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ORIGINAL ARTICLE

Salvage Radiotherapy to the Prostatic Fossa Using Volumetric-modulated Arc Therapy: Early Results

EKC Lee, KK Yuen, WH Mui, GML Law, CMM Lui, MKH Chan, FCS Wong, SY Tung

Department of Clinical Oncology, Tuen Mun Hospital, Tuen Mun, Hong Kong

ABSTRACT

Objectives: *Volumetric-modulated arc therapy (VMAT) is better than intensity-modulated radiotherapy (IMRT) in terms of its plan qualities and efficiency for the treatment of prostate cancer. It remains unclear whether its use in salvage radiotherapy to prostatic fossae is safe and effective. Herein we report the dosimetric and clinical results of salvage radiotherapy to prostatic fossae using VMAT.*

Methods: *Fifteen consecutive patients with a rising prostate-specific antigen after radical prostatectomy in our institution received salvage radiotherapy using VMAT. Prostate-specific antigen control and acute toxicities within 1 year after treatment were retrospectively reviewed. For comparison, IMRT plans were also generated for 12 of these patients and the quality of these plans in terms of organ-at-risk sparing (volume of bladder and rectum receiving 60 and 70 Gy), target coverage (conformation number and the prescribed dose of D90), and the number of monitor units.*

Results: *After salvage radiotherapy using VMAT, all patients had a decrease in their prostate-specific antigen with a complete response rate of 87%. The recorded toxicities were rectal bleeding, tenesmus, urinary frequency, nocturia, and urinary incontinence. After a median follow-up of 20 months, two patients endured treatment failure. There was no significant difference between the VMAT and IMRT plans in terms of quality. The mean number of monitor units by VMAT (488) was significantly smaller than that used by IMRT (519) [$p < 0.001$]. The mean beam-on time was 171 (range, 92-228) seconds with treatment delivered by VMAT.*

Conclusions: *It is efficient, effective, and safe to use VMAT as salvage radiotherapy to the prostatic fossa.*

Key Words: *Prostatic neoplasms; Prostate-specific antigen; Radiotherapy, intensity-modulated; Research design; Salvage therapy*

中文摘要

前列腺窩的挽救性弧形調控放射治療：早期結果報告

李家齊、袁國強、梅永豪、羅文龍、雷鳴明、陳加慶、黃志成、董煜

目的：按質素和效率，弧形調控放射治療（VMAT）醫治前列腺癌比調強適形放射治療（IMRT）優勝。可惜，目前還未清楚VMAT作為挽救性治療前列腺窩是否安全和有效。本文報告使用VMAT作挽救性治療前列腺窩的劑量學和臨床結果。

方法：連續15名在本院接受前列腺癌根治術後，前列腺特異性抗原（PSA）水平上升的患者，他們

Correspondence: *Dr Eric KC Lee, Department of Clinical Oncology, Tuen Mun Hospital, Tuen Mun, Hong Kong.*
Tel: (852) 2468 5087; Fax: (852) 2468 5097; Email: leekc4@ha.org.hk

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均接受使用VMAT作挽救性放射治療。治療後一年內分析患者的PSA水平控制和急性毒性狀況。為方便比較，同時為其中12名患者制定IMRT計劃，根據正常組織照射（膀胱和直腸照射劑量為60及70 Gy）、目標器官覆蓋（構象數量和處方劑量D90）及機器跳數的結果，找出兩個計劃的質素。

結果：使用VMAT作挽救性放射治療後，所有患者的PSA水平均有減少，有87%患者達至完全緩解。患者的毒性反應有直腸出血、裡急後重、尿頻、夜尿和尿失禁。隨訪期中位數20個月後，兩名病人的治療失敗。VMAT和IMRT計劃在質量方面沒有顯著差異。VMAT（488）的平均機器跳數明顯少於IMRT（519）（$p < 0.001$）。VMAT的平均束治療時間為171秒（介乎92-228秒）。

