Technical note

Dose-escalated volumetric modulated arc therapy for total marrow irradiation: A feasibility dosimetric study with 4DCT planning and simultaneous integrated boost

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ABSTRACT

Purpose: To evaluate the planning feasibility of dose-escalated total marrow irradiation (TMI) with simultaneous integrated boost (SIB) to the active bone marrow (ABM) using volumetric modulated arc therapy (VMAT), and to assess the impact of using planning organs at risk (OAR) volumes (PRV) accounting for breathing motion in the optimization.

Methods: Five patients underwent whole-body CT and thoraco-abdominal 4DCT. A planning target volume (PTV) including all bones and ABM was contoured on each whole-body CT. PRV of selected OAR (liver, heart, kidneys, lungs, spleen, stomach) were determined with 4DCT. Planning consisted of 9–10 full 6 MV photon VMAT arcs. Four plans were created for each patient with 12 Gy prescribed to the PTV, with or without an additional 4 Gy SIB to the ABM. Planning dose constraints were set on the OAR or on the PRV. Planning objective was a PTV $D_{mean} < 110\%$ of the prescribed dose, a PTV $V_{110\%} < 50\%$, and OAR $D_{mean} \leq 50\text{--}60\%$.

Results: PTV $D_{mean} < 110\%$ was accomplished for most plans ($n = 18/20$), while all achieved $V_{110\%} < 50\%$. SIB plans succeeded to optimally cover the boost volume (median ABM $D_{mean} = 16.3$ Gy) and resulted in similar OAR sparing compared to plans without SIB (median OAR $D_{mean} = 40\text{--}54\%$ of the ABM prescribed dose). No statistically significant differences between plans optimized with constraints on OAR or PRV were found.

Conclusions: Adding a 4 Gy SIB to the ABM for TMI is feasible with VMAT technique, and results in OAR sparing similar to plans without SIB. Setting dose constraints on PRV does not impair PTV dosimetric parameters.

1. Introduction

Total body irradiation (TBI), associated to supra-lethal doses of chemotherapeutic agents, plays an essential role in the conditioning regimen for bone marrow transplantation (BMT) in patients with hematologic malignancies [1–5]. Slow-cycling bone marrow hematopoietic bone marrow stem cells may have limited radiosensitivity but a relatively high sensitivity to fractionation changes, favoring single-dose TBI or dose escalated protocols [6,7]. There is concern that the dose needed for their eradication in order to improve relapse-free survival figures might result in unacceptable toxicity with standard TBI [8–11]. Of note, randomized trials have shown decreased relapse rates in patients with acute myelogenous leukemia (AML) and chronic myelogenous leukemia (CML) with higher TBI dose [8,9,12]. Overall survival,

however, has remained unchanged because of increased toxicity and treatment related mortality.

The implementation of modern radiotherapy (RT) techniques such as intensity-modulated RT (IMRT) or volumetric modulated arc therapy (VMAT) has introduced the possibility of more targeted forms of TBI, referred to as total marrow (TMI), total lymphoid (TLI) or combined total marrow and lymphoid irradiation (TMLI). Various studies have demonstrated the feasibility of using IMRT or helical tomotherapy (HT) for TMI, and their benefit for dose sparing of organs at risk (OAR) [13–21]. Moreover, dosimetric comparative studies showed that the use of VMAT could further improve the dose sparing of some OAR and significantly decrease the delivery time compared to IMRT or HT [22–26]. In addition to contributing in OAR sparing, the use of more conformal delivery techniques allows dose escalation in (or in selected

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parts of) the target volume as a way to improve survival figures.

The accurate delivery of conformal RT techniques is closely dependent on the correct patient daily repositioning at linac. Modern image-guided RT and efficient immobilization devices are therefore essential to reduce interfraction motion [27,28]. However, to treat tumors the thoraco-abdominal region, it is also crucial to take into account the intrafraction organ motion related to patient breathing.

