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Technical Note

Physical aspects of a spatially fractionated radiotherapy technique for large soft tissue sarcomas

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ABSTRACT

This work demonstrates the safety and feasibility of Lattice Radiotherapy (LRT) for large soft tissue sarcoma in neoadjuvant radiotherapy. The treatment consisted of two courses: the LRT course with a single fraction of 20 Gy delivered to high dose nuclei (HDN) regions and the conventional course with 25 fractions of 2 Gy delivered to the planning target volume. HDN shaped as cylinders with a 1 cm diameter and 1 cm height were placed within the gross tumour volume. The number of HDNs and their position were determined based on tumor size and proximity to organs at risk. Three patients were irradiated using the LRT technique.

1. Introduction

Stereotactic radiosurgery (SBRT/SRS) is a radiation therapy (RT) technique that is usually applied to solid tumors. The application of SBRT for the treatment of large tumors is rather challenging due to toxicity of the nearby organs at risk (OAR). In order to avoid unacceptable toxicity, a spatially fractionated radiotherapy (SFRT) technique with GRID was already proposed in the 1950s [1]. The concept of SFRT consisted of delivering a high ablative dose solely to a small partial volume within a bulky tumor along with constraining the peripheral doses to the surrounding normal tissue. The main characteristic of SFRT is the Peak-and-Valley dose distribution inside the tumor volume. The high ablative dose is delivered to the peaks or vertices while relatively lower doses cover the valley area between the peaks. Initially, in order to apply the GRID technique a special block with holes was needed to generate a radiation field that produced a 2D distribution of peaks and valleys. Application of SFRT using kV machines had obvious disadvantage because of the high entrance dose to the skin. The interest in SFRT was renewed with the implementation of modern megavoltage linear accelerators equipped with a multi-leaf collimator (MLC) [2]. Thus, the 2D GRID approach was logically extended to its 3D version known as Lattice RT (LRT). MLC-based LRT in conjunction with image-guided RT (IGRT) allows to accurately deliver a high radiation dose to a partial tumor volume while the dose at the tumor boundaries is significantly decreased. However many practical aspects of treatment still remain unexplained: for which patients SFRT should be used, what size and form should be the irradiated area and which planning strategy should be chosen.

Also, the effectiveness of SFRT is still not fully explained by radiobiological studies. Initially, SFRT was proposed as a hypofractionation regime for bulky tumor ablation. However, recently researchers have noticed bystander and abscopal effects when applying SFRT techniques [3]. In the era of immunotherapy, these findings caused an intensive exploration of the combination of SFRT ablative potential with immunotherapeutic agents as they are currently being tested with SBRT [4–6]. Classical radiobiology postulates that normal tissues have in general superior repair capabilities over cancer tissues. As reported by Zwicker et al. [7], in theory, if normal cells interspersed in the cancerous cells they may be spared within “valleys” or “cold” areas during SFRT. As a result further they could serve as centers of regrowth for normal tissues. At the same time, in the peak dose zones there is an intensive killing of cancer cells and normal cells as well, consequently the communication between the cancer cells is interrupted throughout the tumor volume.

The safety and efficacy of LRT has been reported for various types of cases and many patients showed benefit from such kind of treatment [8]. However, there are no standardized requirements or treatment protocols for SFRT. The aim of this study was therefore to describe the physical aspects and to evaluate the feasibility and safety of LRT for the treatment of large soft tissue sarcoma in neoadjuvant settings.

2. Materials and methods

Israel Ministry of Health ethical committee approval was obtained prior to study initiation. Eligible for the study were considered 18 years

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or older non-metastatic patients diagnosed with large soft tissue sarcoma 5 cm or more in size, without a personal history of previous malignancy and/or exposure to chemotherapy agents. To date, three patients suitable for this treatment were recruited and presented to a multidisciplinary tumor board meeting and referred to preoperative radiotherapy. All patients signed an informed consent form.

LRT consisted of an initial single fraction of 20 Gy at the first treatment day followed by 50 Gy delivered over 5 weeks in 25 fractions. 20 Gy single fractions are widely used in modern ablative SFRT regimens and considered to be safe and effective [9].

