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Original article

Application of IMRT in adjuvant treatment of soft tissue sarcomas of the thigh—Preliminary results

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ARTICLE INFO

Article history:
Received 29 December 2010
Accepted 22 February 2011

Keywords:
IMRT
3D-CRT
Soft tissue sarcoma

ABSTRACT

Background: Fracture of the femur is the most frequent late complication in patients with soft tissue sarcomas (STS) who receive external beam radiotherapy after limb-sparing surgery.
Aim: To reduce the risk of bone fracture following radiotherapy of STS of the thigh, we minimized the dose to the femur and to surrounding normal tissues by applying intensity modulated radiation therapy (IMRT). We report preliminary results of post-surgery IMRT of the thigh in patients with STS in this extremity.
Materials and methods: 10 adult patients undergoing post-operative radiotherapy of STS of the thigh were treated using IMRT. Clinical IMRT plans with simultaneous integrated boost (SIB) and 3-phase three-dimensional conformal radiotherapy (3D-CRT) were designed to adequately treat the planning target volume and to spare the femur to the largest extent possible. Dose distributions and dose-volume histograms were compared.
Results: For either technique, a comparable target coverage was achieved; however, target volume was better covered and critical structures were better spared in IMRT plans. Mean and maximum doses to OAR structures were also significantly reduced in the IMRT plans. On average, the mean dose to the femur in 3D-CRT plans was about two times higher than that in IMRT plans.
Conclusion: Compared with 3D-CRT, the application of IMRT improves the dose distribution within the concave target volumes and reduces dose to the OAR structures without compromising target coverage.

1. Background

Soft tissue sarcomas (STS) are rare neoplasms originating from mesenchymal tissue. Histologically, they form a heterogeneous group. STS occur in about 1% and 10% of all neoplasms in adults or children, respectively. The incidence of STS in Poland (population of ca. 40 million) is about 800–1000 new cases and is increasing.[1] STS occur most frequently in the extremities (60%). Surgery (limb sparing surgery) is

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doi:10.1016/j.rpor.2011.02.006

the treatment of choice; nevertheless, radiotherapy is important in adjuvant and neoadjuvant approaches.[2] A combined surgery and radiotherapy improve the patient's quality of life and achieve local control rates equivalent to those after amputation.[2–5]

Irradiation of STS may significantly elevate the risk of morbidity, including wound and skin complications, contractures, oedema, or bone fracture and may introduce region-specific complications (genital in the case of thigh, or spinal cord and salivary gland in the case of head and neck sarcomas).[6] Wound complications may be related to the sequence and timing of surgery and irradiation.[3]

The risk due to radiotherapy may be further reduced by using appropriate radiotherapy techniques. It is essential to spare the circumference of the irradiated extremity and to avoid irradiating adjacent areas, such as the contralateral thigh or the genital region. The relative risk of bone fracture after radiotherapy (5%) is lower than that of other complications, but it can exceed 25% if periosteal stripping is performed.[7] Because treatment of such fractures is difficult and prolonged, and causes a decrease in the patient's quality of life, dose to the bone should be minimized.[8]

Because the target volume is large and irregular and lies close to bone structures, 3D-CRT treatment plans become quite complicated and are not always satisfactory. The shape of the lesion around the surrounding bone after complete surgical excision is usually quite irregular. It is therefore technically difficult to treat such a volume homogeneously, while sparing the bone cortex of the adjacent bone. A conventional 3D treatment plan employs fields covering the entire target with large margins and minimal sparing of normal tissue. The application of the IMRT technique permits high doses of radiation to be delivered much more precisely than in the case of conventional radiotherapy.[9]

2. Aim

We explored the possibility of clinically applying IMRT to treat soft tissue sarcoma of the thigh to demonstrate its advantage versus conventional 3D-CRT treatment of this site, in terms of dose distribution, target coverage and normal tissue sparing.