The aim of this pilot study was to evaluate the treatment planning feasibility of a dose-escalated TMI program with simultaneous integrated boost (SIB) to the active bone marrow (ABM) using a VMAT technique. The hypothesis prompting this dosimetric investigation was that delivering a higher dose to the metabolically active part of the marrow could help to improve event-free survival in TMI patients. We intended to compare optimized treatment plans with and without SIB in terms of planning target volume (PTV) dosimetric parameters and OAR sparing. Furthermore, using 4DCT imaging to determine the planning at risk volumes (PRV) of the main OAR in the thoraco-abdominal region, we evaluated the dosimetric impact of sparing the PRV rather than the OAR in the plan optimization. This is the first dosimetric study investigating the feasibility of VMAT TMI including a SIB and the first attempt to set dosimetric constraints on PRV as a way to take into account the OAR breathing motion during treatment delivery.

2. Materials and methods

Five adult patients with hematological malignancies and candidates for conditioning with TBI before allogeneic stem cell transplantation were enrolled in this study. All patients provided a written informed consent and the study was approved by the local ethical committee (CER: 13–138). For treatment planning purposes, all patients underwent a simulation procedure lying supine, arms alongside the body, and ankles placed in a Combifix device (Civco Medical Solutions, Orange City, USA). Thermoplastic contentions to immobilize the head and neck and the pelvic region were not used as this was a dosimetric study. Two CT sets of images were acquired for each patient: a whole-body free-breathing CT (WBFB CT) from top of the head to the mid-thigh with 5 mm axial slice thickness, and a 4DCT of the thoraco-abdominal region with 3 mm axial slice thickness.

Contouring was performed in the corresponding module of the treatment planning system (TPS) Eclipse version 10.0 (Varian Medical Systems, Palo Alto, USA). The clinical target volume (CTV) included the skeleton from the top of the head to mid-femurs, excluding the mandible, maxillary bones and hands. Isolated bones were contoured as a single connected outline, more specifically the ribs, the clavicles, the shoulders and the forearms [22]. The planning target volume (PTV) was defined by adding a 3-mm isotropic expansion to the CTV following guidelines of similar TMI planning studies [14–16,20]. For the plans including a dose escalation with a SIB, the active bone marrow (ABM) volume was defined as the lumbar and thoracic spine as well as the pelvis, except for the sacrum, since the former contain approximately 60% of all active bone marrow [29]. A 1-mm external wall was subtracted from the above mentioned bone structure to obtain the final ABM volume (Fig. 1). No extra PTV margin was added.

The OAR included the brain, eyes, optic nerves, lenses, parotids, oral cavity, larynx, thyroid, lungs, heart, esophagus, liver, spleen, stomach, kidneys, bladder, rectum, uterus and vagina, prostate and external genitals. OAR were defined according to the RTOG guidelines when available. Selected OAR in the thoraco-abdominal region (heart, liver, lungs, kidneys, spleen, and stomach) were contoured on the 10 respiratory phases of the 4DCT. For each of these OAR, a PRV was created on the WBFB CT by accumulation of the OAR contours outlined on the 4DCT phases.

Treatment plans were created on the WBFB CT in Eclipse, optimized with the Progressive Resolution Optimizer (PRO v.10.0) and calculated with Analytical Anisotropic Algorithm AAA algorithm (v.10.0) with a calculation grid size of 2.5 mm. The prescribed dose to the PTV was

Fig. 1. Clinical target volume outline for total marrow irradiation to 12 Gy (yellow outline) with a simultaneous integrated boost to 16 Gy to the active bone marrow (red outline), defined as the lumbar and thoracic spine as well as the pelvis, except for the sacrum. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

12 Gy delivered in 6 fractions of 2 Gy. For the SIB technique, 16 Gy in 6 fractions of 2.67 Gy were planned to be delivered to the ABM simultaneously to the standard dose prescription to the PTV.