結論：使用VMAT作挽救性放射治療前列腺窩是高效、有效和安全的。

INTRODUCTION

Prostate cancer, being the most common non-cutaneous malignancy among men in the western countries, is also the third leading male cancer in Hong Kong.[1] Increasing public and physician awareness in the Chinese community has led to detection of this disease at an earlier stage, when it is still amenable to radical surgery or radiotherapy (RT). Because of recent advances in operative management, such as robotic-assisted laparoscopic prostatectomy, many patients choose radical surgery as the preferred option. Nevertheless, many still endure local failure as a result of positive surgical margins or residual disease from extraprostatic extension (pT3), and need adjuvant radiotherapy (ART) or salvage radiotherapy (SRT) to the prostatic fossa.[2] While ART may run the risk of treating patients who will never experience recurrence, there is Level 2a evidence supporting SRT initiated at the lowest possible prostate-specific antigen (PSA).[3] With a PSA level of 0.2 ng/ml or less before SRT, the 5-year PSA relapse-free survival could reach 64%. In fact, three open randomised controlled trials comparing SRT and ART are now under way: RADICALS,[4] GETUG-17,[5] and RAVES,[6] and their results may provide further information on the optimum timing of SRT.

The challenges of post-prostatectomy RT are the difficulty in determining the clinical target volume (CTV) and its close proximity to the rectum and bladder. Since its introduction in the 1990s, intensity-modulated radiotherapy (IMRT) has enabled radiation oncologists to deliver a higher dose of radiation to treat patients with prostate cancer, including those who have residual disease at the prostatic fossa, without causing much bowel and urinary radiation damage.[7,8] In IMRT, multiple static beams with different beam angles and multileaf collimators are used to create a highly complex and conformal dose profile. In recent years, a novel form of IMRT called volumetric-modulated arc therapy (VMAT) has attracted much interest because of its capability of delivering radiation doses dynamically during rotation of the gantry. With further beam modulations including varying the motions of leaves, gantry speed and dose rate, the radiation intensity from each beam direction is non-uniform in VMAT. While VMAT has the disadvantage of requiring extra time and effort in the inverse planning and optimisation process, several dosimetric studies have shown it is superior to IMRT in terms of its plan qualities and treatment efficiency for prostate cancer treatment.[9-11] However, none of them have reported the acute toxicities and efficacy of using VMAT in the postoperative setting.

Since October 2010, we have started using VMAT to deliver RT to the prostatic fossae of patients who require further local treatment after radical prostatectomy. Here we report the treatment outcomes of patients who received SRT for an increasing PSA after radical prostatectomy. We also compared the dosimetry of VMAT plans and IMRT plans. To our knowledge, this is the first report on the clinical results of using VMAT in this setting.

METHODS

Patient Selection and Contouring

The treatment records and clinical data of 15 patients who had completed a follow-up period of at least 12 months after SRT with VMAT were reviewed. These patients were selected for SRT on the basis of recommendations from Stephenson et al[12]: a pre-SRT PSA higher than 0.2 ng/ml but lower than 4.0 ng/ml. Routine bone scintigraphy and magnetic resonance imaging of the pelvis were not mandatory for these patients. However, the patients had to have recovered fully from the surgery with no significant urinary

incontinence. A planning computed tomography (CT) scan was performed for each patient with 3-mm slice thickness. CTVs were determined with reference to one of the published consensus guidelines.[13-15] The usual boundaries of the CTV are: inferiorly at 5 mm below the urethral anastomosis, anteriorly at the posterior aspect of the symphysis pubis or posterior third of bladder, laterally at the medial border of the obturator internus and levator ani muscles, posteriorly at the anterior mesorectal fascia and superiorly 5 mm above the surgical bed. The planning target volume (PTV) was defined as CTV with a margin of 5 mm posteriorly and 1 cm in all other directions. Organ at risk (OAR) included the rectum, bladder, and both femoral heads. No patient in this cohort received pelvic nodal irradiation or androgen deprivation.

Dosimetric Evaluation and Plan Comparison

VMAT plans were generated by the SmartArc module (version 9.0) of the Pinnacle Treatment Planning System (Philips Medical System, Fitchburg [WI], USA). Plan quality was optimised with the Direct Machine Parameter Optimization algorithm. Step-and-shoot IMRT plans were also generated using the same planning system for 12 of the patients. Target coverage was assessed by comparing the conformation number (CN)[16] and the dose received by 90% of the PTV relative to the prescribed dose (D90). OAR sparing was evaluated by comparing the volume of bladder receiving 60 Gy (VB60) and 70 Gy (VB70), and the volume of rectum receiving 60 Gy (VR60) and 70 Gy (VR70). The numbers of monitor units (MUs) used by IMRT and VMAT were also compared.