3. Materials and methods

Radiotherapy plans for 10 patients with STS of the thigh were examined and compared. All patients underwent limb-sparing surgery. The patients were immobilized as close as possible to their neutral anatomic position. To minimize patient movement, customized foam moulded under their leg and a thermoplastic mask fixed onto the baseboard were used. The surgical scar was marked using CT-compatible wire to delineate the anatomic boundaries of the tumour or scar and a bolus was placed to move the build-up zone closer to the skin surface. 2.5-mm slice CT scans were acquired and transferred to a Varian-Eclipse planning system (Varian Medical Systems, Inc.). Appropriate planning target volumes (PTVs) based on CT, as well as normal tissue and organs at risk structures, were delineated. The tumour bed was defined using pre-operative imaging and surgical clips. The surgical scar was marked over the skin surface. PTV1 consisted of the tumour bed with a 2 cm margin in all directions. PTV2 was formed by adding a 3 cm margin axially to the tumour bed and 5–7 cm superior/inferior margins. PTV3 included PTV1, PTV2 and the whole muscular compartment. PTV was modified to exclude the bone and a 0.5 cm layer beneath the skin surface. In all patients, the entire femur was contoured as a critical structure and normal tissue was defined as the limb, excluding the PTV1 and the femur. The same target volumes of OAR and of normal tissues were used to prepare 3D-CRT and IMRT plans.

For every patient, 3D-CRT plans were developed using 3–4 beams. Targets were treated sequentially and required separate dose plans with different dose prescriptions. The three-phase technique using shrinking fields was employed. The prescribed doses were first to deliver 50 Gy in 25 fractions to PTV3, next 10 Gy in 5 fractions to PTV2, and finally 10 Gy in 5 fractions to PTV1.

IMRT plans employing 7–8 fields were generated using the simultaneous integrated boost (SIB) technique where all targets are treated within a single treatment plan over the entire treatment course.[10] The linear quadratic concept was applied and doses were re-calculated in terms of biologically equivalent dose (BED) in order to provide equivalent doses in the comparison.[11,12]

Patients were treated with 6 MV photons generated by a Varian 2300 C/D accelerator equipped with a Millennium 120-leaf MLC (both from Varian Medical Systems, Inc.). IMRT plans were generated using ECLIPSE/HELIOS software (Varian Medical Systems, Inc.) which includes an inverse planning algorithm. The sliding windows technique[13] was used for delivery. In both techniques, the gantry angles were chosen in such a way as to avoid irradiation of the contralateral leg.

In two of the ten patients treated, fields of lengths exceeding 40 cm were required, thus two separate isocenters had to be introduced. For these two patients, we developed a two-isocenter system, for IMRT and for the initial phases of the 3D-CRT technique.

The 3D and the IMRT plans were generated and dose distributions were first compared visually over axial, sagital and coronal slices with respect to the degree of target conformity within the prescribed dose to the PTVS. Plans were evaluated by comparing dose volume histograms (DVHs) for planning target volumes and organ-at-risk structures.

The minimum dose (D_{min}) and the maximum dose (D_{max}) to the PTVs were evaluated. The optimization goal was to achieve 95–105% of the prescribed dose to PTV1, PTV2 and PTV3. Target coverage was estimated by comparing the percentage of PTV3 receiving at least 95% of dose (V95%). The mean and the maximum dose (D_{mean} and D_{max}, respectively) and the volume of the femur receiving 45 Gy (V_{45}) or more were studied. This dose-volume constraint was chosen because fracture of the femur is more frequent in patients receiving high-dose radiotherapy (60–66 Gy) than in those receiving 50 Gy or less (10% vs. 2%).[14]

A dose to the femur was assessed high if encompassing 5% of the volume (D_5). The dose parameters concerning PTVs and the femur were summarized in the form of mean (including ± SD errors) and median values calculated over all patient treatment plans.