Two different plans were created for each prescription with different optimization strategies on OAR. For the VMAT and VMAT-SIB plans, we set the optimization dose constraints on the OAR, while for VMAT-PRV and VMAT-PRV-SIB, dose constraints were applied to the PRV. The plans without SIB were created before those with SIB, and the same dose values constraints and weights were used for OAR and PRV in the optimization objectives of the plans with or without SIB. This resulted in four treatment plans per patient. All plans were created and optimized by the same physicist (MR).

We planned to treat with 9 to 10 adjacent full VMAT coplanar arcs of 6 MV photon beams arranged along the patient's longitudinal axis, with a 10 cm distance between each isocentre, in a similar way as described by Fogliata *et al.* [22]. All isocenters had the same lateral and anteroposterior (AP) coordinates, hence for the treatment only longitudinal shifts would be needed. There was an overlap region between arcs of approximately 4 cm, depending on patient's size. The collimator angle was set to 90° for all arcs, with jaws set to 40 cm (y-axis) and 14 cm (x-axis). Plans were calculated to be delivered with a Clinac 2300iX (Varian Medical Systems) mounted with a Millenium™ multi-leaf collimator, with leaves of 5 mm width in the central region (20 cm × 20 cm) and of 10 mm in the outer part. We used the maximum available dose-rate of 600 MU/min.

All plans were normalized such that 100% of the prescribed dose was delivered to at least 85% of the PTV ($D_{85\%} = 100\%$ or $V_{100\%} =$

85%) in agreement with published TMI planning studies [20,22,23,30]. Planning aimed to achieve a PTV $D_{\text{mean}} < 110\%$ of the prescribed dose (13.2 Gy), a $V_{110\%} < 50\%$ and a $D_{1\%}$ as low as reasonably achievable. In analogy with other TMI studies [13,16,18,22,23] for the OAR, the present dosimetric study required $D_{\text{mean}} \leq 50\text{--}60\%$ of the prescription dose (i.e., 6 to 7.2 Gy) in order to half the dose received by the same OAR with a TBI and the same prescribed dose.

PTV and ABM volumes as well as the cranio-caudal PTV length were extracted from the WBFB CT for all patients. In the present study, we focused our analysis on the main OAR of the thoraco-abdominal region (heart, liver, lungs, kidneys, spleen, and stomach). OAR and PRV volumes were compared. OAR D_{mean} in each of the four plans were extracted from the TPS and differences between groups analyzed.

Statistical analyses were carried out using the software SPSS (v.24, IBM, Chicago, USA). Significance levels for the difference between dosimetric parameters (plans with or without SIB and plans with or without PRV) were determined using the non-parametric related-samples Wilcoxon signed-rank test, with p -values ≤ 0.05 considered as statistically significant.

All patients in this dosimetric study were treated with standard TBI using a pair of AP-posteroanterior 6 MV photon opposed fields with adequate lung shielding as routinely performed in our department [31,32].

3. Results

Table 1 shows median PTV and ABM volumes, as well as the PTV length of the five patients included in this study. For the patient with the shortest PTV length (i.e. 88.4 cm), we used only 9 isocenters for the planning, while the treatment plans of the other four patients required 10 isocenters. OAR and PTV volumes as contoured on the WBFB are reported in Table 2. Using a 4DCT to create PRV, the average median volume of OAR contoured on WBFB CT increased by 27%. The smallest relative median increase occurred for the liver (10%) and the largest for the heart (39%) (Table 2).

All plans were normalized to ensure that the prescribed dose of 12 Gy covered at least 85% of the PTV. The goal of delivering to the PTV a $D_{\text{mean}} < 13.2$ Gy was respected for all plans but two (for which PTV D_{mean} was 13.3 Gy). Furthermore, all plans achieved the goal of a $V_{110\%} < 50\%$ (Table 3). The SIB plans succeeded to cover the ABM with a D_{mean} close to the prescribed dose of 16 Gy, as well as a $V_{100\%}$ ranging between 60 and 80% of the ABM volume. Regarding the OAR, the constraint $D_{\text{mean}} < 50\text{--}60\%$ was respected in most cases for the heart, kidneys and stomach. There was less compliance for the liver and the spleen ($D_{\text{mean}} \approx 65\%$), and for the lungs ($D_{\text{mean}} \approx 70\text{--}75\%$) (Table 3).

