary sites, only demonstrating slight reductions in mean dose to the brain (4.68%) and spinal cord (2.07%) as seen in Table 5.

This study demonstrates the dosimetric feasibility of the SIB-TBI technique in pediatric patients as an alternative to traditional VMAT-TBI techniques. Further research is needed to study the radiobiological effects to OARs with the reduction in dose attributed to the use of the SIB-TBI approach. Additionally, studies should be conducted to evaluate this technique in adult subjects and to employ methods to increase the speed of acquiring marrow contours. The institution is currently in the process of installing a Varian Halcyon™ treatment machine with Ethos™ adaptive therapy intelligence. The current study has been discontinued in an effort to adapt the SIB-TBI technique for treatment on this equipment. At the completion of installation and acceptance testing, the newly adapted SIB-TBI technique will be used on the Varian Halcyon™ with Ethos™ and future studies will commence.

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Table 1. Target and PTV evaluations defined by volume for VMAT-TBI and SIB-TBI planning.

Target	Target defined - VMAT-TBI	Target defined - SIB-TBI
PTV_BodyEval	Automatically generated external contour with a 5mm uniform retraction away from the skin minus lung volume and optional OARs	
PTV_Upper	The portion of PTV_BodyEval that encompasses the VMAT arc isocenters: head, chest, abdomen & pelvis	
PTV_Lower	The portion of the PTV_BodyEval that encompasses the AP/PA (field in field) isocenters: upper and lower leg	
PTV_Marrow	n/a	Contoured skeletal system
PTV_TotalBody	n/a	PTV_BodyEval minus PTV_Marrow

Table 2. Conventional VMAT-TBI and SIB-TBI planning aims.

Name of Structure	Conventional VMAT-TBI	SIB-TBI 12 Gy/8 Gy
PTV_BodyEval	Dmax < 16 Gy	Dmax < 16 Gy
PTV_TotalBody	V 12 Gy >/= 90%	V 8 Gy >/= 90%
PTV_Marrow	n/a	V 12 Gy >/= 90%
Lungs	Dmean </= 8 Gy	Dmean </= 8 Gy
Heart	D 0.1 cm^3 < 15 Gy	D 0.1 cm^3 < 15 Gy
Kidney (individual)	Dmean < 13 Gy	D 0.1 cm^3 < 13 Gy
SmallBowel	D 0.1 cm^3 < 15 Gy	D 0.1 cm^3 < 15 Gy
WholeBrain	D 0.1 cm^3 < 15 Gy	D 0.1 cm^3 < 15 Gy
SpinalCord	D 0.1 cm^3 < 15 Gy	Dmin >/= 90% D 0.1 cm^3 < 15 Gy

Table 3. Summary of PTV coverage percentages between Conventional VMAT-TBI and SIB-TBI.

Structure	Conventional VMAT-TBI	SIB-TBI 12 Gy/8 Gy
	Coverage (%)	Coverage (%)
PTV_Marrow	100	91.92
PTV_TotalBody	100	93.92

Table 4. Comparison of average mean dose values for OARs between Conventional VMAT-TBI and SIB-TBI.

OAR	Conventional VMAT-TBI	SIB-TBI 12 Gy/8 Gy	Difference	
	Average Mean Dose (Gy)	Average Mean Dose (Gy)	Amount	(%)
Lung	9.25	7.8	1.45	15.68
Heart	12.73	9.46	3.26	25.61
Kidney	11.3	9.73	1.58	13.98
Small Bowel	12.67	10.01	2.66	20.99

Table 5. Max dose values between Conventional VMAT-TBI and SIB-TBI. *Negative values indicate an increase in dose.

Structure	Conventional VMAT-TBI	SIB-TBI 12 Gy/8 Gy	Difference	
	Average Max Dose (Gy)	Average Max Dose (Gy)	Amount	(%)
Body	14.72	14.95	-.23*	-1.56*
Whole Brain	13.86	13.21	.65	4.68
Spinal Cord	14.04	13.75	.29	2.07

Table 6. Proc means table displays the mean, median, maximum, minimum dose, and standard deviations from comparisons between traditional VMAT-TBI and SIB-TBI treatment plans.