A paired *t* test was used to compare each result for IMRT and VMAT plans, with a resulting p value of <0.05 considered statistically significant. All statistics were calculated using the SPSS program for Windows (version 11.0, SBAS, Hong Kong).

Treatment Delivery

For each patient, VMAT was delivered using the Elekta XVI Synergy S model with daily cone beam CT as image-guided radiotherapy (IGRT). Treatment was delivered when the patient was breathing freely. All the patients were treated in the supine position, immobilised in a home-made body frame conformed to the patient's body contour. A bladder scan was performed to ensure that each time he had a comfortably full bladder. The beam-on time of each treatment was retrieved through the MOSAIQ record and verification system.

Clinical Evaluation

Patients were seen weekly by medical officers who recorded their complaints during the treatment period. After SRT, patients were then followed up clinically with the PSA level being monitored about every 3 months. Acute toxicities within the first year of commencing RT were retrospectively reviewed and graded according to Common Terminology Criteria for Adverse Events v3.0. Treatment failure was defined as a PSA level of 0.2 ng/ml greater than the post-salvage nadir, and this had to be confirmed with a second increasing PSA level.[12]

This study was conducted with the approval of our institution's Clinical Research and Ethics Committee.

RESULTS

Patients

The patients' median age was 73 (57-78) years and the median level of their pre-RT PSA was 0.4 (range, 0.2-2.6) ng/ml. Eleven patients had positive or close surgical margins in their prostatectomy specimens. Only one patient had a Gleason sum of 3 + 5 while all the others had a Gleason sum of 7 or less (Table 1). The median time from surgery to start of SRT was 24 (range, 5-84) months.

Treatment Delivery

Seven patients were treated with one arc and eight with two arcs. The mean beam-on time was 171 (range, 92-228) seconds. The mean number of MUs by VMAT (2 Gy per fraction) was 488 (range, 363-703), which was significantly lower than that generated by IMRT plan (mean = 519; range, 384-660; $p < 0.001$).

Table 1. Tumour characteristics by Gleason score and pathological T-stage.

	No. of patients
Gleason score	
3+3	7
3+4	4
4+3	3
3+5	1
Pathological T-stage	
2a	2
2b	1
2c	7
3a	4
3b	1

Target Coverage

The mean PTV was 118 (range, 61-238) cc. The prescribed dose to PTV was 2 Gy per daily fraction to 66 Gy in three patients and 70 Gy in 12. The minimum and maximum point dose in the PTV was 88-99.7% and 103.4-108% of the prescribed dose, respectively. The mean CN by VMAT plans was 0.83 (range, 0.73-0.90) while the mean D90 was 101.8% (range, 101.1-102.6%). IMRT plans were also generated for 12 patients. The mean CN by IMRT plans was 0.83 (range, 0.75-0.91), while the mean D90 was 101.9% (range, 101.1-102.7%). There was no statistically significant difference between the VMAT plans and IMRT plans in terms of their CN and D90.

Organ at Risk

The maximum point dose to the bladder was 73.3 Gy while the maximum point dose to the rectum was 73 Gy. The volume of bladder receiving 60 Gy (VB60) and 70 Gy (VB70), and the volume of rectum receiving 60 Gy (VR60) and 70 Gy (VR70) are illustrated in Figures 1 and 2; their corresponding values using the IMRT plan are also shown for comparison. There was no significant statistical difference between IMRT plans and VMAT