Fig. 2 illustrates the color-wash dose distribution for the standard dose TMI plan (12 Gy) (a) compared to a dose-escalated TMI (16 Gy to the ABM) (b). Median PTV D_{mean} and $V_{110\%}$ were similar in plans with or without SIB (Table 3), while $D_{1\%}$ was higher in plans with SIB in accordance with the prescription. Surprisingly, VMAT-SIB plans resulted in better OAR sparing than plans without SIB, with a statistically

Table 2

Median [min–max] volume of OAR from free-breathing CT scan and PRV from 4DCT scan, and median volume increase from OAR to PRV.

	OAR volume (cm ³)	PRV volume (cm ³)	Median volume increase (%)	Median volume increase (cm ³)
Heart	481.4 [399.0–708.6]	604 [494.7–984.2]	38.9	193.0
Liver	1582.1 [1119.2–2421.1]	1745.34 [1198.4–2542.1]	10.3	163.3
Lungs	2398.0 [1651.7–2986.3]	2441 [2045.1–3946.5]	12.0	325.0
Kidneys	337.1 [233.9–353.6]	419.28 [301.5–453.1]	29.0	88.9
Spleen	137.5 [57.5–991.6]	227.7 [79.8–995.6]	34.3	30.7
Stomach	443.3 [140.6–668.7]	612.3 [271.4–790.7]	38.1	161.0

Abbreviations: OAR: organs at risk; PRV: planning organs at risk volume.

significant reduction (–6%) in median doses to the OAR (Table 3). The number of monitor units (MU) was 33% larger in plans with SIB, as expected since the delivery of a higher dose requires in general more MU.

Finally, our data show that performing the optimization with constraints set on the PRV did not negatively impact the PTV or ABM dosimetric results. Indeed there were no statistically significant differences when comparing the plans VMAT vs. VMAT-PRV and VMAT-SIB vs. VMAT-PRV-SIB, both for the target volumes (Table 2 and Fig. 3) and for the OAR (Table 2).

4. Discussion

TBI is a key component in the treatment management of patients with hematologic malignancies and studies have shown that higher dose may be associated with a reduced post-transplant relapse probability [12]. However, the dose that can be delivered by TBI is limited by toxicity. More targeted irradiation techniques increasing the dose delivered to the target and sculpting the dose around the OAR can represent a treatment strategy able to improve the therapeutic ratio in patients who are candidates for BMT.

Emerging TMI techniques with HT [16–18,20,33] or fixed gantry linac IMRT [13,15] have reported substantial reduction of normal tissue dose relative to conventional TBI, with median doses to OARs about 15–65% of the prescribed target volume dose. Early clinical results have suggested a reduced risk of acute toxicity in patients with targeted TBI (TMI, TLI, TMLI) compared to those receiving standard TBI and other standard conditioning regimens [20,34–36]. In addition, HT has also been used to further increase the dose to the total bone marrow after a standard TBI, a treatment which was associated with a low rate of severe toxicity [37].

In the present study, we undertook a dosimetric optimization effort for five patients planned with VMAT for TMI with or without an SIB to the ABM. Results on this small sample showed that adding an SIB to the ABM did not negatively impact the PTV dose in terms of D_{mean} and $V_{110\%}$ while achieving a fair sparing of OAR in the thoracic region. Patients in this study underwent a 4DCT in order to define, for selected OAR, their respective PRV in the thoraco-abdominal region, thus helping to account for possible organs motion during treatment. Treatment planning with or without SIB was repeated, setting dose constraints on the PRV instead of the OAR during the optimization process. There was no dose distribution impairment to the PTV when setting the constraints on PRV.