Measure	N Obs	Variable	Label	N	Minimum	Median	Maximum	Mean	Std Dev
Body Max Dose	5	Traditional_VMAT	Traditional_VMAT	5	14.22	14.79	15.32	14.72	0.42
		Simultaneous_VMAT	Simultaneous_VMAT	5	14.54	14.92	15.66	14.95	0.44
		diff	TVMAT - SVMAT	5	-0.34	-0.22	-0.13	-0.23	0.10
Bowel Mean Dose	5	Traditional_VMAT	Traditional_VMAT	3	12.54	12.73	12.74	12.67	0.11
		Simultaneous_VMAT	Simultaneous_VMAT	3	9.90	10.00	10.14	10.01	0.12
		diff	TVMAT - SVMAT	3	2.40	2.73	2.84	2.66	0.23
Coverage PTV_Marrow	5	Traditional_VMAT	Traditional_VMAT	5	100.00	100.00	100.00	100.00	0.00
		Simultaneous_VMAT	Simultaneous_VMAT	5	90.80	91.80	93.60	91.92	1.08
		diff	TVMAT - SVMAT	5	6.40	8.20	9.20	8.08	1.08
Coverage PTV_Total Body	5	Traditional_VMAT	Traditional_VMAT	5	100.00	100.00	100.00	100.00	0.00
		Simultaneous_VMAT	Simultaneous_VMAT	5	92.50	93.90	95.40	93.92	1.11
		diff	TVMAT - SVMAT	5	4.60	6.10	7.50	6.08	1.11
Heart Mean Dose	5	Traditional_VMAT	Traditional_VMAT	5	12.28	12.63	13.09	12.73	0.35
		Simultaneous_VMAT	Simultaneous_VMAT	5	9.26	9.47	9.71	9.46	0.17
		diff	TVMAT - SVMAT	5	2.91	3.36	3.62	3.26	0.28
Kidney Mean Dose	5	Traditional_VMAT	Traditional_VMAT	5	9.83	11.76	12.49	11.30	1.18
		Simultaneous_VMAT	Simultaneous_VMAT	5	8.80	9.78	10.39	9.73	0.62
		diff	TVMAT - SVMAT	5	0.32	1.98	2.10	1.58	0.74
Lung Mean Dose	5	Traditional_VMAT	Traditional_VMAT	5	7.71	9.54	10.30	9.25	1.00
		Simultaneous_VMAT	Simultaneous_VMAT	5	6.46	7.88	8.64	7.80	0.88
		diff	TVMAT - SVMAT	5	1.25	1.42	1.67	1.45	0.20
Spinal Cord Max Dose	5	Traditional_VMAT	Traditional_VMAT	5	13.38	14.22	14.71	14.04	0.61
		Simultaneous_VMAT	Simultaneous_VMAT	5	13.07	13.99	14.39	13.75	0.61
		diff	TVMAT - SVMAT	5	0.24	0.30	0.34	0.29	0.05
Spinal Cord Mean Dose	5	Traditional_VMAT	Traditional_VMAT	5	11.36	11.82	12.94	12.01	0.66
		Simultaneous_VMAT	Simultaneous_VMAT	5	11.14	11.56	12.61	11.73	0.64
		diff	TVMAT - SVMAT	5	0.22	0.26	0.35	0.28	0.05
Whole Brain Max Dose	5	Traditional_VMAT	Traditional_VMAT	5	13.15	13.93	14.50	13.83	0.54
		Simultaneous_VMAT	Simultaneous_VMAT	5	12.53	13.27	13.85	13.21	0.52
		diff	TVMAT - SVMAT	5	0.53	0.63	0.66	0.62	0.05
Whole Brain Mean Dose	5	Traditional_VMAT	Traditional_VMAT	5	10.94	12.47	13.45	12.45	0.94
		Simultaneous_VMAT	Simultaneous_VMAT	5	10.42	11.89	12.85	11.88	0.91
		diff	TVMAT - SVMAT	5	0.52	0.58	0.60	0.57	0.03

Table 7. Boxplots representing the average mean dose values for OARs between Conventional VMAT-TBI and SIB-TBI.

