

Volumetric modulated arc radiotherapy for limited osteosclerotic myeloma

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Abstract

AIM: To assess the feasibility of volumetric intensity-modulated arc radiotherapy (VMAT) in patients with limited polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes syndrome.

METHODS: A 70-year-old male with histologically confirmed osteosclerotic myeloma was treated in our department in July 2010 with VMAT. Forty-six Gray in 23 fractions were given on three bone lesions. Doses delivered to target volume and critical organs were compared with a tridimensional conformal radiotherapy (3D-RT) plan. Treatment was well tolerated without any side effects.

RESULTS: VMAT improved dose homogeneity within the target volume, as compared to 3D-RT (standard deviations: 2.9 Gy and 1.6 Gy for 3D and VMAT, respectively). VMAT resulted in a better sparing of critical organs. Dose delivered to 20% of organ volume (D20) was reduced from 22 Gy (3D-RT) to 15 Gy (VMAT) for small bowel, from 24 Gy (3D-RT) to 17 Gy (VMAT) for bladder and from 47 Gy (3D-RT) to 3 Gy (VMAT) for spinal cord. Volumes of critical organs that received at least 20 Gy (V20) were decreased by the use of VMAT, as compared to 3D-RT (V20 bladder: 10% vs 99%; V20 small bowel: 6% vs 21%). One year after treatment completion, no tumor progression has been reported.

CONCLUSION: VMAT improved dose distribution as compared to 3D-RT for limited osteosclerotic myeloma, with better saving of critical organs.

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Key words: Volumetric intensity-modulated arc radiotherapy; Conformal radiotherapy; Critical organs; Osteosclerotic myeloma; Polyneuropathy organomegaly endocrinopathy monoclonal gammopathy and skin change syndrome

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INTRODUCTION

Osteosclerotic myeloma (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes, PO-

EMS syndrome) is a rare paraneoplastic disease resulting from a monoclonal plasma cell disorder^[1,2]. Most frequent diagnostic criteria include polyneuropathy, monoclonal lambda plasma cell proliferative disorder, bone lesions, elevated levels of vascular endothelial growth factor (VEGF) and eventually association with Castleman disease (angiofollicular lymph node hyperplasia). There are other clinical features, such as organomegaly (hepato-splenomegaly, lymphadenopathy), endocrine disorders, skin modifications, papilledema and high extravascular fluid accumulation leading to ascita or pleural effusion^[3]. Although POEMS' pathogenesis remains only partially understood, the overproduction of several pro-inflammatory cytokines [higher levels of interleukine (IL)-1, IL-6, tumor necrosis factor- α] and VEGF has been frequently reported. Moreover, clinical manifestations of POEMS syndrome may be correlated with an increased production of cytokines. Those could potentially be used as surrogate markers of disease activity^[4,5].

There is no strong consensus on the appropriate management of POEMS. Radiation therapy (RT) is generally employed for limited disease, and good response to RT correlates with an increased survival^[6]. On the other hand, prognosis of POEMS is substantially better than that of multiple myeloma and patients may be exposed to late toxicities of treatments^[3]. The delivery of RT in bone lesion is challenging because irradiated fields may include sensitive critical organs. In the era of ballistic optimization, every effort should be made to further improve the efficacy/toxicity ratio. Volumetric intensity-modulated arc radiotherapy (VMAT) is a new RT modality that allows for rapid delivery of highly consistent dose distributions, critical organ sparing and it is currently used for various tumor localizations^[7-12]. Herein, we investigated the use of this new high-tech RT modality for a patient with three sclerotic bone lesions. A dosimetric comparison of a VMAT plan with a conventional tridimensional conformal (3D) plan was performed to evaluate the potential dosimetric benefit of VMAT in sparing critical organs from detrimental irradiation.

MATERIALS AND METHODS

Patient characteristics

A 70-year-old man presented with lower back pain, equilibrium disorders, and a weight loss of 12 kg. He had a past medical history of alcoholism, tobacco and high blood pressure. Initial evaluation included complete history and physical examination, hematological and biochemical profiles, serum protein electrophoresis, bone marrow biopsy and a radiographical skeletal survey. Physical examination showed a symmetric sensorimotor neuropathy of the extremities, endocrine disorders (hyperthyroidism and decrease of testosterone level) and skin changes (melanoderma and hypertrichosis). Biological examinations revealed a plasma cell dyscrasia with an IgA lambda monoclonal gammopathy and an increased VEGF rate of 1275 pg/mL (normal < 5 pg/mL). A myelogram was negative. Total body computed tomog-

raphy (CT) and ¹⁸F-fluorodeoxyglucose positron emission tomography-CT showed organomegaly, mediastinal adenopathies and hypermetabolism of bone sclerotic lesions (T12, L5 vertebra and right ilium). Bone biopsy using immunohistochemical staining demonstrated clonal lambda plasma cell infiltration. POEMS syndrome was retained and this patient received T12 vertebra percutaneous cementoplasty. Due to persistence of lower back pain, he was referred to our department to receive radiation in July 2010.