The role of a VMAT for TMI was investigated in several publications [22,23]. Stated OAR doses were slightly reduced compared to HT and ranged between 5 and 50% of the prescribed dose. Moreover the beam-

Table 1
Geometric characteristics of target volumes for TMI treatment planning.

	Median [min–max]
PTV volume (cm ³)	6828.1 [5982.4–8921.5]
PTV length (cm)	93.0 [88.4–99.1]
ABM volume (cm ³)	660.1 [576.3–965.8]

Abbreviations: TMI: total marrow irradiation; PTV: planning target volume; ABM: active bone marrow.

Table 3

Dosimetric parameters for the four optimization plans (VMAT: plans without SIB and constraints set on the OAR, VMAT-SIB: plans with SIB and constraints set on the OAR, VMAT-PRV: plans without SIB and constraints set on the PRV and VMAT-PRV-SIB: plans with SIB and constraints set on the PRV). Median, minimum and maximum values are presented. The * indicate medians which are significantly different than the corresponding median for the plan without SIB.

		VMAT	VMAT-SIB	VMAT-PRV	VMAT-PRV-SIB
PTV	D_{mean} (Gy)	12.9	13.2	12.9	13.3
		[12.8–13.3]	[13.0–13.2]	[12.8–13.0]	[13.2–13.3]
	$V_{110\%}$ (%)	37.6	33.9	41.4	35.5
		[29.7–48.8]	[30.0–34.6]	[32.4–47.3]	[33.0–38.0]
ABM	$D_{1\%}$ (Gy)	14.3	17.2*	14.5	17.3*
		[14.0–15.2]	[15.7–17.3]	[14.2–14.7]	[17.0–17.5]
	D_{mean} (Gy)	NA	16.3	NA	16.4
			[16.2–16.5]		[16.3–16.5]
OAR	$V_{100\%}$ (%)	NA	62.0	NA	69.0
			[60.1–80.0]		[61.7–80.5]
	$V_{110\%}$ (%)	NA	0.1	NA	0.9
			[0.0–1.3]		[0.1–5.1]
OAR	D_{mean} (Gy)	7.1	6.6*	6.8	6.4*
		[6.9–7.9]	[6.5–6.7]		[6.4–6.6]
	Liver	8.0	7.5*	8.0	7.4*
		[7.7–8.1]	[7.2–7.6]		[7.0–7.8]
	Lungs	9.1	8.6*	9.1	8.6*
		[8.8–9.4]	[8.3–8.7]		[8.3–8.7]
	Kidneys	7.3	7.0*	7.2	6.8*
Total MU number					
per plans					

Abbreviations: OAR: organs at risk; PRV: planning organs at risk volume; SIB: simultaneous integrated boost; PTV: planning target volume; ABM: active bone marrow; D_{mean} : mean dose received by the volume; $V_{X\%}$: volume receiving X% of the prescribed dose; $D_{1\%}$: dose received by 1% of the volume; MU: monitor units.

on time with VMAT was reported to be less than 20 min (e.g. 11, 13, and 18 min reported by Han *et al.* [24], Fogliata *et al.* [22] and Aydogan *et al.* [23], respectively), while a wider range of beam-on times was obtained with HT, from 16 [19] to 50 min [18,20]. The dose to the OAR reported in the literature is, on average, inferior to the dose to the respective OAR in our dosimetric study (Table 1). This might be explained by differences in the definition of PTVs and/or in planning techniques across studies [22,23], as well as by inherent variations in patient's anatomy. This variability, in addition to the relatively small sample size of TMI planning studies, could significantly flaw the comparison with results obtained by other groups.