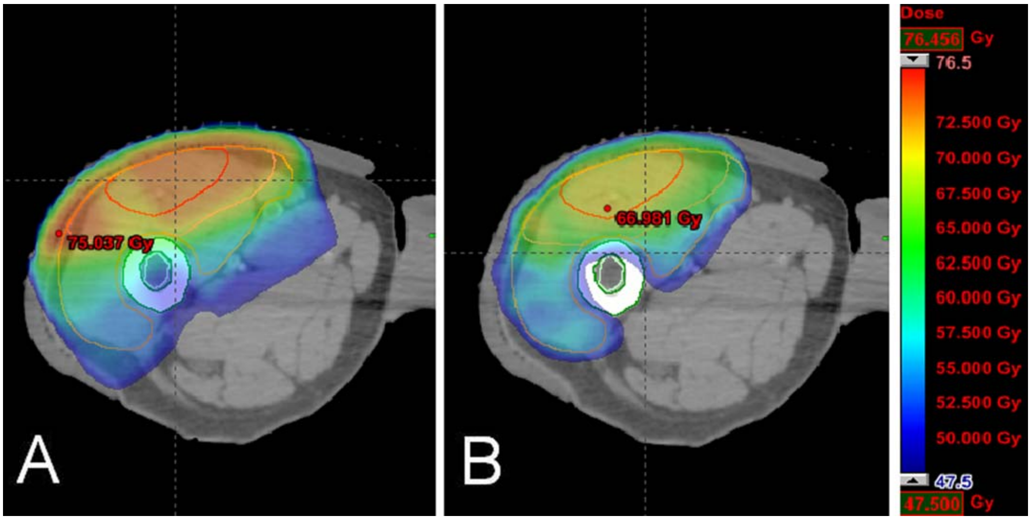

Fig. 1 – Example of transversal isodose distribution for a patient with soft tissue sarcoma of the thigh treated with: (A) 3D-CRT and (B) IMRT techniques.

4. Results

For each patient, the 3D and the IMRT plans met physician-specified clinical criteria concerning target dose and bone sparing. A typical dose distribution for the 3D-CRT and IMRT plans is shown in Fig. 1. Target coverage, as measured by the V_{95} volume, was comparable, the average for PTV3 being 98.1 ± 1.4% (3D-CRT) and 98.5 ± 1.2% (IMRT). The 3D-CRT and IMRT plans showed no significant differences in the PTV regions, with the exception of the average value of D_{max}, which was lower in the case of IMRT (104.7 ± 2.1%) than that for 3D-CRT (107.3 ± 1.3%). The adjustment of dose distribution to the target volumes and conformity within given