Patient immobilization was performed using a BlueBAG BodyFIX (Elekta AB, Sweden) that utilized in our department for most of stereotactic treatments. The LRT treatment session included an IGRT procedure consisting of two CBCTs prior to treatment delivery and one post treatment. The positioning setup was performed using the HexaPOD (Elekta AB, Sweden) 6D system. An Elekta VersaHD clinical linear accelerator (Elekta AB, Sweden) equipped with an Agility HD MLC and the Monaco treatment planning system (TPS) were used. VMAT treatment plans were created using the 6 FFF beam energy in order to shorten the beam-on time. Quality assurance measurements were performed using the Delta4 + phantom (ScandiDos, Sweden) for every treatment plan.

High-dose regions, or nuclei (HDNs), shaped as cylinders with a 1 cm diameter and 1 cm height were placed within the gross tumor volume (GTV). The exact spatial position of each HDN was determined by a senior radiation oncologist and a senior physicist in collaboration with a senior radiologist and an orthopedic surgeon accordingly to the complexity of the GTV and its proximity to deep seated OARs and skin. The treatment planning strategy was similar to a regular SBRT planning approach: 20 Gy were prescribed to the 80% isodose line for HDNs coverage; high dose gradients and conformity were demanded in order to minimize dose to normal tissues and skin areas based on TG-101 AAPM recommendations. An additional goal during LRT planning was to keep the 5–7 Gy isodose region inside the clinical target volume (CTV).

Nerve-vessel bundles, femur, contralateral leg and healthy tissues were considered OARs. Dose constraints for OARs took into account the doses from both parts of treatment. The classical linear quadratic (LQ) model has been found to overestimate cell death at large fraction doses above 10 Gy. Consequently, as a mathematically processed subpart of LQ, equivalent dose (EQD2) has also lack of accuracy when calculated for high single fraction doses. However, taking into account that OARs would receive a dose much smaller than the prescribed 20 Gy for LRT, we could sum the EQD2 dose from a single fraction of 20 Gy and EQD2 values from 25 fractions of 2 Gy to get an estimation of the total EQD2 dose after 26 fraction of irradiation.

The dose heterogeneity was measured as a peak/valley dose ratio (PVDR). Based on previous recommendations [10–11], the traditional definition of PVDR was replaced by the D10/D90 ratio, where D10 and D90 are the doses covering 10% and 90% of GTV respectively. In Table 1 the detailed characteristics of the three LRT plans are summarized.

Three patients with 202, 181 and 132 cm^3 leg sarcomas masses were treated using the LRT technique. The number of HDNs created within the tumor mass were 8, 7 and 5 accordingly to the mass volume.

3. Results

An example of contoured target structures, HDNs and OARs is shown in Fig. 1 (A). The contour of GTV was defined on planning computed tomography (CT) based on fusion with magnetic resonance imaging (MRI), and CTV was defined as GTV plus an additional margin of 8 mm, but excluding the adjacent nerve. Also in Fig. 1 (A), the dose distribution for the 20 Gy LRT plan is presented and demonstrates high dose conformity within the tumor. The spatial arrangement in 3D checkerboard pattern of HDNs for the same leg sarcoma case is demonstrated in Fig. 1 (B). As shown in the Fig. 1, a VMAT plan with partial 220 degrees arc was used in order to avoid irradiating of the healthy leg.

Table 1
Dose-volume parameters of targets and OARs for LRT plans for the first/second/third case. EQD2 is shown for LRT plans only and for total treatment of 26 fractions.