Dosimetric study

Separate dosimetric analyses were performed for conformal 3D-RT and VMAT. The patient was scheduled for CT treatment simulation one week prior to treatment. Planning target volume (PTV) was defined by the tumoral growth volume, as shown on the CT, with a one cm expansion in all dimensions. The dose to be delivered was prescribed in terms of median dose to the PTVs (three sclerotic lesions, two of the rachis and one of the ilium) delivered with 2.0 Gy per fraction, once daily, 5 d per week, with a total dose of radiation 46 Gy in 23 fractions. PTV and critical organs (including kidneys, femoral heads, spinal cord, bone marrow, and bladder) were determined by the same physician. Optimization was performed to spare normal tissues, including spinal cord, bone marrow, kidneys and small bowel.

Treatment plans were created using Rapidarc Planning system software (Rapidarc, Varian Medical System, Palo Alto, CA, United States). After a satisfactory dose distribution was achieved, the plans were accepted and treatment duration was determined. Plan acceptance criteria required that at least 95% of the dose covered 99% of the PTV volume. Dose constraints to the organs at risk were based on the Quantitative Analysis of Normal Tissue Effects in the Clinic recommendations^[13]. A second treatment plan was determined, with 3D conformal system software (Eclipse, Varian; Varian Med Systems, VA, United States). For this phase, a conformal RT technique was used, as routinely used at our Institute. After the two plans were completed, we compared doses delivered to the critical organs, using the VMAT-based or the 3D conformal plan.

Ethical statement

The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) and with the Helsinki Declaration of 1975, as revised in 1983.

RESULTS

The patient was finally treated with VMAT. Tolerance was excellent and no acute or late toxicities were observed. Clinical response consisted of a decreased of the lower back pain following completion of RT. The patient remains free from any tumor progression 18 mo after treatment completion. In the latest evaluation, the

Table 1 Comparison between the treatment plans of critical organs dose exposure

		3D-RT	VMAT
PTV (Gy)	Min	30.5	38.7
	Max	49.1	50.8
	mean \pm SD	46.7 \pm 2.9	47.5 \pm 1.6
Kidney R (Gy)	D10	16.2	18.7
	D20	14.4	14.2
	D30	13.1	11.1
	Dmax	39.6	38
	Dmean	7.9	7.5
	V10	46.7%	33.9%
	V20	2.0%	8.2%
Kidney L (Gy)	V30	0.1%	0.7%
	D10	18.3	19.2
	D20	15.5	14.7
	D30	14.1	11.7
	Dmax	46.7	44.9
	Dmean	9.0	7.6
	V10	44.7%	34.5%
Small bowel (Gy)	V20	7.5%	8.7%
	V30	3.5%	0.7%
	D10	25.8	18.1
	D20	21.6	15.3
	D30	12.4	13.2
	Dmax	46.8	43.1
	Dmean	9.6	8.8
Spinal cord (Gy)	V10	40.6%	43.6%
	V20	20.8%	6.0%
	V30	2.6%	0.2%
	D10	47.3	37.5
	D20	47.1	36.0
	D30	46.8	34.8
	Dmax	47.7	41.0
Femoral head R (Gy)	Dmean	31.8	22.5
	V10	70.5%	64.3%
	V20	67.9%	59.7%
	V30	66.2%	53.8%
	D10	27.2	5.5
	D20	25.8	4.4
	D30	21.5	3.2
Femoral head L (Gy)	Dmax	30.2	7.8
	Dmean	11.6	2.3
	V10	38.8%	0.0%
	V20	31.2%	0.0%
	V30	0.02%	0.0%
	D10	47.4	44.4
	D20	46.8	40.4
Bladder (Gy)	D30	45.9	36.7
	Dmax	47.9	49.3
	Dmean	29.1	21.2
	V10	75.0%	58.4%
	V20	64.0%	48.2%
	V30	52.5%	38.2%
	D10	25.6	19.8
Bladder (Gy)	D20	24.4	16.7
	D30	24.1	14.2
	Dmax	45.0	36.2
	Dmean	24.3	12.5
	V10	100.0%	59.0%
	V20	99.0%	9.5%
	V30	5.3%	0.4%

3D-RT: Conformational radiation therapy; VMAT: Volumetric intensity-modulated arc therapy; PTV: Planned target volume; Gy: Gray; D10, D20, D30: Doses delivered to 10%, 20% and 30% of critical organs volumes, respectively; V10, V20, V30: Volumes of critical organs that received 10 Gy, 20 Gy and 30 Gy, respectively; R: Right; L: Left.