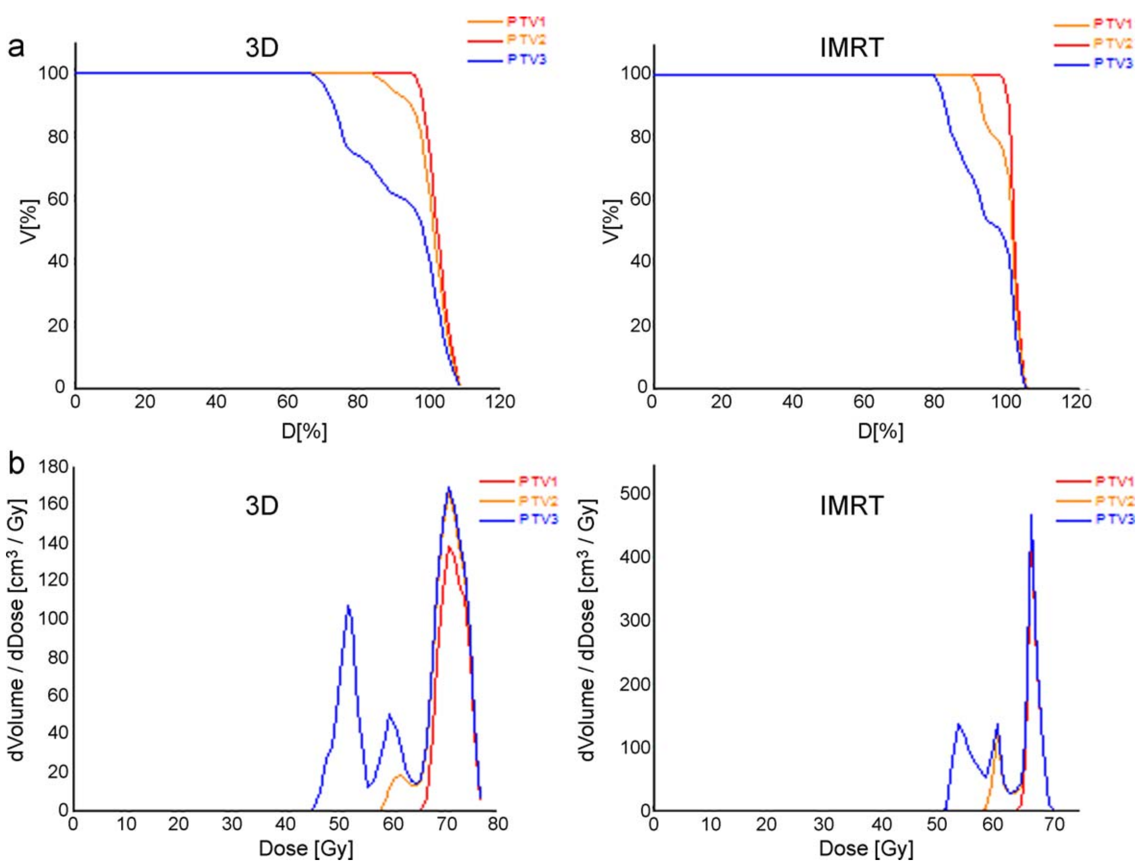

Fig. 2 – Comparison of dose-volume histograms (DVH) for the patient of Fig. 1: (a) cumulative (b) differential in PTV1, PTV2 and PTV3 volumes for 3D-CRT and IMRT techniques used in treatment of this patient.

Table 1 – Dose parameters (Gy) concerning the femur in 10 patients with STS of the thigh treated with 3D-CRT and IMRT techniques: mean (including ±1 SD errors) and median values, calculated for all treatment plans of these patients.

Femur	3D-CRT	IMRT
D_{mean} [Gy]	28.1–37.2	19.6–33.8
Mean (±1 SD)	32.4 (±3.1)	22.2 (±2.2)
Median	30.9	22.2
D_{max} [Gy]	65.1–74	60.4–68.3
Mean (±1 SD)	70.6 (±3.1)	64.9 (±2.3)
Median	71.6	64.9
D_5 [Gy]	57.3–70.2	42.9–60.1
Mean (±1 SD)	64.04 (±4.4)	53.2 (±4.0)
Median	65.65	54.1
V_{45} [%]	37.5–48.6	16–25.5
Mean (±1SD)	41.13 (±3.2)	21.48 (±4.6)
Median	44.62	20.8

planning target volumes (PTV1, PTV2, or PTV3) were better in the IMRT plans. This is also seen in the comparison of dose-volume histograms shown in Fig. 2, where better conformity of the IMRT plan over the target volume is evident.