Structure, Alpha/beta ratio	D95%, Gy	D0.5 cm^3, Gy	Mean dose, Gy	EQD2 (for 0.5 cm^3, LRT treatment), Gy **EQD2 (for 0.5 cm^3, total treatment), Gy**
HDNs, 10	19.0/ 19.0/19.0	23.4/ 22.2/ 24.9	21.3/ 20.9/ 22.3	65.1/59.6/72.4 *113.3/111.9/124.4*
GTV	3.5/2.5/ 2.4	23.4/ 22.2/ 24.9	8.1/9.0/ 7.0	
Nerve, 1.6	<0.5/ <0.5/ <0.5	2.2/5.7/ 4.3	1.4/1.5/ 1.9	2.3/11.6/7.1 *45.3/65.8/52.1*
Femur, 3	<0.5/ <0.5/ <0.5	4.1/ 10.8/ 4.3	1.3/1.9/ 1.6	5.8/29.8/6.3 *62.0/82.9/25.4*
Skin (5 mm inside body), 8.5		4.8/4.4/ 3.3	<0.5/ <0.5/ <0.5	6.1/5.4/3.7 *60.3/44.3/48.4*
Contralateral leg		3.1/2.0/ 1.4	<0.5/ <0.5/ <0.5	
Lymphatic drain	<0.5/ <0.5/ <0.5	2.6/3.6/ 4.7	0.6/0.9/ 1.2	

Dose-volume parameters of three LRT plans are summarized in Table 1. Both for target structures and OARs D95%, D0.5 cm^3 and mean dose were calculated for a whole treatment, while EQD2 was calculated separately for a single LRT fraction in order to emphasize its low dose contribution. In terms of EQD2, the total dose load on the nerves was in the range of 45–52 Gy. Despite the large volumes of tumors of 203, 181, 132 cm^3, it was always possible to guarantee lymphatic drainage region where the maximum dose did not exceed 5 Gy.

QA results showed acceptable values of a gamma-index higher than 95% for a 3%/2 mm criterion for all plans. As a result of the geometric complexity and steep dose gradients, LRT plans consisted of a high number of MU: 9125, 12970 and 9061 monitor units that lengthened the beam-on time up to eleven minutes. In Table 2 the more detailed characteristics of the three LRT plans are summarized.

4. Discussion

The current work describes the application of an LRT technique for large soft tissue sarcomas in neoadjuvant radiotherapy settings. Previous publications in the SFRT field have focused on clinical outcomes. In this paper we describe the physical aspects, planning difficulties and specific dose-volume quantities. Such information will be useful for the exchange of experience for medical centers already using this technique or wishing to know its physical aspects before applying it.

During the optimization of HDNs positions, full plan recalculation is required each time HDNs location is changed. These repeated attempts are due to the fact that there is a number of dose distribution requirements for the HDNs placement and distance between them. Dose peaks cannot be close to the skin surface or OARs, while at the same time they should provide significant ablative effect near nerve bundles and bones to ease the separation of nerve and bone from the tumor during surgery. In order to form dose valleys the average distance between HDNs was 1–2 cm. The D10/D90 values of 3.5, 3.8 and 4.7 demonstrate feasibility to reach very high dose fall-offs inside GTV. For comparison, in other another SFRT studies mean PVDR of 2.7 inside PTV was achieved when using MLC [10] and PVDR of about 5 when using cerrobend GRID collimators [12]. Quality assurance measurements were