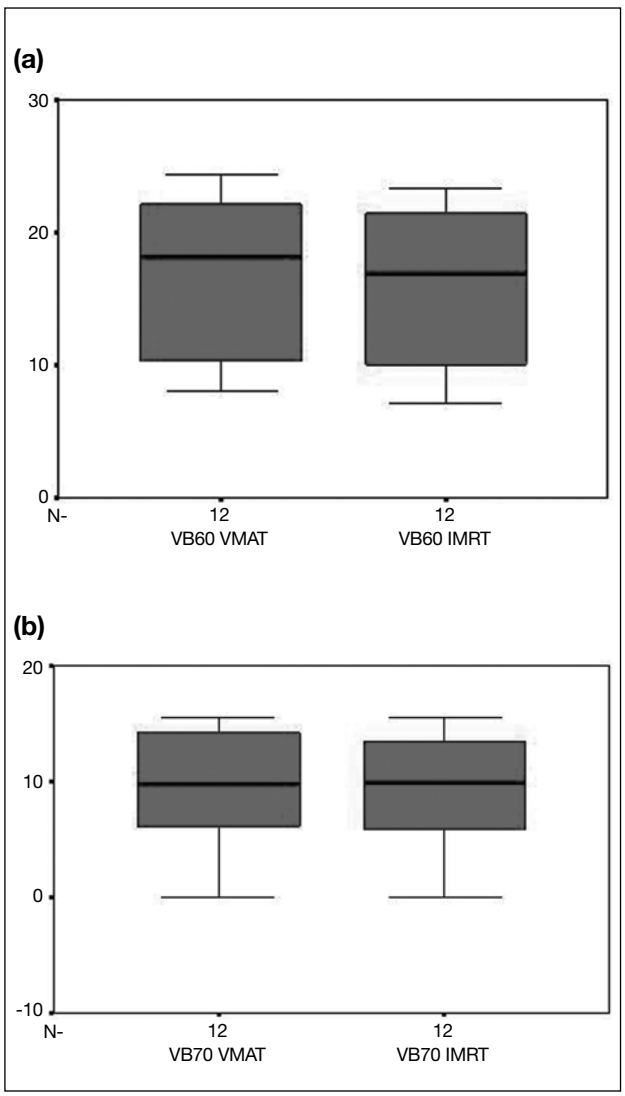

Figure 1. Volume of bladder receiving (a) 60 Gy and (b) 70 Gy by volumetric-modulated arc therapy (VMAT) and intensity-modulated radiotherapy (IMRT). The horizontal lines within the boxes represent the medians, the lower and upper bounds of the boxes represent the 25th and 75th percentiles, and the I bars represent the 5th and 95th percentiles.

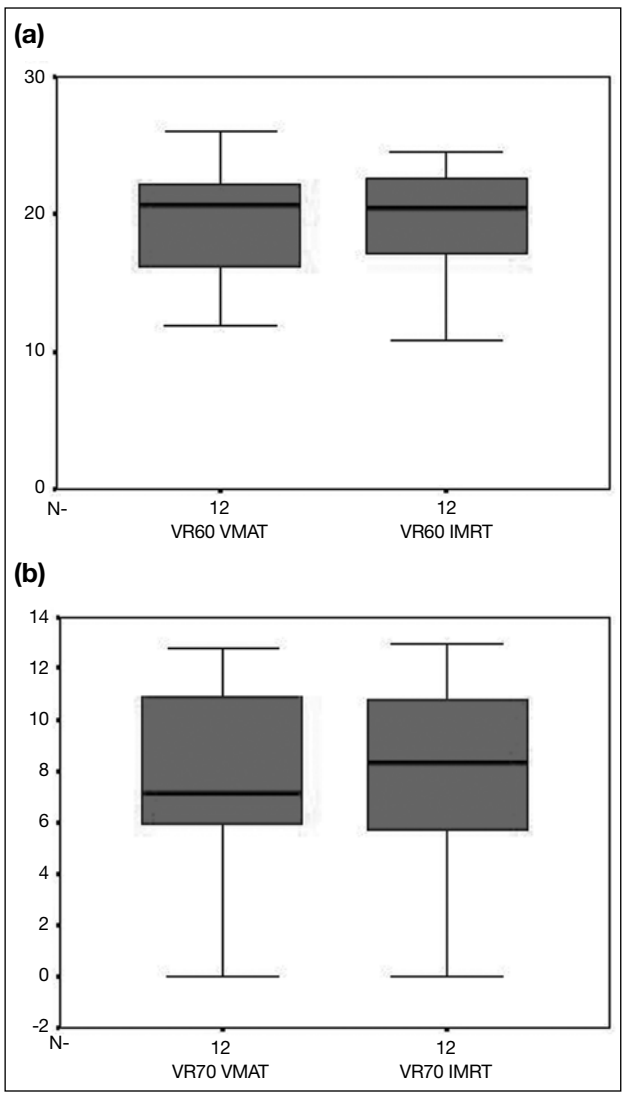

Figure 2. Volume of rectum receiving (a) 60 Gy and (b) 70 Gy by volumetric-modulated arc therapy (VMAT) and intensity-modulated radiotherapy (IMRT). The horizontal lines within the boxes represent the medians, the lower and upper bounds of the boxes represent the 25th and 75th percentiles, and the I bars represent the 5th and 95th percentiles.

plans for each of these parameters. The diagrams of the isodose distributions of the VMAT plans and IMRT plans belonging to one of the patients are also shown in Figure 3.