Although being based on a small patient sample, our results seem to suggest that dose-escalated TMI with a SIB up to 16 Gy to the ABM is feasible and reliable without increasing the dose received by the OAR, and even with a slight dose reduction. The reason for this dose reduction is not clear but might be due to particular implementation in the optimization algorithm of the treatment planning system. The therapeutic benefit from increasing the dose per fraction (> 2 Gy) is suggested by clinical and radio-biological data highlighting that radiation dose and fractionation have a major impact in determining the success of long term marrow engraftment. The fact that the primitive self-renewing stem cells population of the host marrow displays a significant

Fig. 2. An example of dose distribution for one of the patients with a) standard dose TMI (12 Gy) compared to b) a dose-escalated TMI (16 Gy to the ABM) on coronal and sagittal views. Abbreviation: TMI: total marrow irradiation, ABM: active bone marrow.

Fig. 3. Median cumulative dose-volume histogram from patients included in the study for the planning target volume (PTV) and the active bone marrow (ABM) for the four optimization plans: a) VMAT: plans without SIB and constraints set on the OAR vs. VMAT-PRV: plans without SIB and constraints set on the PRV and b) VMAT-SIB: plans with SIB and constraints set on the OAR vs. VMAT-PRV-SIB: plans with SIB and constraints set on the PRV.

sub-lethal damage repair, favors the option of a hypofractionated schedule [6,7,38] to improve tumor control. Indeed, it was shown that patients with CML who received fractionated TBI had a higher risk of relapse [39,40] than those treated with a single fraction, suggesting a role for hypofractionated regimens in this group of patients.

In this study, the volume receiving the escalated dose was defined according to the study by Hayman *et al.* [29], which shows that it contained approximately 60% of all active bone marrow. According to this, the hypothesis at the origin of our dosimetric research was that delivering a boost to the most metabolically active bone marrow regions might translate into a lower relapse rate in patients after undergoing a TMI. On the other hand, 18F-fluoro-L-deoxythymidine (FLT)-PET imaging could be recommended to identify the specific metabolic ABM distribution in an individualized patient. In addition, Magome *et al.* [41,42] employed FLT-PET and dual-energy CT to identify leukemia distribution within the bone marrow. Using treatment planning with HT, they showed that the dose could be escalated in these regions by 2-fold, while maintaining OAR doses at the same level as in standard TMI.

We were unable to observe a negative impact on dose-distribution quality indicators of the target volumes (PTV and ABM) when sparing PRV instead of OAR. Furthermore, a PRV-based optimization taking into account intrafraction motion due to breathing might have more chances to succeed in optimally matching dose calculations vs. dose measurements for the OAR. Nevertheless, PRV delineation requires 4DCT images and contouring on each phase of the respiratory cycle, a time-consuming task. This burden will probably be alleviated in the future with oncoming efficient auto-segmentation tools [43,44]. An alternative solution for the motion management of TMI treatment is respiratory gating to deliver the treatment to a specific breathing phase, with the advantage of an even better targeting of the PTV, but with the drawback of prolonging the treatment time of an already long treatment. Such gating could be potentially implemented with a surface monitoring system, expected to facilitate also the patient setup, in particular for the repositioning of the extremities, and the intrafractional motion control during the relatively long TMI treatment times.

This was a dosimetric feasibility study with a limited number of five patients all simulated for the purpose of the study and that were treated with standard TBI. This reduced number of patients prevents drawing robust and reliable dosimetric conclusions apart from the feasibility of

the technique similar to other TMI planning studies [13,15,17,20,22–24]. Similarly, significance of the statistical results should be interpreted with care, keeping in mind the small sample size. The irradiation of the lower limbs, usually treated with a series of VMAT arcs (or simple open fields) and the patient in feet-first orientation, was not included in our analysis similarly to other TMI planning studies [13,14,16]. In practice, this would add the challenge of managing a treatment involving two plans with different treatment orientations [45,46].

5. Conclusion

In summary, our preliminary study seems to suggest that adding a dose of 4 Gy (ABM-SIB) to a 12 Gy TMI using VMAT techniques should be feasible without any clinically relevant dose increase to the OAR. Further investigations to better quantify the impact of ABM-SIB is warranted. Furthermore, PRV defined from 4DCT could be reliably used without relevant PTV dosimetry drawbacks.

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Declaration of Competing Interest

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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