Significant reduction in the dose to the femur and to surrounding normal tissue was achieved by the IMRT technique. The maximum dose to the bone, which is one of the clinical criteria, was reduced from 70.6 ± 3.1 Gy in the conformal plans to 64.9 ± 2.3 Gy in the IMRT plans. Also the high dose regions (D_5) decreased by an average of 16% from 64.04 ± 4.4 Gy in 3D-CRT to 53.2 ± 4.0 Gy in the IMRT technique. Although, in the low-dose region, the IMRT plans extended over larger volumes than those for conformal plans, the IMRT technique gave a 31.48% decrease of the average dose to the femur, D_{mean} (from 32.4 ± 3.1 Gy for 3D CRT to 22.2 ± 2.2 Gy for IMRT). Furthermore, IMRT delivery led to a significantly lower volume of femur receiving 45 Gy (V_{45}) or more. The mean V_{45} volume in 3D-CRT plans was higher by a factor of almost two than that in IMRT plans (Table 1). The IMRT plans targeted more precisely the prescription dose around the PTVs also reducing hot and cold spots within the target volumes. Due to the larger margins used in the 3D-technique, the irradiated volumes were greater than the target volumes causing higher doses to be delivered to higher volumes of healthy tissues.

5. Discussion

In this study, we demonstrated the superiority of IMRT by comparative evaluation of clinically acceptable 3D-CRT and IMRT plans prepared in our Centre of Oncology to treat patients with soft tissue sarcoma of the thigh. Treatment plans using 3D-CRT and IMRT techniques were evaluated and compared for 10 patients undergoing post-operative radiotherapy for extremity STS. Dose distributions and dose–volume histograms were analyzed.

The comparison of dose distributions revealed that while PTV coverage was comparable between IMRT and 3D-CRT techniques, IMRT treatment plans showed better dose conformity with the target volumes, especially where concave dose distributions were required. Significant reductions in the mean and the maximum doses to the femur in all patients were also achieved. The volume of the femur receiving at least 45 Gy (V_{45}) decreased on average by approximately 50% and hot spots (D_5) were reduced on average by 16%. Reduction of high-dose delivered to the femur resulted in minimizing the risk of bone fracture, a possible late complication of radiation treatment.

The results we obtained agree well both in terms of target coverage and sparing of bone structures with other similar investigations.[15,16] Radiotherapy of STS of the thigh can either be accomplished using 3D-CRT or by IMRT techniques. However, some authors have suggested the use of the IMRT technique to reduce the mean dose to the femur without compromising target coverage.[6,9] Alektiar et al.[9] performed treatment planning for 41 patients with limb sparing surgery and adjuvant IMRT, achieving better sparing of normal tissue and improved local control in treating STS of the extremity. Koshy et al.[17] compared IMRT with 3D-CRT techniques in 15 patients with retroperitoneal sarcoma. Application of IMRT allowed them to improve target coverage and to better spare critical structures: small bowel, liver and kidney. Also, IMRT was well tolerated and acute toxicity decreased.

Due to the variations in their shape and to large and often concave target volumes, conformal dose distribution can seldom be successfully achieved with 3D-CRT techniques. Using the multiple isocenter technique, IMRT can be used not only for small, but also for large tumour volumes, even those exceeding 40 cm in length.

By using simultaneous integrated boost radiotherapy (SIB), multiple target volumes receiving different prescribed doses can be integrated into a single treatment plan. Additionally, the SIB technique offers the possibility of reducing the number of fractions required, thus reducing the complexity and time of treatment delivery. In our Centre, we have observed that IMRT with simultaneous integrated boost is equivalent in terms of dose delivery and more profitable than three-phase 3D-CRT.

Because of the risk of potential complications from a small volume receiving a high dose as compared to that of large volume receiving low dose, the accuracy of patient positioning and immobilization may crucially affect the outcome of IMRT. Therefore, this treatment should be closely observed and controlled through stringent Quality Assurance procedures.

6. Conclusion

The application of IMRT in soft tissue sarcoma of the thigh offers significant benefits with respect to 3D-CRT. IMRT in the treatment of soft tissue sarcoma of the thigh enabled us to improve target dose conformity and to significantly reduce dose to the surrounding normal tissues and bone structure, compared with conventional 3D-CRT planning. Furthermore, IMRT plans achieved more precisely the prescription dose around the target. Longer follow-up is required to determine whether possible late complications of radiation treatment are indeed reduced by the application of IMRT to treat soft tissue sarcomas located in the thigh region.

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