Treatment Outcome

With a median follow-up time of 20 (range, 12.4-24) months, all patients were still alive at the publication of this paper. Table 2 summarises treatment efficacy in terms of PSA responses. All the patients responded to treatment in terms of PSA values at 3 to 5 months after SRT. Thirteen of them (87%) had achieved a complete response according to the definition of Stephenson et al.[17] Furthermore, in 10 patients the PSA still remained undetectable at the last follow-up. Two patients failed treatment but are still asymptomatic and not receiving additional treatment.

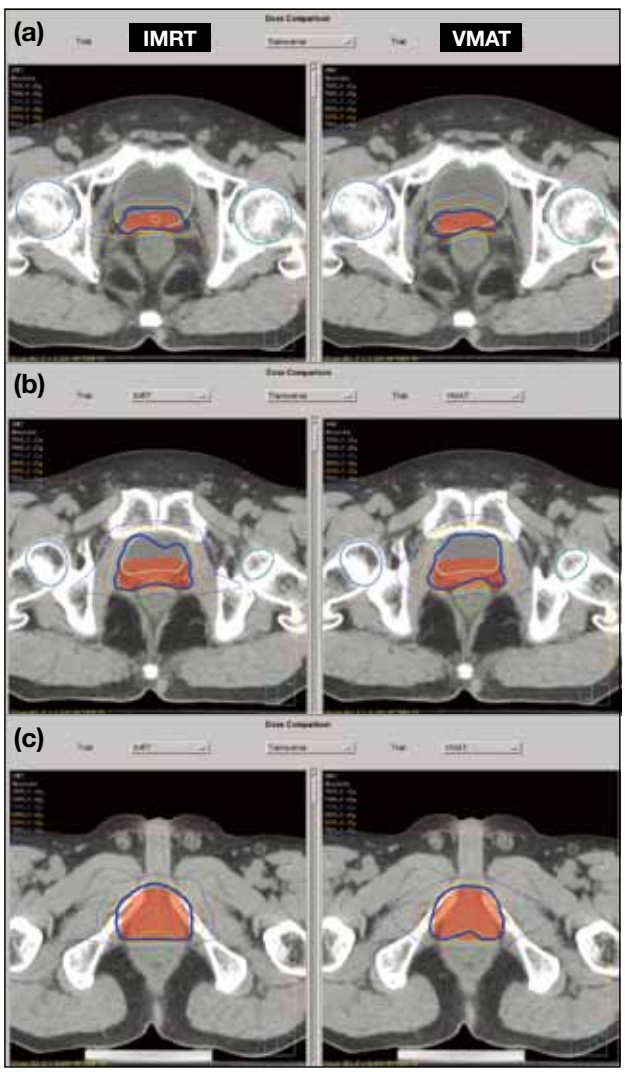

Figure 3. Intensity-modulated radiotherapy (IMRT) and volumetric-modulated arc therapy (VMAT) plans of a patient: (a) most superior, (b) centre, and (c) most inferior of planning target volume.

Acute Toxicities

Table 3 summarises acute toxicities within the first year of SRT. The most common complaints were: rectal bleeding (described as blood-stained toilet paper) in four patients, tenesmus (described as increase in bowel motion to 2 to 3 times per day without change in stool consistency) in two patients, urinary frequency in four patients, nocturia in three patients, and urinary incontinence in one patient.

DISCUSSION

Davidson et al[10] showed that VMAT improves efficiency of delivery for equivalent dosimetric quality as IMRT and helical tomotherapy, across various prostate cancer treatment volumes in the intact and postoperative settings. Kopp et al[9] also demonstrated that VMAT therapy for prostate cancer has dosimetric advantages for critical structures, notably for high-

Table 2. Treatment outcome in terms of prostate-specific antigen (PSA) level control before and after salvage radiotherapy (RT).