VEGF rate has halved (633 pg/mL) and radiological controls showed a local tumoral regression.

Comparing VMAT and 3D-RT plans, 99% of the target volume received 95% of prescribed dose with either technique. However, dose homogeneity was improved for VMAT. For the doses delivered to the PTV, standard deviations were 2.9 Gy and 1.6 Gy for 3D and VMAT, respectively. VMAT resulted in substantial critical organ sparing. Dose delivered to 20% of organ volume (D20) was reduced from 22 Gy (3D-RT) to 15 Gy (VMAT) for small bowel, from 24 Gy (3D-RT) to 17 Gy (VMAT) for bladder and from 47 Gy (3D-RT) to 3 Gy (VMAT) for spinal cord. The volume that received at least 20 Gy (V20) was lower with the use of VMAT than with 3D-RT (V20 bladder: 10% *vs* 99%; V20 small bowel: 6% *vs* 21%). Radiation doses delivered to critical organs according conformal radiotherapy or VMAT are reported in Table 1. Isodoses (Gy) and dose-volume histograms are presented for 3D-RT and VMAT plans in Figures 1 and 2, respectively.

DISCUSSION

In our report, we describe the use of VMAT for localized POEMS syndrome. To our knowledge, there are no previous reports of this technique in the medical literature for osteosclerotic myeloma. The course of POEMS syndrome is frequently chronic and patients may survive four times longer than in multiple myeloma. Dispenzieri *et al*^{3,61} reported a median overall survival of 165 mo in their series of 99 patients. RT given in a dose of 40 to 50 Gy is a commonly accepted first-line treatment for single or multiple osteosclerotic lesions. Indeed, the benefit of radiation correlates with a drastic decrease in symptoms and improvement in survival. However, RT is also associated with acute and chronic toxicities that might potentially affect the quality of life of long-survivor patients. Although we did not have sufficient follow-up to accurately evaluate local control or survival, the risk of long-term severe morbidity increases as the radiation doses delivered to critical organs increases. Highly conformal RT allows efficient target coverage and sparing of organs at risk, such as spinal cord, small bowel or bladder. VMAT is a new form of intensity modulated radiotherapy (IMRT) optimization combining one gantry rotation and variable dose-rate, variable gantry speed and a dynamic multi-leaf collimator. It was recently introduced in clinical practice for comparison to conventional RT modalities in various malignancies, including brain, prostate, head and neck, anal canal, and cervix tumors⁷⁻¹². Our report describes the potential interest of VMAT for osteosclerotic myeloma for both increasing dose homogeneity to the PTV and decreasing the dose to the critical organs. Moreover, sparing of critical organs may allow patients that develop widespread lesions or who did not respond to RT to receive further systemic therapies in the future. Also, as in our case, blood VEGF levels may be used as a surrogate marker

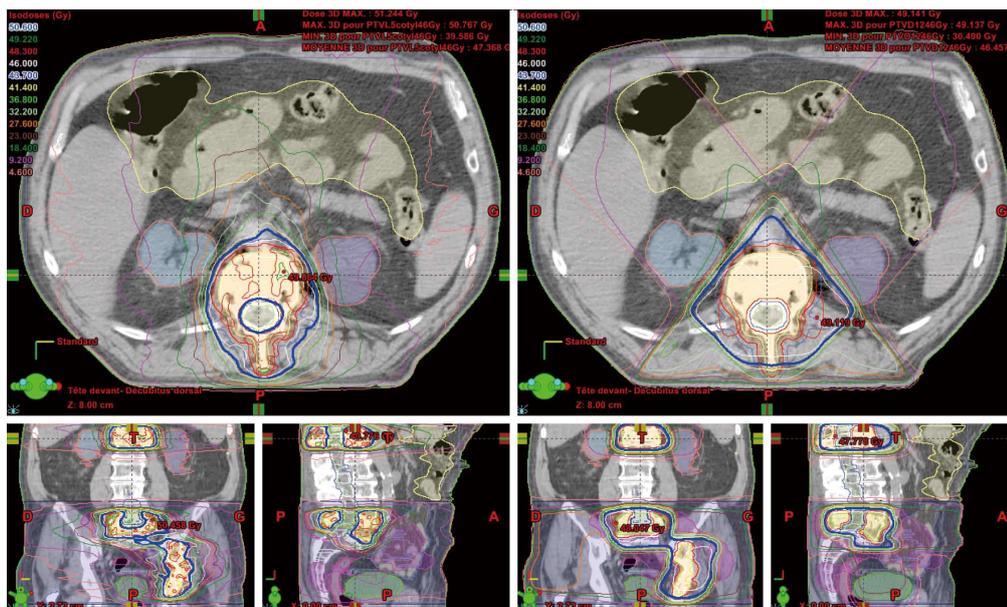


Figure 1 Isodoses (Gray) according to treatment plan: volumetric intensity-modulated arc radiotherapy (right side) and conformal tridimensional radiotherapy (left side).