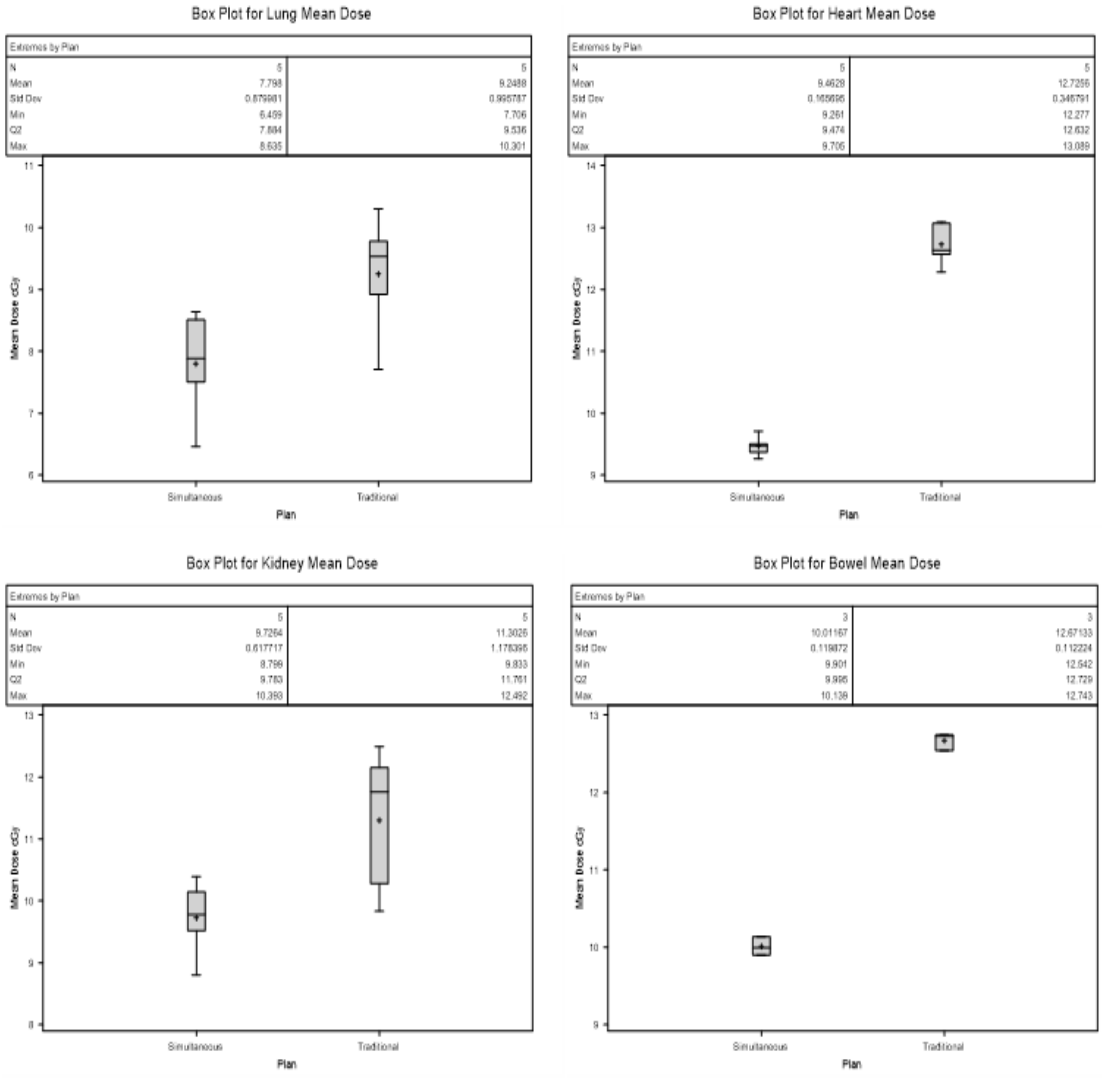

Figure 1. Targets for a representative patient. (Left) Conventional VMAT-TBI target: PTV_BodyEval, (Middle) PTV_Marrow, (Right) SIB-TBI targets: PTV_TotalBody and PTV_Marrow.