Patient No.	PreRT-PSA (ng/ml)	Nadir PSA (ng/ml)	PSA at last follow-up (ng/ml)
1	0.6	0.5	0.8
2	0.9	<0.1	<0.1
3	0.2	<0.1	<0.1
4	2.6	<0.1	<0.1
5	0.7	0.2	0.2
6	0.6	<0.1	<0.1
7	1.5	0.1	0.1
8	0.2	<0.1	<0.1
9	0.3	<0.1	<0.1
10	0.4	<0.1	<0.1
11	0.2	0.1	0.2
12	0.4	<0.1	<0.1
13	0.2	0.1	0.7
14	1.1	<0.1	<0.1
15	0.4	<0.1	<0.1

Table 3. Acute toxicities within the first year of salvage radiotherapy.

Acute toxicity	No. of patients	CTCAE grade
Rectal bleeding	4	1
Proctitis (tenesmus)	2	1
Urinary frequency	4	1
Nocturia	3	1
Urinary incontinence	1	1

Abbreviation: CTCAE = Common Terminology Criteria for Adverse Events.

dose regions compared with fixed-field IMRT, without compromising PTV coverage. The MD Anderson Cancer Centre[11] also demonstrated the superior plan quality as well as the delivery efficiency of VMAT compared with that of IMRT, and agreed that VMAT may be the preferred modality for treating prostate cancer. Although the advantages of VMAT in prostatic cancer management has been shown by many investigators, research providing clinical outcomes from its use in postprostatectomy patients is sparse. Accordingly, the objective of this study was to report the PSA response as well as the acute gastrointestinal and genitourinary toxicity associated with VMAT. Overall, we observed a favourable response rate and toxicity profile among patients receiving SRT with VMAT.

Currently, we do not offer ART on a routine basis because patients often complain of some degree of urinary incontinence after radical prostatectomy, causing concern over increased bladder toxicities after RT. Our policy is to observe patients closely when they are still recovering from surgery and to offer SRT once they have an increasing PSA level. This approach is effective in this patient cohort, when the PSA level before SRT is still low (median, 0.4 ng/ml). All men have responded in that 87% had a complete PSA level response. However, longer follow-up is still needed to draw further conclusions on long-term disease control.

In a recent survey using the Surveillance, Epidemiology, and End Results database, Goldin et al[18] noted a significant increase in IMRT use for postoperative RT in the United States. It was shown that IMRT reduces OAR irradiation compared with 3D conformal radiation therapy. However, drawbacks of IMRT include prolonged beam delivery time and increased number of MUs. The long beam-on time may worsen the accuracy of treatment due to increased intra-fractional patient motion. Furthermore, patient throughput is reduced with economical consequences. Another issue of concern is the increased MUs required in IMRT treatment, which could lead to a higher incidence of secondary malignancies after curative treatment.

Our experience has provided solutions to the above problems. By using VMAT instead of IMRT, the number of MUs was reduced. This has led to shorter beam-on time, which is advantageous in terms of patient comfort and treatment resources. All the VMAT treatment can be completed within 4 minutes, compared with 5-8 minutes when a 7-field static beam IMRT is used. The reduction in MUs can also translate to a lower integral dose, thus minimising the risk of developing radiation-induced malignancy. In fact, VMAT treatment for prostate has been shown to be 55% faster than step-and-shoot IMRT with equivalent or better dosimetric parameters.[19] In this patient cohort, all VMAT plans have met dose constraints in terms of the VR60, VR70, VB60, and VB70. These parameters also remain comparable if the IMRT plan were to be used. Concerning target coverage, VMAT plans are also non-inferior to IMRT plans with similar CN and D90.

In terms of normal tissue complications, our patients did not experience excessive bowel and urinary toxicities after SRT. Since this was a retrospective analysis, we cannot compare patient symptoms and quality of life before and after treatment. Nevertheless, our findings with VMAT confirmed its safety when used in the setting of SRT to the prostatic fossa. In line with the model of King and Kapp[20] for dose escalation in the postoperative setting, we can postulate that greater RT doses in the range of 70-74 Gy are practical and safe, so long as good techniques such as VMAT and IGRT are adopted.

The limitations of our study include the short follow-up time and the small number of patients. Further follow-up is still needed to provide late toxicity data and long-term relapse-free survival, as prostate cancer tends to relapse late. Nonetheless, our clinical experience has demonstrated the efficiency, effectiveness, and safety of using VMAT as SRT to the prostatic fossa. The dosimetric and treatment delivery advantage should lead to its use in future clinical trials.

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