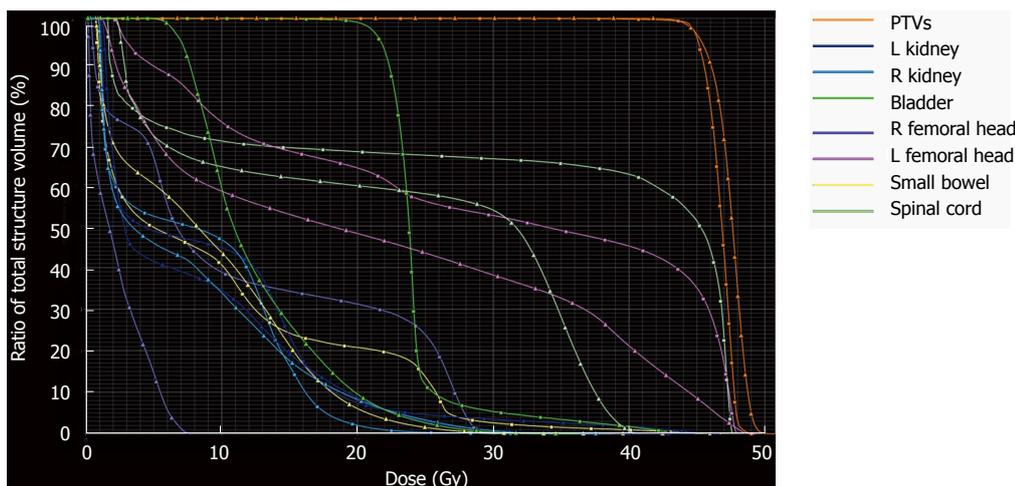


Figure 2 Dose volume histograms for the two treatment plans: Volumetric intensity-modulated arc radiotherapy (triangles) and tridimensional conformal radiotherapy (squares). L: Left; R: Right; Gy: Gray; PTVs: Planning target volumes.

of disease after completion of RT, and then be useful in deciding whether systemic therapy should be added^[14].

VMAT does, however, have some limitations, principally a larger volume of normal tissues receiving low doses irradiation. By using IMRT techniques, it was previously demonstrated that the volume exposed to low doses was increased. This may be particularly important for patients with long survival, where heterogeneous low-dose volume may increase the incidence of second malignancies^[15]. Nevertheless, treatment duration and monitor units are decreased with VMAT compared to conventional IMRT, which can potentially affect the risk of developing a second cancer^[16]. Our study is the first to report the possible use of arc-based RT for POEMS. In other haematological malignancies, Chargari *et al*^[17] reported the feasibility of helical tomotherapy in patients

with paramedullary solitary plasmocytoma. In their experience, helical tomotherapy improved the dose homogeneity within the PTV and resulted in a more efficient sparing of critical organs, when compared to 3D-RT. Although improvement in normal tissue sparing and target coverage is suggested for tomotherapy compared to conventional IMRT, other authors reported that VMAT offered dosimetric qualities comparable to that of helical tomotherapy^[18,19].

In conclusion, VMAT allowed improved dose distribution in comparison to 3D-RT for limited osteosclerotic myeloma. In fact, VMAT achieved higher dose homogeneity within the PTV and better saving of critical organs. The benefit of new highly conformal RT techniques should be further examined in larger series of patients.

COMMENTS

Background

There is no strong consensus on the appropriate management of limited osteosclerotic myeloma. Radiation therapy (RT) is generally employed for limited disease. The authors aimed to assess the feasibility of volumetric intensity-modulated arc radiotherapy (VMAT) in patients with limited polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin change syndrome.

Research frontiers

VMAT is a new RT modality that allows rapid delivery of highly conformal dose distributions, critical organs sparing and is currently used for various tumor localizations. A dosimetric comparison of the VMAT plan with the conventional tridimensional conformal (3D) plan was performed to assess the potential dosimetric benefit of VMAT in sparing critical organs from detrimental irradiation.

Applications

VMAT may provide a clinical and dosimetric benefit over 3D-RT techniques in limited osteosclerotic myeloma.

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VMAT allowed improved dose distribution in comparison to 3D-RT for limited osteosclerotic myeloma. Moreover, VMAT achieved higher dose homogeneity within the planned target volume and better saving of critical organs. The benefit of new highly conformal RT techniques should be further examined in larger series of patients.

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