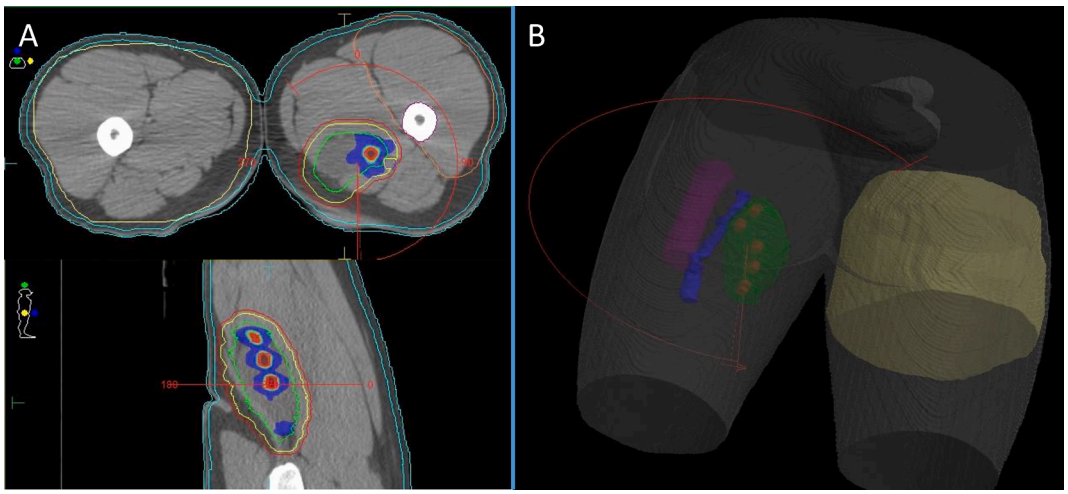

Fig. 1. Illustration of dose (A) and HDN spatial (B) distributions inside leg sarcoma. (A): Isolines legend: brown – 24 Gy, red – 20 Gy, green – 17 Gy, blue – 7 Gy. (B): HDNs (red) are inside GTV (green) that contoured based on MRI and planning CT. CTV (yellow) and PTV (outer red) are used for a treatment of 50 Gy in 25 fractions. OARs: nerve (blue), femur (purple), skin (blue, contralateral leg (light yellow), and avoidance structure for lymphatic drainage (orange) are contoured. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 2
LRT plan characteristics.

Case	# nuclei	GTV volume/HDNs volume, cm^3	Arc length, degrees	# of arcs/segment width, mm	# of segments	MU	Beam-on time	PVDR (D10/D90 for GTV)
1	8	203/6.2	220	4/0.5	262	9125	8:35	3.5
2	7	181/5.5	200	4/0.5	264	12,970	11:06	3.8
3	5	132/3.7	220	4/0.5	215	9061	8:46	4.7

performed with the Delta4 + phantom as this is our regular routine and demonstrated acceptable (more than 95%) gamma passing rates. Total treatment duration including patient positioning and CBCT procedures was up to 30 min and remained in acceptable limits.

During follow-up visits, none of the patients treated with the LRT technique showed functional disorders greater than Grade 1 (accordingly to CTCAEv4). All treated tumors presented in the hip region. So, it defined identical OARs for all three cases: nerves bundle, femur, and skin. Additional attention was paid to minimize the irradiation of healthy soft tissues in order to provide appropriate lymphatic drainage. Since there are no widely accepted tolerances for this aim, the concern was focused to maximally avoid healthy regions in the irradiated extremity and diminish irradiation of the contralateral one using the ALARA principle. Besides that, the additional goal during the building of LRT plans was to achieve maximal dose gradients and isodose compactness. The combination of a conformality cost function in Monaco TPS and a high definition Agility MLC allowed us to create and deliver extremely modulated VMAT plans that exactly met the requirements.

Sarcoma patients receiving neoadjuvant radiotherapy are usually treated with a dose of 50 Gy in 25 fractions. The addition of the LRT fraction of 20 Gy increases the dose load of the OARs. As shown in Table 1 this dose load for the femur bone and nerve bundle is of 2–11 Gy EQD2 in all cases except for the femur (29.6 Gy) in case 2 where the tumor penetrated bone tissue. To control the total dose to nerve bundles, the 50 Gy treatment part was planned with an acceptable PTV undercoverage (of about 90% of the prescription dose) in the nerve region. Skin dose was also recorded but no additional steps were taken to spare it. No complaints were received from patients during the course of treatment. However, one of them had skin healing problems after surgery. All clinical details, outcomes, histological analysis and follow-up will be discussed elsewhere.

As of today, all three patients successfully underwent surgery. The pathology reports show full pathological response for two patients. In the third case the surgery was performed with at least 3-mm clean resection margins.

In this study we demonstrated the technical feasibility and safety of LRT for large soft tissue sarcomas. During HDNs placing and treatment planning it required close collaboration between physicians and physicists. Other aspects were similar to regular SBRT routine. The current clinical outcome showed promising results and encourage us to continue applying LRT techniques for neoadjuvant treatment of large soft tissue sarcomas.

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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