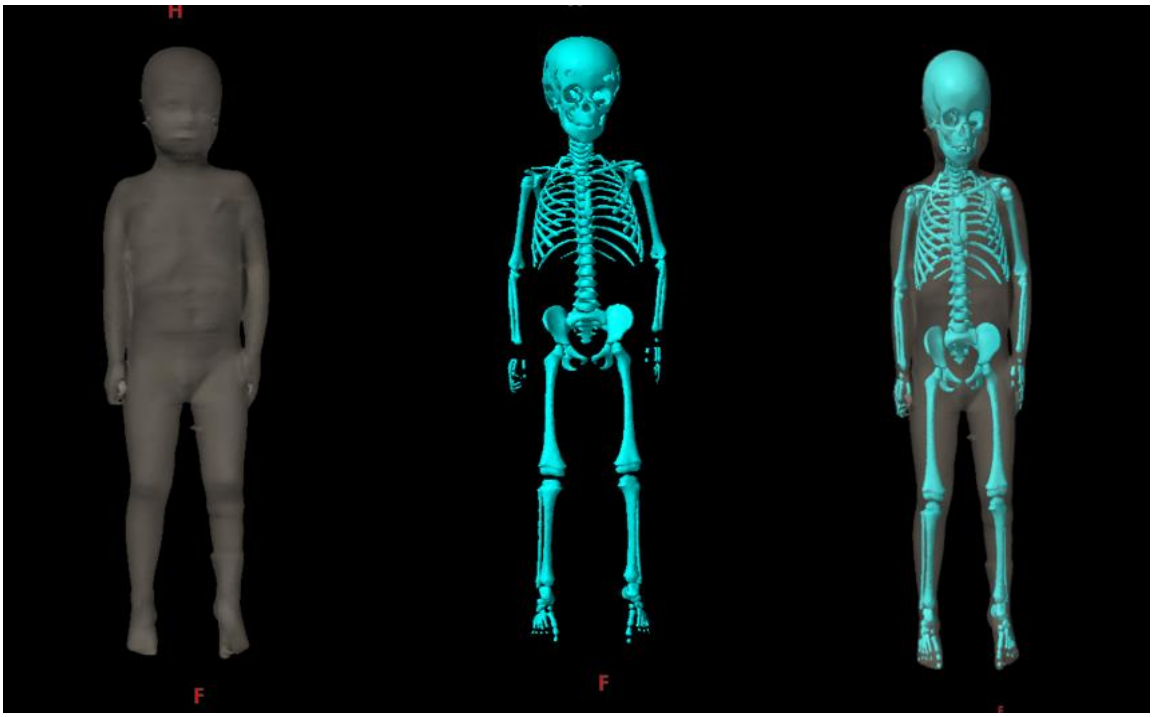

Figure 2. The same treatment fields and isocenters were used for Conventional VMAT-TBI and SIB-TBI.

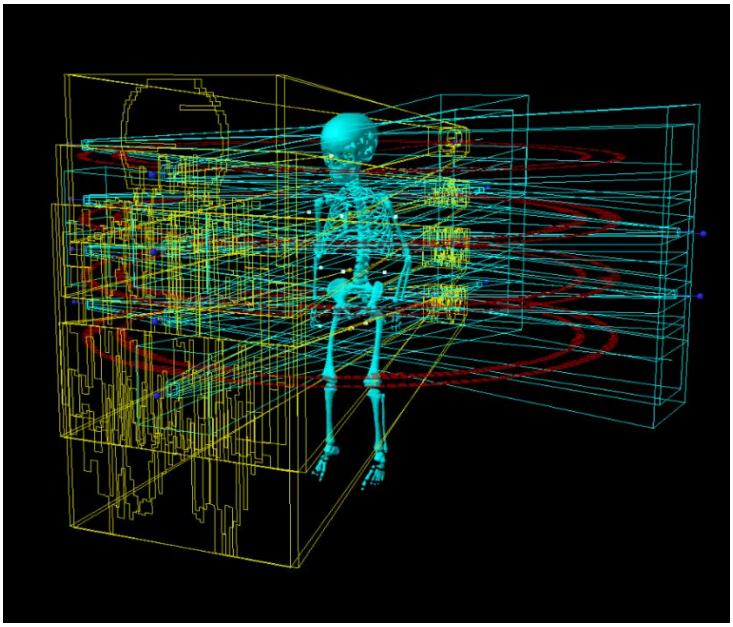

Figure 3. Colorwash presentation of representative axial slice for Conventional VMAT-TBI (top) and SIB-TBI (bottom).